Highly Regio- and Stereoselective Synthesis of Tetracyclic Indoleno-isoxazolidines via Intramolecular 1,3-Dipolar Nitrone Cycloadditions

Manickam Bakthadoss,*[a,b] Govindan Sivakumar,[a] Duddu S. Sharada[c]

[a] Department of Organic Chemistry, University of Madras, Guindy Campus, Chennai, 600 025, India
Fax +91(44)22352494; E-mail: bhakthadoss@yahoo.com

[b] Department of Chemistry, Pondicherry University, Pondicherry 605 014, India

[c] Department of Chemistry, Indian Institute of Technology, Hyderabad 502 205, India

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Abstract: A facile method for the simple synthesis of tetracyclic indoloisoxazolidine frameworks from Baylis–Hillman derivatives through formation of nitrones in situ followed by an intramolecular [3+2]-dipolar cycloaddition reaction sequence is described. High regio- and stereoselectivity, excellent yields, together with the creation of two rings and three contiguous stereogenic centers including one all carbon quaternary center, are the salient features of the present method.

Key words: fused-ring systems, indoles, 1,3-dipolar cycloaddition, stereoselectivity, regioselectivity

The 1,3-dipolar cycloaddition (1,3-DC) reaction has emerged as a powerful tool in organic synthesis.[1a–c] The isoxazolidines formed through 1,3-DC reactions are important intermediates in the preparation of natural products, such as alkaloids and α-amino acids.[1d] Up to three contiguous stereocenters can be formed through 1,3-DC reactions and the challenge of controlling the absolute and relative stereochemistry has attracted much attention in recent years.[1e,f,2]

Due to the labile nature of the N–O bond under mild reducing conditions, isoxazolidines provide easy access to a variety of fascinating 1,3-difunctional amino alcohols.[3] The intramolecular nitrone-olefin cycloaddition reaction is one of the most powerful synthetic methods for the construction of fused bi-, tri- or tetra-cyclic isoxazolidines of either biological significance or as useful synthetic intermediates for target molecules.[4] In fact, certain fused isoxazolines/isoxazoles with indoleno moieties are already known for their antidepressant, antipsychotic, and anti-anxiolytic activities.

Representative examples of indolizidine-containing natural products[4] such as yuremamine,[5] mitomycin C,[6] isatisine A,[7] flindrole C and isoborreverine[8] are shown in Figure 1.

The Baylis–Hillman reaction is one of the most important carbon–carbon bond-forming reactions in the field of organic chemistry.[9] The Baylis–Hillman adducts and their derivatives are useful building blocks for the synthesis of many natural products and biologically active molecules.[10]

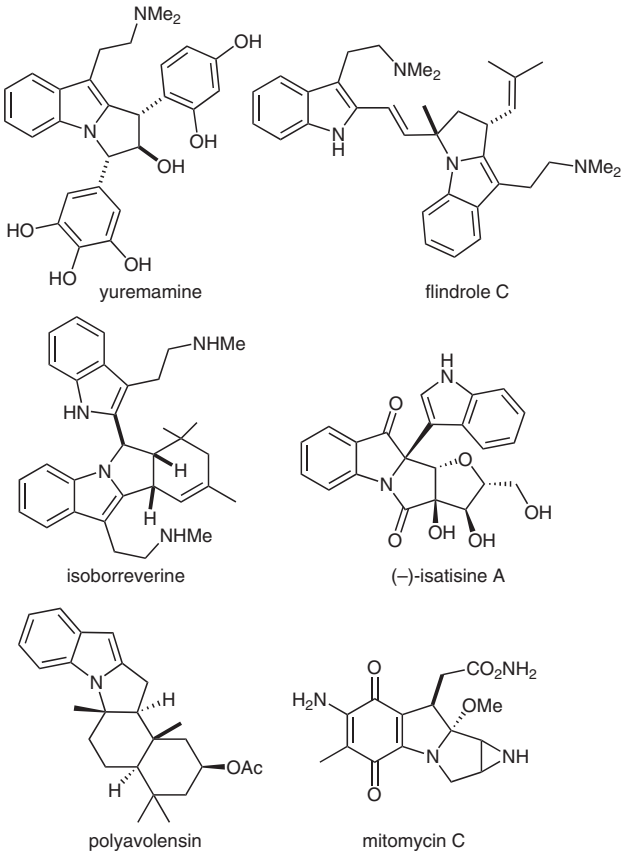

Figure 1 Representative examples of indolizidine-containing natural products

Since indole-fused isoxazoline/isoxazoles are well known for their biological applications, we envisaged that the bromo-derivative of Baylis–Hillman adducts could be exploited to access the skeletons mentioned above. To the best of our knowledge, the Baylis–Hillman derivatives have not been utilized for the synthesis of angularly substituted indole-fused isoxazoline derivatives through nitrone formation followed by intramolecular nitrone cycloaddition. Therefore, we envisaged that Baylis–Hillman derivatives would be suitable substrates for the synthesis of complex angularly substituted tetracyclic indoloisoxazolidines by intramolecular 1,3-dipolar nitrone cycloaddition.

