TÜBİTAK

Turkish Journal of Chemistry

http://journals.tubitak.gov.tr/chem/

Research Article

Turk J Chem
(2016) 40: 434 – 440

doi:10.3906/kim-1507-31

An efficient one-pot, three-component synthesis of 6-cyano-hexahydro-4*H*-thieno[3',2':5,6]pyrimido[1,2-*a*]quinoline-2-carboxylates and their spiro derivatives from *β*-enaminones

Said Ahmed Soliman GHOZLAN, Doaa Mohamed ABDELMONIEM, Amr Mohamed ABDELMONIEM, Ismail Abdelshafy ABDELHAMID*
Department of Chemistry, Faculty of Science, Cairo University, Giza, Egypt

Received: 12.07.2015 • **Accepted/Published Online:** 02.11.2015 • **Final Version:** 17.05.2016

Abstract: A simple and efficient one-pot synthesis of novel thieno[3',2':5,6]pyrimido[1,2-*a*]quinoline-2-carboxylates (**5a**–**d**) and their spirooxindole derivatives (**12a**–**d**) was accomplished. Thus, the Michael addition reaction of the cyclic *β*-enaminone **3** with the corresponding *α*,*β*-unsaturated nitrile derivatives **4a**–**d** in refluxing EtOH in the presence of piperidine afforded **5a**–**d** in good yields. On the other hand, spirooxindole derivatives **12a**–**d** were synthesized by the reaction of cyclic *β*-enaminone **3** with the corresponding 3-cyanomethylidene-2-oxoindoles **11a**–**d** in refluxing EtOH.

Key words: Cyclic enaminones, *α*,*β*-unsaturated nitriles, hexahydroquinolines, multicomponent reaction, spirooxindoles

1. Introduction

Hexahydroquinoline derivatives have received considerable attention as leading pharmaceutical compounds due to their pivotal roles in various biological activities including anti-inflammatory, antibacterial, antihypertensive, antitumor, and antimalarial properties.[1–12] Furthermore, it is known that incorporation of isatin within the molecules can enhance their pharmacological activities, as it constitutes the core structural element of many natural products and biologically active molecules.[13–19]

In recent years, medicinal chemists have modified the quinoline scaffold to optimize its pharmacology. However, a number of modifications have been made to the benzenoid ring; modifications to the pyridinone ring are not common.

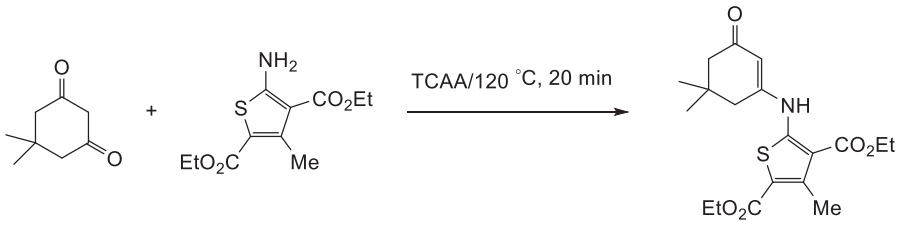
In light of the above-mentioned hypothesis, we assume that integration of the two scaffolds into a spirooxindole incorporating thieno[3',2':5,6]pyrimido[1,2-*a*]quinoline-2-carboxylates can result in the discovery of new active drugs.

2. Results and discussion

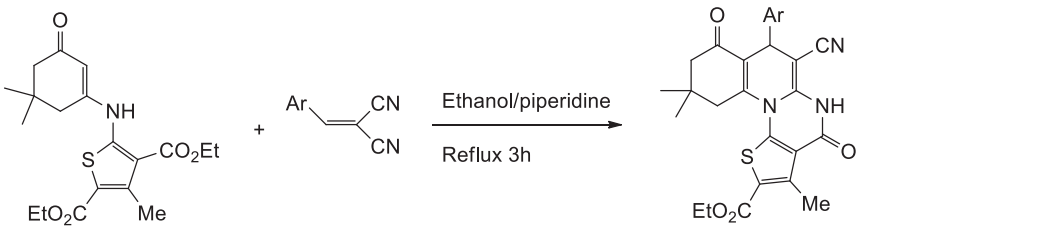
In conjunction with our ongoing research work on enamines[20–30] and spiro-heterocyclic compounds,[25,27,30] we report herein the synthesis of hexahydro-4*H*-thieno[3',2':5,6]pyrimido[1,2-*a*]quinoline-2-carboxylates and their spiro derivatives via the Michael addition reaction of the cyclic *β*-enaminone with *α*,*β*-unsaturated nitrile derivatives. Thus the cyclic enaminone incorporating thiophene moiety **3**, required for the synthesis of the target

