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Synthesis of pyrazole-fused polycyclic systems via intramolecular 1,3-dipolar cycloaddition reactions☆,☆☆

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ABSTRACT

Synthesis of a variety of pyrazole-fused systems starting from 4-iodopyrazolecarbaldehydes is described. The general strategy involves Suzuki coupling of 2-formyl aryl boronic acid with the 4-iodopyrazole derivatives generated from either Morita–Baylis–Hillman, Horner–Wadsworth–Emmons or Knoevenagel reactions followed by 1,3-dipolar cycloaddition reaction either by azomethine ylide or nitrile oxide. Interestingly, the cycloaddition reaction in substrates generated through Morita–Baylis–Hillman and Knoevenagel chemistries were diastereoselective for syn isomer. In contrast, the substrates prepared from Horner–Wadsworth–Emmons chemistry upon cycloaddition reactions afforded a mixture of syn and anti isomers in varying ratios.

1. Introduction

Generation of complexity from readily available simple starting materials has been the mainstay of chemical research. In particular, of significant interest to any medicinal chemistry program is the synthesis of a chemical library incorporating sufficient diversity from readily available substrates via straightforward approaches. In this context, the intramolecular 1,3-dipolar cycloaddition reactions either through azomethine ylide or via nitrile oxide are considered to be convenient approaches for the construction of structurally complex, fused, heterocyclic ring systems with simultaneous generation of several stereogenic centers.[1] The popularity of these strategies have grown manifold since they lead to polycyclic nitrogen-containing compounds, which are represented in various alkaloids and pharmacologically active compounds in a highly regio- and stereocontrolled way.

Pyrazole-derivatives are important from the viewpoint of their pharmacological properties. They have been known to display anti-anxiety, antipyretic, analgesic, PDE-4, antimicrobial, and anti-inflammatory activities.[2] They are also employed as agrochemicals.[3] As a consequence, there has been continued interest to develop methodologies for the synthesis of a variety of pyrazole-based compounds.[4] In this context, halogenated pyrazoles are considered to be of great importance as they provide opportunity for a variety of transition-metal based coupling reactions, which either leads to new fused-pyrazoles or provide a viable intermediate for further complexity generating reactions.[4a] In a project aiming at development of protocols for the preparation of pyrazole-fused architectures we have successfully accomplished the synthesis of pyrazolo[4,3-*b*]pyridin-5-ones,[5] pyrazolo[4,3-*b*]pyridines,[6] pyrazolo-fused benzodiazepines and benzoxazoazepines,[7] pyrazolo[4,3-*d*]pyrimidines and pyrazolo[4,3-*d*]pyrimidin-7(6*H*)-ones,[8] fused-pyrazoloazepines,[9] and pyrrolopyrazoles[10] using either copper-mediated cross coupling reactions or Pd-catalyzed heteroarylation of the heteroarene C–H bonds. Continuing with our exploratory studies to unfold the synthetic potential of 4-iodopyrazolecarbaldehydes we have developed a set of new polycyclic fused-pyrazoles, which may be employed for the biological screening. We envisaged that the derivatives prepared from the Morita–Baylis–Hillman (MBH), Horner–Wadsworth–Emmons (HWE), and Knoevenagel chemistries of 4-iodopyrazolecarbaldehydes upon Suzuki coupling with 2-formyl phenyl boronic acid would result into substrates amenable for intramolecular cycloaddition either through azomethine ylide or nitrile oxide formation.[11] Working toward these goals we observed that the key intramolecular cycloadditions, which employ azomethine ylides derived from MBH derivatives and secondary α-amino esters resulted in

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diastereoselective preparation of polycyclic pyrazoles. In contrast similar cycloadditions, which employ the azomethine ylides derived from HWE derivatives and secondary α-amino esters afforded a mixture of syn and anti diastereomers in varying ratios. The details of results of these studies are being presented herein.

2. Results and discussion

2.1. Studies for synthesis of fused pyrazoles employing the MBH-derivatives

The first stage of this study concerns with use of the MBH derivatives for the desired cycloaddition reactions. The required MBH derivatives **2a**–**d**–**3a**–**c** were prepared from **1a**–**d** following the reported procedure.[5] The Suzuki coupling of **2a**–**d**–**3a**–**c** with 2-formyl phenyl boronic acid in the presence of tetrakis(-triphenylphosphine)palladium (0) proceeded smoothly to give the formyl derivatives **4a**–**d**–**5a**–**c** in good yields (Scheme 1). With **4a**–**d**–**5a**–**c** in hand, the attention was directed toward constructing the polycyclic pyrazoles via intramolecular cycloaddition of azomethine ylide. The investigation for identifying the optimized conditions with respect to solvent and temperature for transformation of **4**–**6** was initiated by reacting **4a** with sarcosine. It was satisfying to note that the reaction of **4a** with sarcosine in toluene under heating at reflux for 2 h was clean and yielded a product, which was readily isolated in pure form by filtering through a small column containing silica gel. Based on the spectral analysis, the structure of the product was established to be **6a**. The reaction was found to be diastereoselective for syn stereochemistry at the ring junction in **6a** as ascertained by result of the X-ray diffraction analysis (Fig. 1).[12] This observation is in line with earlier reports wherein the 1,3-dipolar cycloadditions in MBH derivatives have been disclosed to afford the syn-product exclusively.[11c,e,f,g]

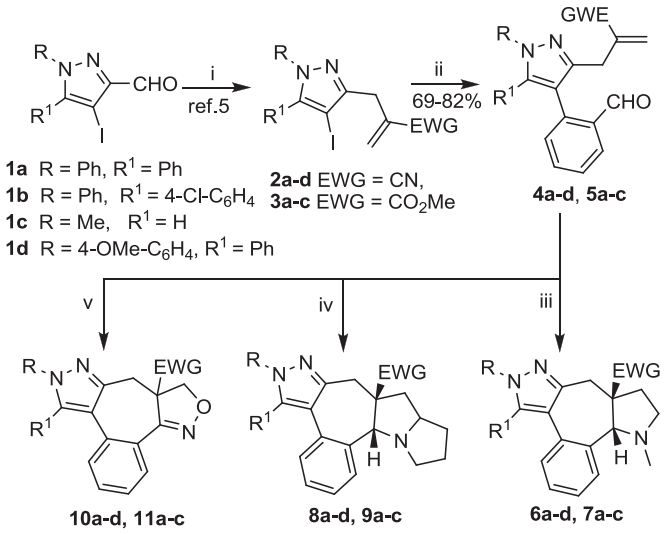
With optimized conditions in hand, the scope of reaction was evaluated by treating **4a**–**d**–**5a**–**c** with sarcosine and proline. It was a delight to note that all reactions were diastereoselective to afford only the syn product of the respective pyrazoloindazole derivatives (**6a**–**d**–**7a**–**c**, **8a**–**d**–**9a**–**c**) in good yields.

Encouraged by the success of the strategy we decided to examine the protocol for the intramolecular 1,3-dipolar cycloaddition via formation of nitrile oxide using **4a**–**d**–**5a**–**c** as the starting materials. Accordingly, compounds **4a**–**d**–**5a**–**c** were treated with hydroxylamine hydrochloride in ethanol at room temperature to afford the corresponding oximes in 30 min, which without any purification were treated with hypochlorite solution in the presence of Et_3N for 16–18 h resulting into the formation of a new 2-isoxazoline systems **10a**–**d**–**11a**–**c** in good yields.

Further, to probe the generality of the protocol with heteroaryl aldehyde in place of benzaldehyde, Suzuki reaction of **2a** with 2-formyl-3-thiopheneboronic acid was carried out to generate **12**. Similar to the earlier results, 1,3-dipolar cycloaddition reactions of **12** with sarcosine and proline afforded the fused-pyrazoles **13** and **14**, respectively, as syn-isomer exclusively whereas the reaction with nitrile oxide gave the isoxazoline **15** (Scheme 2).

2.2. Studies for synthesis of fused pyrazoles employing the HWE-derivatives

In the next stage of the study we turned our attention to another set of substrates, which could be obtained from HWE chemistry of substituted 4-iodo-3-pyrazolecarbaldehydes. Essentially in the first step, aldehydes **1a**,**b**,**e**,**f** were treated with triethylphosphonoacetate to afford the corresponding HWE-products **16.1a**,**b**,**e**,**f**, **16.2a**,**e** (Scheme 3). The Suzuki-coupling of these substrates (**16.1a**,**b**,**e**,**f**, **16.2a**,**e**) with 2-formyl phenyl boronic acid in the presence of Pd(0) yielded the respective coupling products **17.1a**,**b**,**e**,**f**, **17.2a**,**e** in good



Key to R, R , and EWG in compounds present in Scheme 1

Reactant	R	R^1	EWG	Product	Yield[a] [%]
4a	Ph	Ph	CN	**6a**	92
4b	Ph	4-Cl–C_6H_4	CN	**6b**	90
4c	Me	H	CN	**6c**	82
4d	4-MeO–C_6H_4	Ph	CN	**6d**	92
5a	Ph	Ph	CO_2Me	**7a**	87
5b	Ph	4-Cl–C_6H_4	CO_2Me	**7b**	82
5c	Me	H	CO_2Me	**7c**	89
4a	Ph	Ph	CN	**8a**	90
4b	Ph	4-Cl–C_6H_4	CN	**8b**	85
4c	Me	H	CN	**8c**	86
4d	4-MeO–C_6H_4	Ph	CN	**8d**	85
5a	Ph	Ph	CO_2Me	**9a**	88
5b	Ph	4-Cl–C_6H_4	CO_2Me	**9b**	81
5c	Me	H	CO_2Me	**9c**	89
4a	Ph	Ph	CN	**10a**	65
4b	Ph	4-Cl–C_6H_4	CN	**10b**	66
4c	Me	H	CN	**10c**	67
4d	4-MeO–C_6H_4	Ph	CN	**10d**	65
5a	Ph	Ph	CO_2Me	**11a**	70
5b	Ph	4-Cl–C_6H_4	CO_2Me	**11b**	68
5c	Me	H	CO_2Me	**11c**	69
12	Ph	Ph	CN	**13**	91
12	Ph	Ph	CN	**14**	87
12	Ph	Ph	CN	**15**	60

[a] Isolated yields.

Scheme 1. Reagent and conditions: (i) (a) methyl acrylate or acrylonitrile, DABCO, neat, rt, 24–48 h. (b) AcCl, pyridine, 3 h, rt. (c) DABCO, $NaBH_4$, THF/H_2O, rt, 1 h; (ii) 2-formyl phenyl boronic acid (1.1 equiv), $Pd(PPh_3)_4$ (0.05 equiv), Na_2CO_3 (3 equiv), DMF, 90 °C, 3 h; (iii) sarcosine (1.5 equiv), PhMe, 110 °C, 2 h; (iv) L-proline (1.5 equiv), PhMe, 110 °C, 1.5 h; (v) (a) $NH_2OH{\cdot}HCl$ (1.2 equiv), NaOAc (1.2 equiv), EtOH, rt, 30 min; (b) NaOCl (2 equiv), Et_3N (1.5 equiv), CH_2Cl_2, rt, 14 h.

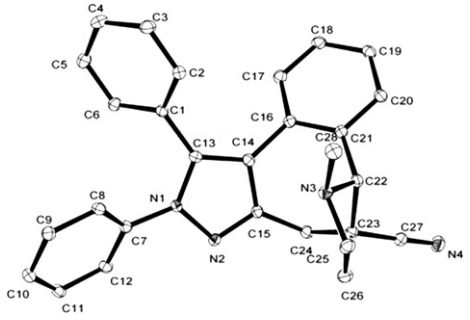
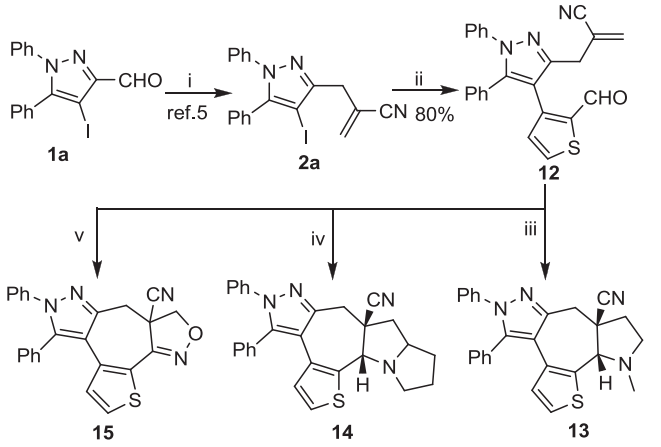


Fig. 1. Ortep diagram for **6a** at 35% probability level.

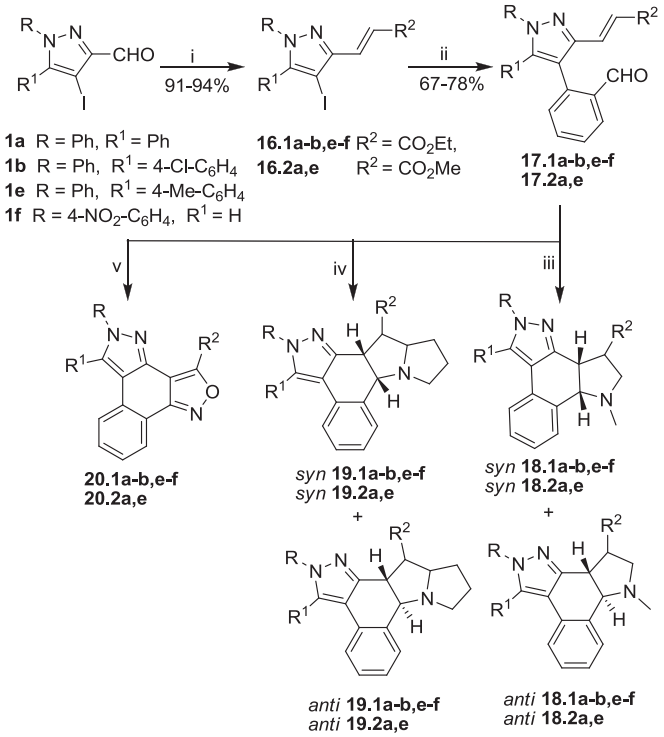


Scheme 2. Reagent and conditions: (i) (a) acrylonitrile, DABCO, neat, rt, 24 h. (b) AcCl, pyridine, 3 h, rt. (c) DABCO, $NaBH_4$, THF/H_2O, rt, 1 h; (ii) 2-formyl 3-thiopheneboronic acid (1.1 equiv), $Pd(PPh_3)_4$ (0.05 equiv), Na_2CO_3 (3 equiv), DMF, 90 °C, 3 h; (iii) sarcosine (1.5 equiv), PhMe, 110 °C, 2 h; (iv) L-proline (1.5 equiv), PhMe, 110 °C, 1.5 h; (v) (a) $NH_2OH·HCl$ (1.2 equiv), NaOAc (1.2 equiv), EtOH, rt, 30 min; (b) NaOCl (2 equiv), Et_3N (1.5 equiv), CH_2Cl_2, rt, 14 h.

yields. With starting material for the envisaged cycloaddition reaction in hand we proceed to optimize the protocol employing **17.1a** and sarcosine as the model substrate. Like the reaction with MBH derivatives, it was found that condensation of **17.1a** with sarcosine was successful in refluxing toluene. However unlike the MBH derivatives, **17.1a** afforded a mixture of two products, which were readily separated via column chromatography. Spectroscopic characterization of the separated products indicated them to be a mixture of relative stereoisomers. Based on the coupling constants of the ring-junction protons the major product (91%) was identified to be *syn*-**18.1a** whereas the minor product (9%), which was relatively polar was identified as *anti*-**18.1a**. In order to test the generality of the protocol compounds **17.1b**,**e**,**f**, **17.2a**,**e** were subjected to similar reaction with sarcosine. Gratifyingly all reactions furnished a mixture of two products, which were readily separated via column chromatography. In each case the major products were identified as *syn*-**18.1b**,**e**,**f**, **18.2a**,**e** while the minor products were the *anti*-**18.1b**,**e**, **18.2a**,**e**. Essentially to unambiguously assign the relative stereochemistry of the products detailed NMR experiments with **18.1e** were carried out (Fig. 2) (see Supplementary data). These results implied that the 1,3-dipolar cycloaddition reactions of these substrates with sarcosine were regio- and diastereoselective in nature and in all cases the syn diastereoisomer is formed in major amount. Such diastereoselectivity in favor of *syn*-isomer during the intramolecular cycloaddition reaction can be explained on the basis of preferential formation of *E*-ylide as compared to *Z*-ylide as reported recently by Ghandi et al. (Fig. 3).[13]

In the next stage the cycloaddition reactions of **17.1a**,**b**,**e**,**f**, **17.2a**,**e** with L-proline were investigated. Accordingly, compounds **17.1a**,**b**,**e**,**f**, **17.2a**,**e** were treated with L-proline in refluxing toluene. Unlike reactions of sarcosine, reactions of L-proline, in each case, yielded a mixture of diastereoisomeric products (*syn*-**19.1a**,**b**,**e**,**f**, **19.2a**,**e** and *anti*-**19.1a**,**b**,**e**,**f**, **19.2a**,**e**) in excellent yields but in ~45:55 diastereoisomeric ratio in favor of *anti*. A detailed NMR experiments with *syn*-**19.1b** and *anti*-**19.1b** confirmed the assigned stereochemistry (Figs. 4 and 5). Finally the stereochemistry was unambiguously assigned on the basis of result of the X-ray diffraction analysis for *syn*-**19.2a** (Fig. 6).[14] The stereochemical outcome for the intramolecular dipolar cycloaddition reaction of proline can be attributed to the preferential formation of W-shaped intermediate over S-shaped intermediate (Fig. 7).[13]

Subsequently **17.1a**,**b**,**e**,**f**, **17.2a**,**e** were also investigated for intramolecular 1,3-dipolar cycloaddition via nitrile oxide



Key to R, R^1, and EWG in compounds present in Scheme 3

Reactant	R	R^1	EWG	Product (*syn*:*anti*)[a]	Yield[b] [%]
17.1a	Ph	Ph	CO_2Et	**18.1a** (91:9)	90
17.1b	Ph	4-Cl–C_6H_4	CO_2Et	**18.1b** (98:2)[c]	96
17.1e	Ph	4-Me–C_6H_4	CO_2Et	**18.1e** (92:8)	92
17.1f	4-NO_2–C_6H_4	H	CO_2Et	**18.1f** (100:0)	95
17.2a	Ph	Ph	CO_2Me	**18.2a** (91:9)	91
17.2e	Ph	4-Me–C_6H_4	CO_2Me	**18.2e** (90:10)	94
17.1a	Ph	Ph	CO_2Et	**19.1a** (37:63)	91
17.1b	Ph	4-Cl–C_6H_4	CO_2Et	**19.1b** (41:59)	97
17.1e	Ph	4-Me–C_6H_4	CO_2Et	**19.1e** (42:58)	95
17.1f	4-NO_2–C_6H_4	H	CO_2Et	**19.1f** (44:56)	96
17.2a	Ph	Ph	CO_2Me	**19.2a** (41:59)	94
172e	Ph	4-Me–C_6H_4	CO_2Me	**19.2e** (40:60)	94
17.1a	Ph	Ph	CO_2Et	**20.1a**	70
17.1b	Ph	4-Cl–C_6H_4	CO_2Et	**20.1b**	68
17.1e	Ph	4-Me–C_6H_4	CO_2Et	**20.1e**	71
17.1f	4-NO_2–C_6H_4	H	CO_2Et	**20.1f**	74
17.2a	Ph	Ph	CO_2Me	**20.2a**	71
17.2e	Ph	4-Me–C_6H_4	CO_2Me	**20.2e**	69

[a] Ratio of *syn*:*anti* in the total isolated yield.
[b] Isolated yields.
[c] The *anti*-**18.1b** was too less to be isolated in a pure form for spectroscopic data.

Scheme 3. Reagents and conditions: (i) $(EtO)_3P(O)CH_2CO_2Et$ (1.2 equiv), NaH (3 equiv), THF, 0 °C–rt, 6 h; (ii) 2-formyl phenyl boronic acid (1.1 equiv), $Pd(PPh_3)_4$ (0.05 equiv), Na_2CO_3 (3 equiv), DMF, 90 °C, 3 h; (iii) sarcosine (1.5 equiv), PhMe, 110 °C, 2 h; (iv) L-Proline (1.5 equiv), PhMe, 110 °C, 1.5 h; (v) (a) $NH_2OH·HCl$ (1.2 equiv), NaOAc (1.2 equiv), EtOH, rt, 30 min; (b) NaOCl (2 equiv), Et_3N (1.5 equiv), CH_2Cl_2, rt, 14–16 h.

