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AN EFFICIENT SYNTHESIS OF 1-(4*H*-1,2,4-TRIAZOL-3-YL)-HEXAHYDROQUINOLINE-3-CARBONITRILE AND THEIR SPIRO DERIVATIVES FROM *β*-ENAMINONES

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Abstract – A series of *N*-((1,2,4-triazol-3-yl)-enamine and *N*-((1,2,3-triazol-4-yl)-enamine were prepared and reacted with *α*,*β*-unsaturated nitriles to yield novel *N*-(4*H*-1,2,4-triazol-3-yl)hexahydroquinoline-3-carbonitriles and their fused and spiro derivatives. Dimroth type rearrangement of the prepared quinoline derivatives **7a,b** and **15a,b** was observed in acetic anhydride leading to the formation of substituted pyrimido[4,5-*b*]quinolines **11a,b**, spiro[indoline-3,5'-pyrimido[4,5-*b*]quinoline] **19** and spiro[indoline-3,5'-[1,3]-oxazino[4,5-*b*]quinoline] **22**.

INTRODUCTION

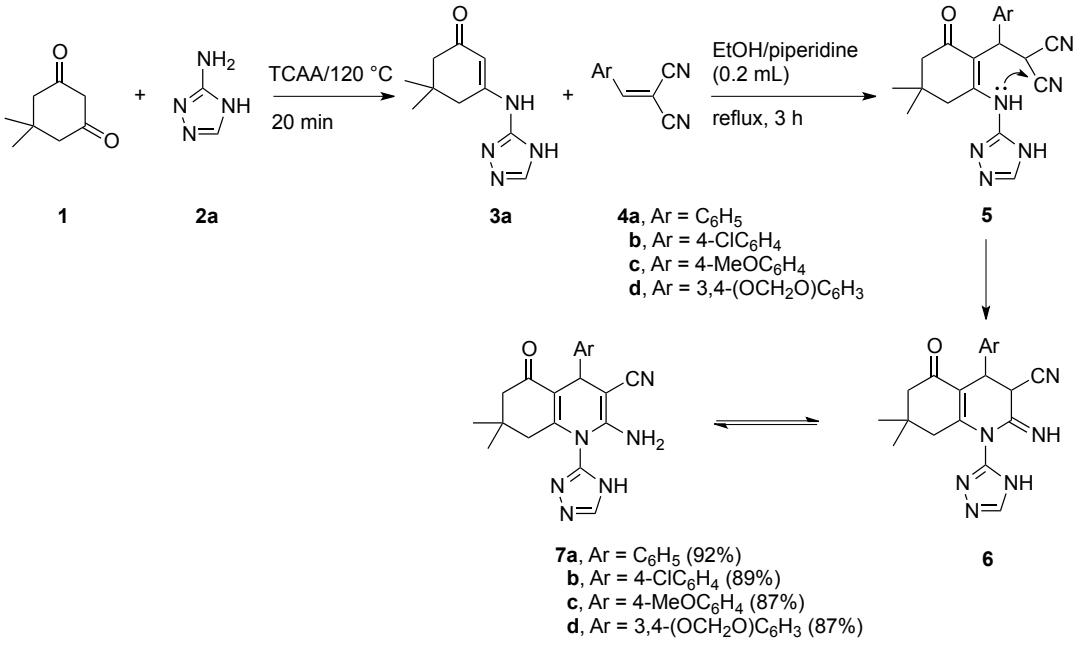
In the last decades, multicomponent cyclocondensations involving aldehydes, activated nitriles and enamines, leading to quinoline and fused quinoline systems, have been widely investigated.[1–7] In addition, quinoline scaffold represents a class of medicinally significant compounds that possess a wide variety of biological properties such as antimicrobial,[8,9] anticancer,[8–17] antiviral[18] and anti-inflammatory agents.[19] Moreover, the spirooxindole system is the core structure of the most distinguished heterocyclic ring systems, which constitutes the core structural element of many pharmacological agents and natural alkaloids, among them, spirotryprostatin B,[20] gelsemine III,[21] horsfiline IV[22] and pteropodine II.[20] As a part of an ongoing research program on Michael addition reactions,[23–28] as well as on the utility of

enamines[29–32] in organic synthesis, we report the results of our investigations concerning the reactivity patterns of the cyclic enamines towards substituted cinnamonitriles aiming at the synthesis of *N*-(4*H*-1,2,4-triazol-3-yl)hexahydroquinoline-3-carbonitriles and their spiro derivatives.