*Correspondence: ismail_shafy@yahoo.com

compounds, was obtained through the reaction of dimedone (**1**) and the diethyl 5-amino-3-methylthiophene-2,4-dicarboxylate (**2**) using a catalytic amount of trichloroacetic acid as a catalyst under solvent-free conditions (Scheme 1). In the next step, Michael addition reaction of the cyclic enamine **3** with arylidenemalononitriles **4a**–**d** in ethanol in the presence of piperidine at reflux for 3 h resulted in the formation of **5** in good yields (Scheme 2). Moreover, we found that compounds **5** could be obtained via the three-component reaction of the cyclic enamine **3**, aldehyde, and malononitrile in ethanol in the presence of piperidine.



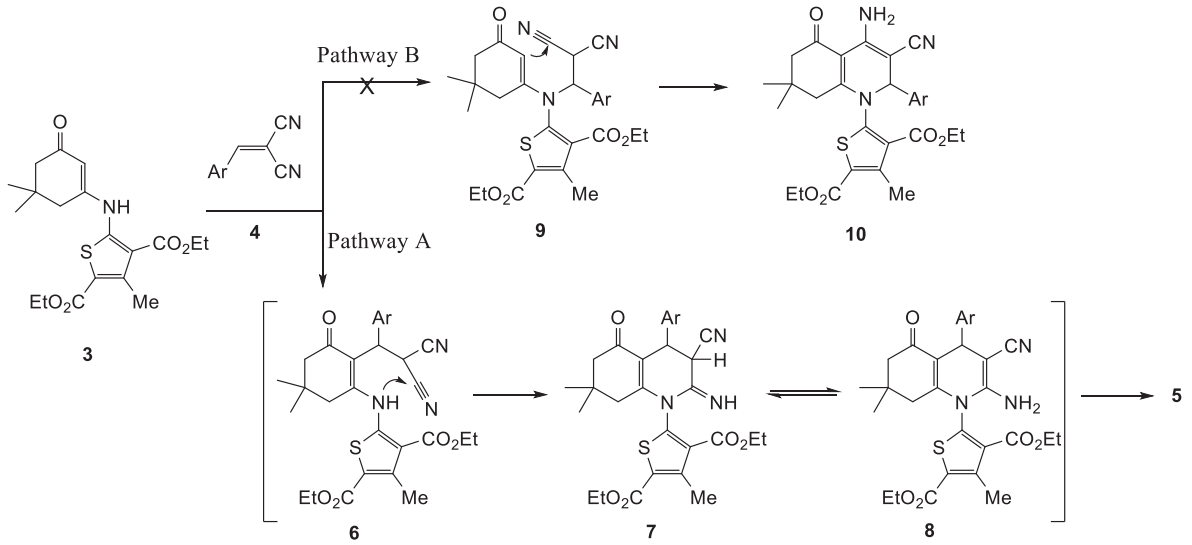
Scheme 1. Synthesis of enamine **3**.



Scheme 2. Synthesis of thieno[3',2':5,6]pyrimido[1,2-*a*]quinoline derivatives **5a**–**d**.

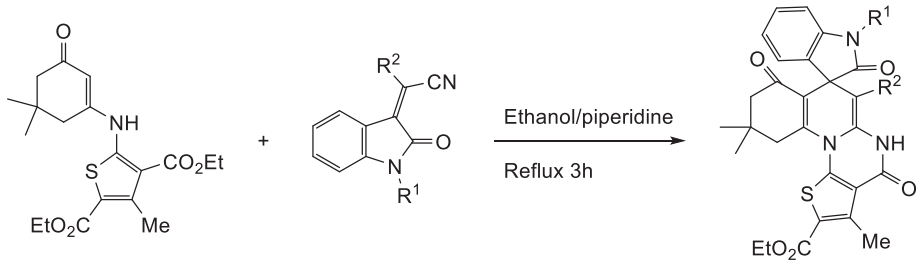
The IR spectra of the hexahydro-4*H*-thieno[3',2':5,6]pyrimido[1,2-*a*]quinoline-2-carboxylate **5a** exhibited characteristic absorption bands at $\nu = 3491$ and 2200 cm^{-1} for NH and CN groups, respectively. The bands at 1696 and 1660 cm^{-1} are assigned for CO groups. The ^{1}H NMR spectra of **5a** revealed the absence of one of the two ester protons. In addition, it displayed two prominent signals at $\delta = 4.65$ and 11.56 ppm due to quinoline ring *H*7 and pyrimidine-N*H*, respectively. The ^{13}C NMR spectrum showed, in addition to the aromatic carbon signals, characteristic peaks at $\delta = 35.5$, 159.2, 161.7, and 194.8 ppm for C-7 and three carbonyl groups, respectively. The mass spectrum of **5a** showed a molecular ion peak at $m/z = 487$ supporting the product formation.