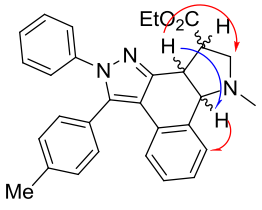


Fig. 2. NOE correlations in *syn*-**18.1e**.

formation. As a consequence **17.1a**,**b**,**e**,**f**, **17.2a**,**e** were treated with hydroxylamine hydrochloride in ethanol at room temperature for 30 min to yield the respective oximes, which without any purification were immediately treated with hypochlorite solution for

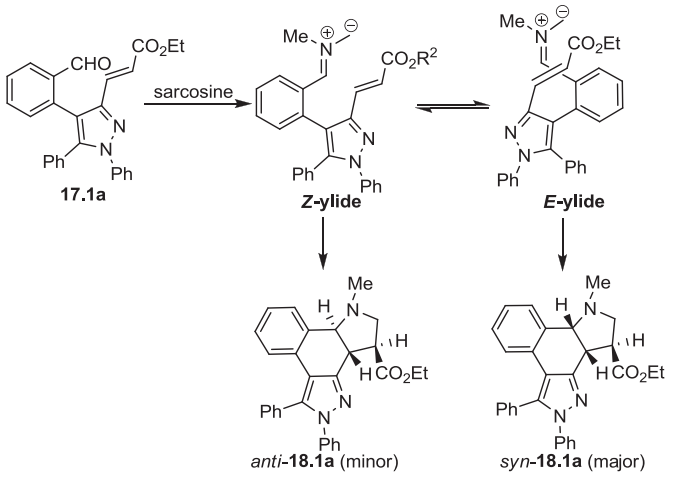


Fig. 3. Transition state model to explain diastereoselectivity during the formation of **18.1**.

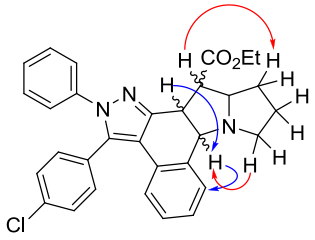


Fig. 4. NOE relations in *syn*-**19.1b**.

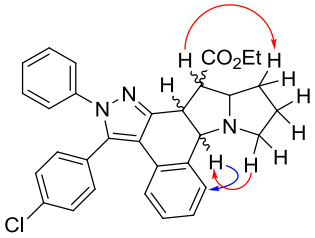


Fig. 5. NOE relations in *anti*-**19.1b**.

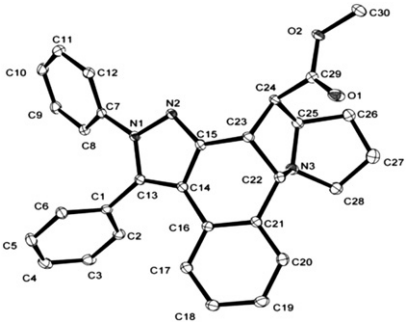


Fig. 6. Ortep diagram for *syn*-**19.2a** at 35% probability level.

16–18 h to furnish the isoxazole derivatives **20.1a**,**b**,**e**,**f**, **20.2a**,**e**, respectively.

The scope of the protocol for accessing fused-pyrazoles was also studied with the regioisomeric pyrazole derivatives **23a**,**b**, which were prepared smoothly via the Suzuki coupling of 2-formyl phenyl boronic acid with 4-iodopyrazole derivatives **22a**,**b** (Scheme 4). Treating **23a**,**b** with sarcosine gave the expected benzo[*e*]pyrrolo [2,3-*g*]indazole derivatives **24a**,**b** in excellent yields in a diastereoselective fashion in favor of syn. On the other hand reactions of

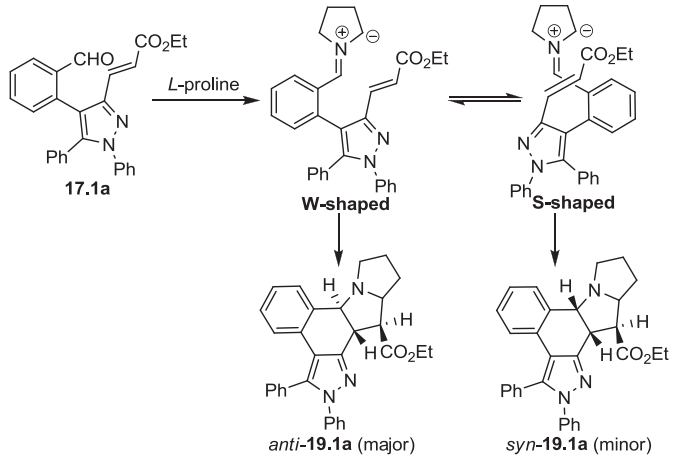
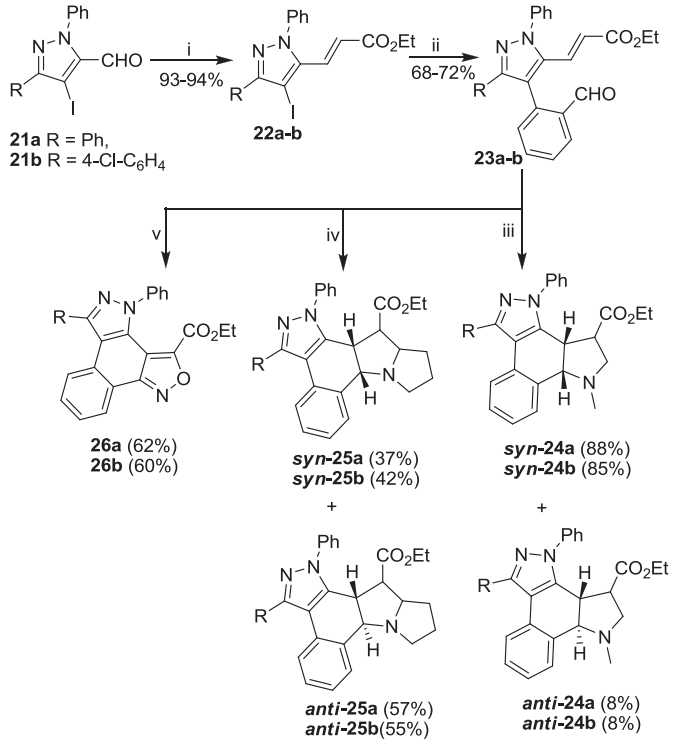


Fig. 7. Transition state model to explain the formation of *anti*- and *syn*-isomers of **19.1**.



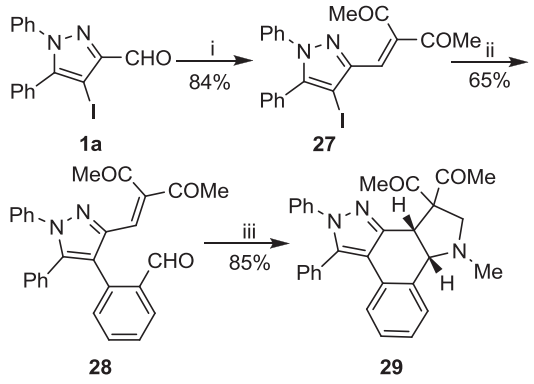
Scheme 4. Reagents and conditions: (i) $(EtO)_3P(O)CH_2CO_2Et$ (1.2 equiv), NaH (3 equiv), THF, 0 °C–rt, 6 h; (ii) 2-formyl phenyl boronic acid (1.1 equiv), $Pd(PPh_3)_4$ (0.05 equiv), Na_2CO_3 (3 equiv), DMF, 90 °C, 3 h; (iii) sarcosine (1.5 equiv), PhMe, 110 °C, 2 h; (iv) L-proline (1.5 equiv), PhMe, 110 °C, 1.5 h; (v) (a) $NH_2OH{\cdot}HCl$ (1.2 equiv), NaOAc (1.2 equiv), EtOH, rt, 30 min; (b) NaOCl (2 equiv), Et_3N (1.5 equiv), CH_2Cl_2, rt, 16–18 h.

23a,**b** with L-proline yielded **25a**,**b**, respectively, in excellent yields as a mixture of syn and anti isomers. As observed earlier, here too the diastereomers were formed in ~45:55 ratio in favor of anti isomer. Similar to earlier results, reactions of **23a**,**b** with hydroxylamine hydrochloride in the presence of sodium acetate gave the corresponding oximes, which were immediately treated with hypochlorite and Et_3N in CH_2Cl_2 to furnish the expected fused-isoxazole derivatives **26a**,**b** in good yields.

2.3. Studies for synthesis of fused pyrazoles employing Knoevenagel derivatives

Finally to illustrate more application of the strategy, the formyl substrate prepared from the Knoevenagel product **27** of **1a** was investigated. In a representative example Knoevenagel reaction of

1a with acetyl acetone was performed to generate **27**, which was subjected to Suzuki coupling as described earlier to obtain **28**. Heating **28** with sarcosine in toluene at reflux temperature resulted into the required product **29** as syn isomer in 85% yields exclusively (Scheme 5).



Scheme 5. Reagents and conditions: (i) acetylacetone (1.2 equiv), piperidine (1 equiv), THF, rt, 5 h; (ii) 2-formyl phenyl boronic acid (1.1 equiv), $Pd(PPh_3)_4$ (0.05 equiv), Na_2CO_3 (3 equiv), DMF, 90 °C, 3 h; (iii) sarcosine (1.5 equiv), PhMe, 110 °C, 3 h.

3. Conclusions

In summary we have disclosed a facile protocol for the synthesis of a variety of pyrazole-fused polycyclic systems from halogenated pyrazoles via cycloaddition chemistry. It was observed that the cycloaddition reaction in the derivatives produced from the MBH or Knoevenagel chemistries are highly diastereoselective to afford only the syn-isomer. Unlike, reactions of the substrates generated from the HWE chemistry gave products as a mixture of diastereomers the ratio of which was influenced by the nature of the reactants. Although we have demonstrated the application of the methodology with substrates derived from MBH, HWE, and Knoevenagel reactions, it is assumed that it should successful with many more substrates, which may carry double bond in the side chain in pyrazole nucleus.

4. Experimental section

4.1. General

General Melting points are uncorrected and were determined in capillary tubes on a Precision melting point apparatus containing silicon oil. IR spectra were recorded using a Perkin Elmer's RX I FTIR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded either on a Bruker DPX-200 or Bruker Avance DRX-300 MHz FT or Bruker 400 MHz spectrometers or Bruker 800 MHz spectrometers, using TMS as an internal standard (chemical shifts in δ). The ESMS were recorded on MICROMASS Quadro-II LCMS system. The HRMS spectra were recorded either as ESI-HRMS on Agilent 6520 Q-TOF, LC–MS/MS mass spectrometer or as DART-HRMS (recorded as ES^+) on a JEOL-AccuTOF JMS-T100LC mass spectrometer having DART (Direct Analysis in Real Time) source. The stereochemistry shown in the structures corresponds to the relative stereochemistry only. One of the compounds *anti*-**18.1b** could be isolated in very low yield and hence data corresponding to it is not included.

4.2. General procedure for the synthesis of compounds 4a–d, 5a–c, 12, 17.1a,b,e,f, 17.2a,e, 23a,b, and 28 as exemplified 4a

A solution of compound **2a** (1.85 mmol, 760 mg) and Na_2CO_3 (5.55 mmol, 2 M) in DMF (10 mL) was degassed with nitrogen for 15 min. Thereafter 2-formyl phenylboronic acid (2.04 mmol, 280 mg) and $Pd(PPh_3)_4$ (0.09 mmol, 10 mg) were added to the reaction mixture under nitrogen atmosphere. The reaction mixture was stirred at 90 °C for 3 h. After completion, the reaction mass was diluted with water (50 mL) and extracted with EtOAc (3×25 mL). The organic layers were pooled, washed with brine dried over Na_2SO_4, and concentrated under reduced pressure to furnish a residue. Column chromatography of the residue over silica gel (hexanes/EtOAc, 85:15, v/v) afforded pure **4a** as a white solid (69%, 496 mg).

*4.2.1. 2-((4-(2-Formylphenyl)-1,5-diphenyl-1H-pyrazol-3-yl)methyl) acrylonitrile (**4a**).* [found: C, 80.00; H, 4.70; N, 11.02. $C_{26}H_{19}N_3O$ (Exact mass: 389.1528) requires C, 80.18; H, 4.92; N, 10.79%]. Mp 130–132 °C; R_f (hexanes/EtOAc, 80:20, v/v) 0.28; ν_{max} (KBr) 1693 (CHO), 2226 (CN) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=3.62 (q, 2H, J=15.3 Hz, CH_2), 5.68 (s, 1H, =CH), 5.84 (s, 1H, =CH), 6.93 (d, 2H, J=7.0 Hz, ArH), 7.13–7.21 (m, 3H, ArH), 7.31–7.36 (m, 6H, ArH), 7.46 (t, 1H, J=7.3 Hz, ArH), 7.61 (t, 1H, J=7.4 Hz, ArH), 7.89 (d, 1H, J=7.6 Hz, ArH), 9.87 (s, 1H, CHO); ^{13}C NMR (50 MHz, $CDCl_3$): δ=32.2, 111.7, 118.4, 120.3, 125.2, 127.8, 128.2, 128.6, 128.6, 128.8, 128.84, 129.1, 130.0, 132.1, 132.6, 134.2, 134.6, 135.8, 139.6, 142.4, 146.5, 191.4; mass (ES^+) m/z=390.3 (M^++1).

*4.2.2. 2-{[5-(4-Chlorophenyl)-4-(2-formylphenyl)-1-phenyl-1H-pyrazol-3-yl]methyl}prop-2-enenitrile (**4b**).* Yield 75% as colorless oil (356 mg from 500 mg); [found: C, 73.89; H, 4.43; N, 9.70. $C_{26}H_{18}ClN_3O$ (Exact mass: 423.1138) requires C, 73.67; H, 4.28; N, 9.91%]; R_f (hexanes/EtOAc, 80:20, v/v) 0.29; ν_{max} (Neat) 1695 (CHO), 2225 (CN) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=3.60 (q, 2H, J=16.0 Hz, CH_2), 5.68 (s, 1H, =CH), 5.84 (s, 1H, =CH), 6.85 (d, 2H, J=8.5 Hz, ArH), 7.13 (d, 2H, J=8.5 Hz, ArH), 7.28–7.38 (m, 6H, ArH), 7.49 (t, 1H, J=7.5 Hz, ArH), 7.62 (dt, 1H, J_1=1.3 Hz, J_2=7.5 Hz, ArH), 7.91 (dd, 1H, J_1=0.9 Hz, J_2=7.7 Hz, ArH), 9.87 (s, 1H, CHO); ^{13}C NMR (50 MHz, $CDCl_3$): δ=32.2, 118.0, 118.3, 120.3, 125.3, 127.4, 128.1, 128.6, 128.8, 129.1, 129.3, 131.2, 132.1, 132.6, 134.3, 134.7, 135.0, 135.3, 139.4, 141.2, 146.7, 191.2; mass (ES^+) m/z=424.4 (M^++1).

*4.2.3. 2-{[4-(2-Formylphenyl)-1-methyl-1H-pyrazol-3-yl]methyl} prop-2-enenitrile (**4c**).* Yield 73% as colorless oil (336 mg from 500 mg); [found: C, 71.62; H, 5.38; N, 16.68. $C_{15}H_{13}N_3O$ (Exact mass: 251.1059) requires C, 71.70; H, 5.21; N, 16.72%]; R_f (hexanes/EtOAc, 70:30, v/v) 0.18; ν_{max} (Neat) 1690 (CHO), 2231 (CN) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=3.52 (s, 2H, CH_2), 3.97 (s, 3H, NCH_3), 5.64 (s, 1H, =CH), 5.82 (s, 1H, =CH), 7.34 (d, 1H, J=7.6 Hz, ArH), 7.40 (s, 1H, ArH), 7.49 (t, 1H, J=7.5 Hz, ArH), 7.62 (dt, 1H, J_1=1.4 Hz, J_2=7.5 Hz, ArH), 7.99 (dd, 1H, J_1=1.0 Hz, J_2=7.8 Hz, ArH); ^{13}C NMR (50 MHz, $CDCl_3$): δ=31.9, 39.4, 117.5, 120.8, 128.1, 128.3, 131.7, 131.9, 134.1, 145.2, 192.2; mass (ES^+) m/z=252.1 (M^++1).

*4.2.4. 2-((4-(2-Formylphenyl)-1-(4-methoxyphenyl)-5-phenyl-1H-pyrazol-3-yl)methyl)acrylonitrile (**4d**).* Yield 82% as yellow oil (522 mg from 670 mg); [found: C, 77.42; H, 5.22; N, 9.93. $C_{27}H_{21}N_3O$ (Exact mass: 419.1634) requires C, 77.31; H, 5.05; N, 10.02.]; R_f (hexanes/EtOAc, 80:20, v/v) 0.28; ν_{max} (Neat) 1691 (CHO), 2227 (CN) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=3.61 (q, 2H, J=19.2 Hz, CH_2), 3.80 (s, 3H, CH_3), 5.68 (s, 1H, =CH), 5.83 (s, 1H, =CH), 6.81–6.85 (m, 2H, ArH), 6.90–6.92 (m, 2H, ArH), 7.13–7.23 (m, 5H, ArH), 7.35 (d, 1H, J=7.6 Hz, ArH), 7.46 (t, 1H, J=7.1 Hz, ArH), 7.59–7.62 (m, 1H, ArH), 7.89 (d, 1H, J=7.7 Hz, ArH), 9.86 (s, 1H, CHO); ^{13}C NMR (75 MHz, $CDCl_3$): δ=32.2, 55.6, 114.3, 120.5, 126.7, 128.1, 128.5, 128.7, 128.9, 130.0, 130.1, 132.0, 132.6, 132.8, 134.2, 134.6, 136.0, 142.4, 146.1, 159.1, 191.5; mass (ES^+) m/z=419.4 (M^++1).

*4.2.5. Methyl 2-{[4-(2-formylphenyl)-1,5-diphenyl-1H-pyrazol-3-yl] methyl}prop-2-enoate (**5a**).* Yield 72% as colorless oil (342 mg from 500 mg); [found: C, 76.99; H, 5.00; N, 6.84. $C_{27}H_{22}N_2O_3$ (Exact mass: 422.1630) requires C, 76.76; H, 5.25; N, 6.63%]; R_f (hexanes/EtOAc,

80:20, v/v) 0.29; ν_{max} (KBr) 1637 (CHO), 1692 (CO_2Me) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=3.62–3.69 (m, 5H, CO_2Me & CH_2), 5.57 (d, 1H, J=1.2 Hz, =CH), 6.21 (d, 1H, J=0.8 Hz, =CH), 6.91 (dd, 2H, J_1=1.1 Hz, J_2=7.8 Hz, ArH), 7.10–7.22 (m, 3H, ArH), 7.27–7.37 (m, 5H, ArH), 7.42 (t, 1H, J=7.5 Hz, ArH), 7.58 (dt, 1H, J_1=1.4 Hz, J_2=7.5 Hz, ArH), 7.86 (dd, 1H, J_1=1.0 Hz, J_2=7.7 Hz, ArH), 9.83 (s, 1H, CHO); ^{13}C NMR (50 MHz, $CDCl_3$): δ=29.3, 52.1, 117.6, 125.2, 127.0, 127.5, 127.7, 128.2, 128.6, 128.6, 128.7, 129.0, 129.2, 130.1, 132.6, 134.0, 136.7, 137.8, 139.8, 142.1, 149.3, 167.2, 191.7; mass (ES^+) m/z=423.2 (M^++1).