RESULTS AND DISCUSSION

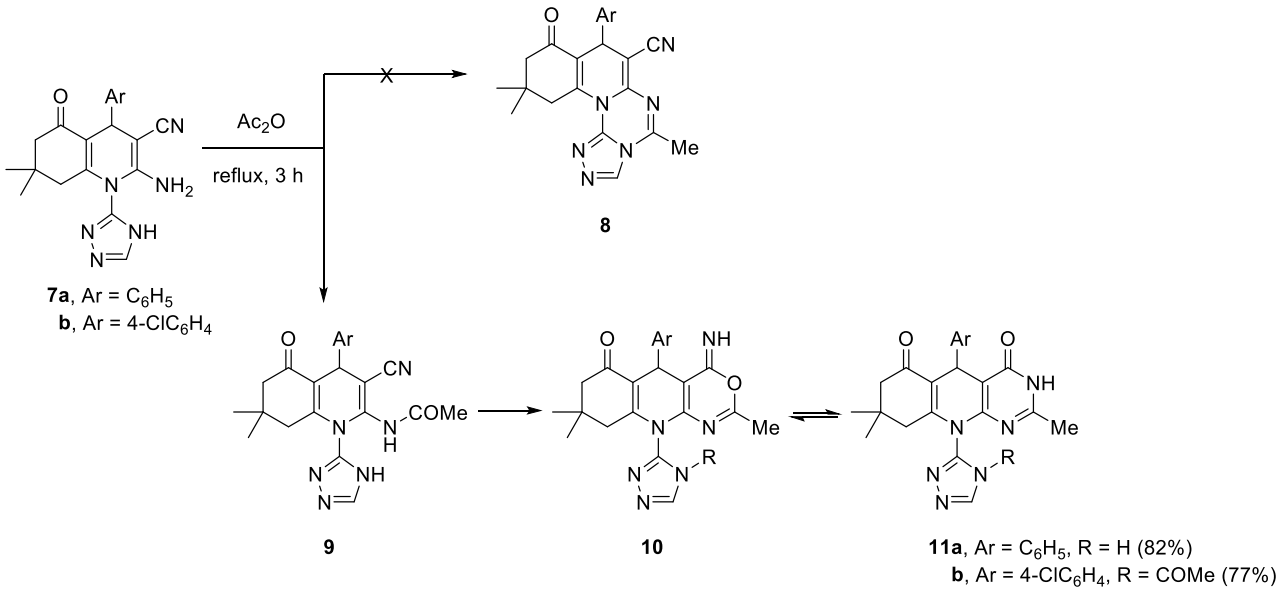
The *N*-(1,2,4-triazol-3-yl)enamine **3a** was obtained through the reaction of dimedone **1** and 3-amino-4*H*-1,2,4-triazole **2a** using a catalytic amount of trichloroacetic acid (TCAA) as a catalyst under solvent-free conditions. When equimolar amounts of **3a** and arylidenemalononitriles **4a-d** were refluxed in alcohol for 3 h, *N*-(4*H*-1,2,4-triazol-3-yl)hexahydroquinoline-3-carbonitrile compounds **7a-d** were obtained in high yields. The formation of compounds **7a-d** apparently involves the formation of Michael adducts **5**, which undergo an intramolecular cyclization into **6**. The formation of the final isolable products **7a-d** is completed *via* isomerization of **6** (Scheme 1).

The constitutions of compounds **7a-d** were established spectroscopically. For example, the IR spectrum of **7a** indicated the presence of a CN group (ν 2185 cm^{-1}), one CO group (ν 1658 cm^{-1}) and characteristic broad bands at ν 3429, 3325 and 3147 cm^{-1}, which refer to the NH_2 and NH groups. The ^{1}H NMR spectrum revealed a singlet signal at δ 4.42 ppm (1 H) assigned to quinoline-H4, as well as two broad singlets at δ 5.81 (2 H) and 14.53 (1 H) ppm referring to NH_2 and triazole-NH, respectively. The multiplet at δ 7.16-7.33 (5 H) ppm was assigned to the aryl protons. The ^{13}C NMR spectrum showed the carbonyl carbon signal at δ 196.0 ppm, that for the quinoline-C4 at δ 36.4 ppm, as well as the other signals of the carbon atoms of the aromatic system.



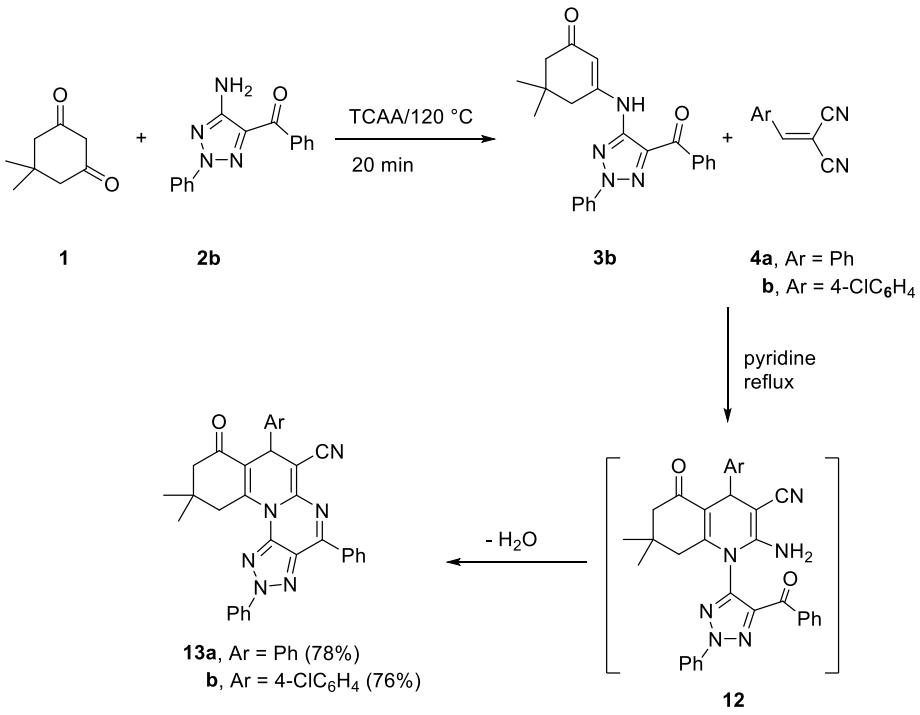
Scheme 1. Synthesis of *N*-(4*H*-1,2,4-triazol-3-yl)hexahydroquinoline-3-carbonitriles **7a-d**

In attempts to produce tetrahydro-8*H*-[1,2,4]triazolo[4',3':5,6][1,3,5]triazino[1,2-*a*]quinoline-7-carbonitrile derivatives **8** by the action of acetic anhydride on compounds **7**, the desired products were not produced, instead the *N*-(1,2,4-triazol-3-yl)tetrahydropyrimido[4,5-*b*]quinoline-4,6-dione derivatives **11** are obtained as sole products. Compounds **11** are assumed to be formed *via* initial acylation of **7** to give **9** that then cyclized into **10** which underwent Dimroth rearrangement into **11**. Similar mechanism was followed under the same conditions.[24] It worth mentioning that boiling compound **7b** in acetic anhydride not only undergoes Dimroth rearrangement but also affects a further acylation of the triazole-NH leading to **11b** (Scheme 2).



