Simple and one-pot synthesis of new heterocyclic compounds in three-component reactions between isoquinoline or phenanthridine and acetylenic esters in the presence of N-heterocycles or 1,3-dicarbonyl compounds

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Abstract

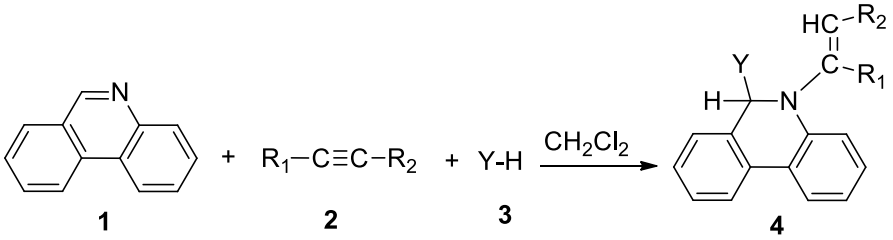
A new class of enamino esters has been isolated in excellent yields from the 1:1:1 addition reaction between phenanthridine or isoquinoline and acetylenic esters such as ethyl propiolate or dialkyl acetylenedicaboxylates in the presence of heterocyclic NH compounds (succinimide, indole, 2-methylindole, 2-benzoxazolinone, 6-chlorobenzoxazolinone, carbazole and 3,6-dibromocarbazole) or 1,3-dicarbonyl compounds like 1,3-dimethylbarbituric acid, acetylacetone and dibenzoylmethane.

Keywords: Enamino esters, phenanthridine, isoquinoline, ethyl propiolate, heterocyclic NH or 1,3-dicarbonyl compounds

Introduction

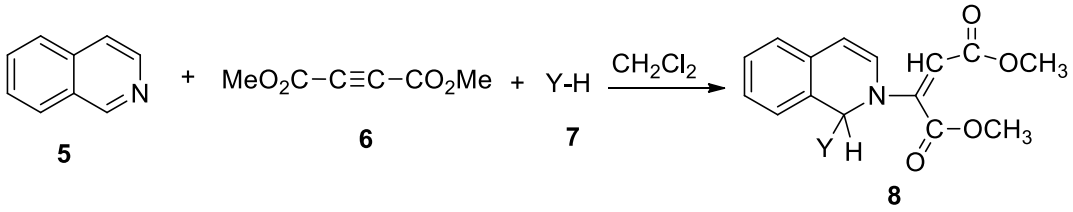
The development of simple synthetic routes for widely used organic compounds from readily available reagents is one of the major tasks in organic synthesis.[1] Phenanthridines are important core structures found in a variety of natural products and other biologically important molecules with a wide range of biological activities and applications,[2-10] including antibacterial, antiprotozoal, anticancer, antimicrobial, anti-inflammatory, antivirial, antioxidant[11-21] and also with applications as drugs,[8] DNA targeting agents,[22] dyes,[23] and probes.[24] Isoquinoline is also present in various natural products such as cryptaustoline and cryptowoline.[25] They are known to exhibit various biological activities[26-34] such as antileukaemic,[35] tubulin polymerization inhibitory[36] and anti-tumour activities.[37] As previously reported,[38] reaction between

phenanthridine and two mol equivalents of dimethyl acetylenedicarboxylate, leads to the formation of a new ring fused to the phenanthridine. In the current work, we now describe an efficient synthesis of a new class of enamino esters (see Scheme 1).