The formation of **5** could be explained by the following plausible mechanism (Scheme 3). The reaction occurs via an initial addition of enamine CH to the activated double bond in **4** to yield **6**, which cyclizes into **7**. Intermediate **7** tautomerizes into **8**, which cyclizes readily into **5** through ethanol elimination (pathway A). On the other hand, the other pathway, which results from initial addition of NH to the activated double bond in **4** (pathway B), was excluded as previously reported.[28,29]



Scheme 3. A plausible mechanism for the reaction of enamine **3** with arylidenemalononitrile derivatives **4**.

Encouraged by the above-mentioned findings and in light of our interest in the synthesis of spiro-heterocyclic compounds,[25,27,30] we also report herein the synthesis of spiro-hexacyclic structures. Thus, we managed to prepare novel spiro cyclic 2-oxoindole derivatives of thieno[3',2':5,6]pyrimido[1,2-*a*]quinolone **12a**–**d** via the reaction of the cyclic enamine **3** with 3-cyanomethylidene-2-oxoindoles **11a**–**d** in the presence of piperidine as catalyst over 5 h (Scheme 4). Compounds **12** were characterized spectroscopically.



3

11a, R^1 = H, R^2 = CN
b, R^1 = H, R^2 = CO_2Et
c, R^1 = Me, R^2 = CN
d, R^1 = Me, R^2 = CO_2Et

12a, R^1 = H, R^2 = CN (83%)
b, R^1 = H, R^2 = CO_2Et (78%)
c, R^1 = Me, R^2 = CN (79%)
d, R^1 = Me, R^2 = CO_2Et (75%)

Scheme 4. Synthesis of spiro[indoline-3,7'-thieno[3',2':5,6]pyrimido[1,2-*a*]quinoline] derivatives **12a**–**d**.

In conclusion, cyclic enamines incorporating thiophene moiety, behaving like *C*-nucleophiles, affect simple and facile Michael addition reactions with various arylidenemalononitriles and 3-cyanomethylidene-2-oxoindoles regioselectively yielding different thieno[3',2':5,6]pyrimido[1,2-*a*]quinoline-2-carboxylate and their spirooxindole derivatives. Full characterization of these compounds is reported. The newly synthesized derivatives are interesting due to their promising pharmacological and biological activities.

3. Materials and methods

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 as solvent on a 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.

Diethyl 5-((5,5-dimethyl-3-oxocyclohex-1-en-1-yl)amino)-3-methylthiophene-2,4-dicarboxylate (3)

The enamine **3** was prepared according to the literature procedure.[31–33]

A mixture of dimedone (**1**) (1 g, 7.14 mmol) and diethyl 5-amino-3-methylthiophene-2,4-dicarboxylate (**2**) (1.84 g, 7.16 mmol) was heated in an oil bath at 120 °C in the presence of trichloroacetic acid (0.2 g, 1.23 mmol) for 20 min. The oily residue was extracted with chloroform (25 mL). The solvent was removed at reduced pressure and the crude solid was crystallized from ethanol to yield compound **3** as yellow crystals (2.30 g, 85%), mp = 172–174 °C, IR (KBr): ν = 3457 (br, NH), 1712 (CO_2Et), 1654 (CO) cm^{-1}, ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.04 (s, 6H, 2CH_3), 1.29 (t, 3H, J = 7.2 Hz, CH_3), 2.17 (s, 2H, CH_2), 2.49 (s, 2H, CH_2), 4.27 (q, 2H, J = 7.2 Hz, CH_2), 5.74 (s, 1H, dimedone =CH), 10.14 (br s, 1H, NH) ppm, ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.2 (CH_3), 14.4 (CH_3), 17.7 (CH_3), 28.2 (2CH_3), 32.8 (C), 44.2 (CH_2), 50.4 (CH_2), 61.0 (CH_2), 61.3 (CH_2), 105.9 (CH), 113.5 (C), 114.9 (C), 146.2 (C), 153.5 (C), 156.1 (C), 162.3 (C), 166.8 (C), 198.6 (C) ppm, MS (EI, 70 eV): m/z (%) = 379 ([M^+], 6), 364 (2), 334 (2), 318 (5), 304 (5), 261 (69), 83 (100), 67 (40), Anal. Calcd for $C_{19}H_{25}NO_5S$: C, 60.14; H, 6.64; N, 3.69; S, 8.45. Found: C, 60.06; H, 6.51; N, 3.49; S, 8.29.