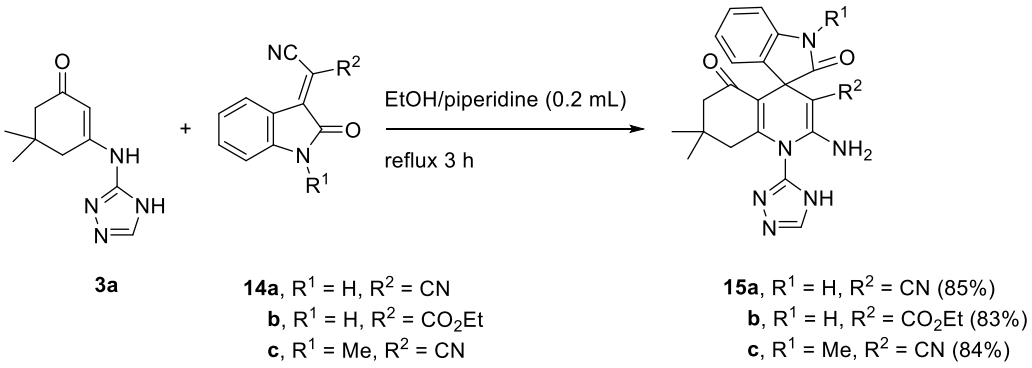
Scheme 2. Synthesis of pyrimido[4,5-*b*]quinoline-4,6-dione derivatives **11a,b**

Encouraged by the results acquired from the enamine **3a**, we attempted to expand the scope of this reaction to prepare tetracyclic structures. Thus the enamine carrying carbonyl group on the triazole ring **3b** was prepared similarly from dimedone **1** and 5-amino-1,2,3-triazole derivative **2b** and reacted with arylidenemalononitriles **4a,b**. The reaction results in the formation of the hexahydro[1,2,3]triazolo[4',5':5,6]pyrimido[1,2-*a*]quinoline-6-carbonitrile derivatives **13** as products of cyclization with water elimination. The reaction proceeds *via* intermediacy of **12**. The structure of compounds **13** was established through inspection of their spectroscopic data. The mass spectrum of **13a** revealed a molecular ion peak as a base peak at *m/z* 522 corresponding to the loss of water. ^{1}H NMR revealed a singlet signal at δ 4.88 ppm corresponding to H-7. All other signals appeared at their expected positions (Scheme 3).



Scheme 3. Synthesis of [1,2,3]triazolo[4',5':5,6]pyrimido[1,2-*a*]quinoline-6-carbonitrile derivatives **13a,b**

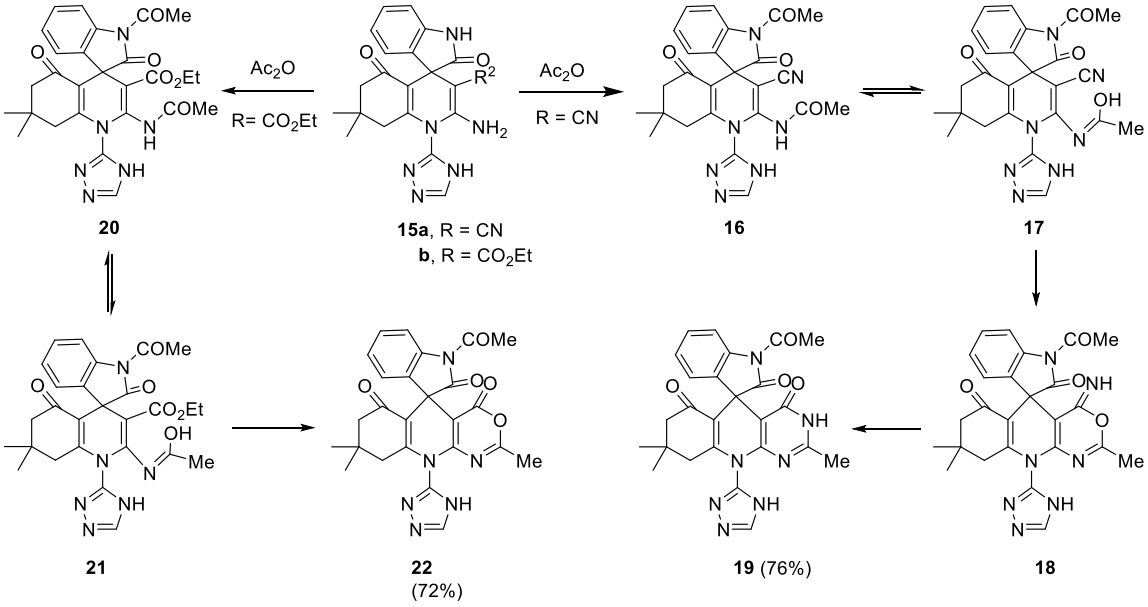
Motivated by these results and in the light of our interest in the synthesis of spiro-heterocyclic compounds,[26–28] we report herein the synthesis of the spiro-tetracyclic structures. Thus, we managed to prepare novel spirocyclic 2-oxoindole derivatives of 2-amino-1-(4*H*-1,2,4-triazol-3-yl)hexahydroquinoline-3-carbonitrile **15a-c** *via* the reaction of the cyclic enamine **3a** with 3-cyanomethylidene-2-oxoindoles **14a-c** in the presence of piperidine as a catalyst over 3 h (Scheme 4). Compounds **15** were characterized spectroscopically.