4(a-c): R_1 = H, R_2 = CO_2Et 4(d,e): R_1 = R_2 = CO_2Me

4(f,g): R_1 = R_2 = CO_2Et 4h: R_1 = R_2 = CO_2Bu^t



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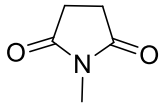
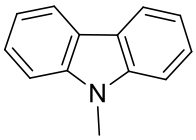
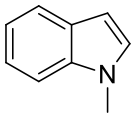
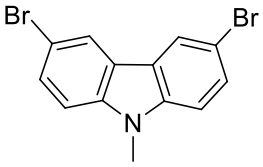
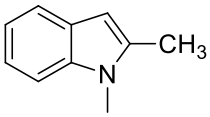
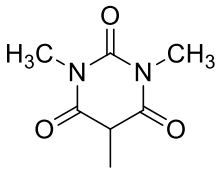
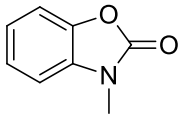
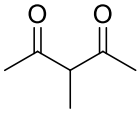
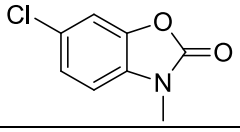
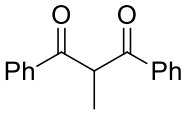
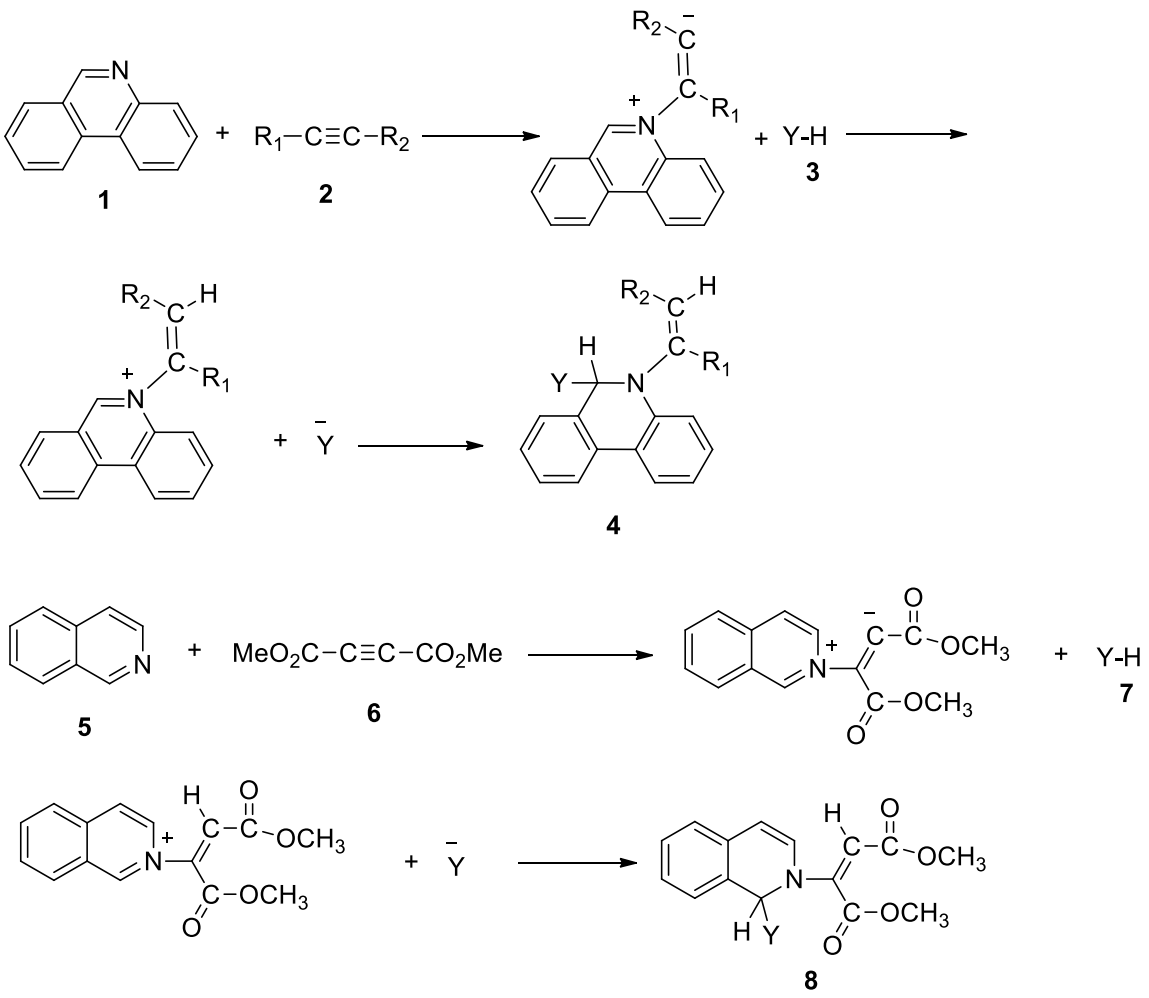
4a		E	92	4f		E	94
4b		E	93	4j		E	95
4c		E	92	4h		E	96
4d		E	94	4i		Z	93
4e		E	92	4j		Z	91