General method for the synthesis of compounds 5a–d and 12a–d:

A mixture of enamine **3** (1 mmol) and activated cinnamonitriles **4a–d** or 3-cyanomethylene-2-oxoindole derivatives **11a–d** (1 mmol) was heated at reflux in ethanol (15 mL) in the presence of piperidine (0.2 mL) for 3 h. The solvent was removed at reduced pressure and the crude products were crystallized from ethanol–dioxane (2:1).

Ethyl 6-cyano-3,10,10-trimethyl-4,8-dioxo-7-phenyl-5,7,8,9,10,11-hexahydro-4*H*-thieno[3',2':5,6] pyrimido[1,2-*a*]quinolone-2-carboxylate (5a)

Yellow crystals (0.42 g, 86%), mp > 300 °C, IR (KBr): ν = 3491 (br, NH), 2200 (CN), 1696 (CO_2Et), 1660 (CO) cm^{-1}, ^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.96 (s, 3H, CH_3), 1.14 (s, 3H, CH_3), 1.30 (t, 3H, J = 7.2 Hz, CH_3), 2.56 (m, 4H, 2CH_2), 2.74 (s, 3H, CH_3), 4.31 (q, 2H, J = 7.2 Hz, CH_2), 4.65 (s, 1H, CH), 7.18–7.30 (m, 5H, ArH), 11.56 (br s, 1H, NH) ppm, ^{13}C NMR (100 MHz, DMSO-d_6): δ = 14.4 (CH_3), 14.7 (CH_3), 25.5 (CH_3), 30.9 (C), 35.5 (CH), 41.9 (CH_2), 50.2 (CH_2), 61.8 (CH_2), 71.5 (C), 112.2 (C), 116.7 (C), 118.9 (C), 126.8 (CH), 127.8 (CH), 129.1 (CH), 140.9 (C), 145.2 (C), 146.4 (C), 149.5 (C), 151.3 (C), 155.6 (C), 159.2 (C), 161.7 (C), 194.8 (C) ppm, MS (EI, 70 eV): m/z (%) = 487 ([M^+], 35), 410 (100), 382 (32), 326 (42), 298 (14), Anal. Calcd for $C_{27}H_{25}N_3O_4S$: C, 66.51; H, 5.17; N, 8.62; S, 6.58. Found: C, 66.48; H, 5.12; N, 8.52; S, 6.49.

Ethyl 7-(4-chlorophenyl)-6-cyano-3,10,10-trimethyl-4,8-dioxo-5,7,8,9,10,11-hexahydro-4*H*-thieno [3',2':5,6]pyrimido[1,2-*a*]quinoline-2-carboxylate (5b)

Yellow crystals (0.44 g, 84%), mp > 300 °C, IR (KBr): ν = 3427 (br, NH), 2197 (CN), 1695 (CO_2Et), 1664 (CO) cm^{-1}, ^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.95 (s, 3H, CH_3), 1.14 (s, 3H, CH_3), 1.30 (t, 3H, J = 7.2 Hz, CH_3), 2.56 (m, 4H, 2CH_2), 2.74 (s, 3H, CH_3), 4.28 (q, 2H, J = 7.2 Hz, CH_2), 4.67 (s, 1H, CH), 7.21–7.34 (m, 4H, ArH), 11.58 (br s, 1H, NH) ppm, ^{13}C NMR (100 MHz, DMSO-d_6): δ = 14.38 (CH_3), 14.66 (CH_3), 25.46 (CH_3), 30.9 (C), 35.4 (CH), 41.9 (CH_2), 50.1 (CH_2), 61.8 (CH_2), 72.7 (C), 111.9 (C), 117.5 (C), 120.8 (C), 128.2 (CH), 129.3 (CH), 133.0 (C), 139.4 (C), 144.3 (C), 145.2 (C), 146.8 (C), 149.5 (C), 153.2 (C), 155.9 (C), 162.0 (C), 194.8 (C) ppm, MS (EI, 70 eV): m/z (%) = 524 ([(M+2)$^+$], 5), 522 ([M$^+$], 15), 521 (40), 410 (100), 382 (36), 326 (45), 298 (16), Anal. Calcd for $C_{27}H_{24}ClN_3O_4S$: C, 62.12; H, 4.63; Cl, 6.79; N, 8.05; S, 6.14. Found: C, 62.05; H, 4.57; Cl, 6.66; N, 8.01; S, 6.03.