*4.2.6. Methyl 2-{[5-(4-chlorophenyl)-4-(2-formylphenyl)-1-phenyl-1H-pyrazol-3-yl]methyl}prop-2-enoate (**5b**).* Yield 73% as yellow oil (348 mg from 500 mg); [found: C, 70.77; H, 4.80; N, 6.35. $C_{27}H_{21}ClN_2O_3$ (Exact mass: 456.1241) requires C, 70.97; H, 4.63; N, 6.13%]; R_f (hexanes/EtOAc, 80:20, v/v) 0.26; ν_{max} (Neat) 1638 (CHO), 1702 (CO_2Me) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=3.60–3.72 (m, 5H, CO_2Me & CH_2), 5.57 (s, 1H, =CH), 6.21 (s, 1H, =CH), 6.84 (d, 2H, J=8.4 Hz, ArH), 7.11 (d, 2H, J=8.4 Hz, ArH), 7.26–7.34 (m, 6H, ArH), 7.45 (t, 1H, J=7.4 Hz, ArH), 7.59 (t, 1H, J=6.8 Hz, ArH), 7.89 (d, 1H, J=7.4 Hz, ArH), 9.83 (s, 1H, CHO); ^{13}C NMR (50 MHz, $CDCl_3$): δ=29.2, 52.0, 117.8, 125.2, 127.0, 127.7, 128.0, 128.4, 129.0, 129.1, 131.2, 132.5, 134.1, 134.5, 134.7, 136.2, 137.6, 139.5, 140.8, 149.3, 167.0, 191.5; mass (ES^+) m/z=457.2 (M^++1).

*4.2.7. Methyl 2-{[4-(2-formylphenyl)-1-methyl-1H-pyrazol-3-yl]methyl}prop-2-enoate (**5c**).* Yield 71% as colorless oil (264 mg from 400 mg); [found: C, 67.80; H, 5.81; N, 9.67. $C_{16}H_{16}N_2O_3$ (Exact mass: 284.1161) requires C, 67.59; H, 5.67; N, 9.85%]; R_f (hexanes/EtOAc, 70:30, v/v) 0.16; ν_{max} (Neat) 1694 (CHO), 1708 (CO_2Me) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=3.59 (s, 2H, CH_2), 3.66 (s, 3H, CO_2Me), 3.93 (s, 3H, NCH_3), 5.47 (d, 1H, J=1.2 Hz, =CH), 6.18 (s, 1H, =CH), 7.34 (t, 2H, J=3.4 Hz, ArH), 7.53–7.70 (m, 2H, ArH), 7.96–7.99 (m, 1H, ArH), 10.0 (s, 1H, CHO); ^{13}C NMR (100 MHz, $CDCl_3$): δ=29.1, 39.1, 52.0, 117.0, 126.7, 127.9, 131.5, 131.8, 132.1, 133.9, 134.6, 136.7, 138.1, 147.8, 167.1, 192.5; mass (ES^+) m/z=285.1 (M^++1).

*4.2.8. 2-((4-(2-Formylthiophen-3-yl)-1,5-diphenyl-1H-pyrazol-3-yl)methyl)acrylonitrile (**12**).* Yield 80% as yellow oil (384 mg from 500 mg); found: [C, 72.76; H, 4.41; N, 10.51. $C_{24}H_{17}N_3OS$ (Exact mass: 395.1092) requires C, 72.89; H, 4.33; N, 10.63.]; R_f (hexanes/EtOAc, 80:20, v/v) 0.26; ν_{max} (Neat) 1694 (CHO), 2229 (CN) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=3.68 (s, 2H, CH_2), 5.77 (s, 1H, =CH), 5.91 (s, 1H, =CH), 6.98 (d, 2H, J=7.3 Hz, ArH), 7.03 (d, 1H, J=4.9 Hz, ArH), 7.19–7.32 (m, 8H, ArH), 7.75 (d, 1H, J=4.9 Hz, ArH), 9.53 (s, 1H, CHO); ^{13}C NMR (75 MHz, $CDCl_3$): δ=32.4, 114.2, 118.4, 120.3, 125.3, 128.0, 128.7, 128.9, 129.1, 129.2, 130.0, 131.6, 132.2, 134.8, 139.5, 139.6, 141.1, 142.7, 146.6, 183.3; mass (ES^+) m/z=396.4 (M^++1).

*4.2.9. Ethyl (2E)-3-[4-(2-formylphenyl)-1,5-diphenyl-1H-pyrazol-3-yl]prop-2-enoate (**17.1a**).* Yield 76% as a white solid (560 mg from 800 mg); mp 149–150 °C; [found: C, 76.95; H, 5.00; N, 6.44. $C_{27}H_{22}N_2O_3$ (Exact mass: 422.1630) requires C, 76.76; H, 5.25; N, 6.63%]; R_f (hexanes/EtOAc, 80:20, v/v) 0.45; ν_{max} (KBr) 1637 (CHO), 1706 (CO_2Et) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=1.27 (t, 3H, J=7.1 Hz, CH_3), 4.19 (q, 2H, J=7.1 Hz, OCH_2), 6.49 (d, 1H, J=16.1 Hz, =CH), 6.91 (d, 2H, J=6.8 Hz, ArH), 7.13–7.23 (m, 3H, ArH), 7.34–7.38 (m, 6H, ArH), 7.47–7.51 (m, 1H, ArH), 7.54 (d, 1H, J=16.1 Hz, =CH), 7.64 (dt, 1H, J_1=1.4 Hz, J_2=7.5 Hz, ArH), 7.92 (dd, 1H, J_1=1.0 Hz, J_2=7.7 Hz, ArH), 9.85 (s, 1H, CHO); ^{13}C NMR (75 MHz, $CDCl_3$): δ=14.4, 60.7, 119.1, 121.0, 125.3, 128.2, 128.3, 128.6, 128.79, 128.93, 129.0, 129.2, 130.1, 132.8, 134.2, 134.24, 134.7, 135.4, 139.6, 143.1, 146.5, 166.9, 191.2; mass (ES^+) m/z=423.2 (M^++1).

*4.2.10. Ethyl (2E)-3-[5-(4-chlorophenyl)-4-(2-formylphenyl)-1-phenyl-1H-pyrazol-3-yl]prop-2-enoate (**17.1b**).* Yield 74% as a white solid (350 mg from 500 mg); mp 144–145 °C; [found: C, 70.75; H, 4.44; N, 6.37. $C_{27}H_{21}ClN_2O_3$ (Exact mass: 456.1241) requires C, 70.97; H, 4.63; N, 6.13%]; R_f (hexanes/EtOAc, 80:20, v/v) 0.31; ν_{max} (KBr) 1648 (CHO), 1700 (CO_2Et) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=1.27 (t, 3H, J=7.1 Hz, CH_3), 4.19 (q, 2H, J=7.1 Hz, OCH_2), 6.46 (d, 1H, J=16.1 Hz, CH), 6.84 (d, 2H, J=8.5 Hz, ArH), 7.13 (d, 2H, J=8.5 Hz, ArH), 7.29–7.34 (m, 6H, ArH), 7.47–7.54 (m, 2H, ArH & =CH), 7.61–7.67 (m, 1H, ArH), 7.94 (d, 1H, J=7.7 Hz, ArH), 9.86 (s, 1H, CHO); ^{13}C NMR (50 MHz, $CDCl_3$): δ=14.4, 60.7, 119.2, 121.0, 125.2, 127.0, 128.4, 128.6, 129.0, 129.2, 129.3, 131.2, 132.7, 133.9, 134.4, 134.5, 134.9, 135.2, 139.2, 141.7, 146.5, 166.9, 191.2; mass (ES^+) m/z=457.2 (M^++1).

*4.2.11. Ethyl (2E)-3-[4-(2-formylphenyl)-5-(4-methylphenyl)-1-phenyl-1H-pyrazol-3-yl]prop-2-enoate (**17.1e**).* Yield 78% as a white solid (304 mg from 500 mg); mp 137–138 °C; [found: C, 77.24; H, 5.78; N, 6.21. $C_{28}H_{24}N_2O_3$ (Exact mass: 436.1787) requires C, 77.04; H, 5.54; N, 6.42%]; R_f (hexanes/EtOAc, 80:20, v/v) 0.30; ν_{max} (KBr) 1649 (CHO), 1706 (CO_2Et) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=1.27 (t, 3H, J=7.1 Hz, CH_3), 2.24 (s, 3H, CH_3), 4.19 (q, 2H, J=7.1 Hz, OCH_2), 6.46 (d, 1H, J=16.1 Hz, =CH), 6.84 (d, 2H, J=8.5 Hz, ArH), 7.13 (d, 2H, J=8.5 Hz, ArH), 7.29–7.34 (m, 6H, ArH), 7.47–7.54 (m, 2H, ArH & =CH), 7.61–7.67 (m, 1H, ArH), 7.94 (d, 1H, J=7.7 Hz, ArH), 9.86 (s, 1H, CHO); ^{13}C NMR (50 MHz, $CDCl_3$): δ=14.4, 60.7, 119.2, 121.0, 125.2, 127.0, 128.4, 128.6, 129.0, 129.2, 129.3, 131.2, 132.7, 133.9, 134.4, 134.5, 134.9, 135.2, 139.2, 141.7, 146.5, 166.9, 191.2; mass (ES^+) m/z=437.2 (M^++1).

*4.2.12. Ethyl (2E)-3-[4-(2-formylphenyl)-1-(4-nitrophenyl)-1H-pyrazol-3-yl]prop-2-enoate (**17.1f**).* Yield 77% as a yellow solid (292 mg from 400 mg); mp 137–138 °C; [found: C, 64.66; H, 4.62; N, 10.53. $C_{21}H_{17}N_3O_5$ (Exact mass: 391.1168) requires C, 64.45; H, 4.38; N, 10.74%]; R_f (hexanes/EtOAc, 80:20, v/v) 0.32; ν_{max} (KBr) 1690 (CHO), 1718 (CO_2Et) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=1.21 (t, 3H, J=7.1 Hz, CH_3), 4.13 (q, 2H, J=7.1 Hz, OCH_2), 5.75 (d, 1H, J=16.2 Hz, =CH), 7.43 (d, 1H, J=7.6 Hz, ArH), 7.48 (d, 1H, J=16.2 Hz, =CH), 7.60 (t, 1H, J=7.4 Hz, ArH), 7.69–7.78 (m, 4H, ArH), 8.08 (d, 1H, J=7.7 Hz, ArH), 8.43 (d, 2H, J=8.9 Hz, ArH); ^{13}C NMR (50 MHz, $CDCl_3$): δ=14.3, 61.3, 121.6, 123.7, 125.2, 125.9, 129.0, 129.1, 129.3, 131.9, 134.2, 134.6, 134.9, 135.7, 143.1, 143.9, 147.3, 165.7, 191.3; mass (ES^+) m/z=392.2 (M^++1).

*4.2.13. Methyl (2E)-3-[4-(2-formylphenyl)-1,5-diphenyl-1H-pyrazol-3-yl]prop-2-enoate (**17.2a**).* Yield 71% as a white solid (67 mg from 100 mg); mp 173–174 °C; [found: C, 76.66; H, 5.10; N, 6.63. $C_{26}H_{20}N_2O_3$ (Exact mass: 408.1474) requires C, 76.45; H, 4.94; N, 6.86%]; R_f (hexanes/EtOAc, 80:20, v/v) 0.52; ν_{max} (KBr) 1647 (CHO), 1697 (CO_2Me) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=3.73 (s, 3H, CO_2Me), 6.50 (d, 1H, J=16.1 Hz, =CH), 6.91 (d, 2H, J=6.8 Hz, ArH), 7.13–7.23 (m, 3H, ArH), 7.31–7.38 (m, 6H, ArH), 7.50 (t, 1H, J=7.4 Hz, ArH), 7.54 (d, 1H, J=16.1 Hz, =CH), 7.64 (dt, 1H, J_1=1.4 Hz, J_2=7.5 Hz, ArH), 7.91–7.94 (m, 1H, ArH), 9.86 (s, 1H, CHO); ^{13}C NMR (50 MHz, $CDCl_3$): δ=51.8, 119.2, 125.3, 128.3, 128.6, 128.8, 129.0, 129.2, 130.1, 132.8, 134.2, 134.4, 134.7, 135.4, 139.5, 143.0, 146.4, 167.3, 191.2; mass (ES^+) m/z=409.2 (M^++1).

*4.2.14. Methyl (2E)-3-[4-(2-formylphenyl)-5-(4-methylphenyl)-1-phenyl-1H-pyrazol-3-yl]prop-2-enoate (**17.2e**).* Yield 67% as a white solid (510 mg from 800 mg); mp 156–157 °C; [found: C, 76.55; H, 5.50; N, 6.85. $C_{27}H_{22}N_2O_3$ (Exact mass: 422.1630) requires C, 76.76; H, 5.25; N, 6.63%]; R_f (hexanes/EtOAc, 80:20, v/v) 0.38; ν_{max} (KBr) 1653 (CHO), 1707 (CO_2Me) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=2.24 (s, 3H, CH_3), 3.73 (s, 3H, CO_2Me), 6.48 (d, 1H, J=16.1 Hz, =CH), 6.78 (d, 2H, J=8.0 Hz, ArH), 6.95 (d, 2H, J=7.9 Hz, ArH), 7.34–7.37 (m, 6H, ArH), 7.49 (t, 1H, J=7.4 Hz, ArH), 7.53 (d, 1H, J=16.1 Hz, =CH), 7.63 (dt, 1H, J_1=1.4 Hz, J_2=7.5 Hz, ArH), 7.93 (dd, 1H, J_1=0.9 Hz, J_2=7.7 Hz, ArH), 9.85 (s, 1H, CHO); ^{13}C NMR (50 MHz, $CDCl_3$): δ=21.4, 51.8, 118.9, 120.3, 125.3, 125.5, 128.1, 128.2, 128.7,

129.1, 129.6, 129.9, 132.8, 134.3, 134.5, 134.6, 135.6, 139.0, 139.6, 143.2, 146.3, 167.4, 191.3; mass (ES^+) m/z=423.3 (M^++1).

*4.2.15. Ethyl (2E)-3-[3-4-(2-formylphenyl)-1,3-diphenyl-1H-pyrazol-5-yl]prop-2-enoate (**23a**).* Yield 72% as a white solid (353 mg from 500 mg); mp 119–120 °C; [found: C, 76.94; H, 5.46; N, 6.40.$C_{27}H_{22}N_2O_3$ (Exact mass: 422.1630) requires C, 76.76; H, 5.25; N, 6.63%]; R_f (hexanes/EtOAc, 80:20, v/v) 0.41; ν_{max} (KBr) 1633 (CHO), 1704 (CO_2Et) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.18 (t, 3H, J=7.1 Hz, CH_3), 4.09 (q, 2H, J=7.1 Hz, OCH_2), 5.53 (d, 1H, J=16.3 Hz, =CH), 7.22 (dd, 3H, J_1=1.6 Hz, J_2=5.1 Hz, ArH), 7.36–7.39 (m, 2H, ArH), 7.42–7.63 (m, 8H, ArH & =CH), 7.69–7.74 (m, 1H, ArH), 8.07 (d, 1H, J=7.7 Hz, ArH), 9.95 (s, 1H, CHO); ^{13}C NMR (50 MHz, $CDCl_3$): δ=14.3, 60.9, 117.5, 121.8, 126.1, 127.8, 128.4, 128.6, 128.7, 129.2, 129.3, 129.7, 130.1, 131.7, 132. 5, 134.6, 134.9, 136.6, 139.1, 151.2, 166.2, 191.4; mass (ES^+) m/z=423.2 (M^++1).

*4.2.16. Ethyl (2E)-3-[3-(4-chlorophenyl)-4-(2-formylphenyl)-1-phenyl-1H-pyrazol-5-yl]prop-2-enoate (**23b**).* Yield 68% as a white solid (356 mg from 500 mg); mp 151–152 °C; [found: C, 71.16; H, 4.41; N, 6.00. $C_{27}H_{21}ClN_2O_3$ (Exact mass: 456.1241) requires C, 70.97; H, 4.63; N, 6.13%]; R_f (hexanes/EtOAc, 80:20, v/v) 0.40; ν_{max} (KBr) 1696 (CHO), 1717 (CO_2Et) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.18 (t, 3H, J=7.1 Hz, CH_3), 4.09 (q, 2H, J=7.1 Hz, OCH_2), 5.53 (d, 1H, J=16.3 Hz, =CH), 7.19 (d, 2H, J=8.6 Hz, ArH), 7.31 (d, 2H, J=8.6 Hz, ArH), 7.40–7.46 (m, 2H, ArH & =CH), 7.49–7.65 (m, 6H, ArH), 7.73 (dt, 1H, J_1=1.1 Hz, J_2=7.4 Hz, ArH), 8.08 (d, 1H, J=6.7 Hz, ArH), 9.93 (s, 1H, CHO); ^{13}C NMR (50 MHz, $CDCl_3$): δ=14.3, 61.0, 117.5, 122.0, 126.1, 128.9, 129.0, 129.3, 129.5, 129.8, 129.9, 130.4, 132.4, 134.4, 134. 6, 135.0, 136.2, 137.0, 139.0, 150.0, 166.1, 191.3; mass (ES^+) m/z=457.2 (M^++1).

*4.2.17. 2-[3-(2-Acetyl-3-oxobut-1-en-1-yl)-1,5-diphenyl-1H-pyrazol-4-yl]benzaldehyde (**28**).* Yield 65% as a white solid (155 mg from 250 mg); mp 155–157 °C; [found C, 77.62; H, 5.29; N, 6.20. $C_{28}H_{22}N_2O_3$ (Exact mass: 434.1630) requires C, 77.40; H, 5.10; N, 6.45%]; R_f (hexanes/EtOAc, 80:20, v/v) 0.26; ν_{max} (KBr) 1668 ($COCH_3$ & CHO) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.28 (s, 3H, $COCH_3$), 2.55 (s, 3H, $COCH_3$), 6.91 (d, 2H, J=7.0 Hz, ArH), 7.05 (s, 1H, =CH), 7.16–7.34 (m, 9H, ArH), 7.51 (t, 1H, J=7.5 Hz, ArH), 7.64 (t, 1H, J=6.9 Hz, ArH), 7.94 (d, 1H, J=6.9 Hz, ArH), 9.86 (s, 1H, CHO); ^{13}C NMR (50 MHz, $CDCl_3$): δ=26.5, 31.4, 120.9, 124.7, 126.5, 128.1, 128.3, 128.5, 128.9, 129.95, 129.1, 129.2, 129.7, 130.0, 132.8, 134.2, 134.4, 134.7, 139.2, 142.6, 143.1, 144.4, 191.0, 196.2, 204.9; mass (ES^+) m/z=435.4 (M^++1).

4.3. General procedure for the synthesis of compounds 6a–d, 7a–c, 13, 18.1a,b,e,f, 18.2a,e, 24a,b and 29 as exemplified 6a

To a stirred solution of compound **4a** (0.26 mmol, 100 mg) in toluene (15 mL) was added sarcosine (0.39 mmol, 30 mg) and stirred at 110 °C for 3 h. Thereafter reaction mixture was cool to room temperature and extracted with EtOAc (3×10 mL) and water (30 mL). The organic layers were combined, washed with brine dried over Na_2SO_4, and concentrated under reduced pressure. Column chromatography of the residue over silica gel (hexanes/EtOAc, 70:30, v/v) afforded pure **6a** as a white solid (92%, 98 mg).

*4.3.1. (2R,6R)-3-Methyl-10,11-diphenyl-3,9,10-triazatetracyclo [11.4.0.0^{2,6}.0^{8,12}]heptadeca-1(13),8,11,14,16-pentaene-6-carbonitrile (**6a**).* Mp 119–120 °C; R_f (hexanes/EtOAc, 70:30, v/v) 0.44; ν_{max} (KBr) 2226 (CN) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.78 (s, 2H, CH_2), 1.93–2.01 (m, 3H, CH_2), 2.34–2.35 (m, 2H, CH_2), 2.75 (d, 1H, J=14.1 Hz, C*H*H), 2.92–3.08 (m, 2H, NCH_2), 3.20 (d, 1H, J=14.0 Hz, CH*H*), 3.66 (s, 1H, NCH), 6.73 (d, 1H, J=7.1 Hz, ArH), 7.06–7.43 (m, 12H, ArH), 7.60 (d, 1H, J=7.5 Hz, ArH); ^{13}C NMR (50 MHz, $CDCl_3$): δ=26.6, 33.3, 34.0, 43.2, 52.4, 55.4, 64.5, 120.3, 124.9, 125.4, 126.6, 127.3, 127.4, 127.8, 128.6, 128.8, 128.82, 128.9, 129.0, 129.4, 129.8, 129.9, 130.2, 130.3, 132.2, 138.5, 139.9, 148.9; mass (ES^+) m/z=443.4 (M^++1); ESI-HRMS: MH^+, found: 443.2283. $C_{30}H_{27}N_4$ requires 443.2236.

