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Multicomponent Cascade Assembly for Quinolinopyranpyrazole Architectures

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Keywords: Domino reactions / Fused ring systems / Multicomponent reactions / Nitrogen heterocycles / Diastereoselectivity

A highly efficient, multicomponent protocol for the construction of functionalized quinolinopyranpyrazole scaffolds with high stereoselectivity has been developed through the application of a domino reaction. All the quinolinopyranpyrazoles were synthesized under solvent- and catalyst-free conditions and required no work-up or column chromatography.

Introduction

Heterocyclic frameworks, especially nitrogen-containing polyheterocycles are the most prevalent class of compounds in the arenas of agrochemical production and pharmaceutics, where they have a wide range of applications. Therefore, the establishment of new synthetic protocols for the construction of nitrogen-based heterocycles possessing enhanced biological as well as pharmacological activities with high molecular diversity and complexity from readily available substrates is one of the major challenges of organic synthesis.[1]

Multicomponent reactions (MCRs)[2] constitute an appealing convergent strategy in which three or more substrates are put together towards the formation of complex target molecules with the inclusion of significant portions of all substrate components. Hence, MCRs facilitate the assembly of three or more starting materials together in a single operational step with high bond-forming efficiency and atom economy, thereby enhancing the structural diversity in a rapid manner. For these reasons, the conceptual development of new multicomponent reactions represents one of the fastest growing areas of organic synthesis.

The utilization of multicomponent domino[3] reactions in organic synthesis is a preferred way to improve synthetic efficiency and selectivity, particularly for the construction of complex molecular units. Such techniques allow the synthesis of complex molecules starting from amenable substrates in a strategically attractive manner. Among various reactions, the domino Knoevenagel–hetero–Diels–Alder reaction[4] is a very useful and convenient tool for the synthesis of fused polyheterocyclic architectures.

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It is clear from the literature that polycyclic quinolinopyran and pyrazole frameworks are widely found in many bioactive compounds and natural products.[5] Pyrazole annulated components are found to be particularly interesting structural units in pharmaceuticals, and are active ingredients in prominent drugs such as Viagra (used for the treatment of erectile dysfunction) and Celebrex (treatment against osteoarthritis, rheumatoid arthritis).[6] Moreover, 3-methyl-1-phenyl-1*H*-pyrazol-5-one [edaravone (**4**)] is a free-radical scavenger as well as potential neuroprotective agent for recovery of acute brain ischemia and subsequent cere-

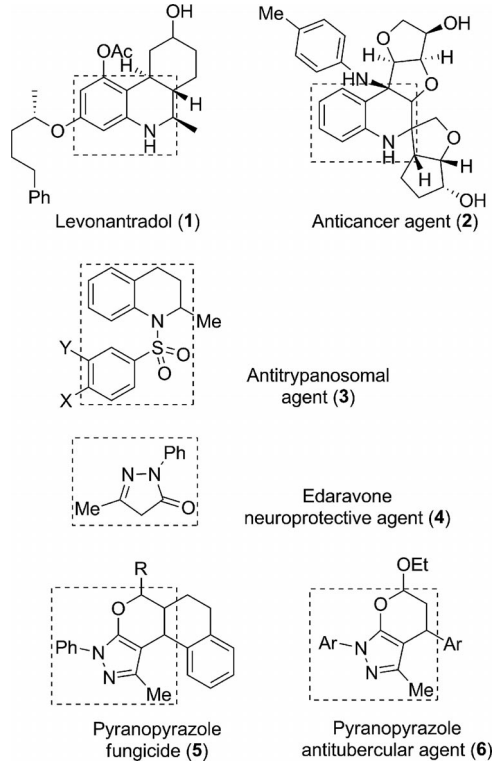


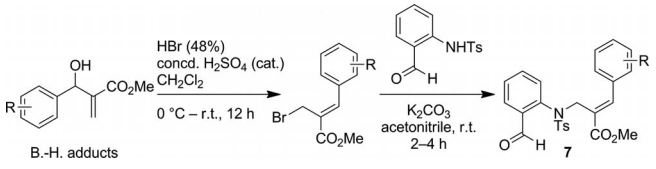
Figure 1. Representative examples of natural products and bioactive molecules containing tetrahydroquinoline and pyranopyrazole motifs.

bral infarction.[7] In fact, many researchers have constructed pyrazole (edaravone), pyranopyrazole and quinolinopyran tethered heterocycles, due to their bioactivities[7] and potential utility in medicinal chemistry such as anticoagulant, anti-HIV, antioxidant, antimalarial and antitubercular activities. Representative natural products and biologically active molecules[8] containing the quinoline and pyranopyrazole structural motif are shown in Figure 1.

The Baylis–Hillman reaction is an important carbon–carbon bond-forming reaction. It is well-documented that the Baylis–Hillman adducts and their derivatives are expedient intermediates for the useful synthesis of several natural products and have been widely employed as a very convenient source for several synthetic manipulations leading to various carbocycles and heterocyclic frameworks of biological interest.[9]

Results and Discussion

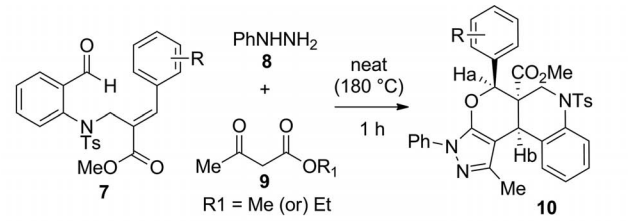
Based on the results detailed in our initial report,[10a] we were prompted to engage *N*-allylated aldehydes **7**, phenylhydrazine (**8**) and ethyl/methyl acetoacetate (**9**) for the efficient construction of tetracyclic quinolino pyranpyrazoles **10** through the generation of pyrazolinone in situ and domino Knoevenagel intramolecular hetero-Diels–Alder (IMHDA). To this end, we treated methyl (2*Z*)-2-(bromomethyl)-3-arylprop-2-enoates bromo derivatives[9f] of the Baylis–Hillman adducts and *N*-tosylated aldehyde with the aid of K_2CO_3 in acetonitrile to generate the required precursor **7**, which we expected would be useful for the construction of the desired tetracyclic quinolino pyranpyrazoles **10** through a multicomponent domino-Knoevenagel intramolecular hetero–Diels–Alder reaction.

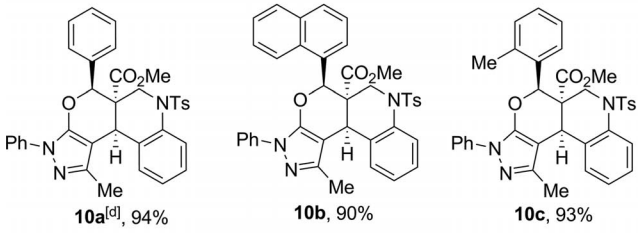


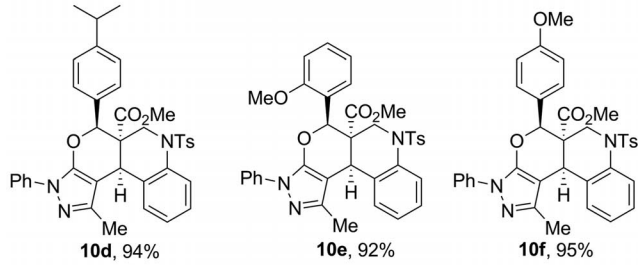
In a continuation of our interest in the field of heterocyclic chemistry,[10] we herein describe an efficient protocol for the synthesis of fused tetracyclic quinolinopyranpyrazole frameworks through a multicomponent domino reaction. Methyl acetoacetate (**9**), phenylhydrazine (**8**) and the Baylis–Hillman derivative **7a** were combined in a round-bottom flask and heated at 180 °C over a period of 1 h under solvent- and catalyst-free conditions, which successfully provided the anticipated tetracyclic quinolinopyranpyrazole **10a** containing an ester moiety at the angular position in excellent yield (94%) without the need for column chromatography purification (Table 1). Washing the crude mass with a mixture of ethyl acetate and hexane (2:48) afforded the pure product.