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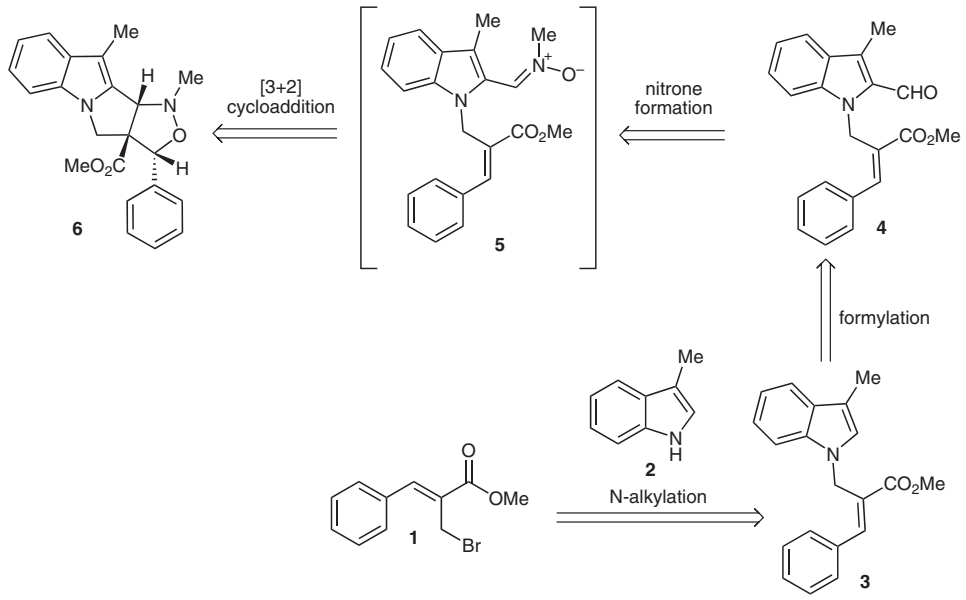
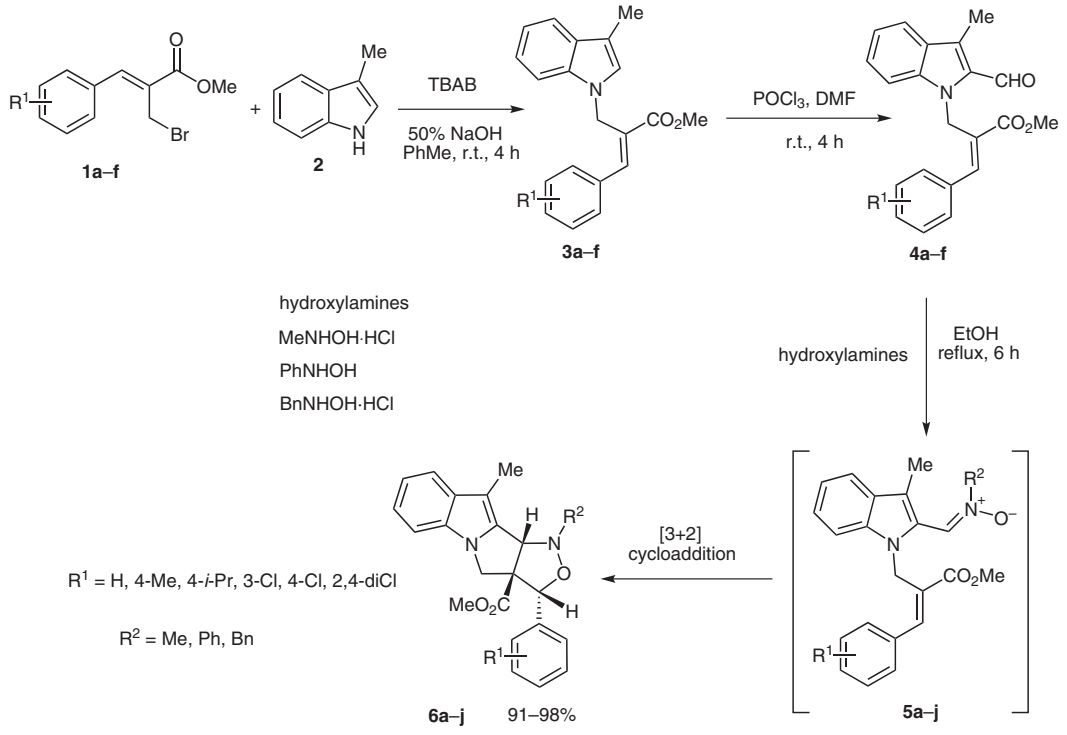


Scheme 1 Retrosynthetic strategy for the synthesis of tetracyclic frameworks

In a continuation of our interest in the field of heterocyclic chemistry,[11] herein we describe a novel protocol for the synthesis of angularly substituted fused tetracyclic indoloisoxazolidines frameworks by using Baylis–Hillman derivatives through formation of nitrone in situ followed by an intramolecular [3+2]-dipolar cycloaddition reaction. Initially we planned to utilize (*Z*)-methyl 2-(bromomethyl)-3-phenylacrylate[11b] (**2**) with 3-methyl indole (**1**) to generate the require N-allylated precursor (**4**) with a view to obtaining the desired tetracyclic frame works **6** through tandem nitrone formation followed by an intramolecular 1,3-dipolar cycloaddition reaction according to the retrosynthetic strategy shown in Scheme 1.

To execute our idea, we first treated (*Z*)-methyl 2-(bromomethyl)-3-phenylacrylate (**1a**) with 3-methylindole (**2**) to obtain N-allylated[12] indole intermediate (**3a**). Further formylation[12] of **3a** led to the corresponding aldehyde **4a** in excellent yield (94%). The catalyst-free reaction of **4a** with *N*-methylhydroxylamine hydrochloride in ethanol at reflux temperature successfully provided the desired tetracyclic indoloisoxazolidine **6a** in excellent yield (95%; Scheme 2).



Scheme 2

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Encouraged by this result, we synthesized a variety of indoloisoxazolidines **6b–j** through application of the intramolecular 1,3-dipolar cycloaddition reaction. Treatment of N-substituted 3-methylindole-2-carboxylaldehydes **4a–f** with *N*-methylhydroxyl amine hydrochloride, *N*-phenylhydroxylamine, or *N*-benzylhydroxylamine hydrochloride in ethanol at reflux temperature successfully provided the desired tetracyclic indoloisoxazolidines **6b–j** in excellent yields (91–98%; Scheme 2, Table 1).

Table 1 Synthesis of Tetracyclic Frameworks **6a–j**

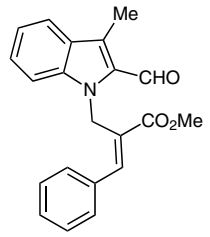
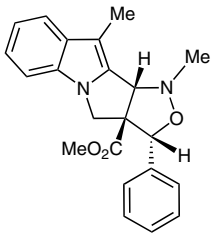
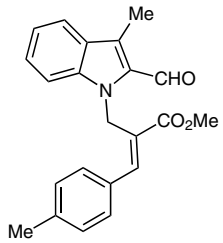
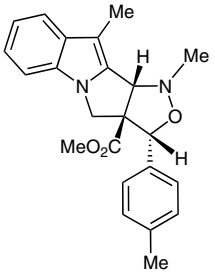
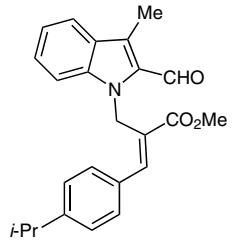
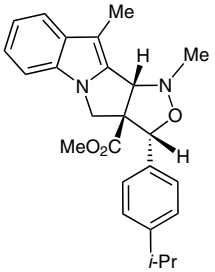
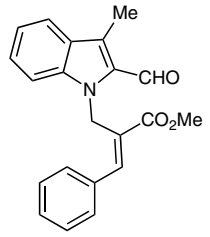
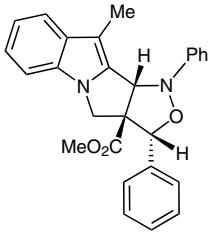
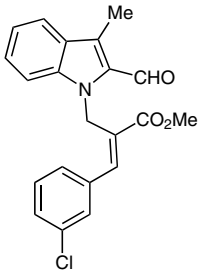
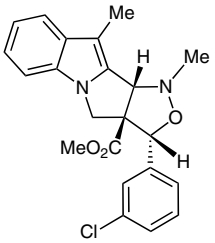
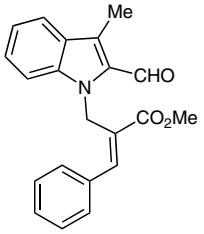
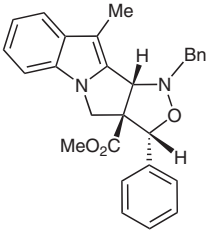
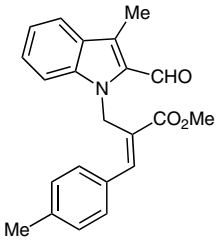
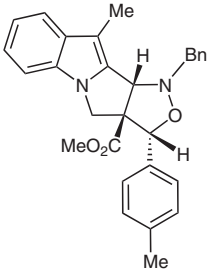
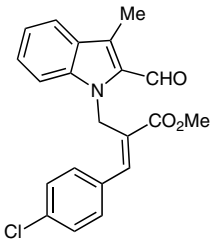
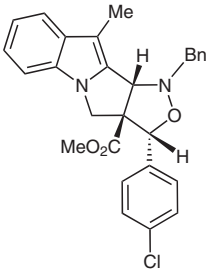
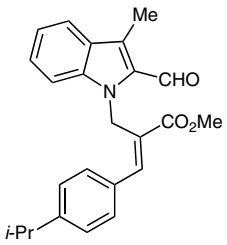
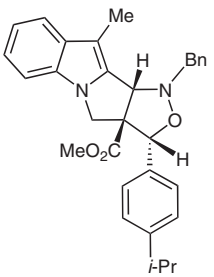
Entry	Substrate	Product[a,b]	Yield (%)[c]
1	 **4a**	 **6a**[d]	95
2	 **4b**	 **6b**	91
3	 **4c**	 **6c**	93
4	 **4a**	 **6d**	97
5	 **4d**	 **6e**	94
6	 **4a**	 **6f**	96
7	 **4b**	 **6g**	98
8	 **4e**	 **6h**	97
9	 **4c**	 **6i**	96