Scheme 1

Results and Discussion

An efficient synthesis of a new class of enamino esters from reaction between phenanthridine **1** or isoquinoline **5** and activated acetylenic esters **2** or **6** as a Michael acceptor[39-46] was undertaken in the presence of heterocyclic NH compounds (succinimide, indole and 2-methylindole, 2-benzoxazolinone, 6-chlorobenzoxazolinone, carbazole and 3,6-dibromocarbazole) or 1,3-dicarbonyl compounds such as 1,3-dimethylbarbituric acid, acetylacetone and dibenzoyl-methane, at ambient temperature. Reactions were carried out by first mixing the phenanthridine or isoquinoline and heterocyclic NH or 1,3-dicarbonyl compounds and then the acetylenic ester was added slowly. The reactions proceeded smoothly in CH_2Cl_2 and then the whole reaction mixture solidified into yellow solid within a few hours. The ^{1}H and ^{13}C NMR spectra of the crude products clearly indicated the formation of enamino esters **4a-h** and **8i,j**. No product other than **4a-h** and **8i,j** could be detected by NMR spectroscopy. The structures of compounds **4a-h** and **8i,j** were confirmed by elemental analyses, mass, IR, ^{1}H NMR and ^{13}C NMR spectra. The ^{1}H NMR spectrum of **4a** exhibited signals for the methyl (δ = 1.29, 3H, t, $^3J_{HH}$ = 7.2 Hz, OCH_2CH_3), methylene (δ = 4.19, 2H, q, $^3J_{HH}$ = 7.2 Hz, OCH_2CH_3), and olefinic (δ = 5.58 and 8.36, 2d, $^3J_{HH}$ = 13.6 Hz, C*H*=C*H*-OCH_2CH_3) protons, along with multiplets at δ = 7.13-8.09 ppm for the aromatic protons. The NC*H*N moieties at δ = 9.03-9.33 ppm in compounds **4a-e** are deshielded due to the anisotropic effect of a benzene ring of phenanthridine.[49] The ^{13}C NMR spectrum of **4a** showed 22 distinct resonances in agreement with the proposed structure. In addition, product **4a** displayed ^{13}C NMR resonances at δ 94.06 ppm, 115.84 and 120.72 ppm, respectively for the N*C*HN, N-CH=*C*H-$CO_2CH_2CH_3$, and N-*C*H=CH-$CO_2CH_2CH_3$ units. The carbonyl group resonances in the ^{13}C NMR spectra of **4a** appeared at δ = 174.78 and 177.16 ppm. The ^{1}H and ^{13}C NMR spectra of compounds **4b-h** and **8i,j** are similar to those of **4a.** Assignment of the configuration (*Z* or *E*) in compounds **4a-h** and **8i,j** was decided on the basis of the chemical shift of the olefinic proton.[34,47-48] With respect to the same employed conditions (effect of same solvent and temperature in our reactions) it seems that, the structural effect of reactants is an important factor for assignment of the configuration (*Z* or *E*) (see Scheme 2).

Briefly, we have developed a new method to access a novel class of heterocyclic derivatives. The present method has the advantage that, not only is the reaction performed under neutral conditions, but also the substances can be mixed without any activation or modifications. It seems that, this procedure is easy and simple approach for synthesis of heterocyclic derivatives.



Scheme 2

Experimental Section

General. Melting points and IR spectra of all compounds were measured on an Electrothermal 9100 apparatus and a Shimadzu IR-460 spectrometer, respectively. The ^{1}H, ^{13}C, and ^{31}P NMR spectra were obtained with a BRUKER DRX-500 AVANCE instrument using $CDCl_3$ as applied solvent and TMS as internal standard at 500.1, 125.8, and 202.4 MHz respectively. In addition, the mass spectra were recorded on a GCMS-QP5050A mass spectrometer operating at an ionization potential of 70 eV. Elemental analysis for C, H and N were performed using a Heraeus CHN-O-Rapid analyzer. Activated acetylenic esters, phenanthridine, isoquinoline, succinimide, indole, 2-methylindole, 2-benzoxazolinone, 6-chloro- benzoxazolinone, carbazole, 3,6-dibromocarbazole, 1,3-dimethylbarbituric acid, acetylacetone and dibenzoylmethane were purchased from Fluka, (Buchs, Switzerland) and used without further purification.