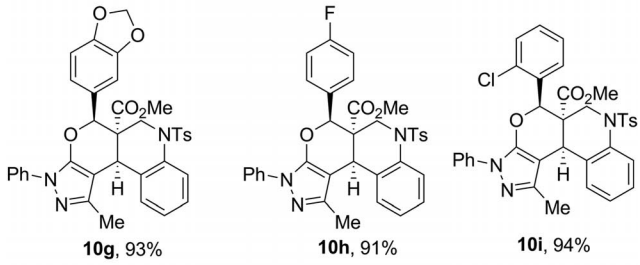
To our surprise, the reaction involves formation of edaravone (**4**) in situ from phenylhydrazine and methyl acetoacetate followed by domino Knoevenagel intramolecular hetero Diels–Alder (IMHDA) reaction, which leads to the formation of three rings encompassing two six-membered rings

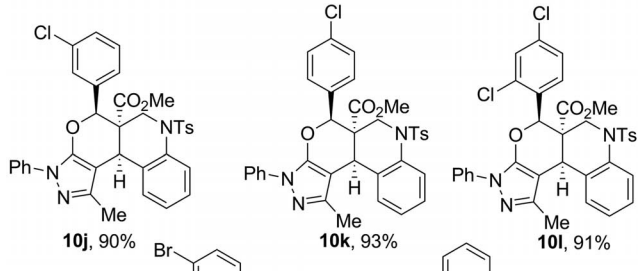
Table 1. Synthesis of novel tetracyclic quinolinopyranpyrazole scaffolds **10a**–**n** through multicomponent cascade reaction.[a]

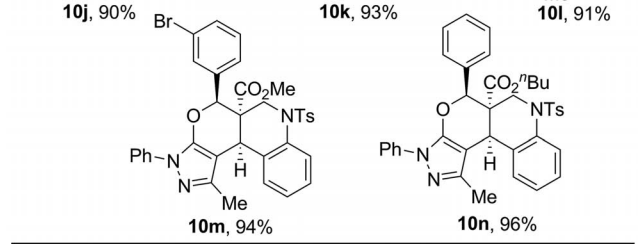












[a] All reactions were carried out on 1 mmol scale of ethyl/methyl acetoacetate, 1 mmol scale of phenylhydrazine and 1 mmol scale of *N*-alkylated compounds **7a**–**n** at 180 °C for 1 h. Isolated yields are given for pure products. All compounds were fully characterized (see the Supporting Information). [b] The structure was further confirmed by single-crystal X-ray analysis.

and one five-membered ring in a stereoselective manner. Similar results were observed when ethyl acetoacetate was used instead of methyl acetoacetate. To the best of our knowledge, there is no report[4g] of this type of domino reaction comprising imine formation, cyclic amide formation, Knovenegel condensation, and intramolecular hetero Diels–Alder reaction for the synthesis of fused tetracyclic quinolinopyranpyrazole architectures through a multicomponent cascade reaction.

To check the generality of the reaction, several Baylis–Hillman derivatives **7b**–**n** were used under the optimized reaction conditions, which effectively led to the formation of the expected angularly substituted (ester moiety) tetracyclic quinolinopyran-pyrazoles **10b**–**n** in 90–96% yields. The isolated yields of the pure products **10a**–**n** are summarized in Table 1. The relative stereochemistry of the molecule **10** was further confirmed by 2D-NMR and single-crystal X-ray analyses (Figure 2).

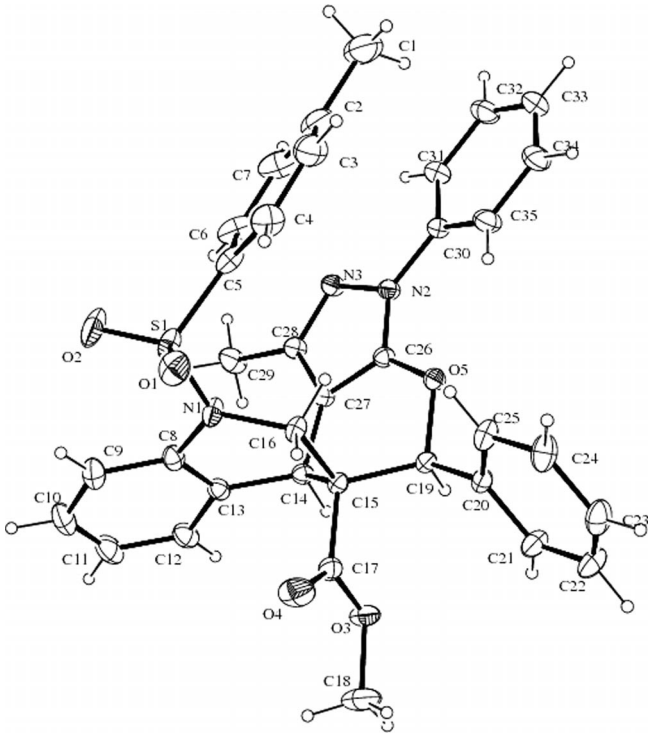


Figure 2. ORTEP diagram[11] of compound **10a**.

Delighted by these successful results, we reacted various Baylis–Hillman derivatives [i.e., (*Z*)-*N*-(2-cyano-3-arylallyl)-*N*-(2-formylphenyl)-4-methylbenzenesulfonamides **11a**–**h**] with phenyl hydrazine (**8**) and ethyl/methyl acetoacetate (**9**) under similar reaction conditions at 200 °C, which successfully provided the desired tetracyclic quinolinopyranpyrazole derivatives (nitrile moiety at the ring junction) **12a**–**h** in excellent yield (90–96%). The isolated yields of the pure products **12a**–**h** are shown in Table 2.

The proposed mechanism probably proceeds through a sequence of pyrazole formation, Knoevenagel condensation, and intramolecular hetero Diels–Alder (IMHDA) reaction, which leads to the construction of tetracyclic quinolinopyranpyrazole as shown in Scheme 1. The nature of the substituent (electron-donating or electron-withdrawing) present in the aryl moiety of the Baylis–Hillman derivatives leads to the quinolinopyranpyrazoles with marginal difference in yields.