Scheme 4. Synthesis of spirocyclic compounds **15a-c**

Boiling compound **15a** in acetic anhydride for a long period results in the formation of **19**. In this respect, the initially formed spiro [1,3]oxazino[4,5-*b*]quinoline]-4-imine **18** undergoes Dimroth rearrangement to give **19**. On the other hand, **15b** containing an ester group in acetic ahydride gives compound **20** that tautomerizes into compound **21**. The cyclization of **21** *via* the loss of EtOH molecule leads to the formation of the spiro[indoline-3,5'-[1,3]oxazino[4,5-*b*]quinoline]-2,4',6'-trione **22** (Scheme 5).

The structure of compounds **19** and **22** were confirmed based on spectral data. Thus the ^{1}H NMR spectrum of **19** indicated the absence of isatin-NH and appearance of acetyl group at δ 2.01 ppm. In addition, it showed the pyrimidine-CH_3 at δ 2.56 ppm. The two signals at δ 12.53 and 14.37 ppm are assigned to pyrimidine-NH and triazole-NH, respectively. On the other hand, ^{1}H NMR spectrum of **19** showed the absence of ester group. The two signals at δ 2.07 and 2.57 ppm are assigned to acetyl and pyrimidine-CH_3 groups, respectively. Moreover, the triazole NH appeared at δ 14.54 ppm. All other signals appeared at their expected positions.



Scheme 5. Synthesis of fused spirocyclic compounds **19** and **22**

CONCLUSIONS

The cyclic enamines incorporating triazole, behaving like *C*-nucleophiles, affect simple and facile Michael addition reactions with various arylidenemalononitriles, and 3-cyanomethylene-2-oxindoles, respectively, to give different *N*-(4*H*-1,2,4-triazol-3-yl)hexahydroquinoline-3-carbonitriles and their spirooxindole derivatives.

EXPERIMENTAL

Melting points were measured with a Stuart melting point apparatus and are uncorrected. The IR spectra were recorded using a FTIR Bruker–vector 22 spectrophotometer as KBr pellets. The ^{1}H and ^{13}C NMR spectra were recorded in DMSO–d_6 and $CDCl_3$ as solvent on Varian Gemini NMR spectrometer at 400 MHz and 100 MHz, respectively, using TMS as internal standard. Chemical shifts are reported as δ values in ppm. Mass spectra were recorded with a Shimadzu GCMS–QP–1000 EX mass spectrometer in EI (70 eV) model. The elemental analyses were performed at the Micro analytical center, Cairo University.

General procedure for synthesis of compounds 3a,b

Enamines **3a,b** are prepared as similar to the method reported in literature.[34]

To a mixture of dimedone (1.00 g, 7.14 mmol) and 3-amino-1,2,4-triazole **2a** (0.60 g, 7.14 mmol) or 5-amino-2*H*-1,2,3-triazole **2b** (1.8 g, 7.14 mmol) was added trichloroacetic acid (0.23 g, 1.41 mmol). The mixture was heated at 120 °C for 20 min. The crude product was separated and crystallized with EtOH to give compounds **3a,b**

3-((4*H*-1,2,4-Triazol-3-yl)amino)-5,5-dimethylcyclohex-2-en-1-one (3a)

Yellow crystals (1.24 g, 84%), Mp 296-298 °C, IR (KBr): *v* 3428, 3280 (2NH), 1579 (CO) cm^{-1}, ^1H NMR (400 MHz, DMSO-d_6): δ 1.00 (*s*, 6H, 2CH_3), 2.05 (*s*, 2H, CH_2), 2.39 (*s*, 2H, CH_2), 6.43 (*s*, 1H, dimedone =C*H*), 8.37 (*s*, 1H, triazole C*H*), 9.53 (*br s*, 1H, enamine N*H*), 13.63 (*br s*, 1H, triazole N*H*) ppm, MS (EI, 70 eV): *m/z* (%) 206 ($[M]^+$, 28), 191 (29), 150 (49), 122 (100), 95 (18), Anal. Calcd for $C_{10}H_{14}N_4O$: C, 58.24; H, 6.84; N, 27.17. Found: C, 58.18; H, 6.76; N, 27.09.

3-((5-Benzoyl-2-phenyl-2*H*-1,2,3-triazol-4-yl)amino)-5,5-dimethylcyclohex-2-en-1-one (3b)

Yellow crystals (2.45 g, 89%), Mp > 300 °C, IR (KBr): *v* 3435 (*br*, NH), 1745, 1623 (2CO) cm^{-1}, ^1H NMR (400 MHz, $CDCl_3$): δ 1.19 (*s*, 6H, 2CH_3), 2.34 (s, 2H, CH_2), 2.54 (s, 2H, CH_2), 6.98 (*s*, 1H, C*H*), 7.44-8.49 (*m*, 10H, Ar*H*), 9.06 (*br s*, 1H, N*H*) ppm, ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.3 ($2CH_3$), 33.0 (C), 43.8 (CH_2), 50.48 (CH_2), 106.9 (CH), 119.2 (CH), 128.6 (CH), 129.5 (CH), 130.4 (CH), 132.5 (C), 133.8 (C), 136.3 (C), 138.9 (C), 151.2 (C), 153.8 (C), 187.6 (C), 199.4 (C) ppm, MS (EI, 70 eV): *m/z* (%) 386 (10), 371 (36), 105 (100), 77 (69), Anal. Calcd for $C_{23}H_{22}N_4O_2$: C, 71.48; H, 5.74; N, 14.50. Found: C, 71.39; H, 5.71; N, 14.42.

General procedure for synthesis of compounds 7a-d

A mixture of enamine **3a** (0.21 g, 1 mmol) and cinnamonitriles **4a-d** (1 mmol) in EtOH (15 mL) is heated at reflux in the presence of piperidine (0.2 mL) for 3 h. The crude products were collected and crystallized from EtOH-dioxane (2:1).