General synthetic procedure, exemplified by (*E*)-ethyl 3-(6-(2,5-dioxopyrrolidin-1-yl)phenanthridine-5(6*H*)-yl)acrylate 4a. To a magnetically stirred solution of phenanthridine (0.18 g, 1 mmol) and succinimide (0.09 g, 1 mmol) in CH_2Cl_2 (10 mL) was added, dropwise, a mixture of ethyl propiolate (1 mmol) in CH_2Cl_2 (5 mL) at -10 °C over 10 min. After a few hours stirring at ambient temperature, the whole reaction mixture solidified into a brown solid, the solvent was then removed under reduced pressure and product washed with cold diethyl ether (2×5 mL). Then the product was recrystallized from a mixture of acetonitrile and acetone.
Brown powder, yield 92%, 0.35 g mp 100-102 ºC, IR (ν_{max}, cm^{-1}): 1707 and 1773 (C=O). ^{1}H NMR (500.1 MHz, $CDCl_3$), δ_H 1.29 (3H, t, $^3J_{HH}$ = 7.2 Hz, OCH_2CH_3), 2.75 (4H, s, $2CH_2$), 4.19 (2H, q, $^3J_{HH}$ = 7.2 Hz, OCH_2CH_3), 5.85 (1H, d, $^3J_{HH}$ = 13.6 Hz, N-CH=C*H*-$CO_2CH_2CH_3$), 7.13-8.09 ($8H_{aro}$, m, 8CH phenanthridine), 8.60 (1H, d, $^3J_{HH}$ = 13.6 Hz, N-C*H*=CH-$CO_2CH_2CH_3$), 9.03 (1H, s, NCHN). ^{13}C NMR (125.8 MHz, $CDCl_3$), δ_C 13.38 (OCH_2CH_3), 26.87 (OCH_2CH_3), 28.51 ($2CH_2$), 94.06 (NCHN), 115.84 (1C, N-CH=*C*H-$CO_2CH_2CH_3$), 120.72 (1C, N-*C*H=CH-$CO_2CH_2CH_3$), 121.09, 122.06, 122.53, 125.68, 126.05, 126.41, 126.92, 127.67, 127.78, 128.65, 130.05 and 152.24 (12C, phenanthridine), 174.78 (C=O, ester), 177.16 (2C=O, succinimide). Anal. Calcd for $C_{22}H_{20}N_2O_4$ (376.16): C, 70.18; H, 5.36; N, 7.44%, Found: C, 70.21; H, 5.31; N, 7.60%.

Ethyl (*E*)-3-(6-(1*H*-indole-1-yl)phenanthridine-5(6*H*)-yl)acrylate 4b. Yellow powder, yield 93%, 0.37 g mp 138-140 ºC, IR (ν_{max}, cm^{-1}): 1718 (C=O). ^{1}H NMR (500.1 MHz, $CDCl_3$), δ_H 1.18 (3H, t, $^3J_{HH}$ = 7.1 Hz, OCH_2CH_3), 4.19 (2H, q, $^3J_{HH}$ = 7.1 HZ, OCH_2CH_3), 5.45 (1H, d, $^3J_{HH}$ = 16.6 HZ, N-CH=C*H*-$CO_2CH_2CH_3$), 6.25 (1H, d, $^3J_{HH}$ = 3.5 Hz, N-CH=C*H*, indole), 6.31 (1H, d, $^3J_{HH}$ 3.5 Hz, N-C*H*=CH, indole), 7.14-8.03 ($12H_{arom}$, m, 12CH), 8.30 (1H, d, $^3J_{HH}$ = 16.6 Hz, N-C*H*=CH-$CO_2CH_2CH_3$), 9.24 (1H, s, NCHN). ^{13}C NMR (125.8 MHz, $CDCl_3$), δ_C 13.43 (OCH_2CH_3), 25.71 (OCH_2CH_3), 63.76 (NCHN), 96.41 (1C, N-CH=*C*H-$CO_2CH_2CH_3$), 111.25, 113.30, 120.19 and 120.29 (4C, indole), 121.85, 122.56 and 122.53 (3C, phenanthridine), 123.26 and 124.30 (2C, indole), 125.66 (1C, N-*C*H=CH-$CO_2CH_2CH_3$), 125.68, 126.35 126.93,127.29, 127.78, 129.65 and 130.15 (7C, phenanthridine), 137.14 (1C, indole), 137.43 and 139.18 (2C, phenanthridine), 153.09 (1C, indole), 172.34 (C=O, ester). MS, m/z (%) = 364 (M-Et and H, 13), 278 ($C_{18}H_{16}NO_2$, 100), 204 (M-C_8H_6N, CO_2Et and H, 48), 179 ($C_{13}H_9N$, 60), 97 ($C_5H_5O_2$, 26). Anal. Calcd for $C_{26}H_{22}N_2O_2$ (394.17): C, 79.15; H, 5.62; N, 7.10%, Found: C, 78.98; H, 5.64; N, 7.18%.