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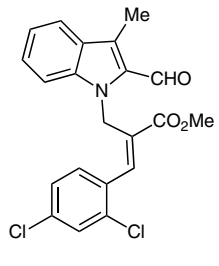
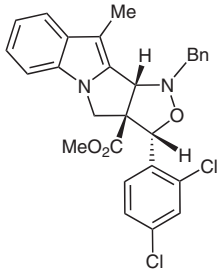
Table 1 Synthesis of Tetracyclic Frameworks **6a–j** (continued)

Entry	Substrate	Product[a,b]	Yield (%)[c]
10	 **4f**	 **6j**	94

[a] Reaction conditions: **4** (1 mmol), *N*-methylhydroxylamine hydrochloride/*N*-phenylhydroxylamine/*N*-benzylhydroxylamine hydrochloride (1.1 mmol), EtOH, reflux, 6 h.
[b] All compounds were fully characterized.
[c] Isolated yield of the pure product.
[d] The structure of the molecule was further confirmed by single-crystal X-ray data.[13]

It is worth mentioning that the highly stereoselective nature of the reaction was clearly shown by ^{1}H NMR spectroscopy and X-ray crystal analyses (Figure 2). The crystal structure of **6a** shows that the phenyl group and the adjacent ester moiety adopt an *anti* orientation, which is presumably due to the initial *trans* geometry of the phenyl group and ester moiety present in the double bond at the vicinal positions of compound **4a**.

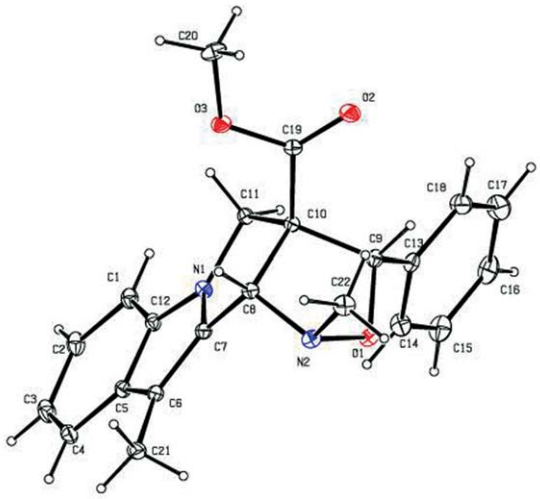


Figure 2 X-ray crystal structure of **6a**

After the successful synthesis of tetracyclic indoloisoxazolidines possessing an ester moiety at the angular position, we planned to synthesize indoloisoxazolidines bearing a nitrile moiety at the angular position. Thus, treatment of N-substituted 3-methylindole-2-carboxylaldehydes **8a–f** with *N*-methylhydroxylamine hydrochloride/*N*-phenylhydroxylamine/*N*-benzylhydroxylamine hydrochloride under similar reaction conditions to those described above successfully provided the anticipated tetracyclic indoloisoxazolidines **11a–j** in excellent yields (92–97%; Scheme 3, Table 2).

Table 2 Synthesis of Tetracyclic Frameworks **11a–j**

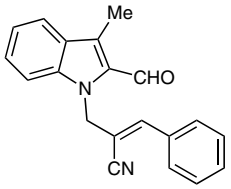
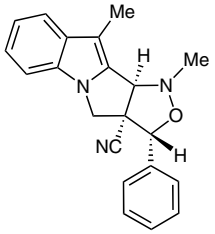
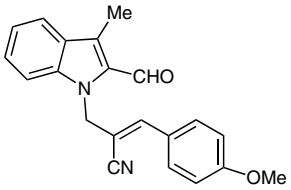
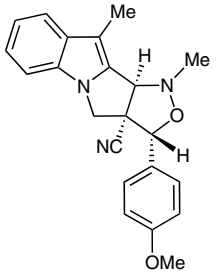
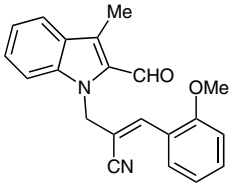
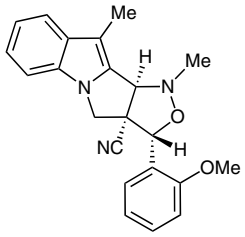
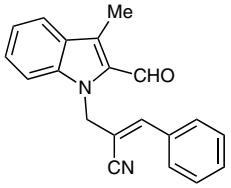
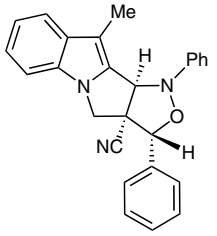
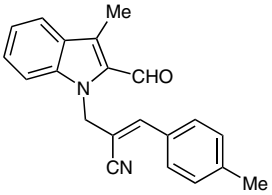
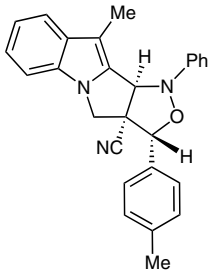
Entry	Substrate	Product[a,b]	Yield (%)[c]
1	 **9a**	 **11a**[d]	95
2	 **9c**	 **11b**	96
3	 **9d**	 **11c**	97
4	 **9a**	 **11d**	95
5	 **9b**	 **11e**	93