*4.3.2. (2R,6R)-11-(4-Chlorophenyl)-3-methyl-10-phenyl-3,9,10-triazatetracyclo[11.4.0.0^{2,6}.0^{8,12}]heptadeca-1(13),8,11,14,16-pentaene-6-carbonitrile (**6b**).* Yield 90% as a white solid (107 mg from 120 mg), mp 224–225 °C; R_f (hexanes/EtOAc, 70:30, v/v) 0.24; ν_{max} (KBr) 2230 (CN) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.01 (s, 3H, NCH_3), 2.32–2.37 (m, 3H, CH_2 & C*H*HN), 2.95–3.08 (m, 3H, CH_2 & CH*H*N), 3.44 (s, 1H, NCH), 6.73 (d, 1H, J=6.5 Hz, ArH), 7.03 (d, 2H, J=8.4 Hz, ArH), 7.12–7.35 (m, 9H, ArH), 7.42 (d, 1H, J=6.7 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ=30.1, 34.2, 34.7, 40.5, 55.3, 77.6, 121.1, 124.8, 125.2, 126.8, 127.4, 128.6, 128.8, 129.1, 129.2, 130.2, 131.6, 132.5, 133.2, 134.8, 135.6, 137.4, 139.6, 147.6; mass (ES^+) m/z=451.4 (M^++1); ESI-HRMS: MH^+, found 451.1670. $C_{28}H_{24}ClN_4$ requires 451.1689.

*4.3.3. (2R,6R)-3,10-Dimethyl-3,9,10-triazatetracyclo[11.4.0.0^{2,6}.0^{8,12}] heptadeca-1(13),8,11,14,16-pentaene-6-carbonitrile (**6c**).* Yield 82% as a white solid (45 mg from 50 mg), mp 119–120 °C; R_f (hexanes/EtOAc, 70:30, v/v) 0.19; ν_{max} (KBr) 2236 (CN) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.79 (s, 3H, NCH_3), 2.11–2.24 (m, 3H, CH_2), 2.80 (d, 1H, J=10.5 Hz, NC*H*H), 2.89–2.96 (m, 2H, NCH*H* & C*H*H), 3.27 (s, 1H, NCH), 3.81 (s, 3H, NCH_3), 7.13–7.19 (m, 3H, ArH), 7.27 (s, 1H, ArH), 7.34 (s, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ=33.8, 34.9, 39.2, 40.8, 49.7, 55.4, 81.0, 121.5, 125.2, 126.6, 127.2, 129.1, 129.3, 133.1, 133.6, 134.7, 146.1; mass (ES^+) m/z=279.2 (M^++1); ESI-HRMS: MH^+, found 279.1617. $C_{17}H_{19}N_4$ requires 279.1610.

*4.3.4. (4bR,7aR)-10-(4-Methoxyphenyl)-5-methyl-11-phenyl-5,6,7,7a,8,10-hexahydro-4bH-benzo[3,4]pyrrolo[2′,3′:5,6]cyclohepta[1,2-c]pyrazole-7a-carbonitrile (**6d**).* Yield 92% as a white solid (98 mg from 100 mg); mp 220–222 °C; R_f (hexanes/EtOAc, 70:30, v/v) 0.27; ν_{max} (KBr) 2227 (CN) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.05 (s, 3H, CH_3), 2.36–2.38 (m, 3H, C*H*HN & CH_2), 2.97–3.11 (m, 3H, CH_2 & CH*H*N), 3.46 (s, 1H, NCH), 3.82 (s, 3H, CH_3), 6.76 (d, 1H, J=7.5 Hz, ArH), 6.84 (d, 2H, J=8.2 Hz, ArH), 7.11–7.21 (m, 6H, ArH), 7.32–7.37 (m, 3H, ArH), 7.43 (d, 1H, J=6.5 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ=34.2, 34.8, 40.4, 49.1, 55.3, 55.6, 56.5, 111.6, 114.1, 120.3, 122.6, 125.0, 126.4, 126.5, 127.2, 128.5, 128.7, 128.9, 130.2, 130.4, 133.1, 135.4, 138.7, 147.0, 158.6; mass (ES^+) m/z=447.3 (M^++1); ESI-HRMS: MH^+, found: 447.2171. $C_{29}H_{27}N_4O$ requires 447.2185.

*4.3.5. Methyl (2R,6R)-3-methyl-10,11-diphenyl-3,9,10-triazatetracyclo[11.4.0.0^{2,6}.0^{8,12}]heptadeca-1(13),8,11,14,16-pentaene-6-carboxylate (**7a**).* Yield 87% as a white solid (88 mg from 100 mg); mp 119–120 °C; R_f (hexanes/EtOAc, 70:30, v/v) 0.25; ν_{max} (KBr) 1730 (CO_2Me) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.98 (s, 3H, NCH_3), 2.14–2.21 (m, 2H, CH_2), 2.27–2.33 (m, 1H, CH*H*N), 2.84–3.05 (m, 3H, CH_2 & CH*H*N), 3.43 (s, 1H, NCH), 3.76 (s, 3H, CO_2Me), 6.71 (d, 1H, J=6.5 Hz, ArH), 7.03–7.08 (m, 1H, ArH), 7.11–7.15 (m, 3H, ArH), 7.19–7.29 (m, 9H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$): δ=33.2, 33.5, 40.8, 52.5, 55.9, 61.7, 79.5, 121.2, 125.1, 126.1, 126.8, 127.8, 128.4, 128.7, 128.8, 130.0, 130.5, 130.7, 133.1, 133.2, 137.8, 138.2, 140.2, 149.4, 177.1; mass (ES^+) m/z=450.3 (M^++1); DART-HRMS: MH^+, found 450.2144. $C_{29}H_{28}N_3O_2$ requires 450.2182.

*4.3.6. Methyl (2R,6R)-11-(4-chlorophenyl)-3-methyl-10-phenyl-3,9,10-triazatetracyclo[11.4.0.0^{2,6}.0^{8,12}]heptadeca-1(13),8,11,14,16-pentaene-6-carboxylate (**7b**).* Yield 82% as a white solid (83 mg from 100 mg); mp 205–206 °C; R_f (hexanes/EtOAc, 70:30, v/v) 0.26; ν_{max} (KBr) 1726 (CO_2Me) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.97 (s, 3H, NCH_3), 2.13–2.19 (m, 2H, CH_2), 2.27–2.33 (m, 1H, CH*H*N),

2.84–3.03 (m, 3H, CH_2 & CH*H*N), 3.43 (s, 1H, NCH), 3.76 (s, 3H, CO_2Me), 6.70 (d, 1H, *J*=7.3 Hz, ArH), 7.05–7.18 (m, 4H, ArH), 7.24–7.32 (m, 8H, ArH); ^{13}C NMR (200 MHz, $CDCl_3$): δ=33.1, 33.4, 40.9, 52.6, 55.9, 61.5, 79.6, 121.4, 125.2, 126.4, 127.1, 128.0, 129.0, 129.1, 129.9, 131.8, 132.8, 133.4, 134.5, 137.0, 137.8, 139.8, 149.5, 177.1; mass (ES^+) *m*/*z*=484.3 (M^++1); ESI-HRMS: MH^+, found 484.1780. $C_{29}H_{27}ClN_3O_2$ requires 484.1792.

*4.3.7. Methyl (2R,6R)-3,10-dimethyl-3,9,10-triazatetracyclo[11.4.0.0^{2,6}.0^{8,12}]heptadeca-1(13),8,11,14,16-pentaene-6-carboxylate (**7c**).* Yield 89% as colorless oil; R_f (hexanes/EtOAc, 50:50, v/v) 0.25, ν_{max} (Neat) 1724 (CO_2Me) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=1.79 (s, 3H, NCH_3), 2.11–2.24 (m, 3H, CH_2), 2.80 (d, 1H, *J*=10.5 Hz, NC*H*H), 2.89–2.96 (m, 2H, NCH*H* & C*H*H), 3.27 (s, 1H, NCH), 3.81 (s, 3H, NCH_3), 7.13–7.19 (m, 3H, ArH), 7.27 (s, 1H, ArH), 7.34 (s, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ=33.8, 34.9, 39.2, 40.8, 49.7, 55.4, 81.0121.5, 125.2, 126.6, 127.2, 129.1, 129.3, 133.1, 133.6, 134.7, 146.1; mass (ES^+) *m*/*z*=312.2 (M^++1); ESI-HRMS: MH^+, found 312.1710. $C_{18}H_{22}N_3O_2$ requires 312.1712.

*4.3.8. (7aR,10aS)-10-Methyl-4,5-diphenyl-7,7a,8,9,10,10a-hexahydro-5H-pyrrolo[2′,3′:5,6]thieno[3′,2′:3,4]cyclohepta[1,2-c]pyrazole-7a-carbonitrile (**13**).* Yield 91% as a white solid (68 mg from 70 mg); mp 194–196 °C; R_f (hexanes/EtOAc, 70:30, v/v) 0.25; ν_{max} (KBr) 2234 (CN) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=2.26–2.30 (m, 2H, CH_2), 2.36 (s, 3H, CH_3), 2.55–2.63 (m, 1H, C*H*HN), 2.94 (d, 1H, *J*=14.0 Hz, C*H*H), 3.17–3.20 (m, 1H, CH*H*N), 3.24 (d, 1H, *J*=14.0 Hz, CH*H*), 3.85 (s, 1H, NCH), 6.48 (d, 1H, *J*=5.1 Hz, ArH), 7.09 (d, 1H, *J*=5.1 Hz, ArH), 7.18 (d, 2H, *J*=7.4 Hz, ArH), 7.29–7.33 (m, 8H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ=34.4, 35.9, 41.6, 52.1, 54.8, 72.2, 117.4, 124.6, 124.8, 125.1, 127.3, 128.4, 128.7, 129.0, 129.9, 130.2, 130.7, 137.8, 138.4, 139.8, 148.0; mass (ES^+) *m*/*z*=423.3 (M^++1); ESI-HRMS: MH^+, found: 423.1670. $C_{26}H_{23}N_4S$ requires 423.1643.

*4.3.9. Ethyl (2S,6R)-3-methyl-9,10-diphenyl-3,8,9-triazatetracyclo[10.4.0.0^{2,6}.0^{7,11}]hexadeca-1(16),7,10,12,14-pentaene-5-carboxylate (syn-**18.1a**).* Yield 82% as a white solid (87 mg from 100 mg); mp 145–146 °C; R_f (hexanes/EtOAc, 70:30, v/v) 0.27; ν_{max} (KBr) 1729 (CO_2Et) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=1.33 (t, 3H, *J*=7.1 Hz, CH_3), 2.31 (s, 3H, NCH_3), 2.54 (t, 1H, *J*=8.6 Hz, CH), 3.40 (d, 1H, *J*=5.6 Hz, CH*H*N), 3.58 (t, 1H, *J*=9.3 Hz, CH), 3.96–4.01 (m, 2H, CH & C*H*HN), 4.25 (q, 2H, *J*=7.1 Hz, OCH_2), 7.05–7.14 (m, 3H, ArH), 7.20–7.22 (m, 6H, ArH), 7.39 (s, 5H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$): δ=14.4, 40.1, 40.8, 46.8, 58.7, 61.1, 69.7, 114.6, 123.3, 125.2, 125.5, 127.0, 128.4, 128.4, 128.8, 130.0, 130.5, 130.7, 131.3, 131.5, 132.0, 138.6, 140.0, 151.7, 175.1; mass (ES^+) *m*/*z*=450.1 (M^++1); DART-HRMS: MH^+, found 450.2186. $C_{29}H_{28}N_3O_3$ requires 450.2182.

*4.3.10. Ethyl (2R,6R)-3-methyl-9,10-diphenyl-3,8,9-triazatetracyclo[10.4.0.0^{2,6}.0^{7,11}]hexadeca-1(16),7,10,12,14-pentaene-5-carboxylate (anti-**18.1a**).* Yield 8% as a white solid (9 mg from 100 mg); mp 168–170 °C; R_f (hexanes/EtOAc, 70:30, v/v) 0.20; ν_{max} (KBr) 1729 (CO_2Et) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=1.31 (t, 3H, *J*=7.1 Hz, CH_3), 2.70 (s, 3H, NCH_3), 3.06–3.12 (m, 1H, CH), 3.51–3.57 (m, 3H, CH & NCH_2), 3.81 (dd, 1H, J_1=6.4 Hz, J_2=12.1 Hz, CH), 4.25 (q, 2H, *J*=7.1 Hz, OCH_2), 6.93 (d, 1H, *J*=7.4 Hz, ArH), 7.00–7.07 (m, 1H, ArH), 7.16–7.39 (m, 11H, ArH), 7.51 (d, 1H, *J*=7.5 Hz, ArH); ^{13}C NMR (50 MHz, $CDCl_3$): δ=14.4, 42.1, 44.0, 44.9, 61.1, 62.0, 72.8, 117.0, 123.3, 124.2, 125.3, 126.2, 126.7, 127.1, 128.8, 129.0, 129.1, 130.2, 130.8, 139.9, 173.5; mass (ES^+) *m*/*z*=450.1 (M^++1); DART-HRMS: MH^+, found 450.2187. $C_{29}H_{28}N_3O_3$ requires 450.2182.

*4.3.11. Ethyl (2S,6R)-10-(4-chlorophenyl)-3-methyl-9-phenyl-3,8,9-triazatetracyclo[10.4.0.0^{2,6}.0^{7,11}]hexadeca-1(16),7,10,12,14-pentaene-5-carboxylate (syn-**18.1b**).* Yield 91% as a white solid (115 mg from 120 mg); mp 149–150 °C; R_f (hexanes/EtOAc, 70:30, v/v) 0.34; ν_{max} (KBr) 1730 (CO_2Et) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=1.32 (t, 3H, *J*=7.1 Hz, CH_3), 2.31 (s, 3H, NCH_3), 2.54 (t, 1H, *J*=8.6 Hz, CH), 3.40 (d, 1H, *J*=5.6 Hz, CH*H*N), 3.57 (dd, 1H, *J*=9.3 Hz, CH), 3.95–3.99 (m, 2H, CH*H*N & NCH), 4.24 (q, 2H, *J*=7.1 Hz, OCH_2), 7.08–7.38 (m, 13H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$): δ=14.5, 40.1, 40.8, 46.8, 58.7, 61.2, 69.7, 114.8, 123.3, 125.4, 125.8, 127.3, 128.5, 129.0, 129.4, 129.8, 130.2, 131.6, 132.1, 135.2, 137.3, 139.8, 151.9, 175.1; mass (ES^+) *m*/*z*=484.1 (M^++1); ESI-HRMS: MH^+, found 484.1800. $C_{29}H_{27}ClN_3O_2$ requires 484.1792.

*4.3.12. Ethyl (2R,6R)-10-(4-chlorophenyl)-3-methyl-9-phenyl-3,8,9-triazatetracyclo[10.4.0.0^{2,6}.0^{7,11}]hexadeca-1(16),7,10,12,14-pentaene-5-carboxylate (anti-**18.1b**).* Yield 2% as a white solid (2 mg from 100 mg); mp 160–161 °C; R_f (hexanes/EtOAc, 70:30, v/v) 0.3; ν_{max} (KBr) 1730 (CO_2Et) cm^{-1}; mass (ES^+) *m*/*z*=484.1 (M^++1); ESI-HRMS: MH^+, found 484.1805. $C_{29}H_{27}ClN_3O_2$ requires 484.1792.

*4.3.13. Ethyl (2S,6R)-3-methyl-10-(4-methylphenyl)-9-phenyl-3,8,9-triazatetracyclo[10.4.0.0^{2,6}.0^{7,11}]hexadeca-1(16),7,10,12,14-pentaene-5-carboxylate (syn-**18.1e**).* Yield 85% as a white solid (90 mg from 100 mg), mp 165–167 °C; R_f (hexanes/EtOAc, 70:30, v/v) 0.31; ν_{max} (KBr) 1730 (CO_2Et) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=1.32 (t, 3H, *J*=7.1 Hz, CH_3), 2.31 (s, 3H, NCH_3), 2.40 (s, 3H, CH_3), 2.53 (t, 1H, *J*=8.7 Hz, CH), 3.39 (d, 1H, *J*=5.8 Hz, CH*H*N), 3.58 (t, 1H, *J*=9.4 Hz, CH), 3.95–4.00 (m, 2H, CH*H*N & NCH), 4.24 (q, 2H, *J*=7.1 Hz, OCH_2), 7.06–7.15 (m, 3H, ArH), 7.17–7.26 (m, 10H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$): δ=14.5, 21.6, 40.1, 40.9, 46.8, 58.8, 61.1, 69.7, 114.4, 123.4, 125.3, 125.4, 126.9, 128.3, 128.4, 128.8, 129.7, 130.5, 130.6, 131.5, 132.0, 138.7, 138.9, 140.2, 151.7, 175.1; mass (ES^+) *m*/*z*=464.1 (M^++1); DART-HRMS: MH^+, found 464.2331. $C_{30}H_{30}N_3O_2$ requires 464.2338.

*4.3.14. Ethyl (2R,6R)-3-methyl-10-(4-methylphenyl)-9-phenyl-3,8,9-triazatetracyclo[10.4.0.0^{2,6}.0^{7,11}]hexadeca-1(16),7,10,12,14-pentaene-5-carboxylate (anti-**18.1e**).* Yield 7% as a white solid (7 mg from 100 mg), mp 154–155 °C; R_f (hexanes/EtOAc, 70:30, v/v) 0.28; ν_{max} (KBr) 1730 (CO_2Et) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=1.32 (t, 3H, *J*=7.1 Hz, CH_3), 1.61 (s, 1H, CH), 1.72 (s, 3H, NCH_3), 1.90 (s, 3H, CH_3), 2.04 (s, 1H, CH), 2.92–2.98 (m, 2H, CH*H*N), 4.20–4.25 (m, 3H, NCH & OCH_2), 7.07 (s, 2H, ArH), 7.11–7.17 (m, 3H, ArH), 7.22–7.26 (m, 3H, ArH), 7.36 (s, 5H, ArH); mass (ES^+) *m*/*z*=464.1 (M^++1); DART-HRMS: MH^+, found 464.2322. $C_{30}H_{30}N_3O_2$ requires 464.2338.

*4.3.15. Ethyl (2S,6R)-3-methyl-9-(4-nitrophenyl)-3,8,9-triazatetracyclo[10.4.0.0^{2,6}.0^{7,11}]hexadeca-1(16),7,10,12,14-pentaene-5-carboxylate (syn-**18.1f**).* Yield 95% as a yellow solid (204 mg from 200 mg), mp 200–201 °C; R_f (hexanes/EtOAc, 70:30, v/v) 0.22; ν_{max} (KBr) 1727 (CO_2Et) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=1.13 (t, 3H, *J*=7.1 Hz, CH_3), 2.18 (s, 3H, NCH_3), 2.23–2.26 (m, 1H, CH), 2.85–2.91 (m, 1H, CH), 3.27 (t, 1H, *J*=9.1 Hz, CH), 3.39 (d, 1H, *J*=6.8 Hz, CH*H*N), 3.94–4.12 (m, 2H, OCH_2), 4.45 (dd, 1H, J_1=2.9 Hz, J_2=6.6 Hz, C*H*HN), 7.21–7.26 (m, 2H, ArH), 7.38–7.42 (m, 1H, ArH), 7.59 (d, 1H, *J*=7.5 Hz, ArH), 7.66 (d, 2H, *J*=8.9 Hz, ArH), 8.05 (s, 1H, ArH), 8.30 (d, 2H, *J*=8.8 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ=14.1, 39.4, 39.5, 47.1, 58.5, 61.4, 69.5, 119.1, 123.4, 124.1, 124.9, 125.9, 129.1, 129.3, 130.0, 130.7, 137.2, 140.1, 144.7, 146.3, 173.7; mass (ES^+) *m*/*z*=419.2 (M^++1); ESI-HRMS: MH^+, found 419.1725. $C_{23}H_{23}N_4O_4$ requires 419.1719.