Ethyl (*E*)-3-(6-(2-methyl-1*H*-indole-1-yl)phenanthridine-5(6*H*)-yl)acrylate 4c. Brown powder, yield 92 %, 0.38g ; mp 136-138 ºC, IR (ν_{max}, cm^{-1}): 1723 (C=O). ^{1}H NMR (500.1 MHz, $CDCl_3$), δH 1.25 (3H, t, $^3J_{HH}$ = 7.2 Hz, OCH_2CH_3), 2.39 (3H, s, CH_3), 4.18 (2H, q, $^3J_{HH}$ = 7.2 Hz, OCH_2CH_3), 5.40 (1H, d, $^3J_{HH}$= 13.3 Hz, N-CH=C*H*-$CO_2CH_2CH_3$), 6.22 (1H, s, indole), 7.08-8.63 ($12H_{aro}$, m, 12CH), 8.70 (1H, d, $^3J_{HH}$ = 13.3 Hz, N-C*H*=CH-$CO_2CH_2CH_3$), 9.30 (1H, NCHN). ^{13}C NMR (125.8 MHz, $CDCl_3$), δC 14.03 (OCH_2CH_3), 26.80 (OCH_2CH_3), 59.41 (NCHN), 97.66 (1C, N-CH=*C*H-$CO_2CH_2CH_3$), 110.18, 113.14, 119.12, 119.75 122.16 and 123.30 (6C, indole), 123.80 and 125.95 (2C, phenanthridine), 126.03 (N-*C*H=CH-$CO_2CH_2CH_3$), 126.81, 126.93, 127.47, 127.70, 129.92 and 131.11 (8C, phenanthridine), 135.18 (1C, indole),

137.23 and 138.10 (2C, phenanthridine), 152.43 (1C, indole), 174.64 (C=O, ester). MS, m/z (%) = 408 (M^+, 3), 379 (M-CH_2CH_3, 7), 335 (M-$CO_2CH_2CH_3$, 39), 179 ($C_{13}H_9N$, 37), 130 (C_9H_8N, 100). Anal. Calcd for $C_{27}H_{24}N_2O_2$ (408.19): C, 79.37; H, 5.93; N, 6.86 %, Found: C, 79.42; H, 6.02; N, 6.91 %.

Dimethyl 2-(6-(2-oxobenzo[*d*]oxazol-3(2*H*)-yl)phenanthridine-5(6*H*)-yl)fumarate 4d. Yellow powder, yield 94%, 0.43 g mp 112-114 ºC, IR (ν_{max}, cm^{-1}): 1722 and 1783 (C=O). ^{1}H NMR (500.1 MHz, $CDCl_3$), δH 3.71 and 3.88 (6H, 2s, 2OCH_3), 7.08 (1H, s, N-C=C*H*-CO_2CH_3), 7.12-8.63 (12H_{arom}, m, 12CH), 9.35 (1H, s, NCHN). ^{13}C NMR (125.8 MHz, $CDCl_3$), δ_C 52.69 and 53.70 (2OCH_3), 109.62 (NCHN), 110.41 (N-C=*C*H-CO_2CH_3), 109.07, 112.98 and 121.71 (3C, benzoxazole), 121.91, 122.33 and 123.40 (3C, phenanthridine), 123.82 (1C, benzoxazole), 124.06 (N-*C*=CH-CO_2CH_3), 124.17, 125.96, 127.79, 128.94, 129.00 and 129.19 (6C, phenanthridine), 142.23 (1C, benzoxazole), 154.32 (1C, benzoxazole, N-C=O), 165.96 and 162.73 (2C=O, ester). Anal. Calcd for $C_{26}H_{20}N_2O_6$ (456.16): C, 68.40; H, 4.42; N, 6.14%, Found: C, 68.49; H, 4.50; N, 6.23%.