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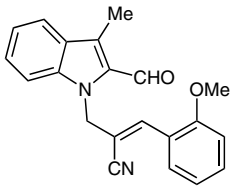
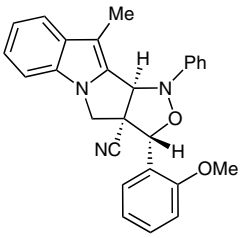
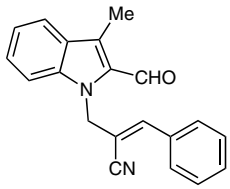
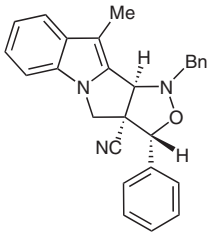
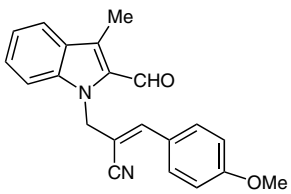
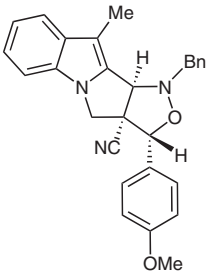
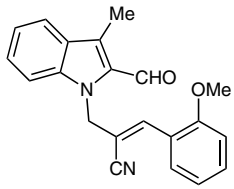
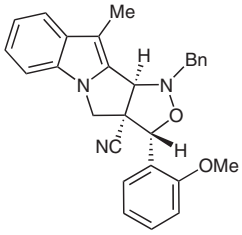
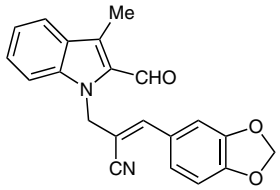
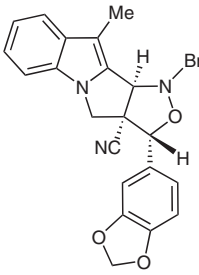
Table 2 Synthesis of Tetracyclic Frameworks **11a–j** (continued)

Entry	Substrate	Product[a,b]	Yield (%)[c]
6	 **9d**	 **11f**	97
7	 **9a**	 **11g**	92
8	 **9c**	 **11h**	94
9	 **9d**	 **11i**	96
10	 **9f**	 **11j**	94

[a] Reaction conditions: **9** (1 mmol), *N*-methylhydroxylamine hydrochloride/*N*-phenylhydroxylamine/*N*-benzylhydroxylamine hydrochloride (1.1 mmol), EtOH, reflux, 6 h

[b] All compounds were fully characterized.

[c] Isolated yield of the pure product.

[d] The structure of the molecule was further confirmed by single-crystal X-ray data.[13]

The relative stereochemistry of compound **11a** was further confirmed by X-ray crystallographic analysis (Figure 3). The X-ray crystal structure of compound **11a** shows that the phenyl group and adjacent nitrile moiety adopt a *syn* orientation, which was presumably due to the initial *cis* geometry of the phenyl group and nitrile moiety present in the double bond at the vicinal positions of compound **8a**.

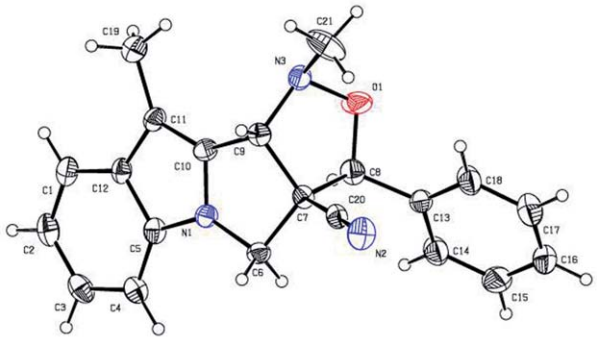


Figure 3 X-ray crystal structure of **11a**

It is important to mention here that the reaction is highly regio- and diastereoselective, as evidenced by NMR spectral data and X-ray crystal data analyses. The negative charge generated on the oxygen atom in intermediates **5** and **10** (see Scheme 2 and Scheme 3) forms an intramolecular bond with the electrophilic carbon at the β-position of the α,β-unsaturated ester/cyano moiety in the same molecule rather than forming a bond at the α-position. Furthermore, if regioisomers **12** and **13** had been formed (Figure 4), two doublets (vicinal coupling constants) corresponding to the H_x and H_y protons would be anticipated in the ^1H NMR spectrum. However, we did not observe such patterns in the spectra of our compounds.

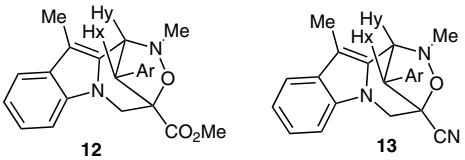


Figure 4 Possible alternative regioisomers

In conclusion, we have successfully developed a simple protocol for the facile synthesis of complex angularly substituted tetracyclic frameworks containing an indoloisoxazolidine ring system involving formation of a nitrone in situ followed by an intramolecular 1,3-dipolar nitrone cycloaddition reaction using Baylis–Hillman derivatives. It is important to mention here that all the indoloisoxazolidines were synthesized under catalyst-free conditions. The new [3+2]-cycloaddition reaction leads to a novel class of angularly substituted fused tetracyclic indoloisoxazolidines, creating two rings, three contiguous stereocenters, one being an all-carbon quaternary center, in a

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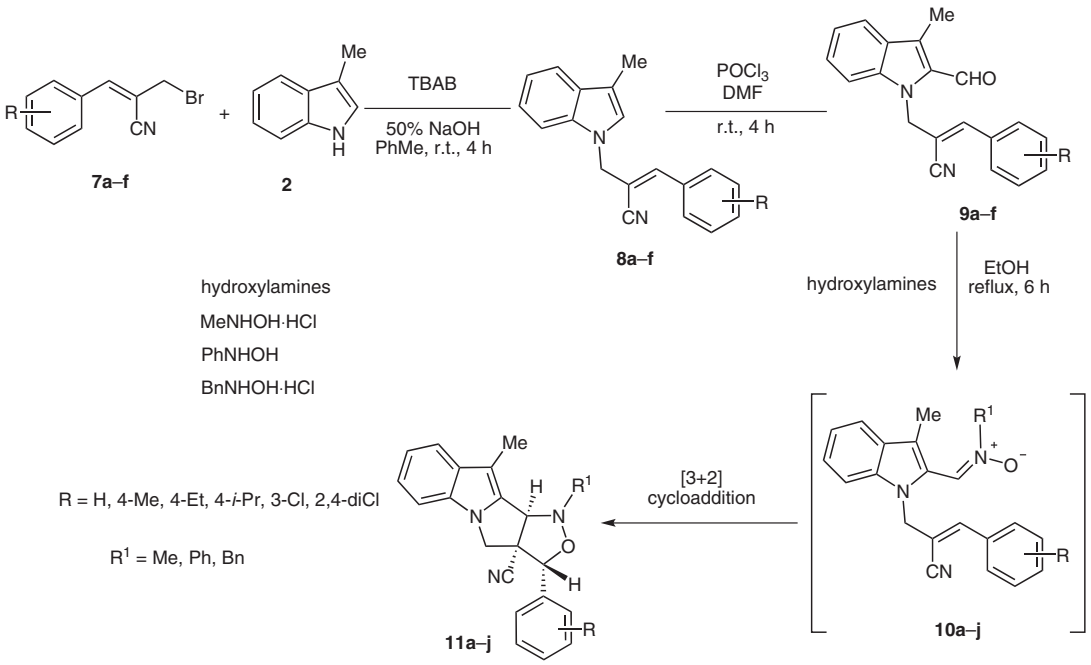

Scheme 3

unique fashion. Angularly substituted tricyclic compounds were obtained in a highly regio- and stereoselective fashion with excellent yields.