Ethyl 6-cyano-7-(4-methoxyphenyl)-3,10,10-trimethyl-4,8-dioxo-5,7,8,9,10,11-hexahydro-4*H*-thieno[3',2':5,6]pyrimido[1,2-*a*]quinoline-2-carboxylate (5c)

Yellow crystals (0.42 g, 81%), mp > 300 °C, IR (KBr): ν = 3434 (br, NH), 2202 (CN), 1716 (CO_2Et), 1663 (CO dimedone), 1610 (CONH) cm^{-1}, ^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.95 (s, 3H, CH_3), 1.14 (s, 3H, CH_3), 1.30 (t, 3H, J = 7.2 Hz, CH_3), 2.54 (m, 4H, 2CH_2), 2.74 (s, 3H, CH_3), 3.68 (s, 3H, CH_3), 4.31 (q, 2H, J = 7.2 Hz, CH_2), 4.58 (s, 1H, CH), 6.81–7.11 (m, 4H, ArH), 11.59 (br s, 1H, NH) ppm, ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.4 (CH_3), 14.7 (CH_3), 25.5 (CH_3), 30.9 (C), 35.4 (CH), 41.9 (CH_2), 50.2 (CH_2), 55.3 (CH_3), 61.8 (CH_2), 77.9 (C), 110.3 (C), 114.5 (CH), 117.7 (C), 121.5 (C), 127.9 (CH), 133.1 (C), 144.9 (C), 145.3 (C), 146.0 (C), 149.5 (C), 155.9 (C), 156.3 (C), 159.1 (C), 161.1 (C), 194.9 (C) ppm, MS (EI, 70 eV): m/z (%) = 517 ([M$^+$], 88), 410 (100), 382 (38), 326 (9), 298 (5), Anal. Calcd for $C_{28}H_{27}N_3O_5S$: C, 64.97; H, 5.26; N, 8.12; S, 6.19. Found: C, 64.85; H, 5.21; N, 8.03; S, 6.06.

Ethyl 7-(benzo[*d*][1,3]dioxol-5-yl)-6-cyano-3,10,10-trimethyl-4,8-dioxo-5,7,8,9,10,11-hexahydro-4*H*-thieno[3',2':5,6]pyrimido[1,2-*a*]quinoline-2-carboxylate (5d)

Yellow crystals (0.44 g, 83%), mp > 300 °C, IR (KBr): ν = 3436 (br, NH), 2199 (CN), 1715 (CO_2Et), 1664 (CO) cm^{-1}, ^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.94 (s, 3H, CH_3), 1.14 (s, 3H, CH_3), 1.30 (t, 3H, J = 7.2 Hz, CH_3), 2.57 (m, 4H, 2CH_2), 2.74 (s, 3H, CH_3), 4.25 (q, 2H, J = 7.2 Hz, CH_2), 4.58 (s, 1H, CH), 5.95 (s, 2H, OCH_2O), 6.66–6.81 (m, 3H, ArH), 11.50 (br s, 1H, NH) ppm, ^{13}C NMR (100 MHz, DMSO-d_6): δ = 14.4 (CH_3), 14.7 (CH_3), 25.4 (CH_3), 30.9 (C), 35.4 (CH), 41.9 (CH_2), 50.2 (CH_2), 61.8 (CH_2), 71.6 (C), 101.2 (CH_2), 106.5 (C), 107.3 (CH), 108.7 (CH), 116.9 (C), 120.2 (CH), 121.3 (C), 134.9 (C), 144.9 (C), 145.3 (C), 146.2 (C), 147.1 (C), 148.2 (C), 149.5 (C), 155.6 (C), 159.8 (C), 161.6 (C), 194.9 (C) ppm, MS (EI, 70 eV): m/z (%) = 531 ([M$^+$], 100), 410 (78), 382 (34), 326 (10), 298 (17), Anal. Calcd for $C_{28}H_{25}N_3O_6S$: C, 63.27; H, 4.74; N, 7.90; S, 6.03. Found: C, 63.18; H, 4.65; N, 7.81; S, 5.91.