The high stereoselectivity observed in the formation of tetracyclic quinolinopyranpyrazole frameworks were clearly evidenced by 2D NMR spectroscopic (NOESY, Figures 4

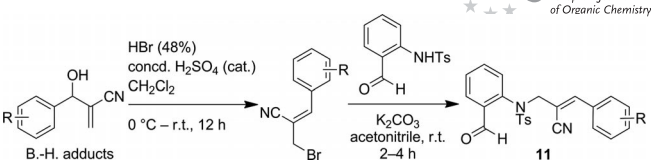
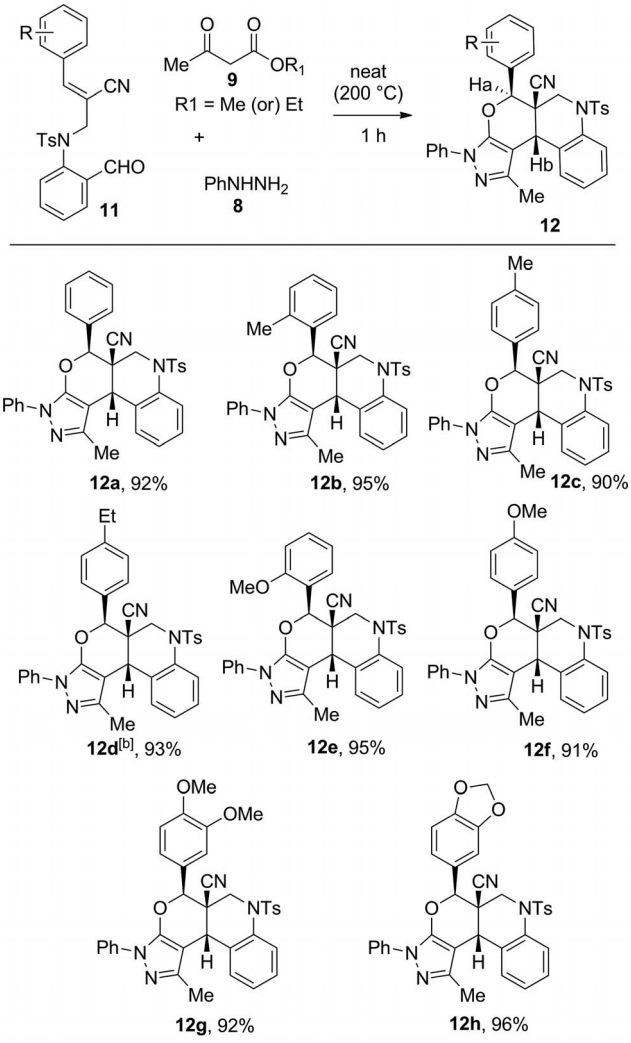
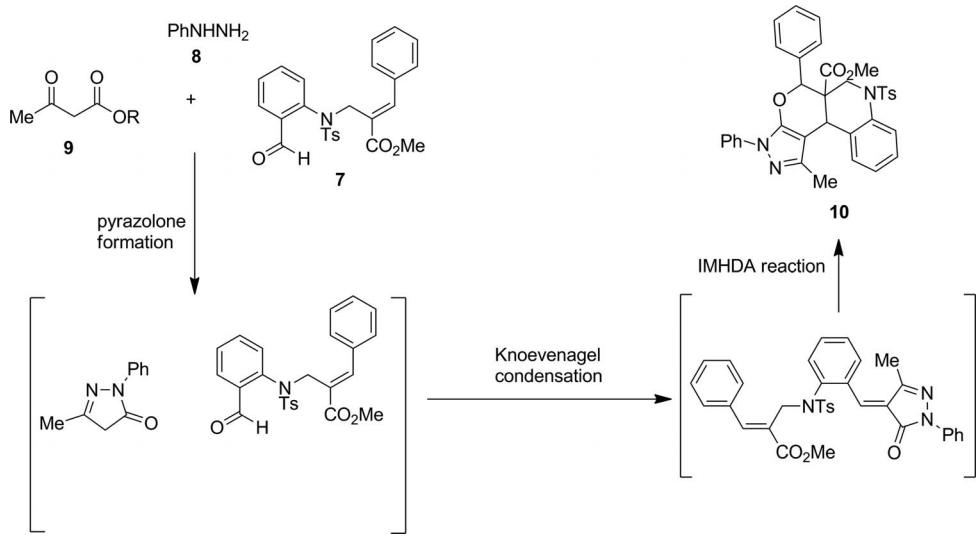


Table 2. Synthesis of novel tetracyclic quinolinopyranpyrazole frameworks **12a**–**h**, containing a nitrile functionality in the ring junction.[a]



[a] All reactions were carried out on 1 mmol scale of ethyl/methyl acetoacetate, 1 mmol scale of phenylhydrazine and 1 mmol scale of *N*-alkylated compounds **11a**–**h** at 200 °C for 1 h. Isolated yields are given for pure products. All compounds were fully characterized (see the Supporting Information). [b] The structure of the molecule was further confirmed by single-crystal X-ray analysis.



Scheme 1. Proposed mechanism for the formation of tetracyclic quinolinopyranpyrazole.

and 5) and X-ray crystal analyses (Figures 2 and 3). The formation of tetracyclic quinolinopyran pyrazole can be explained by considering the various pathways depicted in Scheme 2. It is important to mention here that the stereochemistry of the quinolinopyranpyrazole formed in the IMHDA reaction is controlled[4f] by the geometric nature and attack of dienophiles. In the case of Baylis–Hillman substrates containing an ester group, both *E-endo* (**A**) and *E-exo* (**B**) transition states are possible for the formation of quinolinopyranpyrazole. However, *E-endo* (**A**) is the more favorable. Similarly, *Z-endo* (**C**) and *Z-exo* (**D**) transition states are possible for the Baylis–Hillman substrates tethered with a nitrile functionality, for which *Z-endo* (**C**) is favored. Hence, the *trans* geometry of olefin **7** led to the *anti* product, whereas olefin **11**, having a *cis* geometry, generated the *syn* product.

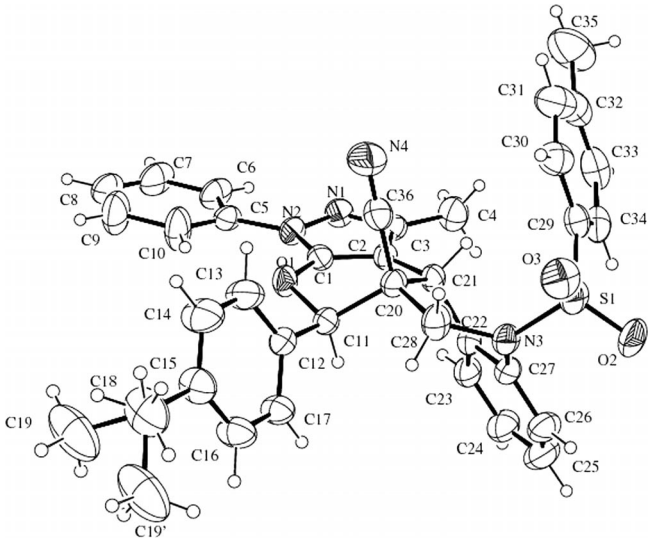
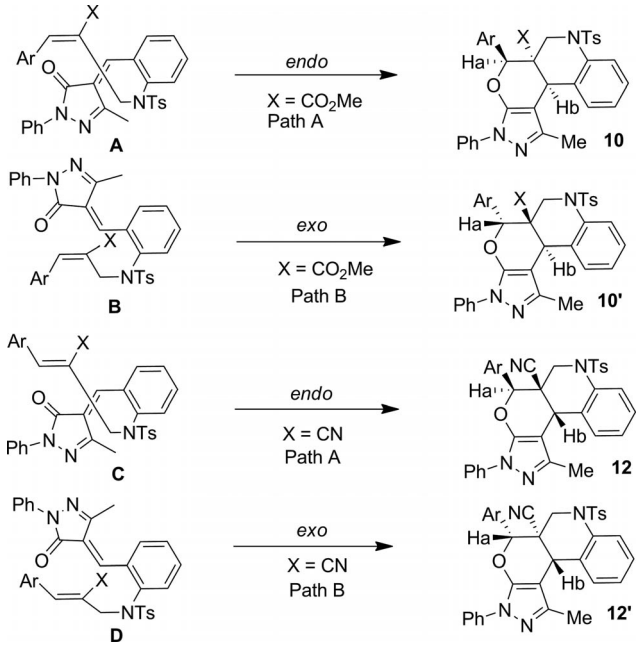


Figure 3. ORTEP diagram[11] of **12d**.