*4.3.16. Methyl (2S,6R)-3-methyl-9,10-diphenyl-3,8,9-triazatetracyclo[10.4.0.0^{2,6}.0^{7,11}]hexadeca-1(16),7,10,12,14-pentaene-5-carboxylate (syn-**18.2a**).* Yield 83% as a white solid (89 mg from 100 mg), mp 145–146 °C; R_f (hexanes/EtOAc, 70:30, v/v) 0.36; ν_{max} (KBr) 1734 (CO_2Me) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=2.31 (s, 3H, NCH_3), 2.56 (t, 1H, *J*=8.7 Hz, CH), 3.39 (d, 1H, *J*=6.0 Hz, CH*H*N), 3.56 (dd, 1H, J_1=9.1 Hz, J_2=9.4 Hz, CH), 3.79 (s, 3H, CO_2Me), 3.95–4.02 (m, 2H, CH*H*N & NCH), 7.06–7.14 (m, 3H, ArH), 7.16–7.24 (m, 6H, ArH), 7.39 (s, 5H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$): δ=21.6, 31.3, 52.3, 63.6, 118.0, 125.7, 126.4, 126.8, 127.9, 128.3, 128.6, 128.7, 129.0, 129.8, 40.1,

40.9, 467, 52.3, 58.6, 69.7, 114.5, 123.4, 125.2, 125.5, 120, 128.5, 128.8, 129.0, 129.1, 130.4, 130.7, 131.3, 131.5, 131.9, 138.6, 140.0, 151.7, 175.5; mass (ES^+) m/z=436.2 (M^++1); DART-HRMS: MH^+, found 436.2020. $C_{28}H_{26}N_3O_2$ requires 436.2025.

*4.3.17. Methyl (2R,6R)-3-methyl-9,10-diphenyl-3,8,9-triazatetracyclo [10.4.0.0^{2,6}.0^{7,11}]hexadeca-1(16),7,10,12,14-pentaene-5-carboxylate (anti-**18.2a**).* Yield 8% as a white solid (8 mg from 100 mg), mp 157–158 °C; R_f (hexanes/EtOAc, 70:30, v/v) 0.30; ν_{max} (KBr) 1734 (CO_2Me) cm^{-1}; ^1H NMR (800 MHz, $CDCl_3$) δ=2.72 (s, 3H, NCH_3), 3.12–3.13 (m, 1H, CH), 3.56 (d, 1H, J=9.2 Hz, CH*H*N), 3.62 (s, 1H, CH), 3.78 (s, 3H, CO_2Me), 3.80–3.82 (s, 2H, CH*H*N & NCH), 6.93 (d, 1H, J=7.4 Hz, ArH), 7.04 (t, 1H, J=7.4 Hz, ArH), 7.19 (t, 1H, J=7.5 Hz, ArH), 7.22–7.30 (m, 7H, ArH), 7.36–7.41 (m, 3H, ArH), 7.52 (d, 1H, J=7.7 Hz, ArH); ^{13}C NMR (200 MHz, $CDCl_3$) δ=41.8, 43.8, 44.8, 52.5, 61.8, 72.7, 117.0, 123.4, 124.3, 125.5, 126.2, 126.8, 127.2, 128.9, 129.0, 129.1, 130.2, 130.3, 130.6, 138.5, 139.8, 151.9, 174.0; mass (ES^+) m/z=436.2 (M^++1); DART-HRMS: MH^+, found 436.2006. $C_{28}H_{26}N_3O_2$ requires 436.2025.

*4.3.18. Methyl (2S,6R)-3-methyl-10-(4-methylphenyl)-9-phenyl-3,8,9-triazatetracyclo[10.4.0.0^{2,6}.0^{7,11}]hexadeca-1(16),7,10,12,14-pentaene-5-carboxylate (syn-**18.2e**).* Yield 85% as a white solid (86 mg from 100 mg); mp 164–165 °C; R_f (hexanes/EtOAc, 70:30, v/v) 0.28; ν_{max} (KBr) 1736 (CO_2Me) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=2.31 (s, 3H, NCH_3), 2.40 (s, 3H, CH_3), 2.56 (t, 1H, J=8.7 Hz, CH), 3.39 (d, 1H, J=5.8 Hz, CH*H*N), 3.56 (t, 1H, J=9.2 Hz, CH), 3.79 (s, 3H, CO_2Me), 3.94–4.02 (m, 2H, CH & C*H*HN), 7.09–7.13 (m, 3H, ArH), 7.17–7.26 (m, 10H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$): δ=21.6, 40.1, 40.9, 46.7, 52.3, 58.7, 69.7, 114.4, 123.4, 125.3, 125.4, 126.9, 128.2, 128.4, 128.7, 129.7, 130.5, 130.6, 131.5, 131.9, 138.7, 138. 9, 140.2, 151.7, 175.6; mass (ES^+) m/z=450.2 (M^++1); DART-HRMS: MH^+, found 450.1796. $C_{27}H_{24}N_3O_3$ requires 450.1818.

*4.3.19. Methyl (2R,6R)-3-methyl-9,10-diphenyl-3,8,9-triazatetracyclo [10.4.0.0^{2,6}.0^{7,11}]hexadeca-1(16),7,10,12,14-pentaene-5-carboxylate (anti-**18.2e**).* Yield 9% as a white solid (10 mg from 100 mg); mp 167–168 °C; R_f (hexanes/EtOAc, 70:30, v/v) 0.18; ν_{max} (KBr) 1735 (CO_2Me) cm^{-1}; ^1H NMR (800 MHz, $CDCl_3$): δ=2.39 (s, 3H, NCH_3), 2.70 (s, 3H, CH_3), 3.08 (s, 1H, CH), 3.54–3.57 (m, 3H, CH & NCH_2), 3.78 (s, 3H, CO_2Me), 3.81 (s, 1H, NCH), 6.97 (d, 1H, J=6.9 Hz, ArH), 7.04 (s, 1H, ArH), 7.17 (s, 5H, ArH), 7.22–7.26 (m, 5H, ArH), 7.51 (d, 1H, J=6.3 Hz, ArH); ^{13}C NMR (200 MHz, $CDCl_3$): δ=21.6, 41.8, 43.9, 44.9, 52.5, 62.0, 72.8, 116.8, 123.2, 124.2, 125.5, 126.1, 126.7, 127.1, 127.5, 128.9, 129.8, 130.0, 130.5, 138.6, 139.0, 139. 9, 152.0, 174.1; mass (ES^+) m/z=450.2 (M^++1); DART-HRMS: MH^+, found 450.1800. $C_{27}H_{24}N_3O_3$ requires 450.1818.

*4.3.20. Ethyl (2S,6R)-3-methyl-8,10-diphenyl-3,8,9-triazatetracyclo [10.4.0.0^{2,6}.0^{7,11}]hexadeca-1(16),7(11),9,12,14-pentaene-5-carboxylate (syn-**24a**).* Yield 88% as a white solid (93 mg from 100 mg), mp 184–185 °C; R_f (hexanes/EtOAc, 70:30, v/v) 0.35; ν_{max} (KBr) 1731 (CO_2Et) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=1.13 (t, 3H, J=7.1 Hz, CH_3), 2.18 (t, 1H, J=9.1 Hz, CH), 2.26 (s, 3H, NCH_3), 2.99 (dd, 1H, J_1=5.8 Hz, J_2=8.5 Hz, CH), 3.29–3.37 (m, 2H, CH*H*N & NCH), 3.87–4.04 (m, 2H, OCH_2), 4.38 (d, 1H, J=3.8 Hz, CH*H*N), 7.14 (d, 2H, J=3.3 Hz, ArH), 7.22–7.23 (m, 1H, ArH), 7.36–7.50 (m, 9H, ArH), 7.74 (d, 2H, J=5.4 Hz, ArH); ^{13}C NMR (50 MHz, $CDCl_3$): δ=14.3, 39.5, 39.7, 47.0, 59.1, 61.1, 70.2, 114.4, 123.7, 125.0, 125.3, 128.1, 128.4, 128.6, 128.7, 129.6, 130.7, 131.1, 131.2, 134.4, 139.9, 141.8, 149.6, 173.9; mass (ES^+) m/z=450.2 (M^++1); DART-HRMS: MH^+, found 450.2178. $C_{29}H_{28}N_3O_3$ requires 450.2182.

*4.3.21. Ethyl (2R,6R)-3-methyl-8,10-diphenyl-3,8,9-triazatetracyclo [10.4.0.0^{2,6}.0^{7,11}]hexadeca-1(16),7(11),9,12,14-pentaene-5-carboxylate (anti-**24a**).* Yield 8% as a white solid (9 mg from 100 mg), mp 145–147 °C; R_f (hexanes/EtOAc, 70:30, v/v) 0.24; ν_{max} (KBr) 1731 (CO_2Et) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=1.13 (t, 3H, J=7.1 Hz, CH_3), 2.63 (s, 3H, NCH_3), 2.85–2.99 (m, 2H, CH & CH_2), 3.39–3.43 (m, 1H, CH), 3.60 (d, 1H, J=13.3 Hz, NCH), 3.76–3.89 (m, 2H, OCH_2), 3.92–4.00 (m, 1H, NCH*H*), 7.15 (t, 1H, J=7.4 Hz, ArH), 7.22 (d, 1H, J=7.5 Hz, ArH), 7.34–7.37 (m, 1H, ArH), 7.42–7.44 (m, 8H, ArH), 7.52 (d, 1H, J=7.5 Hz, ArH), 7.76 (d, 2H, J=7.8 Hz, ArH); ^{13}C NMR (50 MHz, $CDCl_3$): δ=14.1, 41.3, 43.1, 43.5, 61.1, 63.0, 73.2, 116.2, 123.2, 124.5, 125.9, 126.8, 127.1, 128.4, 128.7, 128.9, 129.1, 129.3, 131.3, 133.6, 135.9, 139.5, 143.2, 173.0; mass (ES^+) m/z=450.2 (M^++1); DART-HRMS: MH^+, found 450.2198. $C_{29}H_{28}N_3O_3$ requires 450.2182.

*4.3.22. Ethyl (2S,6R)-10-(4-chlorophenyl)-3-methyl-8-phenyl-3,8,9-triazatetracyclo[10.4.0.0^{2,6}.0^{7,11}]hexadeca-1(16),7(11),9,12,14-pentaene-5-carboxylate (syn-**24b**).* Yield 85% as a white solid (94 mg from 100 mg), mp 190–191 °C; R_f (hexanes/EtOAc, 70:30, v/v) 0.33; ν_{max} (KBr) 1726 (CO_2Et) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=1.13 (t, 3H, J=7.0 Hz, CH_3), 2.18 (t, 1H, J=9.2 Hz, CH), 2.25 (s, 3H, NCH_3), 2.97 (t, 1H, J=7.4 Hz, CH), 3.29–3.37 (m, 2H, CH*H*N & NCH), 3.87–4.04 (m, 2H, OCH_2), 4.37 (d, 1H, J=4.0 Hz, CH*H*N), 7.17–7.26 (m, 3H, ArH), 7.41–7.46 (m, 8H, ArH), 7.69 (d, 2H, J=8.2 Hz, ArH); ^{13}C NMR (50 MHz, $CDCl_3$): δ=14.3, 39.5, 39.7, 47.0, 59.1, 61.1, 70.2, 114.4, 123.6, 124.9, 125.5, 128.2, 128.7, 128.8, 129.6, 130.8, 130.9, 131.3, 132.9, 134.4, 139.8, 142.1, 148.3, 173.8; mass (ES^+) m/z=484.1 (M^++1); ESI-HRMS: MH^+, found 484.1797. $C_{29}H_{27}ClN_3O_2$ requires 484.1792.

*4.3.23. Ethyl (2R,6R)-10-(4-chlorophenyl)-3-methyl-8-phenyl-3,8,9-triazatetracyclo[10.4.0.0^{2,6}.0^{7,11}]hexadeca-1(16),7(11),9,12,14-pentaene-5-carboxylate (anti-**24b**).* Yield 8% as a white solid (10 mg from 100 mg), mp 136–137 °C; R_f (hexanes/EtOAc, 70:30, v/v) 0.26; ν_{max} (KBr) 1726 (CO_2Et) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=1.15 (t, 3H, J=7.1 Hz, CH_3), 2.65 (s, 3H, NCH_3), 2.86–3.00 (m, 2H, CH & C*H*HN), 3.40–3.44 (m, 1H, CH*H*N), 3.60 (d, 1H, J=13.3 Hz, NCH), 3.74–3.89 (m, 2H, OCH_2), 3.93–4.03 (m, 1H, CH), 7.17–7.26 (m, 3H, ArH), 7.33–7.37 (m, 1H, ArH), 7.41–7.46 (m, 6H, ArH), 7.54 (d, 1H, J=7.5 Hz, ArH), 7.73 (d, 2H, J=8.4 Hz, ArH); ^{13}C NMR (50 MHz, $CDCl_3$): δ=14.1, 41.2, 43.1, 43.5, 61.1, 63.0, 73.2, 116.2, 123.3, 124.3, 125.4, 126.1, 126.9, 127.0, 128.9, 129.3, 130.2, 131.0, 132.1, 134.4, 136.0, 139.3, 143.4, 147.9, 172.9; mass (ES^+) m/z=484.1 (M^++1); ESI-HRMS: MH^+, found 484.1782. $C_{29}H_{27}ClN_3O_2$ requires 484.1792.

*4.3.24. 1-[(2S,6R)-5-Acetyl-3-methyl-9,10-diphenyl-3,8,9-triazatetracyclo[10.4.0.0^{2,6}.0^{7,11}]hexadeca-1(16),7,10,12,14-pentaen-5-yl]ethan-1-one (**29**).* Yield 85% as a white solid (90 mg from 100 mg), mp 140–142 °C; [found C, 78.07; H, 5.07; N, 8.89. $C_{30}H_{27}N_3O_2$ (Exact mass: 461.2103) requires C, 78.07; H, 5.90; N, 9.10%]; R_f (hexanes/EtOAc, 70:20, v/v) 0.32; ν_{max} (KBr) 1668 ($COCH_3$) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=2.26 (s, 3H, $COCH_3$), 2.28 (s, 3H, $COCH_3$), 2.41 (s, 3H, NCH_3), 2.60 (d, 1H, J=11.2 Hz, C*H*HN), 3.40 (d, 1H, J=2.2 Hz, CH), 4.11 (d, 1H, J=10.5 Hz, C*H*HN), 4.65 (d, 1H, J=4.4 Hz, CH), 7.00–7.17 (m, 9H, ArH), 7.35–7.41 (m, 5H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ=26.8, 29.8, 40.6, 42.2, 50.9, 57.8, 70.1, 115.8, 123.3, 124.2, 124.8, 125.5, 125.6, 126.6, 128.6, 128.8, 128.9, 129.0, 129.1, 129.2, 130.2, 130.3, 130.5, 130.8, 131.0, 131.4, 138.1, 204.7; mass (ES^+) m/z=462.1 (M^++1).

4.4. General procedure for the synthesis of compounds 8a–d, 9a–c, 14, 19.1a,b,e,f, 19.2a,e and 25a,b as exemplified 8a

To a stirred solution of compound **4a** (0.26 mmol, 0.10 g) in toluene (15 mL) was added L-proline (0.39 mmol, 0.05 g) and stirred at reflux temperature for 4 h. Thereafter reaction mixture was cool to room temperature and extracted with EtOAc (3×10 mL) and water (30 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure.

Column chromatography of the residue over silica gel (hexanes/EtOAc, 70:30, v/v) afforded pure **8a** as white solid (90%, 0.102 g).

*4.4.1. (1R,14R)-9,10-Diphenyl-10,11,20-triazapentacyclo[12.6.0.0^{2,7}.0^{8,12}.0^{16,20}]icosa-2,4,6,11-tetraene-14-carbonitrile (**8a**).* Mp 119–120 °C; R_f (hexanes/EtOAc, 70:30, v/v) 0.44; ν_{max} (KBr) 2226 (CN) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.78 (s, 2H, CH_2), 1.93–2.01 (m, 3H, CH_2), 2.34–2.35 (m, 2H, CH_2), 2.75 (d, 1H, J=14.1 Hz, C*H*H), 2.92–3.08 (m, 2H, NCH_2), 3.20 (d, 1H, J=14.0 Hz, CH*H*), 3.66 (s, 1H, NCH), 6.73 (d, 1H, J=7.1 Hz, ArH), 7.06–7.43 (m, 12H, ArH), 7.60 (d, 1H, J=7.5 Hz, ArH); ^{13}C NMR (50 MHz, $CDCl_3$): δ=26.6, 33.3, 34.0, 43.2, 52.4, 55.4, 64.5, 120.3, 124.9, 125.4, 126.6, 127.3, 127.4, 127.8, 128.6, 128.8, 128.82, 128.9, 129.0, 129.4, 129.8, 129.9, 130.2, 130.3, 132.2, 138.5, 139.9, 148.9; mass (ES^+) m/z=443.4 (M^++1); ESI-HRMS: MH^+, found 443.2283. $C_{30}H_{27}N_4$ requires 443.2236.

*4.4.2. (1R,14R)-9-(4-Chlorophenyl)-10-phenyl-10,11,20-triazapentacyclo[12.6.0.0^{2,7}.0^{8,12}.0^{16,20}]icosa-2,4,6,11-tetraene-14-carbonitrile (**8b**).* Yield 85% as a white solid (143 mg from 150 mg), mp 193–194 °C; R_f 0.42 (hexanes/EtOAc, 70:30, v/v); ν_{max} (KBr) 2234 (CN) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ=1.76 (s, 2H, CH_2), 2.00 (m, 2H, CH_2), 2.35–2.37 (m, 2H, CH_2), 2.77 (d, 1H, J=14.0 Hz, C*H*H), 2.91 (m, 1H, NCH_2), 3.02 (s, 1H, CH_2), 3.18 (d, 1H, J=14.1 Hz, C*H*H), 3.61 (m, 1H, CH_2), 4.37 (s, 1H, NCH), 6.73 (d, 1H, J=7.2 Hz, ArH), 7.06–7.14 (m, 3H, ArH), 7.20–7.34 (m, 8H, ArH), 7.60 (d, 1H, J=7.5 Hz, ArH); ^{13}C NMR (50 MHz, $CDCl_3$): δ=26.5, 33.3, 34.0, 43.2, 52.4, 55.3, 64.5, 120.6, 124.8, 125.5, 126.8, 127.6, 127.9, 128.4, 129.1, 129.3, 130.0, 131.6, 131.9, 134.7, 137.4, 138.5, 139.6, 149.0; mass (ES^+) m/z=477.4 (M^++1); ESI-HRMS: MH^+, found 477.1846. $C_{30}H_{26}ClN_4$ requires 477.1846.

*4.4.3. (1R,14R)-10-Methyl-10,11,20-triazapentacyclo[12.6.0.0^{2,7}.0^{8,12}.0^{16,20}]icosa-2,4,6,11-tetraene-14-carbonitrile (**8c**).* Yield 86% as a white solid (52 mg from 50 mg), mp 119–120 °C; R_f (hexanes/EtOAc, 50:50, v/v) 0.26; ν_{max} (KBr) 2231 (CN) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.60–1.68 (m, 2H, CH_2), 2.09–2.15 (m, 2H, CH_2), 2.49 (d, 1H, J=14.2 Hz, CH_2), 2.67–2.70 (m, 1H, CHH), 2.79 (s, 1H, CHH), 2.94 (d, 1H, J=14.1 Hz, C*H*H), 3.11–3.36 (m, 1H, NCHH), 3.45–3.48 (m, 1H, NCHH), 3.77 (s, 4H, NCH_3 & NCHH), 4.04 (s, 1H, NCH), 7.04–7.16 (m, 4H, ArH), 7.05–7.15 (m, 4H, ArH), 7.43 (d, 1H, J=7.1 Hz, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ=26.2, 32.9, 33.9, 39.1, 42.9, 52.7, 55.4, 64.6, 76.2, 121.2, 126.7, 127.0, 127.9, 128.2, 128.4, 130.1, 132.4, 137.7, 147.7; mass (ES^+) m/z=305.2 (M^++1); ESI-HRMS: MH^+, found 305.1760. $C_{19}H_{21}N_4$ requires 305.1766.