All reagents were purchased from commercial sources and used without further purification. Solvents were distilled prior to use. Column chromatography was performed on silica gel. IR spectra were recorded with an FTIR-8300 Shimadzu spectrometer. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded with a Bruker spectrometer using $CDCl_3$ as solvent and TMS as internal standard. MS were recorded with a Jeol-JMS-DX 303 HF mass spectrometer. Elemental analyses were recorded with a Perkin–Elmer 240C-CHN analyzer. Melting points are uncorrected. Thin-layer chromatography (TLC) was performed using glass plates coated with silica gel (ACME, 254F). Spots were visualized using iodine vapor and a UV lamp.

Methyl 8,11-Dimethyl-13-phenyl-12-oxa-1,11-diazatetracyclo[7.6.0.0^{2,7}.0^{10,14}]pentadeca-2(7),3,5,8-tetraene-14-carboxylate (6a); Typical Procedure

A mixture of **4a** (1 mmol) and *N*-methylhydroxylamine hydrochloride (1.1 mmol) and EtOH (5 mL) were placed in a round-bottom flask and heated at reflux for 6 h. After completion of the reaction, as indicated by TLC, the reaction mixture was concentrated under reduced pressure, H_2O (10 mL) was added and the mixture was extracted with EtOAc (20 mL). The organic layer washed with brine (10 mL) and concentrated. The crude product was purified by column chromatography (EtOAc–hexane, 10%) to provide the desired pure product **6a**.

Yield: 0.344 g (95%); white solid; mp 195–197 °C.

IR (KBr): 1729, 1625, 1519, 1217 cm^{-1}.

^{1}H NMR (300 MHz): δ = 2.37 (s, 3 H), 3.03 (s, 3 H), 3.78 (d, *J* = 10.5 Hz, 1 H), 3.88 (s, 3 H), 4.07 (d, *J* = 10.8 Hz, 1 H), 5.16 (s, 1 H), 5.88 (s, 1 H), 7.01–7.56 (m, 9 H).

^{13}C NMR (75 MHz): δ = 9.69, 42.02, 56.73, 52.34, 71.30, 72.21, 83.39, 109.43, 110.56, 118.72, 118.89, 121.38, 121.63, 124.54, 127.09, 128.90, 129.34, 134.42, 136.45, 173.26.

MS: *m*/*z* = 363 [M + 1]$^+$.

Anal. Calcd for $C_{22}H_{22}N_2O_3$: C, 72.91; H, 6.12; N, 7.73. Found: C, 73.19; H, 6.47; N, 7.98.

Methyl 8,11-Dimethyl-13-(4-methylphenyl)-12-oxa-1,11-diazatetracyclo[7.6.0.0^{2,7}.0^{10,14}]pentadeca-2(7),3,5,8-tetraene-14-carboxylate (6b)

Yield: 0.342 g (91%); white solid; mp 201–203 °C.

IR (KBr): 1728, 1625, 1516, 1221 cm^{-1}.

^{1}H NMR (300 MHz): δ = 2.35 (s, 3 H), 2.36 (s, 3 H), 3.03 (s, 3 H), 3.82 (d, *J* = 11.1 Hz, 1 H), 3.87 (s, 3 H), 4.07 (d, *J* = 11.1 Hz, 1 H), 5.16 (s, 1 H), 5.83 (s, 1 H), 7.03–7.56 (m, 8 H).

^{13}C NMR (75 MHz): δ = 9.25, 21.22, 43.99, 47.47, 53.24, 72.59, 72.65, 83.57, 109.62, 119.03, 119.15, 119.24, 121.30, 126.18, 126.61, 129.27, 129.57, 132.30, 133.30, 138.27, 173.16.

MS: *m*/*z* = 377 [M + 1]$^+$.

Anal. Calcd for $C_{23}H_{24}N_2O_3$: C, 73.38; H, 6.43; N, 7.44. Found: C, 73.59; H, 6.55; N, 7.86.

Methyl 8,11-Dimethyl-13-[4-(propan-2-yl)phenyl]-12-oxa-1,11-diazatetracyclo[7.6.0.0^{2,7}.0^{10,14}]pentadeca-2(7),3,5,8-tetraene-14-carboxylate (6c)

Yield: 0.375 g (93%); white solid; mp 209–211 °C.

IR (KBr): 1727, 1621, 1523, 1220 cm^{-1}.

^{1}H NMR (300 MHz): δ = 1.24 (d, *J* = 6.9 Hz, 6 H), 2.36 (s, 3 H), 2.83–3.04 (m, 4 H), 3.88–4.16 (m, 5 H), 5.16 (s, 1 H), 5.84 (s, 1 H), 7.04–7.56 (m, 8 H).

^{13}C NMR (75 MHz): δ = 9.02, 23.90, 23.96, 33.87, 38.76, 47.47, 53.22, 72.63, 77.24, 109.62, 119.01, 119.24, 119.85, 121.26, 124.10, 126.64, 126.69, 127.73, 132.59, 133.31, 149.24, 173.12.

MS: *m*/*z* 405 [M + 1]$^+$.

Anal. Calcd for $C_{25}H_{28}N_2O_3$: C, 74.23; H, 6.98; N, 6.93. Found: C, 73.95; H, 6.91; N, 7.01.

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Methyl 8-Methyl-11,13-diphenyl-12-oxa-1,11-diazatetracyclo[7.6.0.0^{2,7}.0^{10,14}]pentadeca-2(7),3,5,8-tetraene-14-carboxylate (6d)
Yield: 0.411 g (97%); white solid; mp 199–201 °C.

IR (KBr): 1727, 1628, 1514, 1216 cm^{-1}.

^{1}H NMR (300 MHz): δ = 2.39 (s, 3 H), 3.71 (s, 3 H), 3.91 (d, *J* = 10.8 Hz, 1 H), 4.17 (d, *J* = 11.1 Hz, 1 H), 5.73 (s, 1 H), 5.99 (s, 1 H), 7.02–7.59 (m, 14 H).

^{13}C NMR (75 MHz): δ = 8.57, 47.30, 53.17, 72.72, 73.13, 84.61, 109.56, 114.56, 119.15, 119.39, 121.36, 122.50, 126.80, 128.68, 128.79, 129.34, 132.36, 133.49, 134.36, 136.98, 149.65, 172.27.

MS: *m*/*z* = 425 [M + 1]$^+$.

Anal. Calcd for $C_{27}H_{24}N_2O_3$: C, 76.39; H, 5.70; N, 6.60. Found: C, 76.47; H, 5.82; N, 6.52.

Methyl 13-(3-Chlorophenyl)-8-methyl-11-phenyl-12-oxa-1,11-diazatetracyclo[7.6.0.0^{2,7}.0^{10,14}]pentadeca-2(7),3,5,8-tetraene-14-carboxylate (6e)
Yield: 0.373 g (94%); white solid; mp 117–119 °C.

IR (KBr): 1724, 1629, 1523, 1216 cm^{-1}.