Scheme 2. Plausible pathway for the formation of tetracyclic quinolinopyranpyrazoles (**10**/**12**).

According to the NOESY spectrum of compound **10n**, the observed correlation between Ha and Hb protons clearly denotes the *cis* orientation (Figure 4). Similarly, the orientation of the aryl and ester moieties are *trans* to each other due to the initial *E*-geometry of the alkene in **7n**. Therefore, the relative stereochemistry of the ester group and Ha proton are *cis* to each other. Likewise, in compound **12e**, no correlation was observed between the Ha and Hb protons due to their *anti* orientation (Figure 5). The aryl and cyano groups are orientation *syn* due to the initial *Z*-geometry of alkene **11e**. Hence, the stereochemistry of the cyano group and Ha proton must be *cis*. As per the ORTEP

diagram of the quinolinopyranpyrazole **10a**, shown in Figure 2, the relative stereochemistry of the phenyl group and the adjacent ester moiety are in *anti* orientation, and the ester moiety and the ring junction proton exist in a *syn* orientation. In the X-ray crystal structure of tetracyclic quinolinopyranpyrazole **12d**, it was clear that the *p*-ethylphenyl group, adjacent nitrile moiety, and ring junction proton are in *syn* orientation (Figure 3). Thus, it is apparent that the *anti* product was formed when olefin **7**, having a *trans* geometry (aryl and ester groups present in the *vicinal* positions of compound **7**), was utilized. Similarly, olefin **11**, having a *cis* geometry (aryl and nitrile moieties present in the *vicinal* positions of compound **11**), led to formation of the *syn* product, which confirmed the stereoselectivity observed in the IMHDA reaction.

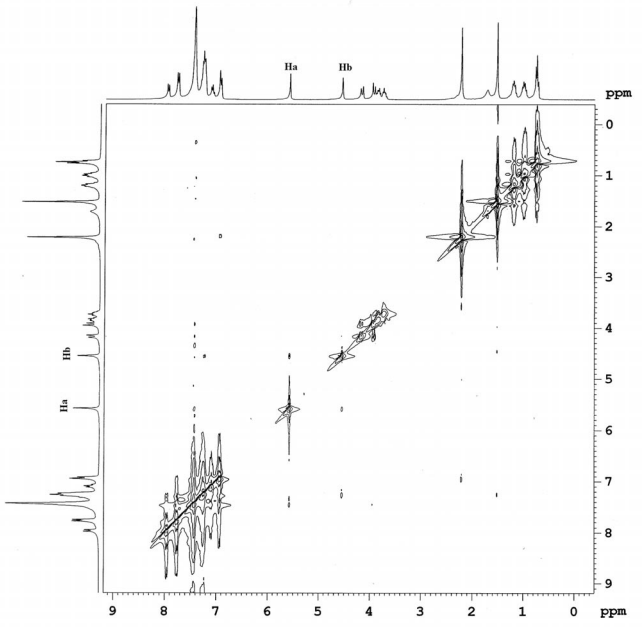


Figure 4. NOESY spectrum of **10n**.

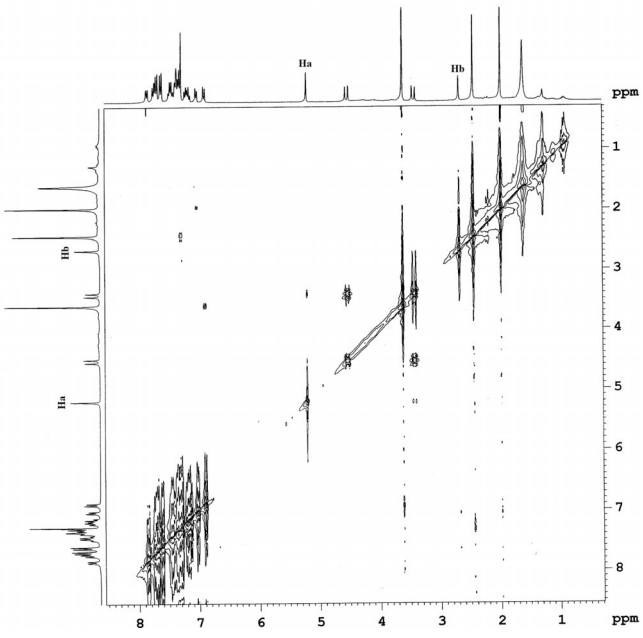


Figure 5. NOESY spectrum of **12e**.

Conclusions

We have established an efficient, multicomponent reaction for the highly stereoselective synthesis of novel tetracyclic quinolinopyranpyrazole frameworks through a cascade sequence comprising pyrazole ring formation, Knoevenagel condensation, and intramolecular hetero–Diels–Alder reaction. The stereoselective construction of the tetracyclic quinolinopyranpyrazole involves the formation of three rings and three contiguous stereogenic centers (two N–C bonds, two C–C bonds, and one O–C bond), one of which is an all carbon quaternary center, in a unique manner. This muticomponent reaction features several interesting aspects such as carrying out reactions under catalyst- and solvent-free conditions, and isolation of the pure products without work-up or column chromatography purification. Formation of a wide variety of tetracyclic quinolinopyranpyrazole frameworks in excellent yields with high stereoselectivity highlights the efficiency of the reaction. The present methodology also provides new avenues for the synthesis of libraries of compounds with a quinolinopyranpyrazole framework for biological testing.

Experimental Section

Synthesis of Methyl 16-Methyl-8-[(4-methylphenyl)sulfonyl]-11,14-diphenyl-12-oxa-8,14,15-triazatetracyclo[8.7.0.0^{2,7}.0^{13,17}]heptadeca-2,4,6,13(17),15-pentaene-10-carboxylate (10a). Typical Procedure: A mixture of methyl (2*E*)-2-{[*N*-(2-formylphenyl)(4-methylphenyl)sulfonamido]methyl}-3-phenylprop-2-enoate (**7a**; 1 mmol), ethyl/methyl acetoacetate (**9**; 1 mmol), and phenylhydrazine (**8**; 1 mmol) was placed in a round-bottomed flask and heated at 180 °C for 1 h. After completion of the reaction (indicated by TLC), the crude product was washed with a mixture of ethyl acetate and hexane (2:48, 5 mL), which successfully provided the pure product **10a** as a colorless solid.

Tetracyclic Quinolinopyranpyrazoles (10a): Yield 0.570 g (94%); colorless solid; m.p. 227–229 °C. IR (neat): $\tilde{\nu}$ = 1735, 1596, 1510 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.50 (s, 3 H), 2.19 (s, 3 H), 3.36 (s, 3 H), 3.92 (d, J = 12.3 Hz, 1 H), 4.15 (d, J = 12.6 Hz, 1 H), 4.54 (s, 1 H), 5.54 (s, 1 H), 6.90–7.94 (m, 18 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.84, 21.41, 40.46, 42.70, 52.25, 52.60, 84.31, 96.86, 119.66, 120.71, 123.66, 124.10, 125.60, 126.33, 126.42, 126.54, 128.81, 129.11, 129.42, 129.94, 130.77, 134.77, 134.53, 135.92, 138.35, 144.14, 145.84, 147.68, 171.52 ppm. MS: *m*/*z* = 607 [M$^+$ + 1]. $C_{35}H_{31}N_3O_5S$ (605.71): calcd. C 69.40, H 5.16, N 6.94; found C 69.31, H 5.24, N 6.86.