Ethyl 6'-cyano-3',10',10'-trimethyl-2,4',8'-trioxo-4',5',8',9',10',11'-hexahydrospiro[indoline- 3,7'-thieno[3',2':5,6]pyrimido[1,2-*a*]quinoline]-2'-carboxylate (12a)

Yellow crystals (0.44 g, 83%), mp > 300 °C, IR (KBr): ν = 3258, 3191 (2NH), 2201 (CN), 1732 (CO_2Et), 1694 (CO), 1658 (CO) cm^{-1}, ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.05 (d, 6H, 2CH_3), 1.31 (t, 3H, J = 7.2

Hz, $CO_2CH_2CH_3$), 2.09–2.41 (m, 2H, CH_2), 2.75 (s, 3H, CH_3), 2.83–3.28 (m, 2H, CH_2), 4.33 (q, J = 7.2 Hz, $CO_2CH_2CH_3$), 6.80–7.17 (m, 4H, ArH), 10.54 (br s, 1H, NH), 11.45 (br s, 1H, NH) ppm, MS (EI, 70 eV): m/z (%) = 528 ([M^+], 16), 467 (30), 444 (67), 415 (11), 371 (16), 149 (53), 97 (66), 71 (100), 57 (86), Anal. Calcd for $C_{28}H_{24}N_4O_5S$: C, 63.62; H, 4.58; N, 10.60; S, 6.07. Found: C, 63.51; H, 4.44; N, 10.55; S, 6.02.

Diethyl 3',10',10'-trimethyl-2,4',8'-trioxo-4',5',8',9',10',11'-hexahydrospiro[indoline-3,7'-thieno[3',2':5,6]pyrimido[1,2-*a*]quinoline]-2',6'-dicarboxylate (12b)

Yellow crystals (0.45 g, 78%), mp > 300 °C, IR (KBr): ν = 3436, 3281 (2NH), 1729, 1664 ($2CO_2Et$) cm^{-1}, ^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.94 (t, 3H, J = 7.2 Hz, $CO_2CH_2CH_3$), 1.02 (m, 6H, $2CH_3$), 1.29 (t, 3H, J = 7.2 Hz, $CO_2CH_2CH_3$), 2.05–2.39 (m, 2H, CH_2), 2.77 (s, 3H, CH_3), 3.17–3.29 (m, 2H, CH_2), 3.86 (q, J = 7.2 Hz, $CO_2CH_2CH_3$), 4.31 (q, J = 7.2 Hz, $CO_2CH_2CH_3$), 6.72–7.10 (m, 4H, ArH), 10.29 (br s, 1H, NH), 12.04 (br s, 1H, NH) ppm, MS (EI, 70 eV): m/z (%) = 575 ([M^+], 2), 561 (4), 502 (57), 474 (13), 80 (100), 64 (83), Anal. Calcd for $C_{30}H_{29}N_3O_7S$: C, 62.60; H, 5.08; N, 7.30; S, 5.57. Found: C, 62.53; H, 5.01; N, 7.22; S, 5.54.

Ethyl 6'-cyano-1,3',10',10'-tetramethyl-2,4',8'-trioxo-4',5',8',9',10',11'-hexahydrospiro[indoline-3,7'-thieno[3',2':5,6]pyrimido[1,2-*a*]quinoline]-2'-carboxylate (12c)

Yellow crystals (0.43 g, 79%), mp > 300 °C, IR (KBr): ν = 3437 (NH), 2205 (CN), 1715 (CO_2Et), 1691 (CO), 1659 (CO) cm^{-1}, ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.05 (d, 6H, $2CH_3$), 1.29 (t, 3H, J = 7.2 Hz, $CO_2CH_2CH_3$), 2.05–2.35 (m, 2H, CH_2), 2.75 (s, 3H, CH_3), 2.82–3.25 (m, 2H, CH_2), 3.17 (s, 3H, N-CH_3), 4.31 (q, J = 7.2 Hz, $CO_2CH_2CH_3$), 6.94–7.28 (m, 4H, ArH), 11.54 (br s, 1H, NH) ppm, MS (EI, 70 eV): m/z (%) = 542 ([M^+], 38), 481 (27), 459 (100), 458 (99), 431 (22), 385 (23), 192 (22), 146 (29), 83 (65), 64 (67), Anal. Calcd for $C_{29}H_{26}N_4O_5S$: C, 64.19; H, 4.83; N, 10.33; S, 5.91. Found: C, 64.08; H, 4.72; N, 10.21; S, 5.83.