*4.4.4. (8aR,13aR)-6-(4-Methoxyphenyl)-5-phenyl-8,8a,9,9a,10,11,12,13a-octahydro-6H-benzo[3,4]pyrazolo[4′,3′:5,6]cyclohepta[1,2-b]pyrrolizine-8a-carbonitrile (**8d**).* Yield 85% as a white solid (96 mg from 100 mg); mp 202–204 °C; [found: C, 78.95; H, 5.88; N, 11.70. $C_{31}H_{28}N_4O$ (Exact mass: 472.2263) requires C, 78.79; H, 5.97; N, 11.86.]; R_f (hexanes/EtOAc, 70:30, v/v) 0.24; ν_{max} (KBr) 2236 (CN) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.78–1.84 (m, 2H, CH_2), 2.00–2.04 (m, 2H, CH_2), 2.30–2.40 (m, 2H, CH_2), 2.75 (d, 1H, J=14.0 Hz, C*H*H), 2.91–2.93 (m, 1H, NCH_2), 3.04–3.07 (m, 1H, NCH_2), 3.18 (d, 1H, J=14.0 Hz, C*H*H), 3.64 (s, 1H, CH), 3.80 (s, 3H, CH_3), 4.38 (s, 1H, NCH), 6.74 (dd, 1H, J_1=1.0 Hz, J_2=7.5 Hz, ArH), 6.82 (d, 2H, J=9.0 Hz, ArH), 7.06–7.10 (m, 1H, ArH), 7.13–7.17 (m, 2H, ArH), 7.17–7.22 (m, 3H, ArH), 7.28–7.34 (m, 3H, ArH), 7.60 (d, 1H, J=7.5 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ=26.6, 33.3, 34.0, 43.1, 52.5, 55.4, 55.6, 64.5, 76.2, 114.1, 119.9, 125.0, 126.5, 126.8, 127.8, 128.5, 128.7, 129.4, 129.7, 130.0, 130.3, 132.4, 133.1, 138.5, 138.8, 148.5, 158.7; mass (ES^+) m/z=473.3 (M^++1).

*4.4.5. Methyl (1R,14R)-9,10-diphenyl-10,11,20-triazapentacyclo[12.6.0.0^{2,7}.0^{8,12}.0^{16,20}]icosa-2(7),3,5,8,11-pentaene-14-carboxylate (**9a**).* Yield 88% as a yellow solid (119 mg from 120 mg); mp 119–120 °C; R_f (hexanes/EtOAc, 70:30, v/v) 0.34; ν_{max} (KBr) 1727 (CO_2Me) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ=1.60–1.67 (m, 1H, C*H*H), 1.72–1.77 (m, 1H, C*H*H), 1.84–1.89 (m, 1H, C*H*H), 1.94–2.04 (m, 1H, CH*H*), 2.19–2.25 (m, 1H, CH*H*), 2.31 (t, 1H, J=11.1 Hz, CH*H*), 2.43–2.49 (m, 1H, C*H*H), 2.79–2.88 (m, 1H, NCH), 3.03 (s, 3H, CO_2Me), 3.28–3.36 (m, 2H, NCH_2), 3.68 (s, 1H, NCH), 3.76–3.82 (m, 1H, NCH*H*), 6.71 (d, 1H, J=7.7 Hz, ArH), 6.82 (t, 1H, J=7.0 Hz, ArH), 7.08–7.14 (m, 3H, ArH), 7.18–7.22 (m, 4H, ArH), 7.24–7.32 (m, 4H, ArH), 7.41 (d, 1H, J=7.6 Hz, ArH); ^{13}C NMR (50 MHz, $CDCl_3$): δ=26.0, 28.8, 38.1, 39.8, 47.6, 51.6, 61.3, 70.9, 71.4, 118.2, 125.5, 125.6, 125.9, 127.2, 128.6, 128.8, 128.9, 129.2, 130.2, 131.1, 131.4, 136.6, 140.0, 140.6, 149.1, 175.3; mass (ES^+) m/z=476.3 (M^++1); ESI-HRMS: MH^+, found 476.2348. $C_{31}H_{30}N_3O_2$ requires 476.2338.

*4.4.6. Methyl (1R,14R)-9-(4-chlorophenyl)-10-phenyl-10,11,20-triazapentacyclo[12.6.0.0^{2,7}.0^{8,12}.0^{16,20}]icosa-2(7),3,5,8,11-pentaene-14-carboxylate (**9b**).* Yield 81% as a white solid (90 mg from 100 mg), mp 175–176 °C; R_f (hexanes/EtOAc, 70:30, v/v) 0.33; ν_{max} (KBr) 1725 (CO_2Me) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ=1.83–1.95 (m, 2H, CH_2), 2.16–2.41 (m, 2H, CH_2), 2.55–2.79 (m, 2H, CH_2), 2.98 (dd, 2H, J_1=13.8 Hz, J_2=26.9 Hz, C*H*H), 3.21–3.35 (m, 1H, NCH_2), 3.73 (s, 3H, CO_2Me), 4.30 (s, 1H, NCH), 6.72 (d, 1H, J=7.3 Hz, ArH), 7.04–7.16 (m, 4H, ArH), 7.19–7.38 (m, 9H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$): δ=25.9, 28.7, 38.0, 39.7, 47.6, 51.5, 61.2, 70.9, 71.3, 118.4, 125.6, 126.0, 127.2, 127.5, 128.9, 129.0, 129.2, 129.5, 129.8, 131.6, 132.3, 134.7, 136.6, 139.2, 139.6, 149.2, 175.2; mass (ES^+) m/z=510.3 (M^++1); ESI-HRMS: MH^+, found 510.1954. $C_{31}H_{29}ClN_3O_2$ requires 510.1948.

*4.4.7. Methyl (1R,14R)-10-methyl-10,11,20-triazapentacyclo[12.6.0.0^{2,7}.0^{8,12}.0^{16,20}]icosa-2(7),3,5,8,11-pentaene-14-carboxylate (**9c**).* Yield 89% as yellow oil (53 mg from 50 mg); R_f (hexanes/EtOAc, 50:50, v/v) 0.16; ν_{max} (Neat) 1728 (CO_2Me) cm^{-1}; ^{1}H NMR (800 MHz, $CDCl_3$): δ=1.59–1.64 (m, 1H, C*H*H), 1.77 (s, 1H, CH*H*), 1.83 (s, 2H, CH_2), 2.11–2.17 (m, 1H, NC*H*H), 2.23 (t, 1H, J=11.1 Hz, NCH*H*), 2.42 (s, 1H, NC*H*H), 2.78 (s, 1H, NCH*H*), 3.07 (s, 3H, CO_2Me), 3.16 (d, 1H, J=16.2 Hz, C*H*H), 3.29 (s, 1H, NCH*H*), 3.40 (s, 1H, NCH), 3.60 (d, 1H, J=16.2 Hz, C*H*H), 3.90 (s, 3H, NCH_3), 7.17–7.21 (m, 2H, ArH), 7.38 (d, 1H, J=7.1 Hz, ArH), 7.41 (d, 1H, J=7.0 Hz, ArH), 7.57 (s, 1H, ArH); ^{13}C NMR (200 MHz, $CDCl_3$): δ=22.9, 28.6, 29.9, 37.7, 39.1, 39.7, 48.0, 51.6, 72.1, 77.4, 119.9, 125.8, 126.0, 126.9, 128.9, 130.3, 147.6, 175.0; mass (ES^+) m/z=338.2 (M^++1); ESI-HRMS: MH^+, found 338.1863. $C_{20}H_{24}N_3O_2$ requires 338.1869.

*4.4.8. (7aR,12aS)-4,5-Diphenyl-7,7a,8,8a,9,10,11,12a-octahydro-5H-pyrazolo[4′,3′:5,6]thieno[2′,3′:3,4]cyclohepta[1,2-b]pyrrolizine-7a-carbonitrile (**14**).* Yield 87% as a white solid (69 mg from 70 mg); mp 200–202 °C; R_f (hexanes/EtOAc, 70:30, v/v) 0.22; ν_{max} (KBr) 2231 (CN) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.84–1.89 (m, 2H, CH_2), 2.01 (s, 2H, CH_2), 2.36–2.45 (m, 2H, CH_2), 2.72 (d, 1H, J=11.7 Hz, C*H*H), 3.03 (s, 1H, NCH_2), 3.32 (d, 2H, J=14.2 Hz, C*H*H), 3.86 (s, 1H, CH), 4.54 (s, 1H, NCH), 6.43 (d, 1H, J=5.2 Hz, ArH), 6.97 (d, 1H, J=5.0 Hz, ArH), 7.14–7.27 (m, 10H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ=22.9, 26.6, 32.5, 34.9, 43.5, 56.6, 64.9, 72.6, 116.8, 124.5, 125.3, 127.4, 128.0, 128.7, 128.8, 128.9, 130.0, 130.3, 138.8, 139.9, 142.9, 148.7; mass (ES^+) m/z=449.3 (M^++1); ESI-HRMS: MH^+, found: 449.1826. $C_{28}H_{25}N_4S$ requires 449.1800.

*4.4.9. Ethyl (1R,13S)-4,5-diphenyl-3,4,14-triazapentacyclo[11.6.0.0^{2,6}.0^{7,12}.0^{14,18}]nonadeca-2,5,7,9,11-pentaene-19-carboxylate (syn-**19.1a**).* Yield 34% as a white solid (38 mg from 100 mg), mp 160–161 °C; [found: C, 78.36; H, 6.04; N, 8.71. $C_{31}H_{29}N_3O_2$ (Exact mass: 475.2260) requires C, 78.29; H, 6.15; N, 8.84%]; R_f (hexanes/EtOAc, 70:30, v/v) 0.24; ν_{max} (KBr) 1722 (CO_2Et) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.18–1.26 (m, 1H, CH*H*), 1.32 (t, 3H, J=7.1 Hz, CH_3), 1.90–2.04 (m, 3H, C*H*H & CH_2), 2.92–3.02 (m, 2H, CH), 3.99–4.02 (m, 3H, NCH & NCH_2), 4.20–4.24 (m, 3H, NCH & OCH_2), 6.99–7.11 (m, 3H, ArH), 7.14–7.26 (m, 5H, ArH), 7.35–7.39 (m, 6H, ArH); ^{13}C NMR (50 MHz,

$CDCl_3$): δ=14.5, 27.4, 28.9, 42.5, 45.6, 53.4, 60.7, 66.2, 68.2, 115.2, 123.3, 125.3, 126.1, 127.1, 127.9, 128.8, 128.9, 129.0, 129.8, 130.8, 131.4, 140.1, 174.0; mass (ES^+) m/z=476.2 (M^++1).

*4.4.10. Ethyl (1R,13R)-4,5-diphenyl-3,4,14-triazapentacyclo[11.6.0.0^{2,6}.0^{7,12}.0^{14,18}]nonadeca-2,5,7,9,11-pentaene-19-carboxylate (anti-**19.1a**).* Yield 57% as a white solid (64 mg from 100 mg), mp 171–172 °C; R_f (hexanes/EtOAc, 70:30, v/v) 0.15; ν_{max} (KBr) 1723 (CO_2Et) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.34 (t, 3H, J=7.1 Hz, CH_3), 1.18–1.26 (m, 1H, CH*H*), 1.90–2.04 (m, 3H, C*H*H & CH_2), 2.92–3.02 (m, 2H, CH), 3.99–4.02 (m, 3H, NCH & NCH_2), 4.20–4.24 (m, 3H, NCH & OCH_2), 6.99–7.11 (m, 3H, ArH), 7.14–7.26 (m, 5H, ArH), 7.35–7.39 (m, 6H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$): δ=14.5, 27.4, 28.9, 42.5, 45.6, 53.4, 60.7, 66.2, 68.2, 115.2, 123.3, 125.3, 126.1, 127.1, 127.9, 128.8, 128.9, 129.0, 129.8, 130.8, 131.4, 140.1, 174.0; mass (ES^+) m/z=476.2 (M^++1); ESI-HRMS: MH^+, found 476.2346. $C_{31}H_{30}N_3O_2$ requires 476.2338.

*4.4.11. Ethyl (1R,13S)-5-(4-chlorophenyl)-4-phenyl-3,4,14-triazapentacyclo[11.6.0.0^{2,6}.0^{7,12}.0^{14,18}]nonadeca-2,5,7,9,11-pentaene-19-carboxylate (syn-**19.1b**).* Yield 40% as a white solid (67 mg from 150 mg), mp 140–142 °C; R_f (hexanes/EtOAc, 70:30, v/v) 0.22; ν_{max} (KBr) 1720 (CO_2Et) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.24–1.26 (m, 1H, CH*H*), 1.32 (t, 3H, J=7.1 Hz, CH_3), 1.90–2.04 (m, 3H, C*H*H & CH_2), 2.92–3.01 (m, 2H, CH_2), 3.92–4.01 (m, 3H, NCH & NCH_2), 4.20–4.25 (m, 3H, NCH & OCH_2), 7.07 (s, 2H, ArH), 7.11–7.18 (m, 3H, ArH), 7.22–7.29 (m, 3H, ArH), 7.36 (s, 5H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$): δ=14.5, 27.4, 28.9, 42.5, 50.5, 53.4, 60.7, 66.2, 68.1, 115.4, 123.2, 125.3, 126.3, 127.3, 127.9, 128.0, 129.1, 129.3, 129.8, 129.9, 132.1, 135.1, 135.4, 137.3, 139.8, 150.3, 174.0; mass (ES^+) m/z=510.2 (M^++1); ESI-HRMS: MH^+, found 510.1937. $C_{31}H_{29}ClN_3O_2$ requires 510.1948.

*4.4.12. Ethyl (1R,13R)-5-(4-chlorophenyl)-4-phenyl-3,4,14-triazapentacyclo[11.6.0.0^{2,6}.0^{7,12}.0^{14,18}]nonadeca-2,5,7,9,11-pentaene-19-carboxylate (anti-**19.1b**).* Yield 57% as a white solid (96 mg from 150 mg), mp 150–151 °C; R_f (hexanes/EtOAc, 70:30, v/v) 0.14; ν_{max} (KBr) 1723 (CO_2Et) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.34 (t, 3H, J=7.1 Hz, CH_3), 1.65–1.69 (m, 1H, CH*H*), 1.84–1.93 (m, 2H, CH_2), 2.09–2.21 (m, 1H, CH), 2.71–2.80 (m, 1H, CH), 3.40–3.47 (m, 2H, CH_2), 3.58–3.66 (m, 1H, CH), 4.21–4.35 (m, 4H, NCH, NCH*H* & OCH_2), 6.95 (d, 1H, J=7.5 Hz, ArH), 7.04 (t, 1H, J=7.4 Hz, ArH), 7.18–7.29 (m, 8H, ArH), 7.36 (d, 2H, J=8.5 Hz, ArH), 7.58 (d, 2H, J=7.6 Hz, ArH); ^{13}C NMR (50 MHz, $CDCl_3$): δ=14.5, 26.2, 28.7, 39.1, 49.2, 50.7, 60.9, 67.9, 68.9, 116.7, 123.8, 125.4, 126.28, 126.34, 126.9, 127.3, 128.9, 129.4, 129.5, 130.4, 131.7, 135.1, 135.3, 137.3, 139.6, 150.9, 173.0; mass (ES^+) m/z=510.2 (M^++1); ESI-HRMS: MH^+, found 510.1938. $C_{31}H_{29}ClN_3O_2$ requires 510.1948.

*4.4.13. Ethyl (1R,13S)-5-(4-methylphenyl)-4-phenyl-3,4,14-triazapentacyclo[11.6.0.0^{2,6}.0^{7,12}.0^{14,18}]nonadeca-2,5,7,9,11-pentaene-19-carboxylate (syn-**19.1e**).* Yield 40% as a white solid (45 mg from 100 mg), mp 198–199 °C; R_f (hexanes/EtOAc, 70:30, v/v) 0.23; ν_{max} (KBr) 1726 (CO_2Et) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.32 (t, 3H, J=7.1 Hz, CH_3), 1.60 (s, 1H, CH*H*), 1.90–2.04 (m, 3H, CH_2), 2.40 (s, 3H, CH_3), 2.92–3.01 (m, 3H, C*H*H), 3.98–4.01 (m, 3H, NC*H*H & NCH), 4.20–4.24 (m, 3H, NCH & NCH*H*), 7.02 (t, 1H, J=7.5 Hz, ArH), 7.11 (t, 2H, J=7.4 Hz, ArH), 7.18–7.28 (m, 9H, ArH), 7.35 (d, 1H, J=7.4 Hz, ArH); ^{13}C NMR (50 MHz, $CDCl_3$): δ=14.5, 21.6, 27.4, 28.9, 42.5, 50.6, 53.4, 60.6, 66.1, 68.2, 115.0, 123.3, 125.2, 125.9, 126.9, 127.8, 128.2, 128.8, 129.5, 129.6, 129.8, 130.6, 135.2, 138.77, 138.84, 140.1, 150.0, 174.1; mass (ES^+) m/z=490.2 (M^++1); DART-HRMS: MH^+, found 490.2505. $C_{32}H_{32}N_3O_2$ requires 490.2494.

*4.4.14. Ethyl (1R,13R)-5-(4-methylphenyl)-4-phenyl-3,4,14-triazapentacyclo[11.6.0.0^{2,6}.0^{7,12}.0^{14,18}]nonadeca-2,5,7,9,11-pentaene-19-carboxylate (anti-**19.1e**).* Yield 55% as a white solid (61 mg from 100 mg), mp 166–167 °C; R_f (hexanes/EtOAc, 70:30, v/v) 0.14, ν_{max} (KBr) 1726 (CO_2Et) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.34 (t, 3H, J=7.1 Hz, CH_3), 1.65–1.72 (m, 1H, CH*H*), 1.84–1.93 (m, 2H, CH_2), 2.09–2.18 (m, 1H, C*H*H), 2.39 (s, 3H, CH_3), 2.77 (dd, 1H, J_1=7.7 Hz, J_2=17.5 Hz, CH), 3.41–3.48 (m, 2H, NC*H*H & NCH), 3.63 (dd, 1H, J_1=11.1 Hz, J_2=13.6 Hz, CH), 4.21–4.28 (m, 4H, NCH & NCH*H*), 7.00–7.04 (m, 2H, ArH), 7.19–7.22 (m, 10H, ArH), 7.56 (d, 1H, J=7.2 Hz, ArH); ^{13}C NMR (50 MHz, $CDCl_3$): δ=14.5, 21.6, 26.2, 28.7, 39.2, 49.2, 50.7, 60.9, 67.9, 69.0, 116.4, 123.9, 125.3, 126.0, 126.2, 126.8, 126.9, 128.0, 128.7, 129.8, 130.2, 130.9, 135.1, 138.8, 138.9, 140.0, 150.8, 173.1; mass (ES^+) m/z=490.2 (M^++1); DART-HRMS: MH^+, found 490.2505. $C_{32}H_{32}N_3O_2$ requires 490.2494.

*4.4.15. Ethyl (1R,13S)-4-(4-nitrophenyl)-3,4,14-triazapentacyclo[11.6.0.0^{2,6}.0^{7,12}.0^{14,18}]nonadeca-2,5,7,9,11-pentaene-19-carboxylate (syn-**19.1f**).* Yield 42% as a yellow solid (42 mg from 100 mg), mp 157–158 °C; R_f (hexanes/EtOAc, 70:30, v/v) 0.21; ν_{max} (KBr) 1724 (CO_2Et) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.11 (t, 3H, J=6.9 Hz, CH_3), 1.43–1.50 (m, 1H, CH*H*), 1.75–1.86 (m, 2H, CH_2), 1.99–2.00 (m, 1H, C*H*H), 2.88–2.93 (m, 1H, CH), 3.05–3.06 (m, 2H, CH), 3.59–3.67 (m, 1H, NCH), 3.94–3.96 (m, 2H, OCH_2), 4.29–4.31 (m, 1H, NCH*H* & NCH) 7.24–7.36 (m, 2H, ArH), 7.49–7.54 (m, 2H, ArH), 7.72 (d, 2H, J=8.6 Hz, ArH), 8.04 (s, 1H, ArH), 8.34 (d, 2H, J=8.7 Hz, ArH); ^{13}C NMR (50 MHz, $CDCl_3$): δ=14.3, 25.5, 28.1, 39.5, 51.8, 52.9, 61.1, 65.0, 66.6, 119.8, 123.2, 125.0, 126.8, 128.4, 129.1, 133.6, 137.3, 149.2, 145.1, 146.5, 172.6; mass (ES^+) m/z=445.3 (M^++1); ESI-HRMS: MH^+, found 445.1879. $C_{25}H_{25}N_4O_4$ requires 445.1876.