Methyl 16-Methyl-8-[(4-methylphenyl)sulfonyl]-11-(naphthalen-1-yl)-14-phenyl-12-oxa-8,14,15-triazatetracyclo[8.7.0.0^{2,7}.0^{13,17}]-heptadeca-2(7),3,5,13(17),15-pentaene-10-carboxylate (10b): Yield 0.590 g (90%); colorless solid; m.p. 230–232 °C. IR (neat): $\tilde{\nu}$ = 1744, 1589, 1522 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.55 (s, 3 H), 2.22 (s, 3 H), 2.87 (s, 3 H), 4.17 (d, J = 12.3 Hz, 1 H), 4.42 (d, J = 12 Hz, 1 H), 4.80 (s, 1 H), 6.38 (s, 1 H), 6.92–7.92 (m, 20 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.95, 21.44, 40.34,

43.59, 51.50, 52.45, 79.94, 97.26, 119.57, 112.58, 123.51, 124.10, 125.26, 125.44, 125.54, 125.87, 126.40, 126.66, 126.82, 129.03, 129.10, 130.06, 130.35, 130.44, 131.02, 133.65, 134.16, 135.72, 138.40, 144.17, 145.95, 148.08, 170.64 ppm. MS: *m*/*z* = 657 [M$^+$ + 1]. $C_{39}H_{33}N_3O_5S$ (655.77): calcd. C 71.43, H 5.07, N 6.41; found C 71.53, H 5.01, N 6.52.

Methyl 16-Methyl-8-[(4-methylphenyl)sulfonyl]-11-(2-methylphenyl)-14-phenyl-12-oxa-8,14,15-triazatetracyclo[8.7.0.0^{2,7}.0^{13,17}]heptadeca-2(7),3,5,13(17),15-pentaene-10-carboxylate (10c): Yield 0.576 g (93%); colorless solid; m.p. 230–232 °C. IR (neat): $\tilde{\nu}$ = 1735, 1596, 1510 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.57 (s, 3 H), 2.21 (s, 3 H), 2.29 (s, 3 H), 3.28 (s, 3 H), 4.10–4.14 (m, 1 H), 4.53–4.62 (m, 2 H), 5.78 (s, 1 H), 6.93–7.95 (m, 17 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.90, 19.41, 21.40, 40.85, 43.40, 51.39, 52.63, 81.13, 97.27, 119.63, 123.56, 124.10, 125.53, 126.31, 126.63, 127.32, 128.70, 129.07, 129.33, 129.43, 130.93, 131.14, 132.85, 134.06, 135.67, 136.11, 138.34, 144.18, 145.87, 171.16 ppm. MS: *m*/*z* = 620 [M$^+$ + 1]. $C_{36}H_{33}N_3O_5S$ (619.73): calcd. C 69.77, H 5.37, N 6.78; found C 69.85, H 5.30, N 6.84.

Methyl 16-Methyl-8-[(4-methylphenyl)sulfonyl]-14-phenyl-11-[4-(propan-2-yl)phenyl]-12-oxa-8,14,15-triazatetracyclo[8.7.0.0^{2,7}.0^{13,17}]heptadeca-2(7),3,5,13(17),15-pentaene-10-carboxylate (10d): Yield 0.609 g (94%); colorless solid; m.p. 227–229 °C. IR (neat): $\tilde{\nu}$ = 1738, 1592, 1518 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.27 (d, *J* = 6.9 Hz, 6 H), 1.50 (s, 3 H), 2.19 (s, 3 H), 2.94 (sept, *J* = 6.9 Hz, 1 H), 3.37 (s, 3 H), 3.89 (d, *J* = 12.6 Hz, 1 H), 4.15 (d, *J* = 12.3 Hz, 1 H), 4.53 (s, 1 H), 5.52 (s, 1 H), 6.90–7.95 (m, 17 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.84, 21.39, 23.82, 23.96, 33.89, 40.43, 42.73, 52.24, 52.57, 84.21, 96.81, 119.64, 123.68, 124.07, 125.53, 126.33, 126.47, 126.84, 128.76, 129.16, 129.41, 130.76, 131.82, 134.10, 135.93, 138.38, 144.13, 145.80, 147.77, 150.17, 171.48 ppm. MS: *m*/*z* = 649 [M$^+$ + 1]. $C_{38}H_{37}N_3O_5S$ (647.79): calcd. C 70.46, H 5.76, N 6.49; found C 70.54, H 5.63, N 6.60.

Methyl 11-(2-Methoxyphenyl)-16-methyl-8-[(4-methylphenyl)sulfonyl]-14-phenyl-12-oxa-8,14,15-triazatetracyclo[8.7.0.0^{2,7}.0^{13,17}]heptadeca-2(7),3,5,13(17),15-pentaene-10-carboxylate (10e): Yield 0.585 g (92%); colorless solid; m.p. 238–240 °C. IR (neat): $\tilde{\nu}$ = 1745, 1586, 1520 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.54 (s, 3 H), 2.22 (s, 3 H), 3.37 (s, 3 H), 3.79 (s, 3 H), 4.04 (d, *J* = 12.3 Hz, 1 H), 4.36 (d, *J* = 12.3 Hz, 1 H), 4.71 (s, 1 H), 5.95 (s, 1 H), 6.89–7.93 (m, 17 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.01, 21.53, 39.25, 43.76, 51.35, 52.38, 55.30, 78.33, 96.95, 110.32, 119.58, 121.05, 123.18, 123.52, 123.99, 125.42, 126.38, 127.29, 127.94, 128.44, 129.05, 129.38, 130.38, 131.10, 134.12, 135.68, 138.45, 144.09, 145.89, 147.95, 156.37, 170.40 ppm. MS: *m*/*z* = 637 [M$^+$ + 1]. $C_{36}H_{33}N_3O_6S$ (635.73): calcd. C 68.01, H 5.23, N 6.61; found C 68.11, H 5.16, N 6.70.

Methyl 11-(4-Methoxyphenyl)-16-methyl-8-[(4-methylphenyl)sulfonyl]-14-phenyl-12-oxa-8,14,15-triazatetracyclo[8.7.0.0^{2,7}.0^{13,17}]heptadeca-2(7),3,5,13(17),15-pentaene-10-carboxylate (10f): Yield 0.604 g (95%); colorless solid; m.p. 237–239 °C. IR (neat): $\tilde{\nu}$ = 1736, 1591, 1528 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.49 (s, 3 H), 2.19 (s, 3 H), 3.37 (s, 3 H), 3.84 (s, 3 H), 3.91 (d, *J* = 12.6 Hz, 1 H), 4.17 (d, *J* = 12.3 Hz, 1 H), 4.51 (s, 1 H), 5.49 (s, 1 H), 6.90–7.95 (m, 17 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.84, 21.40, 40.44, 42.76, 52.34, 52.60, 55.33, 84.13, 96.83, 114.16, 119.63, 123.61, 124.65, 125.53, 126.32, 126.47, 126.54, 127.90, 128.75, 129.08, 129.41, 130.74, 134.21, 135.95, 138.41, 144.10, 145.81, 147.84, 160.29, 171.63 ppm. MS: *m*/*z* = 637 [M$^+$ + 1]. $C_{36}H_{33}N_3O_6S$ (635.73): calcd. C 68.01, H 5.23, N 6.61; found C 68.09, H 5.14, N 6.72.