Diethyl 1,3',10',10'-tetramethyl-2,4',8'-trioxo-4',5',8',9',10',11'-hexahydrospiro[indoline-3,7'-thieno[3',2':5,6]pyrimido[1,2-*a*]quinoline]-2',6'-dicarboxylate (12d)

Yellow crystals (0.44 g, 75%), mp = 250–252 °C, IR (KBr): ν = 3444 (NH), 1722, 1663 ($2CO_2Et$), 1607 (CO) cm^{-1}, ^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.85 (t, 3H, J = 7.2 Hz, $CO_2CH_2CH_3$), 1.01 (m, 6H, $2CH_3$), 1.29 (t, 3H, J = 7.2 Hz, $CO_2CH_2CH_3$), 2.01–2.39 (m, 2H, CH_2), 2.78 (s, 3H, CH_3), 3.16 (s, 3H, N-CH_3), 3.26–3.29 (m, 2H, CH_2), 3.83 (q, J = 7.2 Hz, $CO_2CH_2CH_3$), 4.29 (q, J = 7.2 Hz, $CO_2CH_2CH_3$), 6.84–7.20 (m, 4H, ArH), 12.25 (br s, 1H, NH) ppm, ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.6 (CH_3), 14.4 (CH_3), 14.7 (CH_3), 25.8 (CH_3), 31.0 (C), 33.9 (CH_3), 43.0 (CH_2), 48.5 (C), 50.2 (CH_2), 61.1 (CH_2), 61.7 (CH_2), 87.2 (C), 107.5 (C), 119.6 (CH), 120.2 (C), 122.1 (CH), 122.7 (C), 122.9 (C), 128.8 (CH), 133.0 (CH), 144.5 (C), 145.1 (C), 146.4 (C), 146.9 (C), 149.1 (C), 155.9 (C), 161.9 (C), 167.0 (C), 178.4 (C), 194.1 (C) ppm, MS (EI, 70 eV): m/z (%) = 589 ([M^+], 14), 516 (100), 488 (16), 460 (8), 83 (20), Anal. Calcd for $C_{31}H_{31}N_3O_7S$: C, 63.14; H, 5.30; N, 7.13; S, 5.44. Found: C, 63.09; H, 5.23; N, 7.07; S, 5.37.