2-Amino-7,7-dimethyl-5-oxo-4-phenyl-1-(4*H*-1,2,4-triazol-3-yl)-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (7a)

Yellowish white crystals (0.33 g, 92%), Mp > 300 °C, IR (KBr): *v* 3429, 3325, 3147 (NH_2 and NH), 2185 (CN), 1658 (CO) cm^{-1}, ^1H NMR (400 MHz, DMSO-d_6): δ 0.83 (*s*, 3H, CH_3), 0.92 (*s*, 3H, CH_3), 1.94-2.19 (*m*, 4H, 2CH_2), 4.42 (*s*, 1H, C*H*), 5.81 (*br s*, 2H, NH_2), 7.16-7.33 (*m*, 5H, Ar*H*), 8.78 (s, 1H, triazole C*H*), 14.53 (*br s*, 1H, triazole N*H*) ppm, ^{13}C NMR (100 MHz, DMSO-d_6): δ 27.0 (CH_3), 28.3 (CH_3), 32.3 (C), 36.4 (CH), 40.2 (CH_2), 49.6 (CH_2), 61.4 (C), 114.0 (C), 121.0 (C), 126.5 (CH), 126.8 (CH), 128.4 (CH), 145.9 (C), 149.8 (C), 154.6 (C), 156.2 (CH), 161.2 (C), 195.0 (C) ppm, MS (EI, 70 eV): *m/z* (%) 360 ($[M]^+$, 39), 283 (100), Anal. Calcd for $C_{20}H_{20}N_6O$: C, 66.65; H, 5.59; N, 23.32. Found: C, 66.56; H, 5.49; N, 23.29.

2-Amino-4-(4-chlorophenyl)-7,7-dimethyl-5-oxo-1-(4*H*-1,2,4-triazol-3-yl)-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (7b)

Yellow crystals (0.35 g, 89%), Mp > 300 °C, IR (KBr): *v* 3440, 3322, 3115 (NH_2 and NH), 2187 (CN), 1659 (CO) cm^{-1}, ^1H NMR (400 MHz, DMSO-d_6): δ 0.81 (*s*, 3H, CH_3), 0.91 (*s*, 3H, CH_3), 1.91-2.25 (*m*, 4H, 2CH_2), 4.43 (*s*, 1H, C*H*), 5.86 (*br s*, 2H, NH_2), 7.25-7.38 (*m*, 4H, Ar*H*), 8.77 (*s*, 1H, triazole C*H*), 14.49 (*br s*, 1H, triazole N*H*) ppm, ^{13}C NMR (100 MHz, DMSO-d_6): δ 27.7 (CH_3), 28.1 (CH_3), 32.5 (C), 36.0 (CH), 40.1 (CH_2), 49.9 (CH_2), 61.7 (C), 114.4 (C), 120.7 (C), 128.2 (CH), 128.6 (CH), 131.5 (C), 144.0 (C), 144.9 (C), 149.8 (C), 150.5 (CH), 161.6 (C), 195.0 (C) ppm, MS (EI, 70 eV): *m/z* (%) 396 ([$(M+2)^+$], 1.4), 394 ([M^+], 4), 283 (100), Anal. Calcd for $C_{20}H_{19}ClN_6O$: C, 60.84; H, 4.85; Cl, 8.98; N, 21.28. Found: C, 60.77; H, 4.79; Cl, 8.91; N, 21.23.

2-Amino-4-(4-methoxyphenyl)-7,7-dimethyl-5-oxo-1-(4*H*-1,2,4-triazol-3-yl)-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (7c)

Bright yellow crystals (0.34 g, 87%), Mp > 300 °C, IR (KBr): *v* 3444, 3329, 3128 (NH_2 and NH), 2187 (CN), 1659 (CO) cm^{-1}, ^1H NMR (400 MHz, DMSO-d_6): δ 0.82 (*s*, 3H, CH_3), 0.91 (*s*, 3H, CH_3), 1.93-2.18 (*m*, 4H, 2CH_2), 3.71 (*s*, 3H, OCH_3), 4.38 (*s*, 1H, C*H*), 5.77 (*br s*, 2H, NH_2), 6.84-7.28 (*m*, 4H, Ar*H*), 8.78 (*s*, 1H, triazole C*H*), 14.51 (*br s*, 1H, triazole N*H*) ppm, ^{13}C NMR (100 MHz, DMSO-d_6): δ 26.9 (CH_3), 28.2 (CH_3), 32.2 (C), 35.5 (CH), 40.3 (CH_2), 49.5 (CH_2), 55.0 (CH_2), 61.6 (C), 113.7 (CH), 114.2 (C), 121.0 (C), 127.8 (CH), 138.0 (C), 145.6 (C), 149.4 (C), 150.3 (C), 154.3 (CH), 157.8 (C), 195.0 (C) ppm, MS (EI, 70 eV): *m/z* (%) 390 ([M^+], 39), 283 (100), Anal. Calcd for $C_{21}H_{22}N_6O_2$: C, 64.60; H, 5.68; N, 21.52. Found: C, 64.55; H, 5.52; N, 21.44.

2-Amino-4-(benzo[*d*][1,3]dioxol-5-yl)-7,7-dimethyl-5-oxo-1-(4*H*-1,2,4-triazol-3-yl)-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (7d)

Yellow crystals (0.35 g, 87%), Mp > 300 °C, IR (KBr): *v* 3450, 3330, 3129 (NH_2 and NH), 2188 (CN), 1662 (CO) cm^{-1}, ^1H NMR (400 MHz, DMSO-d_6): δ 0.83 (*s*, 3H, CH_3), 0.92 (*s*, 3H, CH_3), 1.93-2.24 (*m*, 4H, 2CH_2), 4.35 (*s*, 1H, C*H*), 5.80 (*br s*, 2H, NH_2), 5.95 (*s*, 2H, OCH_2O), 6.71-6.84 (*m*, 3H, Ar*H*), 8.78 (*s*, 1H, triazole C*H*), 14.53 (*br s*, 1H, triazole N*H*) ppm, ^{13}C NMR (100 MHz, DMSO-d_6): δ 27.0 (CH_3), 28.1 (CH_3), 32.2 (C), 36.0 (CH), 41.4 (CH_2), 49.5 (CH_2), 61.5 (C), 100.7 (CH_2), 114.1 (C), 107.0 (CH), 107.9 (CH), 119.8 (C), 120.9 (CH), 139.9 (C), 145.8 (C), 147.3 (C), 149.5 (C), 150.3 (C), 154.3 (CH), 161.2 (C), 195.0 (C) ppm, MS (EI, 70 eV): *m/z* (%) 404 ([$M]^+$, 46), 283 (100), Anal. Calcd for $C_{21}H_{20}N_6O_3$: C, 62.37; H, 4.98; N, 20.78. Found: C, 62.29; H, 4.93; N, 20.71.