^{1}H NMR (300 MHz): δ = 2.37 (s, 3 H), 3.03 (s, 3 H), 3.78 (d, *J* = 10.8 Hz, 1 H), 3.88 (s, 3 H), 4.07 (d, *J* = 11.1 Hz, 1 H), 5.16 (s, 1 H), 5.87 (s, 1 H), 7.01–7.56 (m, 8 H).

^{13}C NMR (75 MHz): δ = 8.34, 41.82, 47.17, 52.30, 71.32, 72.21, 82.27, 120.33, 121.06, 126.22, 126.94, 127.14, 127.28, 128.80, 130.49, 130.83, 131.40, 131.76, 133.70, 134.65, 137.20, 173.26.

MS: *m*/*z* = 398 [M + 2]$^+$.

Anal. Calcd for $C_{22}H_{21}ClN_2O_3$: C, 66.58; H, 5.33; N, 7.06. Found: C, 66.69; H, 5.27; N, 7.15.

Methyl 11-Benzyl-13-phenyl-8-methyl-12-oxa-1,11-diazatetracyclo[7.6.0.0^{2,7}.0^{10,14}]pentadeca-2(7),3,5,8-tetraene-14-carboxylate (6f)
Yield: 0.420 g (96%); white solid; mp 202–204 °C.

IR (KBr): 1727, 1622, 1512, 1223 cm^{-1}.

^{1}H NMR (300 MHz): δ = 2.06 (s, 3 H), 3.78 (d, *J* = 11.1 Hz, 1 H), 3.94 (s, 3 H), 4.07 (d, *J* = 10.8 Hz, 1 H), 4.39 (dd, *J* = 12.3, 19.5 Hz, 2 H), 5.31 (s, 1 H), 5.99 (s, 1 H), 6.94–7.58 (m, 14 H).

^{13}C NMR (75 MHz): δ = 8.30, 47.43, 53.35, 60.29, 71.45, 72.36, 84.55, 104.10, 109.40, 118.91, 119.22, 121.09, 126.82, 127.92, 128.61, 129.90, 132.24, 133.48, 135.15, 136.38, 136.43, 137.43, 173.33.

MS: *m*/*z* = 439 [M + 1]$^+$.

Anal. Calcd for $C_{28}H_{26}N_2O_3$: C, 76.69; H, 5.98; N, 6.39. Found: C, 76.58; H, 5.83; N, 6.76.

Methyl 11-Benzyl-13-(4-methylphenyl)-8-methyl-12-oxa-1,11-diazatetracyclo[7.6.0.0^{2,7}.0^{10,14}]pentadeca-2(7),3,5,8-tetraene-14-carboxylate (6g)
Yield: 0.443 g (98%); white solid; mp 198–200 °C.

IR (KBr): 1732, 1627, 1518, 1219 cm^{-1}.

^{1}H NMR (300 MHz): δ = 2.04 (s, 3 H), 2.34 (s, 3 H), 3.82 (d, *J* = 11.1 Hz, 1 H), 3.92 (s, 3 H), 4.07 (d, *J* = 11.1 Hz, 1 H), 4.39 (dd, *J* = 12, 17.1 Hz, 2 H), 5.30 (s, 1 H), 5.95 (s, 1 H), 6.96–7.58 (m, 13 H).

^{13}C NMR (75 MHz): δ = 8.24, 21.24, 47.40, 53.32, 60.25, 71.37, 72.33, 84.65, 103.96, 109.43, 118.88, 119.21, 121.04, 126.78, 127.91, 128.62, 129.29, 129.94, 131.97, 132.26, 133.49, 136.46, 137.58, 138.45, 173.40.

MS: *m*/*z* = 454 [M + 1]$^+$.

Anal. Calcd for $C_{29}H_{28}N_2O_3$: C, 76.97; H, 6.24; N, 6.19. Found: C, 76.77; H, 6.18; N, 6.59.

Methyl 11-Benzyl-13-(4-chlorophenyl)-8-methyl-12-oxa-1,11-diazatetracyclo[7.6.0.0^{2,7}.0^{10,14}]pentadeca-2(7),3,5,8-tetraene-14-carboxylate (6h)
Yield: 0.459 g (97%); white solid; mp 202–204 °C.

IR (KBr): 1725, 1628, 1516, 1219 cm^{-1}.

^{1}H NMR (300 MHz): δ = 2.08 (s, 3 H), 3.72 (d, *J* = 11.1 Hz, 1 H), 3.93 (s, 3 H), 4.06 (d, *J* = 11.1 Hz, 1 H), 4.36 (dd, *J* = 12, 26.4 Hz, 2 H), 5.32 (s, 1 H), 5.94 (s, 1 H), 6.95–7.56 (m, 13 H).

^{13}C NMR (75 MHz): δ = 8.30, 47.59, 53.42, 60.22, 71.34, 72.15, 83.84, 104.36, 109.41, 119.07, 119.26, 121.27, 127.92, 127.98, 128.27, 128.64, 128.82, 129.79, 132.25, 133.50, 133.77, 134.52, 136.30, 173.16.

MS: *m*/*z* = 474 [M + 1]$^+$.

Anal. Calcd for $C_{28}H_{25}ClN_2O_3$: C, 71.10; H, 5.33; N, 5.92. Found: C, 71.03; H, 5.44; N, 5.86.

Methyl 11-Benzyl-13-[4-(propane-2-yl)phenyl]-8-methyl-12-oxa-1,11-diazatetracyclo[7.6.0.0^{2,7}.0^{10,14}]pentadeca-2(7),3,5,8-tetraene-14-carboxylate (6i)
Yield: 0.461 g (96%); white solid; mp 212–214 °C.

IR (KBr): 1731, 1629, 1516, 1220 cm^{-1}.

^{1}H NMR (300 MHz): δ = 1.17 (d, *J* = 6.9 Hz, 6 H), 1.97 (s, 3 H), 2.81 (sept, *J* = 6.9 Hz, 1 H), 3.77 (d, *J* = 10.8 Hz, 1 H), 3.86 (s, 3 H), 4.02 (d, *J* = 10.8 Hz, 1 H), 4.32 (dd, *J* = 11.4, 16.2 Hz, 2 H), 5.23 (s, 1 H), 5.89 (s, 1 H), 6.89–7.48 (m, 13 H).

^{13}C NMR (75 MHz): δ = 6.69, 22.33, 22.38, 22.31, 45.81, 51.74, 69.90, 70.82, 83.04, 102.44, 107.86, 117.29, 117.64, 119.45, 125.09, 125.26, 126.32, 127.04, 127.25, 128.37, 130.69, 131.91, 134.89, 136.00, 147.82, 171.82.

MS: *m*/*z* = 481 [M + 1]$^+$.

Anal. Calcd for $C_{31}H_{32}N_2O_3$: C, 77.47; H, 6.71; N, 5.83. Found: C, 77.59; H, 6.62; N, 5.95.

Methyl 11-Benzyl-13-(2,4-dichlorophenyl)-8-methyl-12-oxa-1,11-diazatetracyclo[7.6.0.0^{2,7}.0^{10,14}]pentadeca-2(7),3,5,8-tetraene-14-carboxylate (6j)
Yield: 0.477 g (94%); white solid; mp 195–197 °C.

IR (KBr): 1729, 1625, 1519, 1217 cm^{-1}.