Methyl 11-(2*H*-1,3-Benzodioxol-5-yl)-16-methyl-8-[(4-methylphenyl)sulfonyl]-14-phenyl-12-oxa-8,14,15-triazatetracyclo[8.7.0.0^{2,7}.0^{13,17}]heptadeca-2(7),3,5,13(17),15-pentaene-10-carboxylate (10g): Yield 0.605 g (93%); colorless solid; m.p. 240–242 °C. IR (neat): $\tilde{\nu}$ = 1785, 1576, 1530 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.49 (s, 3 H), 2.18 (s, 3 H), 3.40 (s, 3 H), 3.86 (d, *J* = 12.3 Hz, 1 H), 4.19 (d, *J* = 12.3 Hz, 1 H), 4.50 (s, 1 H), 5.44 (s, 1 H), 6.03 (d, *J* = 4.5 Hz, 2 H), 6.80–7.95 (m, 16 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.79, 21.35, 40.53, 42.79, 52.33, 52.75, 84.20, 96.89, 101.48, 106.90, 108.41, 119.64, 120.51, 123.69, 124.09, 125.60, 126.33, 128.15, 128.80, 129.13, 129.42, 130.72, 134.11, 135.89, 138.33, 144.14, 145.80, 147.57, 148.06, 148.38, 171.48 ppm. MS: *m*/*z* = 651 [M$^+$ + 1]. $C_{36}H_{31}N_3O_7S$ (649.72): calcd. C 66.55, H 4.81, N 6.47; found C 66.63, H 4.70, N 6.58.

Methyl 11-(4-Fluorophenyl)-16-methyl-8-[(4-methylphenyl)sulfonyl]-14-phenyl-12-oxa-8,14,15-triazatetracyclo[8.7.0.0^{2,7}.0^{13,17}]heptadeca-2(7),3,5,13(17),15-pentaene-10-carboxylate (10h): Yield 0.569 g (91%); colorless solid; m.p. 224–226 °C. IR (neat): $\tilde{\nu}$ = 1792, 1586, 1546 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.49 (s, 3 H), 2.20 (s, 3 H), 3.38 (s, 3 H), 3.90 (d, *J* = 12.3 Hz, 1 H), 4.13 (d, *J* = 12.3 Hz, 1 H), 4.52 (s, 1 H), 5.53 (s, 1 H), 6.91–7.95 (m, 17 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.94, 21.53, 40.48, 42.65, 52.25, 52.82, 83.75, 96.80, 115.77, 116.05, 119.68, 123.63, 124.16, 125.70, 126.31, 128.41, 128.52, 128.86, 129.15, 129.44, 130.43, 130.75, 134.10, 135.85, 138.28, 144.19, 145.85, 147.50, 171.54 ppm. MS: *m*/*z* = 625 [M$^+$ + 1]. $C_{35}H_{30}FN_3O_5S$ (623.70): calcd. C 67.40, H 4.85, N 6.74; found C 67.51, H 4.93, N 6.66.

Methyl 11-(2-Chlorophenyl)-16-methyl-8-[(4-methylphenyl)sulfonyl]-14-phenyl-12-oxa-8,14,15-triazatetracyclo[8.7.0.0^{2,7}.0^{13,17}]heptadeca-2(7),3,5,13(17),15-pentaene-10-carboxylate (10i): Yield 0.602 g (94%); colorless solid; m.p. 230–232 °C. IR (neat): $\tilde{\nu}$ = 1789, 1566, 1556 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.49 (s, 3 H), 2.20 (s, 3 H), 3.41 (s, 3 H), 3.88 (d, *J* = 12.3 Hz, 1 H), 4.07 (d, *J* = 12.6 Hz, 1 H), 4.53 (s, 1 H), 5.54 (s, 1 H), 6.91–7.90 (m, 17 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.68, 21.39, 40.24, 42.42, 52.06, 52.60, 83.42, 96.77, 119.49, 123.39, 124.18, 125.60, 126.12, 126.16, 127.83, 128.48, 128.77, 128.98, 129.06, 129.38, 130.64, 132.98, 133.98, 135.24, 135.66, 138.15, 144.16, 145.67, 147.28, 171.93 ppm. MS: *m*/*z* = 641 [M$^+$ + 1]. $C_{35}H_{30}ClN_3O_5S$ (640.15): calcd. C 65.67, H 4.72, N 6.56; found C 65.78, H 4.63, N 6.63.

Methyl 11-(3-Chlorophenyl)-16-methyl-8-[(4-methylphenyl)sulfonyl]-14-phenyl-12-oxa-8,14,15-triazatetracyclo[8.7.0.0^{2,7}.0^{13,17}]heptadeca-2(7),3,5,13(17),15-pentaene-10-carboxylate (10j): Yield 0.576 g (90%); colorless solid; m.p. 230–232 °C. IR (neat): $\tilde{\nu}$ = 1758, 1591, 1538 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.49 (3 H), 2.21 (s, 3 H), 3.39 (s, 3 H), 3.89 (d, *J* = 12.3 Hz, 1 H), 4.11 (d, *J* = 12.3 Hz, 1 H), 4.52 (s, 1 H), 5.53 (s, 1 H), 6.91–7.94 (m, 17 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.84, 21.60, 40.63, 42.68, 52.13, 52.92, 83.62, 96.81, 119.67, 123.63, 124.17, 125.73, 126.19, 126.31, 127.96, 128.89, 129.10, 129.16, 129.45, 130.74, 133.04, 134.12, 135.45, 135.45, 135.84, 138.26, 144.19, 145.85, 147.41, 171.49 ppm. MS: *m*/*z* = 641 [M$^+$ + 1]. $C_{35}H_{30}ClN_3O_5S$ (640.15): calcd. C 65.67, H 4.72, N 6.56; found C 65.56, H 4.63, N 6.62.

Methyl 11-(4-Chlorophenyl)-16-methyl-8-[(4-methylphenyl)sulfonyl]-14-phenyl-12-oxa-8,14,15-triazatetracyclo[8.7.0.0^{2,7}.0^{13,17}]heptadeca-2(7),3,5,13(17),15-pentaene-10-carboxylate (10k): Yield 0.595 g (93%); colorless solid; m.p. 228–230 °C. IR (neat): $\tilde{\nu}$ = 1745, 1588, 1529 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.52 (s, 3 H), 2.21 (s, 3 H), 3.40 (s, 3 H), 4.11 (d, *J* = 12 Hz, 1 H), 4.44 (d, *J* = 12 Hz, 1 H), 4.71 (s, 1 H), 6.02 (s, 1 H), 6.91–7.92 (m, 17 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.90, 21.42, 39.64, 43.69, 51.16, 52.90, 80.26, 97.17, 119.72, 123.43, 124.14, 125.65,

126.37, 126.85, 127.57, 128.63, 128.84, 129.10, 129.44, 129.96, 130.63, 131.05, 132.53, 133.18, 134.17, 135.52, 138.29, 144.19, 145.94, 147.65, 169.98 ppm. MS: m/z = 641 [M^+ + 1]. $C_{35}H_{30}ClN_3O_5S$ (640.15): calcd. C 65.67, H 4.72, N 6.56; found C 65.74, H 4.60, N 6.64.

Methyl 11-(2,4-Dichlorophenyl)-16-methyl-8-[(4-methylphenyl)sulfonyl]-14-phenyl-12-oxa-8,14,15-triazatetracyclo[8.7.0.0^{2,7}.0^{13,17}]-heptadeca-2(7),3,5,13(17),15-pentaene-10-carboxylate (10l): Yield 0.614 g (91%); colorless solid; m.p. 233–235 °C. IR (neat): $\tilde{\nu}$ = 1763, 1586, 1542 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.50 (s, 3 H), 2.19 (s, 3 H), 3.36 (s, 3 H), 3.92 (d, J = 12.3 Hz, 1 H), 4.14 (d, J = 12 Hz, 1 H), 4.54 (s, 1 H), 5.54 (s, 1 H), 6.90–7.94 (m, 16 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.84, 21.41, 40.46, 42.70, 52.25, 52.60, 84.30, 96.85, 119.66, 121.15, 123.65, 124.10, 125.60, 126.33, 126.42, 126.53, 127.29, 128.61, 128.81, 129.11, 129.42, 130.77, 134.17, 134.42, 134.53, 135.92, 138.35, 144.14, 145.84, 147.68, 171.51 ppm. MS: m/z = 676 [M^+ + 1]. $C_{35}H_{29}Cl_2N_3O_5S$ (674.60): calcd. C 62.32, H 4.33, N 6.23; found C 62.41, H 4.25, N 6.30.