General procedure for synthesis of compounds 11a,b

Compound **7a** or **7b** (10 mmol) was heated at reflux in acetic anhydride (5 mL) for 3 h. The excess solvent was evaporated under vacuum and the residue was washed with 0.2 *N* aq. $NaHCO_3$ (20 mL). The crude product was crystallized from EtOH-dioxane (3:1).

2,8,8-Trimethyl-5-phenyl-10-(4*H*-1,2,4-triazol-3-yl)-5,8,9,10-tetrahydropyrimido[4,5-*b*]quinoline-4,6(3*H*,7*H*)-dione (11a)

Yellowish white crystals (0.33 g, 82%), Mp > 300 °C, IR (KBr): *v* 3368, 3133 (2NH), 1659, 1626 (2CO) cm^{-1}, ^1H NMR (400 MHz, DMSO-d_6): δ 0.78 (*s*, 3H, CH_3), 0.93 (*s*, 3H, CH_3), 1.75 (*m*, 2H, 2CH_2), 2.04 (*s*, 3H, CH_3), 2.24 (*m*, 2H, 2CH_2), 5.04 (*s*, 1H, C*H*), 7.09-7.34 (*m*, 5H, Ar*H*), 8.66 (s, 1H, triazole C*H*), 12.29 (*br s*, 1H, pyrimidine N*H*), 14.51 (*br s*, 1H, triazole N*H*) ppm, ^{13}C NMR (100 MHz, DMSO-d_6): δ 21.0 (CH_3), 26.2 (CH_3), 29.1 (CH_3), 31.8 (C), 34.3 (CH), 40.3 (CH_2), 49.5 (CH_2), 101.6 (C), 112.2 (C), 126.1 (CH), 127.6 (CH), 127.8 (CH), 145.3 (C), 145.6 (C), 149.3 (C), 150.7 (C), 152.8 (C), 157.0 (CH), 161.4 (C), 194.8 (C) ppm, MS (EI, 70 eV): *m/z* (%) 402 ([M^+], 30), 325 (100), Anal. Calcd for $C_{22}H_{22}N_6O_2$: C, 65.66; H, 5.51; N, 20.88. Found: C, 65.58; H, 5.44; N, 20.79.

10-(4-Acetyl-4*H*-1,2,4-triazol-3-yl)-5-(4-chlorophenyl)-2,8,8-trimethyl-5,8,9,10-tetrahydropyrimido-[4,5-*b*]quinoline-4,6(3*H*,7*H*)-dione (11b)

Yellow crystals (0.37 g, 77%), Mp > 300 °C, IR (KBr): *v* 3101 (2NH), 1761, 1663, 1602 (3CO) cm^{-1}, ^1H NMR (400 MHz, DMSO-d_6): δ 0.81 (*s*, 3H, CH_3), 0.96 (*s*, 3H, CH_3), 1.91 (*m*, 2H, 2CH_2), 2.07 (*s*, 3H, CH_3), 2.27 (*m*, 2H, 2CH_2), 2.72 (*s*, 3H, COCH_3), 5.03 (*s*, 1H, C*H*), 7.18-7.42 (*m*, 4H, Ar*H*), 9.49 (s, 1H, triazole C*H*), 12.36 (*br s*, 1H, pyrimidine N*H*) ppm, ^{13}C NMR (100 MHz, DMSO-d_6): δ 21.4 (CH_3), 22.3 (CH_3), 27.2 (CH_3), 29.5 (CH_3), 32.5 (C), 33.7 (CH), 40.5 (CH_2), 50.1 (CH_2), 102.7 (C), 114.0 (C), 128.2 (CH), 129.7 (CH), 132.2 (C), 143.4 (C), 144.3 (C), 149.3 (C), 153.7 (C), 157.4 (CH), 163.4 (C), 167.6 (C), 195.5 (C) ppm, MS (EI, 70 eV): *m/z* (%) 463 ([$(M-15)^+$], 0.5), 436 (10), 367 (74), 325 (100), Anal. Calcd for $C_{24}H_{23}ClN_6O_3$: C, 60.19; H, 4.84; Cl, 7.40; N, 17.55. Found: C, 60.11; H, 4.69; Cl, 7.31; N, 17.48.

General method for synthesis of compounds 13a,b

A mixture of enamine **3b** (0.21 g, 1 mmol) and cinnamonitriles **4a,b** (1 mmol) in pyridine (5 mL) is heated at reflux for 3 h. The excess pyridine was removed at reduced pressure and the resulting residue was treated with aq. HCl (0.2 N, 10 mL). The crude products were collected and crystallized from EtOH-dioxane (2:1).