^{1}H NMR (300 MHz): δ = 2.17 (s, 3 H), 3.66 (d, *J* = 11.1 Hz, 1 H), 3.90 (s, 3 H), 4.22–4.58 (m, 3 H), 5.16 (s, 1 H), 6.20 (s, 1 H), 6.99–7.56 (m, 12 H).

^{13}C NMR (75 MHz): δ = 8.45, 46.68, 53.39, 60.06, 72.32, 73.10, 82.52, 104.43, 109.45, 119.04, 119.30, 121.40, 127.47, 127.94, 128.58, 128.81, 129.27, 129.87, 132.37, 132.49, 132.93, 133.25, 134.91, 136.12, 136.44, 172.80.

MS: *m*/*z* = 508 [M + 1]$^+$.

Anal. Calcd for $C_{28}H_{24}Cl_2N_2O_3$: C, 66.28; H, 4.77; N, 5.52. Found: C, 66.19; H, 4.47; N, 5.98.

8,11-Dimethyl-13-phenyl-12-oxa-1,11-diazatetracyclo[7.6.0.0^{2,7}.0^{10,14}]pentadeca-2(7),3,5,8-tetraene-14-carbonitrile (11a)
Yield: 0.313 g (95%); white solid; mp 185–187 °C.

IR (KBr): 2214, 1629, 1514, 1217 cm^{-1}.

^{1}H NMR (300 MHz): δ = 2.36 (s, 3 H), 3.09 (s, 3 H), 4.44 (d, *J* = 10.8 Hz, 1 H), 4.62 (d, *J* = 10.5 Hz, 1 H), 4.73 (s, 1 H), 5.23 (s, 1 H), 7.13–7.58 (m, 9 H).

^{13}C NMR (75 MHz): δ = 9.17, 44.44, 51.74, 63.48, 87.23, 106.26, 109.63, 119.14, 119.79, 119.84, 122.65, 126.80, 128.89, 129.76, 132.79, 133.20, 133.55, 134.11.

MS: *m*/*z* = 330 [M + 1]$^+$.

Anal. Calcd for $C_{21}H_{19}N_3O$: C, 76.57; H, 5.81; N, 12.76. Found: C, 76.92; H, 5.66; N, 12.45.

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13-(4-Methoxyphenyl)-8,11-dimethyl-12-oxa-1,11-diazatetracyclo[7.6.0.0^{2,7}.0^{10,14}]pentadeca-2(7),3,5,8-tetraene-14-carbonitrile (11b)
Yield: 0.345 g (96%); white solid; mp 213–215 °C.

IR (KBr): 2217, 1626, 1514, 1221 cm^{-1}.

^{1}H NMR (300 MHz): δ = 2.37 (s, 3 H), 3.03 (s, 3 H), 3.97 (s, 3 H), 4.50 (s, 1 H), 4.58 (d, *J* = 10.8 Hz, 2 H), 5.48 (s, 1 H), 6.97–7.58 (m, 8 H).

^{13}C NMR (75 MHz): δ = 8.20, 42.42, 52.82, 54.43, 63.23, 76.19, 82.45, 105.14, 108.51, 109.22, 118.49, 118.69, 120.04, 121.48, 122.76, 124.81, 128.81, 131.73, 132.22, 154.63.

MS: *m*/*z* = 360 [M + 1]$^+$.

Anal. Calcd for $C_{22}H_{21}N_3O_2$: C, 73.52; H, 5.89; N, 11.69. Found: C, 73.61; H, 5.79; N, 11.75.

13-(2-Methoxyphenyl)-8,11-dimethyl-12-oxa-1,11-diazatetracyclo[7.6.0.0^{2,7}.0^{10,14}]pentadeca-2(7),3,5,8-tetraene-14-carbonitrile (11c)
Yield: 0.348 g (97%); white solid; mp 179–181 °C.

IR (KBr): 2218, 1631, 1522, 1215 cm^{-1}.

^{1}H NMR (300 MHz): δ = 2.37 (s, 3 H), 3.03 (s, 3 H), 3.97 (s, 3 H), 4.50 (s, 1 H), 4.58 (d, *J* = 10.8 Hz, 1 H), 4.80 (d, *J* = 10.8 Hz, 1 H), 5.48 (s, 1 H), 6.97–7.58 (m, 8 H).

^{13}C NMR (75 MHz): δ = 9.23, 53.85, 55.13, 55.46, 57.61, 64.26, 83.47, 109.55, 109.89, 110.25, 119.52, 119.71, 121.07, 121.87, 122.51, 123.79, 125.84, 129.83, 132.76, 132.87, 133.24, 155.66.

MS: *m*/*z* = 360 [M + 1]$^+$.

Anal. Calcd for $C_{22}H_{21}N_3O_2$: C, 73.52; H, 5.89; N, 11.69. Found: C, 73.41; H, 5.97; N, 11.58.

8-Methyl-11,13-diphenyl-12-oxa-1,11-diazatetracyclo[7.6.0.0^{2,7}.0^{10,14}]pentadeca-2(7),3,5,8-tetraene-14-carbonitrile (11d)
Yield: 0.371 g (95%); white solid; mp 185–187 °C.

IR (KBr): 2218, 1627, 1521, 1219 cm^{-1}.

^{1}H NMR (300 MHz): δ = 2.05 (s, 3 H), 3.83 (d, *J* = 10.8 Hz, 1 H), 4.08 (d, *J* = 11.1 Hz, 1 H), 5.30 (s, 1 H), 5.96 (s, 1 H), 6.96–7.58 (m, 14 H).

^{13}C NMR (75 MHz): δ = 9.57, 42.30, 52.31, 58.59, 72.44, 85.40, 105.30, 109.48, 110.46, 118.49, 118.69, 121.15, 124.64, 125.25, 125.32, 126.52, 126.72, 126.84, 128.70, 129.61, 130.62, 131.42, 131.70, 133.55, 136.32, 141.76.

MS: *m*/*z* = 392 [M + 1]$^+$.

Anal. Calcd for $C_{26}H_{21}N_3O$: C, 79.77; H, 5.41; N, 10.73. Found: C, 79.85; H, 5.30; N, 10.82.

8,11-Dimethyl-13-(4-methylphenyl)-12-oxa-1,11-diazatetracyclo[7.6.0.0^{2,7}.0^{10,14}]pentadeca-2(7),3,5,8-tetraene-14-carbonitrile (11e)
Yield: 0.377 g (93%); white solid; mp 206–208 °C.

IR (KBr): 2215, 1625, 1518, 1217 cm^{-1}.

^{1}H NMR (300 MHz): δ = 2.36 (s, 3 H), 2.39 (s, 3 H), 4.01 (d, *J* = 11.1 Hz, 1 H), 4.10 (d, *J* = 10.8 Hz, 1 H), 5.62 (s, 1 H), 6.05 (s, 1 H), 7.02–7.59 (m, 13 H).

^{13}C NMR (75 MHz): δ = 8.49, 21.29, 48.73, 58.41, 73.89, 85.78, 105.54, 109.60, 114.87, 119.72, 120.17, 122.07, 123.56, 126.44, 129.13, 129.71, 129.79, 132.42, 133.63, 135.20, 139.67, 148.36.