Methyl 11-(3-Bromophenyl)-16-methyl-8-[(4-methylphenyl)sulfonyl]-14-phenyl-12-oxa-8,14,15-triazatetracyclo[8.7.0.0^{2,7}.0^{13,17}]-heptadeca-2(7),3,5,13(17),15-pentaene-10-carboxylate (10m): Yield 0.644 g (94%); colorless solid; m.p. 232–234 °C. IR (neat): $\tilde{\nu}$ = 1729, 1578, 1546 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.49 (s, 3 H), 2.20 (s, 3 H), 3.42 (s, 3 H), 3.87 (d, J = 12.3 Hz, 1 H), 4.10 (d, J = 12.3 Hz, 1 H), 4.53 (s, 1 H), 5.49 (s, 1 H), 6.91–7.93 (m, 17 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.90, 21.55, 40.33, 42.54, 53.23, 52.87, 83.39, 96.85, 119.71, 122.75, 123.63, 124.21, 124.93, 125.77, 126.22, 126.37, 128.90, 129.19, 129.47, 129.71, 130.56, 130.75, 132.56, 134.10, 135.84, 136.73, 138.23, 144.21, 145.88, 147.31, 171.03 ppm. MS: m/z = 687 [M^+ + 2]. $C_{35}H_{30}BrN_3O_5S$ (684.60): calcd. C 61.40, H 4.42, N 6.14; found C 61.32, H 4.55, N 6.22.

Butyl 16-Methyl-8-[(4-methylphenyl)sulfonyl]-11,14-diphenyl-12-oxa-8,14,15-triazatetracyclo[8.7.0.0^{2,7}.0^{13,17}]heptadeca-2(7),3,5,13(17),15-pentaene-10-carboxylate (10n): Yield 0.622 g (96%); colorless solid; m.p. 220–224 °C. IR (neat): $\tilde{\nu}$ = 1740, 1568, 1553 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.69–1.22 (m, 7 H), 1.50 (s, 3 H), 2.19 (s, 3 H), 3.68–3.93 (m, 3 H), 4.14 (d, J = 12.3 Hz, 1 H), 4.52 (s, 1 H), 5.55 (s, 1 H), 6.90–7.95 (m, 18 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.45, 13.84, 18.69, 21.40, 30.12, 40.70, 42.76, 52.03, 65.52, 84.35, 96.88, 119.63, 123.76, 124.03, 125.55, 126.32, 126.48, 126.73, 128.71, 128.76, 129.09, 129.32, 129.41, 130.84, 134.16, 134.57, 136.03, 138.40, 144.10, 145.80, 147.70, 171.15 ppm. MS: m/z = 649 [M^+ + 1]. $C_{38}H_{37}N_3O_5S$ (647.79): calcd. C 70.46, H 5.76, N 6.49; found C 70.55, H 5.68, N 6.38.

Synthesis of 16-Methyl-8-[(4-methylphenyl)sulfonyl]-11,14-diphenyl-12-oxa-8,14,15-triazatetracyclo[8.7. 0.0^{2,7}.0^{13,17}]heptadeca-2,4,6,13(17),15-pentaene-10-carbonitrile (12a): A mixture of (2*Z*)-2-{[*N*-(2-formylphenyl)(4-methylphenyl)sulfonamido]methyl}-3-phenylprop-2-enenitrile (**11a**; 1 mmol), ethyl/methyl acetoacetate (**9**; 1 mmol) and phenylhydrazine (**8**; 1 mmol) was placed in a round-bottomed flask and melted at 200 °C for 1 h. After completion of the reaction (indicated by TLC), the crude product was washed with a mixture of ethyl acetate and hexane (2:48, 5 mL), which provided the pure product **12a** as a colorless solid.

Tetracyclic Quinolinopyranpyrazoles (12a): Yield 0.527 g (92%); colorless solid; m.p. 223–225 °C. IR (neat): $\tilde{\nu}$ = 2228, 1557, 1524 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.97 (s, 3 H), 2.43 (s, 3 H), 2.64 (s, 1 H), 3.05 (d, J = 16. 2 Hz, 1 H), 4.60 (d, J = 15.9 Hz, 1 H), 4.81 (s, 1 H), 7.00–7.92 (m, 18 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.43, 19.36, 21.74, 37.36, 46.06, 50.53, 75.87, 93.79, 120.15, 126.00, 127.31, 127.48, 127.59, 127.92, 128.27, 128.47, 129.07, 129.20, 130.13, 130.22, 130.95, 130.98, 133.15, 136.11, 136.37, 138.08, 144.60, 147.18, 150.00 ppm. MS: m/z = 574 [M^+ + 1]. $C_{34}H_{28}N_4O_3S$ (572.68): calcd. C 71.31, H 4.93, N 9.78; found C 71.40, H 4.85, N 9.86.

16-Methyl-8-[(4-methylphenyl)sulfonyl]-11-(2-methylphenyl)-14-phenyl-12-oxa-8,14,15-triazatetracyclo[8.7.0.0^{2,7}.0^{13,17}]heptadeca-2,4,6,13(17),15-pentaene-10-carbonitrile (12b): Yield 0.558 g (95%); colorless solid; m.p. 228–230 °C. IR (neat): $\tilde{\nu}$ = 2258, 1537, 1544 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.86 (s, 3 H), 1.97 (s, 3 H), 2.43 (s, 3 H), 2.64 (s, 1 H), 3.05 (d, J = 15.9 Hz, 1 H), 4.60 (d, J = 16.2 Hz, 1 H), 4.81 (s, 1 H), 6.97–7.94 (m, 17 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.34, 19.27, 21.61, 37.25, 46.03, 50.57, 75.87, 93.80, 118.90, 120.23, 120.33, 126.00, 127.32, 127.47, 127.59, 127.91, 128.25, 128.47, 128.69, 129.07, 129.91, 130.13, 130.21, 130.95, 133.15, 136.11, 136.38, 138.08, 144.65, 147.04, 149.85 ppm. MS: m/z = 588 [M^+ + 1]. $C_{35}H_{30}N_4O_3S$ (586.71): calcd. C 71.65, H 5.15, N 9.55; found C 71.76, H 5.24, N 9.63.

16-Methyl-8-[(4-methylphenyl)sulfonyl]-11-(4-methylphenyl)-14-phenyl-12-oxa-8,14,15-triazatetracyclo[8.7.0.0^{2,7}.0^{13,17}]heptadeca-2,4,6,13(17),15-pentaene-10-carbonitrile (12c): Yield 0.528 g (90%); colorless solid; m.p. 229–231 °C. IR (neat): $\tilde{\nu}$ = 2246, 1528, 1536 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.96 (s, 3 H), 2.40 (s, 3 H), 2.41 (s, 3 H), 2.73 (s, 1 H), 3.20 (d, J = 15.6 Hz, 1 H), 4.44–4.49 (m, 2 H), 7.00–7.73 (m, 17 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.38, 21.24, 21.64, 36.89, 46.00, 51.30, 80.52, 93.11, 120.22, 125.96, 127.36, 128.05, 128.33, 129.02, 129.07, 129.62, 129.74, 130.12, 132.61, 136.52, 137.16, 138.16, 140.66, 144.61, 147.09, 149.53 ppm. MS: m/z = 588 [M^+ + 1]. $C_{35}H_{30}N_4O_3S$ (586.71): calcd. C 71.65, H 5.15, N 9.55; found C 71.76, H 5.08, N 9.61.