10,10-Dimethyl-8-oxo-2,4,7-triphenyl-2,7,8,9,10,11-hexahydro-[1,2,3]triazolo[4',5':5,6]pyrimido[1,2-*a*]quinoline-6-carbonitrile (13a)

Yellow crystals (0.41 g, 78%), Mp > 300 °C, IR (KBr): *v* 2198 (CN), 1640 (CO) cm^{-1}, ^1H NMR (400 MHz, DMSO-d_6): δ 1.01 (*s*, 3H, CH_3), 1.15 (*s*, 3H, CH_3), 2.23, 2.47, 2.84, 3.64 (4 *m*, 4H, 2CH_2), 4.88 (*s*, 1H, C*H*), 7.33-8.61 (*m*, 15H, Ar*H*) ppm, MS (EI, 70 eV): *m/z* (%) 522 ([M^+], 24), 445 (100), 77 (63), Anal. Calcd for $C_{33}H_{26}N_6O$: C, 75.84; H, 5.01; N, 16.08. Found: C, 75.69; H, 4.93; N, 16.01.

7-(4-Chlorophenyl)-10,10-dimethyl-8-oxo-2,4-diphenyl-2,7,8,9,10,11-hexahydro-[1,2,3]triazolo[4',5':5,6]pyrimido[1,2-*a*]quinoline-6-carbonitrile (13b)

Yellow crystals (0.42 g, 76%), Mp = 293-295 °C, IR (KBr): *v* 2199 (CN), 1638 (CO) cm^{-1}, ^1H NMR (400

MHz, DMSO-d_6): δ 1.06 (*s*, 3H, CH_3), 1.14 (*s*, 3H, CH_3), 2.23, 2.46, 2.84, 3.62 (4 *m*, 4H, 2CH_2), 4.90 (*s*, 1H, C*H*), 7.36-8.61 (*m*, 14H, Ar*H*) ppm, MS (EI, 70 eV): *m/z* (%) 558 ([$(M+2)^+$], 13), 556 ([M^+], 36), 445 (100), 77 (73), Anal. Calcd for $C_{33}H_{25}ClN_6O$: C, 71.15; H, 4.52; Cl, 6.36; N, 15.09. Found: C, 71.09; H, 4.44; Cl, 6.19; N, 15.03.

General procedure for synthesis of compounds 15a-c

A mixture of enamine **3a** (0.21 g, 1 mmol) and 3-cyanomethylene-2-oxindoles 1**4a-c** (1 mmol) in EtOH (15 mL) is heated at reflux in the presence of piperidine (0.2 mL) for 3 h. The crude products were collected and crystallized from EtOH-dioxane (2:1).

2'-Amino-7',7'-dimethyl-2,5'-dioxo-1'-(4*H*-1,2,4-triazol-3-yl)-5',6',7',8'-tetrahydro-1'*H*-spiro[indoline-3,4'-quinoline]-3'-carbonitrile (15a)

Red crystals (0.34 g, 85%), Mp > 300 °C, IR (KBr): *v* 3442, 3315, 3213, 3137 (NH_2 and 2NH), 2198 (CN), 1708, 1634 (2CO) cm^{-1}, ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.86 (*s*, 3H, CH_3), 0.91 (*s*, 3H, CH_3), 1.88-2.15 (*m*, 4H, 2CH_2), 5.78 (*br s*, 2H, NH_2), 6.76-7.14 (*m*, 4H, Ar*H*), 8.79 (*s*, 1H, triazole C*H*), 10.25 (*br s*, 1H, oxindole N*H*), 13.85 (*br s*, 1H, triazole N*H*) ppm, ^{13}C NMR (100 MHz, DMSO-d_6): δ 26.7 (CH_3), 27.9 (CH_3), 32.0 (C), 41.4 (CH_2), 49.3 (C), 50.1 (CH_2), 61.0 (C), 102.2 (C), 109.0 (CH), 111.4 (C), 118.4 (CH), 120.8 (CH), 121.5 (C), 122.7 (CH), 136.2 (C), 141.6 (C), 145.9 (C), 150.4 (C), 151.3 (C), 153.5 (CH), 156.5 (C), 194.0 (C) ppm, MS (EI, 70 eV): *m/z* (%) 401 ([M^+], 20), 384 (9), 375 (17), 358 (31), 347 (51), 325 (27), 317 (100), 300 (21), 290 (38), Anal. Calcd for $C_{21}H_{19}N_7O_2$: C, 62.83; H, 4.77; N, 24.42. Found: C, 62.77; H, 4.63; N, 24.31.

Ethyl 2'-amino-7',7'-dimethyl-2,5'-dioxo-1'-(4*H*-1,2,4-triazol-3-yl)-5',6',7',8'-tetrahydro-1'*H*-spiro-[indoline-3,4'-quinoline]-3'-carboxylate (15b)

Orange crystals (0.37 g, 83%), Mp > 300 °C, IR (KBr): *v* 3451, 3322, 3173, 3122 (NH_2 and 2NH), 1678, 1658, 1640 (3CO) cm^{-1}, ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.79 (*s*, 3H, CH_3), 0.87 (*s*, 3H, CH_3), 0.87 (*t*, 3H, *J* = 7.2 Hz, $CO_2CH_2CH_3$), 1.79-2.12 (*m*, 4H, 2CH_2), 3.67 (*q*, 2H, *J* = 7.2 Hz, $CO_2CH_2CH_3$), 6.64-7.05 (*m*, 4H, Ar*H*), 7.24 (*br s*, 2H, NH_2), 8.83 (*s*, 1H, triazole C*H*), 9.97 (*br s*, 1H, oxindole N*H*), 14.58 (*br s*, 1H, triazole N*H*) ppm, ^{13}C NMR (100 MHz, DMSO-d_6): δ 13.0 (CH_3), 26.5 (CH_3), 27.9 (CH_3), 31.5 (C), 40.4 (CH_2), 48.6 (C), 50.2 (CH_2), 58.6 (CH_2), 79.2 (C), 107.8 (C), 113.7 (CH), 120.3 (CH), 122.1 (CH), 122.2 (C), 126.8 (CH), 137.3 (C), 143.7 (C), 145.9 (C), 149.7 (C), 151.9 (CH), 154.2 (C), 168.4 (C), 193.6 (C) ppm, MS (EI, 70 eV): *m/z* (%) 448 ([M^+], 9), 402 (11), 375 (100), Anal. Calcd for $C_{23}H_{24}N_6O_4$: C, 61.60; H, 5.39; N, 18.74. Found: C, 61.53; H, 5.34; N, 18.68.