Dimethyl 2-(6-(6-chloro-2-oxobenzo[*d*]oxazol-3(2*H*)-yl)phenanthridine-5(6*H*(-yl)fumarate 4e. Yellow powder, yield 92%, 0.45 g mp 126-128 ºC, IR (ν_{max}, cm^{-1}): 1712 and 1773 (C=O). ^{1}H NMR (500.1 MHz, $CDCl_3$), δ_H 3.69 and 3.85 (6H, 2s, 2OCH_3), 6.65 (1H, s, N-C=C*H*-CO_2CH_3), 7.09-8.55 (11H_{aro}, m, 11CH), 9.33 (1H, s, NCHN). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ_C 52.48 and 53.50 (2OCH_3), 76.69 (NCHN), 110.10 (N-C=*C*H-CO_2CH_3), 110.95, 114.23 and 122.70 (3C, benzoxazole), 122.91, 122.86 and 124.24 (3C, phenanthridine), 123.06 (1C, benzoxazole), 123.92 (N-*C*=CH-CO_2CH_3), 125.47, 127.42, 127.66, 128.13, 128.45, 128.92, 129.14 and 129.25 (7C, phenanthridine), 131.67 (1C, benzoxazole), 132.20 and 132.61 (2C, phenanthridine), 142.75 (1C, benzoxazole), 152.38 (1C, benzoxazole, N-C=O), 161.43 and 162.33 (2C=O, ester). Anal. Calcd for $C_{26}H_{19}ClN_2O_6$ (490.65): C, 63.59; H, 3.90; N, 5.71%, Found: C, 63.67; H, 3.98; N, 5.81%.

Diethyl 2-(6-(9*H*-carbazole-9-yl)phenanthridine-5(6*H*)-yl)fumarate 4f. Yellow powder, yield 94%, 0.49 g mp 121-123 ºC, IR (ν_{max}, cm^{-1}): 1716 and 1756 (C=O). ^{1}H NMR (500.1 MHz, $CDCl_3$), δ_H 0.75 and 0.98 (6H, 2t, $^3J_{HH}$ = 6.9 Hz, 2OCH_2CH_3), 3.75 and 3.86 (4H, 2m, 2ABX3 system, 2OCH_2CH_3), 6.30 (1H, s, N-C=C*H*-$CO_2CH_2CH_3$), 7.28 (1H, s, NCHN), 7.04-8.07 (16H_{arom}, m, 16CH). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ_C 14.11 and 14.84 (2OCH_2CH_3), 59.12 and 61.51 (2OCH_2CH_3), 69.18 (NCHN), 107.72 (1C, N-C=*C*H-$CO_2CH_2CH_3$), 114.75, 119.35, 121.18 and 121.89 (4C, phenanthridine), 122.07 and 122.69 (2C, carbazole), 124.84 (1C, N-*C*=CH-$CO_2CH_2CH_3$), 125.06 and 126.63 (2C, phenanthridine), 126.39 (1C, carbazole), 127.11, 129.28, 130.17, 131.40 and 132.17 (5C, phenanthridine), 134.56, 135.46, 136.20, 137.12, 138.71, 139.53, 139.60, 139.94 and 142.07 (9C, carbazole), 142.01 (1C, phenanthridine), 164.19 and 165.14 (2C=O, ester). MS, m/z (%) = 350 (M-carbazole, 100), 204 (M-carbazole and 2CO_2Et, 21), 179 ($C_{13}H_9N$, 38). Anal. Calcd for $C_{33}H_{28}N_2O_4$ (516.22): C, 76.71; H, 5.47; N, 5.42%, Found: C, 76.80; H, 5.52; N, 5.36%.