Acknowledgment

I. A. Abdelhamid gratefully acknowledges the Alexander von Humboldt Foundation for a research fellowship.

References

1. Yamada, N.; Kadowaki, S.; Takahashi, K.; Umezu, K. *Biochem. Pharmacol.* **1992**, *44*, 1211-1213.
2. Faber, K.; Stueckler, H.; Kappe, T. *J. Heterocycl. Chem.* **1984**, *21*, 1177-1178.
3. Johnson, J. V.; Rauckman, B. S.; Baccanari, P. D.; Roth, B. *J. Med. Chem.* **1989**, *32*, 1942-1949.
4. Abdel-Gawad, S. M.; El-Gaby, M. S. A.; Heiba, H. I.; Ali, H. M.; Ghorab, M. M. *J. Chin. Chem. Soc.* **2005**, *52*, 1227-1236.
5. El-Gaby, M. S. A.; Abdel-Gawad, S. M.; Ghorab, M. M.; Heiba, H. I.; Ali, H. M. *Phosphorus, Sulfur, Silicon Relat. Elem.* **2006**, *181*, 279-297.
6. Ghorab, M. M.; Abdel-Hamide, S. G.; Farrag, H. A. *Acta Pol. Pharm. Drug Res.* **2001**, *58*, 175-184.
7. Ghorab, M. M.; Ragab, F. A.; Noaman, E.; Heiba, H. I.; Aboulmagd, S. A. *Arzneim.-Forsch.* **2009**, *59*, 96-103.
8. Zhao, Y. L.; Chen, Y. L.; Chang, F. S.; Tzeng, C. C. *Eur. J. Med. Chem.* **2005**, *40*, 792-797.
9. Rose, U.; Drager, M. *J. Med. Chem.* **1992**, *35*, 2238-2243.
10. Li, S. Y.; Chen, Y. L.; Wang, C; Tzeng, C. C. *Bioorg. Med. Chem.* **2006**, *14*, 7370-7376.
11. Tseng, C. H.; Chen, Y. L.; Lu, P. J.; Yang, C. N.; Tzeng, C. C. *Bioorg. Med. Chem.* **2008**, *16*, 3153-3162.
12. Chen, Y. L.; Chen, I. L.; Wang, T. C.; Han, C. H.; Tzeng, C. C. *Eur. J. Med. Chem.* **2005**, 40, 928-934.
13. Galliford, C. V.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 8748-8758.
14. Kang, T. H.; Murakami, Y.; Matsumoto, K.; Takayama, H.; Kitajima, M.; Aimi, N.; Watanabe, H. *Eur. J. Pharmacol.* **2002**, *455*, 27-34.
15. Vine, K. L.; Matesic, L.; Locke, J. M.; Ranson, M.; Skropeta, D. *Anticancer Agents Med. Chem.* **2009**, *9*, 397-414.
16. Lin, H.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 36-51.
17. Marti, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2003**, 2209-2219.
18. Rottmann, M.; McNamara, C.; Yeung, B. K. S.; Lee, M. C. S.; Zou, B.; Russell, B.; Seitz, P.; Plouffe, D. M.; Dharia, N. V.; Tan, J.; et al. *Science* **2010**, *329*, 1175-1180.
19. Yeung, B. K. S.; Zou, B.; Rottmann, M.; Lakshminarayana, S. B.; Ang, S. H.; Leong, S. Y.; Tan, J.; Wong, J.; Keller-Maerki, S.; Fischli, C.; et al. *J. Med. Chem.* **2010**, *53*, 5155-5164.
20. Ghozlan, S. A. S.; Abdelmoniem, A. M.; Butenschön, H.; Abdelhamid, I. A. *Tetrahedron* **2015**, *71*, 1413-1418.
21. Al-Mousawi, S. M.; Moustafa, M. S.; Abdelhamid, I. A. *Curr. Org. Chem.* **2011**, *15*, 3503-3513.
22. Ghozlan, S. A. S.; Abdelmoniem, A. M.; Abdelhamid, I. A. *Curr. Org. Chem.* **2011**, *15*, 3098-3119.
23. Abdelhamid, I. A.; Darwish, E. S.; Nasra, M. A.; Abdel-Gallil, F. M.; Fleita, D. H. *Synthesis* **2010**, *2010*, 1107-1112.
24. Elnagdi, M. H.; Al-Awadi, N. A.; Abdelhamid, I. A. *Adv. Heterocycl. Chem.* **2009**, *97*, 1-43.
25. Abdelhamid, I. A.; Mohamed, M. H.; Abdelmoniem, A. M.; Ghozlan, S. A. S. *Tetrahedron* **2009**, *65*, 10069-10073.
26. Ghozlan, S. A. S.; Mohamed, M. H.; Abdelmoniem, A. M.; Abdelhamid, I. A. *Arkivoc* **2009**, *10*, 302-311.
27. Abdelhamid, I. A. *Synlett* **2009**, *2009*, 625-627.
28. Ghozlan, S. A. S.; Abdelhamid, I. A.; Hassaneen, H. M.; Elnagdi, M. H. *J. Heterocycl. Chem.* **2007**, *44*, 105-108.
29. Ghozlan, S. A. S.; Abdelhamid, I. A.; Elnagdi, M. H. *Arkivoc* **2006**, *13*, 147-157.
30. Ghozlan, S. A. S.; Mohamed, M. F.; Ahmed, A. G.; Shouman, S. A.; Attia, Y. M.; Abdelhamid, I. A. *Archiv. Pharm.* **2015**, *348*, 113-124.
31. Karimi-Jaberi, Z.; Takmilifard, Z. *Eur. Chem. Bull.* **2013**, *2*, 211-213.
32. Cui, B.; Wang, R. H.; Chen, L. Z.; Jin, Y.; Cui, B.; Wang, R. H.; Chen, L. Z.; Jin, Y.; Han G. F. *Synth. Commun.* **2011**, *41*, 1064-1070.
33. Lichitsky, B. V.; Ivanov, S. N.; Dudinov, A. A.; Woznesensky, S. A.; Krayushkin, M. M. *Russ. Chem. Bull.* **2001**, *50*, 2428-2432.