16-Methyl-8-[(4-methylphenyl)sulfonyl]-11-(4-ethylphenyl)-14-phenyl-12-oxa-8,14,15-triazatetracyclo[8.7.0.0^{2,7}.0^{13,17}]heptadeca-2,4,6,13(17),15-pentaene-10-carbonitrile (12d): Yield 0.559 g (93%); colorless solid; m.p. 228–230 °C. IR (neat): $\tilde{\nu}$ = 2264, 1567, 1524 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.27 (t, J = 7.5 Hz, 3 H), 1.96 (s, 3 H), 2.42 (s, 3 H), 2.66–2.72 (m, 3 H), 3.20 (d, J = 12.6 Hz, 1 H), 4.46–4.50 (m, 2 H), 7.00–7.73 (m, 17 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 12.44, 15.27, 21.59, 28.64, 36.82, 45.96, 51.34, 80.55, 93.10, 120.26, 125.97, 127.36, 128.04, 128.35, 128.39, 128.56, 129.01, 129.06, 129.80, 130.11, 132.59, 136.50, 137.15, 138.13, 144.56, 146.86, 147.04, 149.58 ppm. MS: m/z = 602 [M^+ + 1]. $C_{36}H_{32}N_4O_3S$ (600.73): calcd. C 71.98, H 5.37, N 9.33; found C 71.86, H 5.44, N 9.42.

11-(2-Methoxyphenyl)-16-methyl-8-[(4-methylphenyl)sulfonyl]-14-phenyl-12-oxa-8,14,15-triazatetracyclo[8.7.0.0^{2,7}.0^{13,17}]heptadeca-2,4,6,13(17),15-pentaene-10-carbonitrile (12e): Yield 0.573 g (95%); colorless solid; m.p. 224–226 °C. IR (neat): $\tilde{\nu}$ = 2289, 1597, 1532 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.96 (s, 3 H), 2.42 (s, 3 H), 2.63 (s, 1 H), 3.41 (d, J = 15.3 Hz, 1 H), 3.59 (s, 3 H), 4.51 (d, J = 15.6 Hz, 1 H), 5.18 (s, 1 H), 6.86–7.84 (m, 17 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.83, 21.60, 37.13, 47.26, 50.63, 55.59, 72.69, 93.43, 110.60, 120.22, 121.41, 121.76, 125.90, 127.32, 127.47, 127.97, 128.27, 128.33, 128.85, 129.04, 129.72, 130.11, 131.20, 132.96, 136.50, 136.86, 138.17, 144.48, 147.03, 149.79, 156.08 ppm. MS: m/z = 604 [M^+ + 1]. $C_{35}H_{30}N_4O_4S$ (602.71): calcd. C 69.75, H 5.02, N 9.30; found C 69.68, H 5.09, N 9.22.

11-(4-Methoxyphenyl)-16-methyl-8-[(4-methylphenyl)sulfonyl]-14-phenyl-12-oxa-8,14,15-triazatetracyclo[8.7.0.0^{2,7}.0^{13,17}]heptadeca-2,4,6,13(17),15-pentaene-10-carbonitrile (12f): Yield 0.549 g (91%); colorless solid; m.p. 222–224 °C. IR (neat): $\tilde{\nu}$ = 2278, 1591,

1542 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.96 (s, 3 H), 2.42 (s, 3 H), 2.64 (s, 1 H), 3.40 (d, J = 15.3 Hz, 1 H), 3.59 (s, 3 H), 4.51 (d, J = 15.6 Hz, 1 H), 5.18 (s, 1 H), 6.86–7.84 (m, 17 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.41, 21.60, 36.79, 46.69, 50.01, 55.41, 72.65, 93.43, 110.60, 120.22, 121.41, 121.76, 125.90, 127.32, 127.47, 127.97, 128.33, 128.85, 129.04, 130.11, 131.20, 132.96, 136.50,136.86, 138.17, 144.48, 147.03, 149.79, 156.08 ppm. MS: *m/z* = 604 [M^+ + 1]. $C_{35}H_{30}N_4O_4S$ (602.71): calcd. C 69.75, H 5.02, N 9.30; found C 69.86, H 5.11, N 9.24.

11-(3,4-Dimethoxyphenyl)-16-methyl-8-[(4-methylphenyl)sulfonyl]-14-phenyl-12-oxa-8,14,15-triazatetracyclo[8.7.0.0^{2,7}.0^{13,17}]heptadeca-2,4,6,13(17),15-pentaene-10-carbonitrile (12g): Yield 0.582 g (92%); colorless solid; m.p. 218–220 °C. IR (neat): $\tilde{\nu}$ = 2268, 1581, 1529 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.97 (s, 3 H), 2.42 (s, 3 H), 2.76 (s, 1 H), 3.19 (d, J = 15.6 Hz, 1 H), 3.91 (s, 6 H), 4.43–4.51 (m, 2 H), 6.83–7.73 (m, 16 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.48, 21.74, 36.76, 45.79, 51.42, 55.96, 56.26, 60.99, 80.56, 93.16, 110.78, 110.84, 120.11, 120.52, 121.58, 124.84, 125.95, 127.25, 127.37, 128.01, 128.36, 129.00, 129.10, 130.11, 132.49, 136.47, 137.15, 138.20, 144.58, 147.07, 149.54, 149.63, 150.76 ppm. MS: *m/z* = 634 [M^+ + 1]. $C_{36}H_{32}N_4O_5S$ (632.73): calcd. C 68.34, H 5.10, N 8.85; found C 68.25, H 5.17, N 8.78.

11-(2*H*-1,3-Benzodioxol-5-yl)-16-methyl-8-[(4-methylphenyl)sulfonyl]-14-phenyl-12-oxa-8,14,15-triazatetracyclo[8.7.0.0^{2,7}.0^{13,17}]-heptadeca-2,4,6,13(17),15-pentaene-10-carbonitrile (12h): Yield 0.592 g (96%); colorless solid; m.p. 217–219 °C. IR (neat): $\tilde{\nu}$ = 2259, 1578, 1543 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.95 (s, 3 H), 2.42 (s, 3 H), 2.72 (s, 1 H), 3.21 (d, J = 15.9 Hz, 1 H), 4.39 (s, 1 H), 4.52 (d, J = 15.6 Hz, 1 H), 6.04 (s, 2 H), 6.81–7.73 (m, 16 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.55, 21.66, 36.80, 45.94, 51.25, 80.52, 93.11, 101.74, 108.28, 108.37, 120.28, 122.90, 126.03, 126.13, 127.35, 128.06, 128.32, 129.05, 129.10, 130.13, 132.48, 136.47, 137.11, 138.08, 144.59, 147.05, 148.53, 149.46 ppm. MS: *m/z* = 618 [M^+ + 1]. $C_{35}H_{30}N_4O_5S$ (618.71): calcd. C 68.17, H 4.58, N 9.09; found C 68.10, H 4.46, N 9.17.

Supporting Information (see footnote on the first page of this article): Experimental procedures (with all spectroscopic data), ^1H and ^{13}C NMR spectra of all compounds.

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[11] Structures were confirmed by single-crystal X-ray data. CCDC-903000 (for **10a**) and -902999 (for **12d**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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