Diethyl 2-(6-(3,6-diboromo-9*H*-carbazole-9-yl)phenanthridine-5(6*H*)-yl)fumarate 4g.Yellow powder, yield 95%, 0.64 g mp 181-183 ºC, IR (ν_{max}, cm^{-1}): 1716 and 1756 (C=O). ^{1}H NMR

(500.1 MHz, $CDCl_3$), δ_H 0.82 and 1.03(6H, 2t, $^3J_{HH}$ = 7.1 Hz, 2OCH$_2$*CH$_3$*), 3.56 and 3.84 (4H, 2m, 2ABX3system, 2O*CH$_2$*CH$_3$), 6.38 (1H, s, N-C=C*H*-CO$_2$CH$_2$CH$_3$), 7.99-8.10 (14H$_{aro}$, m, 14CH), 8.13 (1H, s, NCHN). ^{13}C NMR (125.8 MHz, $CDCl_3$), 13.53 and 13.74 (2OCH$_2$*CH$_3$*), 60.96 and 61.91 (2O*CH$_2$*CH$_3$), 69.53 (NCHN), 112.23 (1C, N-C=*C*H-CO$_2$CH$_2$CH$_3$), 113.44, 115.73, 121.19 and 122.59 (5C, phenanthridine), 122.94, 123.09, 123.30, 123.69 and 123.86 (5C, carbazole), 124.41 (1C, N-*C*=CH-CO$_2$CH$_2$CH$_3$), 124.70, 125.25, 125.30 and 127.82 (4C, phenanthridine), 129.08, 129.18 and 129.32 (3C, carbazole), 130.38, 130.56 and 131.41 (3C, phenanthridine), 138.41, 140.90, 140.99 and 141.49 (4C, carbazole), 163.30 and 163.41 (2C=O, ester). Anal. Calcd for $C_{33}H_{26}Br_2N_2O_4$ (674.20): C, 58.74; H, 3.89; N, 4.15%, Found: C, 58.88; H, 3.92; N, 4.30%.

Di-tert-butyl 2- (6-(1,3-dimethyl-2,4,6-trioxo-hexahydropyrimidin-5-yl)phenanthridine-5(6*H*)-yl)fumarate 4h. Pink powder, yield 96%, 0.54 g mp 135-137 ºC, IR (ν_{max}, cm^{-1}): 1681 and 1740 (C=O). ^{1}H NMR (500.1 MHz, $CDCl_3$), δ_H 1.30 and 1.57 (18H, 2s, 2OC(*CH$_3$*)$_3$), 2.73 and 3.38 (6H, 2s, 2NCH$_3$), 4.69 (1H, d, $^3J_{HH}$ = 7.4 Hz, NC*H*CH), 5.01 (1H, d, $^3J_{HH}$ = 7.4 Hz, O=C-C*H*-C=O), 5.64 (1H, s, N-C=C*H*-CO$_2$C(CH$_3$)$_3$), 6.66-7.80 (8H$_{aro}$, m, 8CH).^{13}C NMR (125.8 MHz, $CDCl_3$) δ_C 26.71 and 26.99 (6C, 2CO$_2$C(*CH$_3$*)$_3$), 27.02 and 27.94 (2C, 2NCH$_3$), 65.79 (1C, N*C*HCH), 67.05 (1C, O=C-*C*H-C=O), 73.20 (1C, N-C=*C*H-CO$_2$C(CH$_3$)$_3$), 81.62 and 81.78 (2C, 2CO2*C*(CH$_3$)$_3$), 111.65, 116.09, 118.11, 121.00 and 121.06 (6C, phenanthridine), 124.14 (1C, N-*C*=CH-CO$_2$C(CH$_3$)$_3$), 124.39, 125.99, 128.79, 129.20, 129.67 and 143.55 (6C, phenanthridine),149.49 (1C, N-CO-N), 166.45 and 167.04 (2C, 2C-*C*O-C), 167.21 and 169.93 (2C, 2C=O, ester). Anal. Calcd for $C_{31}H_{35}N_3O_7$ (561.27): C, 66.28; H, 6.28; N, 7.48%, Found: C, 65.96; H, 6.37; N, 7.58%.