MS: *m*/*z* = 406 [M + 1]$^+$.

Anal. Calcd for $C_{27}H_{23}N_3O$: C, 79.97; H, 5.72; N, 10.36. Found: C, 79.85; H, 5.63; N, 10.22.

13-(2-Methoxyphenyl)-8-methyl-11-phenyl-12-oxa-1,11-diazatetracyclo[7.6.0.0^{2,7}.0^{10,14}]pentadeca-2(7),3,5,8-tetraene-14-carbonitrile (11f)
Yield: 0.408 g (97%); white solid; mp 201–203 °C.

IR (KBr): 2215, 1625, 1518, 1217 cm^{-1}.

^{1}H NMR (300 MHz): δ = 2.18 (s, 3 H), 3.97 (d, *J* = 10.8 Hz, 1 H), 4.06 (s, 3 H), 4.21 (d, *J* = 11.1 Hz, 1 H), 5.43 (s, 1 H), 6.09 (s, 1 H), 7.12–7.71 (m, 13 H).

^{13}C NMR (75 MHz): δ = 9.67, 52.27, 59.49, 73.33, 83.61, 105.30, 109.45, 118.68, 118.82, 118.87, 119.10, 121.34, 121.86, 124.42, 126.73, 127.21, 128.43, 128.77, 129.60, 136.60, 144.08, 146.21.

MS: *m*/*z* = 422 [M + 1]$^+$.

Anal. Calcd for $C_{27}H_{23}N_3O_2$: C, 76.94; H, 5.50; N, 9.97. Found: C, 76.79; H, 5.88; N, 9.69.

11-Benzyl-8-methyl-13-phenyl-12-oxa-1,11-diazatetracyclo[7.6.0.0^{2,7}.0^{10,14}]pentadeca-2(7),3,5,8-tetraene-14-carbonitrile (11g)
Yield: 0.373 g (92%); white solid; mp 166–168 °C.

IR (KBr): 2218, 1627, 1521, 1218 cm^{-1}.

^{1}H NMR (300 MHz): δ = 2.33 (s, 3 H), 4.33–4.65 (m, 4 H), 5.08 (s, 1 H), 5.17 (s, 1 H), 7.17–7.59 (m, 14 H).

^{13}C NMR (75 MHz): δ = 9.07, 51.09, 61.77, 62.17, 74.20, 86.97, 106.32, 109.57, 118.96, 119.75, 119.83, 122.58, 126.88, 127.87, 128.50, 128.81, 129.24, 129.72, 132.74, 133.27, 133.54, 134.48, 136.09.

MS: *m*/*z* = 406 [M + 1]$^+$.

Anal. Calcd for $C_{27}H_{23}N_3O$: C, 79.97; H, 5.72; N, 10.36. Found: C, 80.17; H, 5.82; N, 10.52.

11-Benzyl-13-(4-methoxyphenyl)-8-methyl-12-oxa-1,11-diazatetracyclo[7.6.0.0^{2,7}.0^{10,14}]pentadeca-2(7),3,5,8-tetraene-14-carbonitrile (11h)
Yield: 0.409 g (94%); white solid; mp 171–173 °C.

IR (KBr): 2218, 1617, 1518, 1215 cm^{-1}.

^{1}H NMR (300 MHz): δ = 1.99 (s, 3 H), 3.60 (d, *J* = 14.1 Hz, 1 H), 3.77–3.83 (m, 6 H), 4.39 (d, *J* = 11.7 Hz, 2 H), 7.59–8.64 (m, 13 H).

^{13}C NMR (75 MHz): δ = 7.24, 28.68, 53.76, 54.29, 57.35, 57.48, 60.02, 83.17, 107.83, 108.38, 113.07, 118.37, 119.01, 121.92, 126.39, 126.83, 127.26, 127.37, 127.53, 128.29, 129.31, 129.53, 134.69, 135.42, 158.80.

MS: *m*/*z* = 436 [M + 1]$^+$.

Anal. Calcd for $C_{28}H_{25}N_3O_2$: C, 77.22; H, 5.79; N, 9.65. Found: C, 77.66; H, 5.89; N, 9.87.

11-Benzyl-13-(2-methoxyphenyl)-8-methyl-12-oxa-1,11-diazatetracyclo[7.6.0.0^{2,7}.0^{10,14}]pentadeca-2(7),3,5,8-tetraene-14-carbonitrile (11i)
Yield: 0.418 g (96%); white solid; mp 167–169 °C.

IR (KBr): 2223, 1625, 1517, 1221 cm^{-1}.

^{1}H NMR (300 MHz): δ = 2.07 (s, 3 H), 3.68 (d, *J* = 14.1 Hz, 1 H), 3.82–3.87 (m, 4 H), 4.51 (d, *J* = 11.7 Hz, 1 H), 4.56 (s, 1 H), 4.67–4.71 (m, 2 H), 6.94–8.20 (m, 13 H).

^{13}C NMR (75 MHz): δ = 8.29, 50.58, 54.98, 55.42, 58.48, 60.12, 84.45, 108.86, 109.15, 115.63, 119.37, 119.96, 120.95, 122.83, 123.89, 127.37, 128.30, 128.38, 129.64, 130.84, 135.76, 136.55, 156.80.

MS: *m*/*z* = 436 [M + 1]$^+$.

Anal. Calcd for $C_{28}H_{25}N_3O_2$: C, 77.22; H, 5.79; N, 9.65. Found: C, 77.45; H, 5.87; N, 9.78.

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13-(2*H*-1,3-Benzodioxol-4-yl)-11-benzyl-8-methyl-12-oxa-1,11-diazatetracyclo[7.6.0.0^{2,7}.0^{10,14}]pentadeca-2(7),3,5,8-tetraene-14-carbonitrile (11j)
Yield: 0.422 g (94%); white solid; mp 179–181 °C.

IR (KBr): 2220, 1619, 1515, 1218 cm^{-1}.

^{1}H NMR (300 MHz): δ = 2.32 (s, 3 H), 4.32 (d, *J* = 13.8 Hz, 1 H), 4.46 (dd, *J* = 10.8, 13.2 Hz, 2 H), 4.59 (d, *J* = 10.8 Hz, 1 H), 5.05 (s, 1 H), 5.08 (s, 1 H), 6.01 (s, 2 H), 6.83–7.58 (m, 12 H).

^{13}C NMR (75 MHz): δ = 9.04, 51.15, 58.41, 61.78, 62.13, 74.08, 86.81, 101.45, 106.32, 107.32, 108.46, 109.56, 118.99, 119.74, 120.78, 122.58, 127.87, 128.49, 129.23, 132.75, 133.25, 134.45, 136.05, 148.08, 148.72.

MS: *m*/*z* = 450 [M + 1]$^+$.

Anal. Calcd for $C_{28}H_{23}N_3O_3$: C, 74.82; H, 5.16; N, 9.35. Found: C, 74.99; H, 5.58; N, 9.10.

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(13) The structures were confirmed by single-crystal X-ray data. CCDC 902963 (**6a**) and 902964 (**11a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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