*4.4.16. Ethyl (1R,13R)-4-(4-nitrophenyl)-3,4,14-triazapentacyclo[11.6.0.0^{2,6}.0^{7,12}.0^{14,18}]nonadeca-2,5,7,9,11-pentaene-19-carboxylate (anti-**19.1f**).* Yield 54% as a yellow solid (61 mg from 100 mg), mp 162–163 °C; R_f (hexanes/EtOAc, 70:30, v/v) 0.13; ν_{max} (KBr) 1724 (CO_2Et) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.10 (t, 3H, J=7.1 Hz, CH_3), 1.42–1.45 (m, 1H, CH*H*), 1.77–1.88 (m, 2H, CH_2), 2.00–2.10 (m, 1H, C*H*H), 2.74 (dd, 1H, J_1=7.7 Hz, J_2=17.2 Hz, CH), 2.99 (t, 1H, J=10.4 Hz, CH), 3.37–3.44 (m, 1H, NC*H*H), 3.55–3.66 (m, 1H, NCH), 3.77–3.99 (m, 2H, OCH_2), 4.11–4.18 (m, 1H, NCH*H*), 4.36 (d, 1H, J=14.0 Hz, NCH), 7.30–7.36 (m, 2H, ArH), 7.53–7.60 (m, 4H, ArH), 7.99 (s, 1H, ArH), 8.30 (d, 1H, J=8.7 Hz, ArH); ^{13}C NMR (50 MHz, $CDCl_3$): δ=14.1, 25.6, 28.5, 39.4, 48.9, 50.7, 61.0, 68.6, 70.1, 120.8, 123.2, 124.5, 126.1, 126.8, 127.7, 128.1, 129.2, 129.9, 130.3, 133.0, 134.6, 137.0, 140.6, 145.0, 147.7, 172.8; mass (ES^+) m/z=445.3 (M^++1); ESI-HRMS: MH^+, found 445.1885. $C_{25}H_{25}N_4O_4$ requires 445.1876.

*4.4.17. Methyl (1R,13S)-4,5-diphenyl-3,4,14-triazapentacyclo[11.6.0.0^{2,6}.0^{7,12}.0^{14,18}]nonadeca-2,5,7,9,11-pentaene-19-carboxylate (syn-**19.2a**).* Yield 41% as a white solid (93 mg from 200 mg), mp 210–211 °C; R_f (hexanes/EtOAc, 70:30, v/v) 0.30; ν_{max} (KBr) 1732 (CO_2Me) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.58–1.63 (m, 2H, CH*H*), 1.90 (s, 2H, CH_2), 2.92–3.01 (m, 3H, C*H*H), 3.77 (s, 3H, CO_2Me), 3.96–4.02 (m, 3H, NC*H*H & NCH), 4.26–4.27 (m, 1H, NCH), 7.01–7.23 (m, 9H, ArH), 7.35–7.39 (m, 6H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$): δ=27.4, 28.9, 42.5, 50.6, 51.8, 53.5, 66.1, 68.2, 115.1, 123.3, 125.2, 126.1, 127.0, 127.8, 128.8, 128.9, 129.0, 129.3, 129.8, 130.7, 131.3, 135.1, 138.6, 140.0, 149.9, 174.5; mass (ES^+) m/z=462.2 (M^++1); DART-HRMS: MH^+, found 462.2146. $C_{30}H_{28}N_3O_2$ requires 462.2185.

*4.4.18. Methyl (1R,13R)-4,5-diphenyl-3,4,14-triazapentacyclo[11.6.0.0^{2,6}.0^{7,12}.0^{14,18}]nonadeca-2,5,7,9,11-pentaene-19-carboxylate (anti-**19.2a**).* Yield 59% as a white solid (133 mg from 200 mg), mp 185–186 °C; R_f (hexanes/EtOAc, 70:30, v/v) 0.15; ν_{max} (KBr) 1732 (CO_2Me) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.60–1.68 (m, 1H, CH*H*), 1.84–1.91 (m, 2H, CH_2), 2.10–2.21 (m, 1H, C*H*H), 2.74–2.82 (m, 1H, CH), 3.41–3.52 (m, 2H, NC*H*H & NCH), 3.60–3.68 (dd, 1H, J=11.0, 13.3 Hz, CH), 3.81 (s, 3H, CO_2Me), 4.28–4.35 (m, 2H, NCH & NCH*H*), 6.95–7.03 (m, 2H, ArH), 7.15–7.28 (m, 9H, ArH), 7.37–7.39

(m, 3H, ArH), 7.57 (d, 1H, J=7.6 Hz, ArH); ^{13}C NMR (50 MHz, $CDCl_3$): δ=21.6, 26.1, 28.9, 39.2, 49.2, 50.4, 52.1, 68.0, 68.9, 116.4, 123.9, 125.3, 125.7, 126.0, 126.2, 126.9, 127.0, 127.8, 128.7, 129.8, 130.2, 130.8, 134.6, 138.9, 139.0, 149.9, 150.4, 173.3; DART-HRMS: MH^+, found 462.2176. $C_{30}H_{28}N_3O_2$ requires 462.2185.

*4.4.19. Methyl (1R,13S)-5-(4-methylphenyl)-4-phenyl-3,4,14-triazapentacyclo[11.6.0.0^{2,6}.0^{7,12}.0^{14,18}]nonadeca-2,5,7,9,11-pentaene-19-carboxylate (syn-**19.2e**).* Yield 38% as a white solid (88 mg from 200 mg), mp 167–168 °C; R_f (hexanes/EtOAc, 70:30, v/v) 0.29; ν_{max} (KBr) 1730 (CO_2Me) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.26–1.34 (m, 1H, CHH), 1.89–2.04 (m, 3H, CH_2), 2.40 (s, 3H, CH_3), 2.94–3.01 (m, 3H, C*H*H), 3.77 (s, 3H, CO_2Me), 3.99–4.01 (m, 3H, NC*H*H & NCH), 4.25 (s, 1H, NCH), 7.04 (d, 1H, J=6.8 Hz, ArH), 7.11 (t, 2H, J=6.3 Hz, ArH), 7.20–7.26 (m, 9H, ArH), 7.36 (d, 1H, J=6.9 Hz, ArH); ^{13}C NMR (50 MHz, $CDCl_3$): δ=21.6, 27.4, 28.9, 42.5, 50.6, 51.7, 53.5, 66.2, 68.2, 115.0, 123.3, 125.2, 126.0, 127.0, 127.8, 128.2, 128.7, 129.5, 129.7, 129.8, 130.6, 138.9, 140.1, 150.1, 174.5; mass (ES^+) m/z=476.2 (M^++1); DART-HRMS: MH^+, found 476.2333. $C_{31}H_{30}N_3O_2$ requires 476.2338.

*4.4.20. Methyl (1R,13R)-5-(4-methylphenyl)-4-phenyl-3,4,14-triazapentacyclo[11.6.0.0^{2,6}.0^{7,12}.0^{14,18}]nonadeca-2,5,7,9,11-pentaene-19-carboxylate (anti-**19.2e**).* Yield 56% as a white solid (122 mg from 200 mg), mp 187–188 °C; R_f (hexanes/EtOAc, 70:30, v/v) 0.14; ν_{max} (KBr) 1730 (CO_2Me) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.61–1.67 (m, 1H, CH*H*), 1.88–1.93 (m, 2H, CH_2), 2.10–2.20 (m, 1H, C*H*H), 2.39 (s, 3H, CH_3), 2.80 (dd, 1H, J_1=7.0 Hz, J_2=16.5 Hz, CH), 3.47–3.53 (m, 2H, NC*H*H & NCH), 3.65 (t, 1H, J=12.3 Hz, CH), 3.81 (s, 3H, CO_2Me), 4.33–4.38 (m, 2H, NCH & NCH*H*), 7.01 (d, 2H, J=5.6 Hz, ArH), 7.16–7.26 (m, 9H, ArH), 7.57 (d, 1H, J=7.4 Hz, ArH); ^{13}C NMR (50 MHz, $CDCl_3$): δ=21.6, 26.1, 28.8, 39.2, 49.2, 50.4, 52.1, 68.0, 68.9, 116.3, 123.9, 125.3, 125.4, 126.0, 126.2, 126.9, 127.0, 127.8, 128.7, 129.8, 130.2, 130.8, 134.6, 138.9, 139.0, 149.9, 150.4, 173.3; mass (ES^+) m/z=476.2 (M^++1); DART-HRMS: MH^+, found 476.2339. $C_{31}H_{30}N_3O_2$ requires 476.2338.

*4.4.21. Ethyl (1R,13S)-3,5-diphenyl-3,4,14-triazapentacyclo[11.6.0.0^{2,6}.0^{7,12}.0^{14,18}]nonadeca-2(6),4,7,9,11-pentaene-19-carboxylate (syn-**25a**).* Yield 37% as a white solid (42 mg from 100 mg), mp 143–144 °C; R_f (hexanes/EtOAc, 70:30, v/v) 0.29; ν_{max} (KBr) 1727 (CO_2Et) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.12 (t, 3H, J=7.1 Hz, CH_3), 1.51–1.53 (m, 1H, CH*H*), 1.73–1.84 (m, 2H, CH_2), 1.98–2.00 (m, 1H C*H*H), 2.97–3.13 (m, 3H, CH & CH*H*N), 3.63–3.66 (m, 1H, NCH), 3.89–3.92 (m, 2H, NCH), 4.23–4.33 (m, 2H, OCH_2), 7.09–7.16 (m, 2H, ArH), 7.38–7.53 (m, 10H, ArH), 7.73–7.75 (m, 2H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$): δ=14.4, 25.3, 27.8, 39.7, 51.2, 52.4, 60.7, 65.4, 66.6, 114.8, 123.5, 125.1, 125.9, 127.9, 128.1, 128.4, 128.6, 129.2, 129.5, 130.1, 134.4, 140.0, 149.5, 172.8; mass (ES^+) m/z=476.2 (M^++1); DART-HRMS: MH^+, found 476.2322. $C_{31}H_{30}N_3O_2$ requires 476.2338.

*4.4.22. Ethyl (1R,13R)-3,5-diphenyl-3,4,14-triazapentacyclo[11.6.0.0^{2,6}.0^{7,12}.0^{14,18}]nonadeca-2(6),4,7,9,11-pentaene-19-carboxylate (anti-**25a**).* Yield 7% as a white solid (64 mg from 100 mg), mp 199–200 °C; R_f (hexanes/EtOAc, 70:30, v/v) 0.19; ν_{max} (KBr) 1727 (CO_2Et) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.12 (t, 3H, J=7.2 Hz, CH_3), 1.43–1.49 (m, 1H, CH*H*), 1.77–1.87 (m, 2H, CH_2), 2.00–2.10 (m, 1H, C*H*H), 2.74 (dd, 1H, J_1=8.0 Hz, J_2=16.2 Hz, CH), 3.00 (t, 1H, J=10.3 Hz, CH), 3.36–3.44 (m, 1H, NC*H*H), 3.56–3.67 (m, 1H, NCH), 3.76–3.95 (m, 2H, OCH_2), 4.11–4.16 (m, 1H, NCH*H*), 4.41 (d, 1H, J=13.7 Hz, NCH), 7.11 (t, 1H, J=7.5 Hz, ArH), 7.20 (t, 1H, J=7.3 Hz, ArH), 7.34 (d, 1H, J=7.7 Hz, ArH), 7.40–7.44 (m, 8H, ArH), 7.54 (d, 1H, J=7.5 Hz, ArH), 7.66–7.68 (m, 2H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$): δ=14.1, 25.5, 28.1, 39.6, 48.5, 50.4, 60.6, 69.1, 70.1, 115.5, 124.3, 125.8, 126.0, 126.9, 128.0, 128.4, 128.6, 129.1, 129.2, 131.1, 133.8, 139.5, 142.4, 149.2, 172.6; mass (ES^+) m/z=476.2 (M^++1); DART-HRMS: MH^+, found 476.2322. $C_{31}H_{30}N_3O_2$ requires 476.2338.

*4.4.23. Ethyl (1R,13S)-5-(4-chlorophenyl)-3-phenyl-3,4,14-triazapentacyclo[11.6.0.0^{2,6}.0^{7,12}.0^{14,18}]nonadeca-2(6),4,7,9,11-pentaene-19-carboxylate (syn-**25b**).* Yield 42% as a white (49 mg from 100 mg) solid, mp 209–210 °C; R_f (hexanes/EtOAc, 70:30, v/v) 0.31; ν_{max} (KBr) 1718 (CO_2Et) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.12 (t, 3H, J=6.8 Hz, CH_3), 1.50–1.53 (m, 1H, CH*H*), 1.76–1.84 (m, 2H, CH_2), 1.99–2.04 (m, 1H, C*H*H), 2.99–3.10 (m, 3H, CH &CH*H*N), 3.62–3.65 (m, 1H, NCH), 3.90–3.92 (m, 2H, NCH), 4.23–4.29 (m, 2H, OCH_2), 7.14 (s, 2H, ArH), 7.35–7.49 (m, 9H, ArH), 7.70 (d, 2H, J=7.7 Hz, ArH); ^{13}C NMR (50 MHz, $CDCl_3$): δ=14.4, 25.3, 27.8, 39.6, 51.1, 52.3, 60.8, 65.4, 66.5, 114.9, 123.4, 125.0, 126.1, 127.9, 128.3, 128.8, 129.4, 129.5, 129.8, 130.8, 132.9, 133.9, 134.3, 139.9, 141.0, 148.3, 172.7; mass (ES^+) m/z=510.2 (M^++1); ESI-HRMS: MH^+, found 510.1932. $C_{31}H_{29}ClN_3O_2$ requires 510.1948.

*4.4.24. Ethyl (1R,13R)-5-(4-chlorophenyl)-3-phenyl-3,4,14-triazapentacyclo[11.6.0.0^{2,6}.0^{7,12}.0^{14,18}]nonadeca-2(6),4,7,9,11-pentaene-19-carboxylate (anti-**25b**).* Yield 55% as a yellow solid (59 mg from 100 mg), mp >250 °C; R_f (hexanes/EtOAc, 70:30, v/v) 0.19; ν_{max} (KBr) 1718 (CO_2Et) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.11 (t, 3H, J=7.1 Hz, CH_3), 1.43–1.47 (m, 1H, CH*H*), 1.77–1.85 (m, 2H, CH_2), 2.00–2.13 (m, 1H, C*H*H), 2.74 (dd, 1H, J_1=8.2 Hz, J_2=16.6 Hz, CH), 2.99 (t, 1H, J=10.3 Hz, CH), 3.36–3.44 (m, 1H, NC*H*H), 3.55–3.66 (m, 1H, NCH), 3.75–3.95 (m, 2H, OCH_2), 4.12–4.17 (m, 1H, NCH*H*), 4.40 (d, 1H, J=13.7 Hz, NCH), 7.14 (t, 1H, J=7.4 Hz, ArH), 7.20 (d, 1H, J=7.6 Hz, ArH), 7.31 (d, 1H, J=7.3 Hz, ArH), 7.38–7.44 (m, 7H, ArH), 7.55 (d, 1H, J=7.4 Hz, ArH), 7.62 (m, 2H, J=8.3 Hz, ArH); ^{13}C NMR (50 MHz, $CDCl_3$): δ=14.1, 25.5, 28.1, 39.6, 48.5, 50.3, 60.6, 69.1, 70.0, 115.6, 124.1, 125.9, 126.2, 127.0, 128.0, 128.9, 129.2, 129.3, 130.5, 130.9, 132.4, 133.8, 134.3, 139.5, 142.6, 148.0, 172.5; mass (ES^+) m/z=510.2 (M^++1); ESI-HRMS: MH^+, found 510.1952. $C_{31}H_{29}ClN_3O_2$ requires 510.1948.

4.5. General procedure for the synthesis of compounds 10a–d, 11a–c, 15, 20.1a,b,e,f, 20.2a,e and 26a,b as exemplified 10a

To a stirred solution of compound **4a** (0.51 mmol, 200 mg) in EtOH (15 mL) was added hydroxylamine hydrochloride (0.62 mmol, 43 mg) and sodium acetate (0.62 mmol, 51 mg) and the reaction was continued at room temperature for 30 min. Thereafter EtOH was evaporated and the residue was extracted with EtOAc (3×15 mL) and water (30 mL). The organic layers were combined washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. Subsequently the reaction mixture was diluted with CH_2Cl_2 (15 mL) followed by addition of Et_3N (0.77 mmol, 0.11 mL) and NaOCl (1.02 mmol, 0.068 mL) and stirred at rt for overnight. After completion of the reaction water (30 mL) was added and layers were separated. The aqueous layer was again extracted with CH_2Cl_2 (2×15 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Column chromatography of the residue over silica gel (hexanes/EtOAc, 90:10, v/v) afforded pure **10a** as a white solid (65%, 134 mg).

*4.5.1. 10,11-Diphenyl-4-oxa-3,9,10-triazatetracyclo[11.4.0.0^{2,6}.0^{8,12}]heptadeca-1(17),2,8,13,15-pentaene-6-carbonitrile (**10a**).* Mp 158–159 °C; R_f (hexanes/EtOAc, 80:20, v/v) 0.57; ν_{max} (KBr) 2212 (CN) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=3.40–3.50 (m, 2H, CH_2), 4.41 (d, 1H, J=9.3 Hz, OCH*H*), 5.00 (d, 1H, J=9.2 Hz, OC*H*H), 6.86 (d, 1H, J=7.7 Hz, ArH), 7.09 (d, 2H, J=6.9 Hz, ArH), 7.19–7.35 (m, 10H, ArH), 7.73 (d, 1H, J=6.8 Hz, ArH); ^{13}C NMR (50 MHz, $CDCl_3$): δ=29.8, 30.4, 56.7, 117.9, 119.0, 125.4, 125.7, 127.4, 127.9, 128.6, 129.0, 129.1, 129.2, 129.3, 129.8,

130.4, 130.9, 132.0, 139.3, 141.9, 145.3, 156.8; mass (ES^+) m/z=403.3 (M^++1); ESI-HRMS $[MH]^+$, found 403.1572. $C_{26}H_{19}N_4O$ requires 403.1559.

*4.5.2. 11-(4-Chlorophenyl)-10-phenyl-4-oxa-3,9,10-triazatetracyclo [11.4.0.0^{2,6}.0^{8,12}]heptadeca-1(17),2,8,13,15-pentaene-6-carbonitrile (**10b**).* Yield 66% as a white solid (102 mg from 150 mg), mp 121–122 °C; R_f (hexanes/EtOAc, 80:20, v/v) 0.54; ν_{max} (KBr) 2235 (CN) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=3.38–3.49 (m, 2H, CH_2), 4.39 (d, 1H, J=9.2 Hz, OCH*H*), 4.99 (d, 1H, J=9.2 Hz, OC*H*H), 6.86 (d, 1H, J=6.9 Hz, ArH), 7.02 (d, 2H, J=8.5 Hz, ArH), 7.18–7.37 (m, 9H, ArH), 7.75 (dd, 1H, J_1=1.2 Hz, J_2=7.5 Hz, ArH); ^{13}C NMR (50 MHz, $CDCl_3$): δ=29.9, 30.3, 56.8, 117.8, 119.2, 125.3, 125.5, 125.8, 127.7, 128.2, 128.9, 129.1, 129.3, 129.4, 129.9, 131.1, 131.7, 132.0, 135.5, 139.1, 140.6, 145.4, 156.7; mass (ES^+) m/z=437.3 (M^++1); ESI-HRMS: MH^+, found 437.1180. $C_{26}H_{18}ClN_4O$ requires 437.1169.

*4.5.3. 10-Methyl-4-oxa-3,9,10-triazatetracyclo[11.4.0.0^{2,6}.0^{8,12}]heptadeca-1(17),2,8,13,15-pentaene-6-carbonitrile (**10c**).* Yield 67% as a white solid (142 mg from 200 mg), mp 136–137 °C; R_f (hexanes/EtOAc, 70:30, v/v) 0.24; ν_{max} (KBr) 2234 (CN) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=3.27 (d, 1H, J=15.4 Hz, CH*H*), 3.52 (d, 1H, J=15.4 Hz, C*H*H), 3.92 (s, 3H, NCH_3), 4.69 (d, 1H, J=8.8 Hz, OC*H*H), 4.86 (d, 1H, J=8.8 Hz, OCH*H*), 7.28 (s, 1H, ArH), 7.45 (t, 1H, J=7.2 Hz, ArH), 7.64 (d, 1H, J=7.8 Hz, ArH), 7.87 (d, 2H, J=11.6 Hz, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ=35.5, 39.4, 48.9, 79.2, 117.1, 119.3, 122.6, 126.6, 126.8, 130.2, 130.3, 130.4, 131.6, 143.8, 157.4; mass (ES^+) m/z=265.0 (M^++1); ESI-HRMS: MH^+, found 265.1095. $C_{15}H_{13}N_4O$ requires 265.1089.