2'-Amino-1,7',7'-trimethyl-2,5'-dioxo-1'-(4*H*-1,2,4-triazol-3-yl)-5',6',7',8'-tetrahydro-1'*H*-spiro[indoline-3,4'-quinoline]-3'-carbonitrile (15c)

Brick-red crystals (0.35 g, 84%), Mp > 300 °C, IR (KBr): *v* 3444, 3335, 3141 (NH_2 and NH), 2190 (CN), 1689, 1653 (2CO) cm^{-1}, ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.85 (*s*, 3H, CH_3), 0.91 (*s*, 3H, CH_3),

1.90-2.13 (*m*, 4H, 2CH_2), 3.14 (*s*, 3H, NCH_3), 5.84 (*br s*, 2H, NH_2), 6.95-7.26 (*m*, 4H, Ar*H*), 8.79 (s, 1H, triazole C*H*), 14.33 (*br s*, 1H, triazole N*H*) ppm, ^{13}C NMR (100 MHz, DMSO-d_6): δ 18.2 (CH_3), 26.3 (CH_3), 27.4 (CH_3), 28.0 (CH_3), 32.2 (C), 40.6 (CH_2), 48.2 (C), 49.7 (CH_2), 56.9 (C), 107.6 (C), 118.1 (CH), 122.3 (CH), 122.8 (CH), 128.1 (CH), 134.6 (C), 142.8 (C), 144.6 (C), 150.4 (C), 151.3 (C), 154.2 (CH), 165.5 (C), 194.3 (C) ppm, MS (EI, 70 eV): *m/z* (%) 415 ([M^+], 13), 372 (8), 361 (15), 331 (78), 304 (47), 234 (32), 146 (64), 83 (100), Anal. Calcd for $C_{22}H_{21}N_7O_2$: C, 63.60; H, 5.10; N, 23.60. Found: C, 63.55; H, 5.06; N, 23.49.

General procedure for synthesis of compounds 19 and 22

Compound **15a** or **15b** (10 mmol) was heated at reflux in acetic anhydride (5 mL) for 3 h. The excess solvent was evaporated under vacuum and the residue was washed with 0.2 *N* aq. $NaHCO_3$ (20 mL). The crude product was crystallized from EtOH-dioxane (3:1)**.**

1-Acetyl-2',8',8'-trimethyl-10'-(4*H*-1,2,4-triazol-3-yl)-8',9'-dihydro-3'*H*-spiro[indoline-3,5'-pyrimido-[4,5-*b*]quinoline]-2,4',6'(7'*H*,10'*H*)-trione (19)

Red crystals (0.37 g, 76%), Mp > 300 °C, IR (KBr): *v* 3432 (*br*, 2NH), 1762, 1658, 1601 (3CO) cm^{-1}, ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.82 (*s*, 3H, CH_3), 0.93 (*s*, 3H, CH_3), 1.85-1.91 (*m*, 2H, CH_2), 2.01 (*s*, 3H, COCH_3), 2.15-2.34 (*m*, 2H, CH_2), 2.56 (*s*, 3H, pyrimidine CH_3), 7.08-8.07 (*m*, 4H, Ar*H*), 8.75 (*s*, 1H, triazole C*H*), 12.53 (*br s*, 1H, pyrimidine N*H*), 14.37 (*br s*, 1H, triazole N*H*) ppm, ^{13}C NMR (100 MHz, DMSO-d_6): δ 21.2 (CH_3), 26.4 (CH_3), 26.8 (CH_3), 29.1 (CH_3), 32.1 (C), 40.2 (CH_2), 49.6 (C), 49.9 (CH_2), 101.5 (C), 115.4 (C), 123.1 (CH), 121.6 (CH), 128.3 (CH), 128.4 (C), 133.1 (CH), 140.4 (C), 143.9 (C), 145.0 (C), 153.6 (C), 153.7 (C), 157.9 (CH), 161.8 (C), 171.2 (C), 179.3 (C), 194.8 (C) ppm, MS (EI, 70 eV): *m/z* (%) 485 ([M^+], 22), 442 (100), 359 (23), Anal. Calcd for $C_{25}H_{23}N_7O_4$: C, 61.85; H, 4.78; N, 20.20. Found: C, 61.79; H, 4.65; N, 20.09.

1-Acetyl-2',8',8'-trimethyl-10'-(4*H*-1,2,4-triazol-3-yl)-8',9'-dihydrospiro[indoline-3,5'-[1,3]oxazino-[4,5-*b*]quinoline]-2,4',6'(7'*H*,10'*H*)-trione (22)

Orange crystals (0.37 g, 72%), Mp > 300 °C, IR (KBr): *v* 3198 (NH), 1736, 1649, 1615 (3CO) cm^{-1}, ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.84 (*s*, 3H, CH_3), 0.93 (*s*, 3H, CH_3), 1.93-2.02 (*m*, 2H, CH_2), 2.07 (*s*, 3H, COCH_3), 2.16-2.34 (*m*, 2H, CH_2), 2.57 (*s*, 3H, oxazine CH_3), 7.14-8.09 (*m*, 4H, Ar*H*), 8.81 (*s*, 1H, triazole C*H*), 14.54 (*br s*, 1H, triazole N*H*) ppm, MS (EI, 70 eV): *m/z* (%) 486 ([M^+], 19), 443 (100), 401 (15), 360 (22), Anal. Calcd for $C_{25}H_{22}N_6O_5$: C, 61.72; H, 4.56; N, 17.28. Found: C, 61.64; H, 4.43; N, 17.16.

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