*4.5.4. 10-(4-Methoxyphenyl)-11-phenyl-7,7a,8,10-tetrahydrobenzo [6,7]pyrazolo[3′,4′:4,5]cyclohepta[1,2-c]isoxazole-7a-carbonitrile (**10d**).* Yield 65% as a white solid (67 mg from 100 mg); mp 134–135 °C; R_f (hexanes/EtOAc, 80:20, v/v) 0.43; ν_{max} (KBr) 2238 (CN) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=3.44 (s, 2H, CH_2), 3.78 (s, 3H, CH_3), 4.41 (d, 1H, J=9.2 Hz, OCH*H*), 4.99 (d, 1H, J=9.4 Hz, OC*H*H), 6.80–6.87 (m, 3H, ArH), 7.07–7.17 (m, 4H, ArH), 7.22 (d, 1H, J=8.0 Hz, ArH), 7.31–7.37 (m, 4H, ArH), 7.73 (d, 1H, J=7.4 Hz, ArH); ^{13}C NMR (50 MHz, $CDCl_3$): δ=30.4, 32.1, 55.6, 56.8, 114.3, 118.6, 125.7, 126.8, 127.4, 129.0, 129.1, 129.8, 130.4, 130.9, 132.1, 141.9, 144.9, 159.2; mass (ES^+) m/z=433.3 (M^++1); ESI-HRMS: MH^+, found: 433.1642. $C_{27}H_{21}N_4O_2$ requires 433.1665.

*4.5.5. Methyl 10,11-diphenyl-4-oxa-3,9,10-triazatetracyclo[11.4.0.0^{2,6}.0^{8,12}]heptadeca-1(17),2,8,11,13,15-hexaene-6-carboxylate (**11a**).* Yield 70% as a white (72 mg from 100 mg) solid, mp 108–110 °C; R_f (hexanes/EtOAc, 80:20, v/v) 0.47; ν_{max} (KBr) 1735 (CO_2Me) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=3.25–3.36 (m, 2H, CH_2), 3.80 (s, 3H, CO_2Me), 4.38 (d, 1H, J=9.1 Hz, OCH*H*), 4.98 (d, 1H, J=9.0 Hz, OC*H*H), 6.79 (d, 1H, J=7.1 Hz, ArH), 7.07–7.10 (m, 2H, ArH), 7.19–7.33 (m, 10H, ArH), 7.61–7.64 (m, 1H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$): δ=29.1, 30.8, 53.2, 69.7, 119.2, 125.3, 127.0, 127.6, 128.4, 128.7, 128.8, 128.9, 129.0, 129.5, 129.6, 129.9, 130.4, 132.1, 133.5, 139.5, 141.2, 146.9, 160.0, 171.9; mass (ES^+) m/z=436.2 (M^++1); ESI-HRMS: MH^+, found 436.1665. $C_{27}H_{22}N_3O_3$ requires 436.1661.

*4.5.6. Methyl 11-(4-chlorophenyl)-10-phenyl-4-oxa-3,9,10-triazatetracyclo[11.4.0.0^{2,6}.0^{8,12}]heptadeca-1(17),2,8,11,13,15-hexaene-6-carboxylate (**11b**).* Yield 68% as a white solid (84 mg from 120 mg), mp 154–155 °C; [found C, 69.12; H, 4.36; N, 8.71. $C_{27}H_{20}ClN_3O_3$ (Exact mass: 469.1193) requires C, 69.01; H, 4.29; N, 8.94%]; R_f (hexanes/EtOAc, 80:20, v/v) 0.46; ν_{max} (KBr) 1737 (CO_2Me) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=3.24–3.35 (m, 2H, CH_2), 3.79 (s, 3H, CO_2Me), 4.36 (d, 1H, J=9.0 Hz, OCH*H*), 4.98 (d, 1H, J=9.0 Hz, OC*H*H), 6.79 (d, 1H, J=7.4 Hz, ArH), 7.01 (d, 2H, J=8.3 Hz, ArH), 7.19–7.31 (m, 9H, ArH), 7.63 (d, 1H, J=7.3 Hz, ArH); ^{13}C NMR (50 MHz, $CDCl_3$): δ=29.0, 53.3, 69.7, 119.4, 125.4, 127.2, 127.9, 128.5, 129.2, 129.8, 130.0, 131.7, 135.1, 139.2, 139.9, 147.1, 159.8, 171.8; mass (ES^+) m/z=470.1 (M^++1).

*4.5.7. Methyl 10-methyl-4-oxa-3,9,10-triazatetracyclo[11.4.0.0^{2,6}.0^{8,12}] heptadeca-1(17),2,8,11,13,15-hexaene-6-carboxylate (**11c**).* Yield 69% as a white solid (144 mg from 200 mg), mp 167–168 °C; R_f (hexanes/EtOAc, 70:30, v/v) 0.34; ν_{max} (KBr) 1724 (CO_2Me) cm^{-1}; ^1H NMR (800 MHz, $CDCl_3$): δ=3.17 (d, 1H, J=14.9 Hz, CH*H*), 3.54 (s, 3H, CO_2Me), 3.58 (d, 1H, J=15.6 Hz, C*H*H), 3.88 (s, 3H, NCH_3), 4.50 (d, 1H, J=5.8 Hz, OC*H*H), 4.77 (d, 1H, J=5.9 Hz, OCH*H*), 7.24 (s, 1H, ArH), 7.38 (s, 1H, ArH), 7.52 (d, 1H, J=4.3 Hz, ArH), 7.70 (s, 1H, ArH), 7.88 (d, 2H, J=4.3 Hz, ArH); ^{13}C NMR (200 MHz, $CDCl_3$): δ=33.3, 39.2, 53.0, 62.3, 79.4, 119.4, 125.5, 126.3, 126.6, 129.5, 129.9, 130.3, 130.5, 145.6, 159.8, 171.1; mass (ES^+) m/z=298.0 (M^++1); ESI-HRMS: MH^+, found 298.1198. $C_{16}H_{16}N_3O_3$ requires 298.1192.

*4.5.8. 4,5-Diphenyl-5,7,7a,8-tetrahydropyrazolo[3′,4′:4,5]thieno [3′,2′:6,7]cyclohepta[1,2-c]isoxazole-7a-carbonitrile (**15**).* Yield 60% as a white solid (124 mg from 200 mg), mp 136–138 °C; R_f (hexanes/EtOAc, 80:20, v/v) 0.42, ν_{max} (KBr) 2242 (CN) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ=3.72 (s, 2H, CH_2), 4.82 (s, 1H, OCH*H*), 5.95 (s, 1H, OC*H*H), 6.01 (s, 1H, ArH), 6.48 (s, 1H, ArH), 7.00 (s, 1H, ArH), 7.25–7.32 (m, 9H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ=32.7, 33.8, 60.0, 107.2, 118.7, 121.1, 125.4, 125.6, 126.9, 127.7, 128.5, 128.6, 128.8, 129.1, 130.3, 131.9, 140.0, 144.5, 147.9; mass (ES^+) m/z=409.3 (M^++1); ESI-HRMS calcd for $C_{24}H_{17}N_4OS$ $[MH]^+$: 409.1123; found: 409.1127.

*4.5.9. Ethyl 9,10-diphenyl-4-oxa-3,8,9-triazatetracyclo [10.4.0.0^{2,6}.0^{7,11}]hexadeca-1(16),2,5,7,10,12,14-heptaene-5-carboxylate (**20.1a**).* Yield 70% as a yellow solid (68 mg from 100 mg); R_f=0.37 (hexanes/EtOAc, 80:20, v/v); ν_{max} (KBr) 1736 (CO_2Et) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=1.52 (t, 3H, J=7.1 Hz, CH_3), 4.60 (q, 2H, J=7.1 Hz, OCH_2), 7.27–7.52 (m, 13H, ArH), 8.54 (d, 1H, J=7.7 Hz, ArH); ^{13}C NMR (50 MHz, $CDCl_3$): δ=14.4, 62.5, 112.3, 117.0, 121.0, 123.6, 125.2, 125.7, 126.6, 127.9, 128.8, 129.4, 129.6, 129.8, 130.5, 130.9, 138.4, 139.0, 139.9, 152.9, 157.6, 158.7; mass (ES^+) m/z=434.2 (M^++1); ESI-HRMS: MH^+, found 434.1518. $C_{27}H_{20}N_3O_3$ requires 434.1505.

*4.5.10. Ethyl 10-(4-chlorophenyl)-9-phenyl-4-oxa-3,8,9-triazatetracyclo[10.4.0.0^{2,6}.0^{7,11}]hexadeca-1(16),2,5,7,10,12,14-heptaene-5-carboxylate (**20.1b**).* Yield 68% as a yellow solid (66 mg from 100 mg); R_f (hexanes/EtOAc, 80:20, v/v) 0.38; ν_{max} (KBr) 1728 (CO_2Et) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=1.51 (t, 3H, J=7.1 Hz, CH_3), 4.59 (q, 2H, J=7.1 Hz, OCH_2), 7.33–7.50 (m, 12H, ArH), 8.55 (d, 1H, J=7.4 Hz, ArH); ^{13}C NMR (50 MHz, $CDCl_3$): δ=14.4, 62.5, 112.1, 117.0, 121.1, 123.4, 125.3, 125.5, 125.8, 126.8, 128.0, 128.2, 129.0, 129.3, 129.8, 130.5, 131.8, 132.3, 136.0, 137.7, 138.5, 139.6, 153.0, 157.5, 158.6; mass (ES^+) m/z=468.1 (M^++1); ESI-HRMS: MH^+, found 468.1117. $C_{27}H_{19}ClN_3O_3$ requires 468.1115.

*4.5.11. Ethyl 10-(4-methylphenyl)-9-phenyl-4-oxa-3,8,9-triazatetracyclo[10.4.0.0^{2,6}.0^{7,11}]hexadeca-1(16),2,5,7,10,12,14-heptaene-5-carboxylate (**20.1e**).* Yield 71% as a yellow solid (69 mg from 100 mg); R_f (hexanes/EtOAc, 80:20, v/v) 0.36; ν_{max} (KBr) 1720 (CO_2Et) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=1.52 (t, 3H, J=7.1 Hz, CH_3), 4.60 (q, 2H, J=7.1 Hz, OCH_2), 7.26–7.44 (m, 11H, ArH), 7.50 (d, 1H, J=8.0 Hz, ArH), 8.54 (d, 1H, J=7.5 Hz, ArH); ^{13}C NMR (50 MHz, $CDCl_3$): δ=14.4, 21.7, 62.5, 117.0, 121.0, 123.6, 125.2, 125.7, 126.6, 127.8, 127.9, 128.8, 129.8, 130.2, 130.5, 130.7, 139.2, 139.8, 140.0, 152.9, 157.7, 158.8; mass (ES^+) m/z=448.1 (M^++1); ESI-HRMS: MH^+, found 448.1671. $C_{28}H_{22}N_3O_3$ requires 448.1661.

4.5.12. Ethyl 9-(4-nitrophenyl)-4-oxa-3,8,9-triazatetracyclo[10.4.0. 0^{2,6}.0^{7,11}]hexadeca-1(16),2,5,7,10,12,14-heptaene-5-carboxylate

(***20.1f***). Yield 74% as a yellow solid (72 mg from 100 mg); R_f (hexanes/EtOAc, 80:20, v/v) 0.32; ν_{max} (KBr) 1720 (CO_2Et) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ=1.27 (t, 3H, J=7.1 Hz, CH_3), 4.01 (q, 2H, J=7.1 Hz, OCH_2), 7.58–7.65 (m, 1H, ArH), 7.72–7.79 (m, 3H, ArH), 8.10 (d, 1H, J=7.9 Hz, ArH), 8.37 (d, 2H, J=9.0 Hz, ArH), 8.52 (s, 1H, ArH), 8.61 (d, 1H, J=7.7 Hz, ArH); ^{13}C NMR (50 MHz, $CDCl_3$): δ=14.2, 63.0, 107.8, 120.1, 122.6, 123.8, 124.1, 125.2, 127.7, 128.2, 128.6, 131.4, 137.3, 146.8, 147.0, 153.2, 157.4, 157.8; mass (ES^+) m/z=403.1 (M^++1); ESI-HRMS: MH^+, found 403.1031. $C_{21}H_{15}N_4O_5$ requires 403.1042.

*4.5.13. Methyl 9,10-diphenyl-4-oxa-3,8,9-triazatetracyclo[10.4.0.0^{2,6}.0^{7,11}]hexadeca-1(16),2,5,7,10,12,14-heptaene-5-carboxylate (**20.2a**).* Yield 71% as a yellow solid (73 mg from 100 mg); R_f (hexanes/EtOAc, 80:20, v/v) 0.36; ν_{max} (KBr) 1725 (CO_2Me) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=4.13 (s, 3H, CO_2Me), 7.28–7.51 (m, 13H, ArH), 8.54 (d, 1H, J=7.1 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ=52.9, 112.1, 116.8, 120.8, 123.4, 125.0, 125.5, 126.4, 127.7, 128.6, 129.2, 129.4, 129.6, 130.3, 130.7, 138.2, 138.8, 139.7, 152.7, 157.4, 158.5; mass (ES^+) m/z=420.2 (M^++1); ESI-HRMS: MH^+, found 420.1348. $C_{26}H_{18}N_3O_3$ requires 420.1348.

*4.5.14. Methyl 10-(4-methylphenyl)-9-phenyl-4-oxa-3,8,9-triazatetracyclo[10.4.0.0^{2,6}.0^{7,11}]hexadeca-1(16),2,5,7,10,12,14-heptaene-5-carboxylate (**20.2e**).* Yield 69% as a yellow solid (71 mg from 100 mg); R_f (hexanes/EtOAc, 80:20, v/v) 0.36; ν_{max} (KBr) 1728 (CO_2Me) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=2.46 (s, 3H, CH_3), 4.13 (s, 3H, CO_2Me), 7.29–7.44 (m, 11H, ArH), 7.50 (d, 1H, J=8.0 Hz, ArH), 8.53 (d, 1H, J=7.9 Hz, ArH); ^{13}C NMR (50 MHz, $CDCl_3$): δ=21.6, 53.1, 116.9, 120.9, 123.6, 125.2, 125.7, 126.6, 127.7, 127.9, 128.9, 129.8, 130.2, 130.5, 130.7, 138.3, 139.3, 139.8, 140.0, 158.0, 158.8; mass (ES^+) m/z=434.1 (M^++1); ESI-HRMS: MH^+, found 434.1505. $C_{27}H_{20}N_3O_3$ requires 434.1505.

*4.5.15. Ethyl 8,10-diphenyl-4-oxa-3,8,9-triazatetracyclo[10.4.0.0^{2,6}.0^{7,11}]hexadeca-1(16),2,5,7(11),9,12,14-heptaene-5-carboxylate (**26a**).* Yield 62% as a white solid (64 mg from 100 mg); R_f (hexanes/EtOAc, 80:20, v/v) 0.52; ν_{max} (KBr) 1734 (CO_2Et) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=1.21 (t, 3H, J=7.2 Hz, CH_3), 3.82 (q, 2H, J=7.2 Hz, OCH_2), 7.43–7.60 (m, 8H, ArH), 7.63 (d, 2H, J=7.2 Hz, ArH), 7.70–7.73 (m, 2H, ArH), 7.84–7.87 (m, 1H, ArH), 8.60 (dd, 1H, J_1=1.7 Hz, J_2=7.2 Hz, ArH); ^{13}C NMR (50 MHz, $CDCl_3$): δ=14.1, 62.8, 106.8, 117.9, 120.2, 123.76, 124.0, 125.2, 126.8, 128.4, 129.0, 129.2, 129.8, 129.9, 130.0, 130.7, 134.0, 141.8, 150.4, 153.8, 157.9, 158.0; mass (ES^+) m/z=434.3 (M^++1); ESI-HRMS: MH^+, found 434.1527. $C_{27}H_{20}N_3O_3$ requires 434.1505.

*4.5.16. Ethyl 10-(4-chlorophenyl)-8-phenyl-4-oxa-3,8,9-triazatetracyclo[10.4.0.0^{2,6}.0^{7,11}]hexadeca-1(16),2,5,7(11),9,12,14-heptaene-5-carboxylate (**26b**).* Yield 60% as a yellow solid (62 mg from 100 mg); R_f (hexanes/EtOAc, 80:20, v/v) 0.51; ν_{max} (KBr) 1731 (CO_2Et) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=1.21 (t, 3H, J=7.1 Hz, CH_3), 3.83 (q, 2H, J=7.1 Hz, OCH_2), 7.44–7.55 (m, 7H, ArH), 7.61 (d, 2H, J=7.4 Hz, ArH), 7.67 (d, 2H, J=8.4 Hz, ArH), 7.82–7.85 (m, 1H, ArH), 8.59–8.62 (m, 1H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$): δ=14.1, 62.9, 106.7, 117.8, 120.2, 123.7, 123.8, 125.3, 126.9, 128.5, 129.1, 129.2, 129.5, 130.0, 130.8, 131.4, 132.4, 135.3, 141.7, 149.2, 153.9, 157.9, 158.0; mass (ES^+) m/z=468.2 (M^++1); ESI-HRMS: MH^+, found: 468.1117. $C_{27}H_{19}ClN_3O_3$ requires 468.1115.

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Supplementary data

Remaining spectroscopic data and copies of ^1H and ^{13}C NMR spectra of all new compounds are provided. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.03.099. These data include MOL files and InChiKeys of the most important compounds described in this article.

References and notes

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12. Crystal data of compound **6a**: $C_{28}H_{24}N_4$, M=416.51, Monoclinic, P 21/n, a=8.8122(17), b=19.571(4), c=12.739(2) Å, α=90, β=93.974(4), γ=90, V=2191.8(7) Å^3, Z=4, D_{calcd}=1.262 mg/m^3, m (Mo-K$_\alpha$)=0.076 mm^{-1}, F (000)=880, colorless block, dimension 0.21×0.2×0.19 mm, 14,415 reflections measured (R_{int}=0.0687), 5388 unique, wR_2=0.2140, conventional R=0.0698 on F^2 values of 3132 reflections with $I>2s(I)$, $(\Delta/\sigma)_{max}$=000), S=1.095 for all data and 289 parameters. Unit cell determination and intensity data collection (2θ=50°) were performed on a Bruker P4 diffractometer at 293(2) K. Structure solutions by direct methods and refinements by full-matrix least-squares methods on F^2. Programs: XSCANS (Siemens Analytical X-ray Instrument Inc.: Madison, WI, USA, 1996) for data collection and data processing; SHELXTL-NT (Bruker AXS Inc.: Madison, Wisconsin, USA, 1997) for structure determination, refinements and molecular graphics. Further details of the crystal structure investigation can be obtained from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK (CCDC deposition no. 927231).
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14. Crystal data of compound **19.2a**: $C_{30}H_{27}N_3O_2$, M=461.55, triclinic, P–1, a=9.233(2), b=10.647(2), c=13.105(3) Å, α=99.208(3), β=108.350(4), γ=100.080(4), V=1171.5(4) Å^3, Z=2, D_{calcd}=1.308 g cm^{-3}, m (Mo-K$_\alpha$)=0.083 mm^{-1}, F (000)=488, yellow block, dimension 0.42×0.40×0.38 mm, 6660 reflections measured (R_{int}=0.0347), 4510 unique, wR_2=0.2095, conventional R=0.0669 on F^2 values of 2817 reflections with $I>2s(I)$, S=1.003 for all data and 316 parameters. Unit cell determination and intensity data collection (2θ=50°) were performed on a Bruker P4 diffractometer at 100 (2) K. Structure solutions by direct methods and refinements by full-matrix least-squares methods on F^2. Programs: ZSCANS (Siemens Analytical X-ray Instrument Inc.: Madison, WI, USA, 1996) for data collection and data processing; SHELXTL-NT (Bruker AXS Inc.: Madison, Wisconsin, USA, 1997) for structure determination, refinements and molecular graphics. Further details of the crystal structure investigation can be obtained from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK (CCDC deposition no. 927230).