Dimethyl 2-(1-(2,4-dioxopentan-3-yl)isoquinolin-2(1*H*)-yl)maleate 8i. Brown powder, yield 93%, 0.35 g mp 141-143 ºC, IR (ν_{max}, cm^{-1}): 1620 and 1731 (C=O). ^{1}H NMR (500.1 MHz, $CDCl_3$), δH 1.79 and 2.23 (6H, 2s, 2CH$_3$), 3.60 and 3.80 (6H, 2s, 2OCH$_3$), 3.90 (1H, d, $^3J_{HH}$ = 10.3 Hz, O=C-C*H*-C=O), 5.24 (1H, s, N-C=C*H*-CO$_2$CH$_3$), 5.54 (1H, d, $^3J_{HH}$ =10.3 Hz, NC*H*CH), 6.12 (1H, d, $^3J_{HH}$ = 7.6 Hz, N-CH=C*H*, isoquinoline), 6.61(1H, d, $^3J_{HH}$ = 7.6 Hz, N-C*H*=CH, isoquinoline), 7.04-7.40 (4H$_{aro}$, m, 4CH, isoquinoline), ^{13}C NMR (125.8 MHz, $CDCl_3$) δ_C 51.79 and 53.73 (2OCH$_3$), 59.41 (N*C*HCH), 69.90 (O=C-*C*H-C=O), 95.23 (N-C=*C*H-CO$_2$CH$_3$), 123.14 (N- *C*=CH-CO$_2$CH$_3$), 124.78, 125.70, 126.17, 127.22, 127.94, 128.22, 128.76 and 130.11 (8C, isoquinoline), 163.90 and 165.13 (2C=O, ester), 198.82 and 199.61 (2C=O). MS, m/z (%) = 228 ($C_{14}H_{14}NO_2$, 66), 208 ($C_{13}H_6NO_2$, 47), 143 ($C_6H_7O_4$, 14), 129 (C_9H_7N, 46), 99 ($C_5H_7O_2$, 10), 59 (CO_2CH_3, 22). Anal. Calcd for $C_{20}H_{21}NO_6$ (371.16): C, 64.66; H, 5.70; N, 3.77%, Found: C, 64.71; H, 5.63; N, 3.81%.

Dimethyl 2-(1-(1,3-dioxo-1,3-diphenylpropan-2-yl)isoquinolin-2(1*H*)-yl)maleate 8j. Brown powder, yield 91 %, 0.45g mp 156-158 ºC, IR (ν_{max}, cm^{-1}): 1618 and 1736 (C=O). ^{1}H NMR (500.1 MHz, $CDCl_3$), δH 3.62 and 3.78 (6H, 2s, 2OCH$_3$), 5.75 (1H, d, $^3J_{HH}$ = 9.9 Hz, O=C-C*H*-C=O), 5.86 (1H, s, N-C=C*H*-CO$_2$CH$_3$), 6.03 (1H, d, $^3J_{HH}$ = 9.9 Hz, NC*H*CH), 6.19 (1H, d, $^3J_{HH}$ = 7.5 Hz, N-CH=C*H*, isoquinoline), 6.56 (1H, d, $^3J_{HH}$ = 7.5 Hz, N-C*H*=CH, isoquinoline), 7.10-8.45 (14H$_{aro}$, m, 14CH, isoquinoline and 2C$_6$H$_5$), ^{13}C NMR (125.8 MHz, $CDCl_3$) δ_C 51.27 and

52.81 (2OCH_3), 58.32 (N*C*HCH), 63.12 (O=C-*C*H-C=O), 97.11 (N-C=*C*H-CO_2CH_3), 124.09 (N-*C*=CH-CO_2CH_3), 125.90, 126.70 and126.84, (3C, isoquinoline), 127.16 (1C, 2C_6H_5), 128.22 and 128.67 (2C, isoquinoline), 128.80 and 128.84 (2C, 2C_6H_5), 128.76 and 128. 89 (2C, isoquinoline), 129.17, 129.94 and 130.28 (3C, 3C_6H_5), 130.64 (1C, isoquinoline), 164.75 and 166.80 (2C=O, ester), 191.81 and 191.90 (2C=O). MS, m/z %= 180 ($C_{12}H_6NO$, 12), 143 ($C_6H_7O_4$, 54), 129 (C_9H_7N, 100), 128 ($C_5H_4O_4$, 29), 102 (C_7H_2O, 51), 97 (C_4HO_3, 9), 76 (C_6H_4, 15), 59 (CO_2CH_3, 27). Anal. Calcd for $C_{30}H_{25}NO_6$ (495.20): C, 72.70; H, 5.09; N, 2.83 %, Found: C, 72.85; H, 4.94; N, 2.97 %.

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References

1. Laszlo, P. *Organic Reactions*: *Simplisity and Logic*; Wiley: New York, 1995.
2. Xie, C.; Zhang, Y.; Huang, Z.; Xu, P. *J. Org. Chem*. **2007**, *72*, 5431.
3. Ishikawa, T. *Med. Res. Rev*. **2001**, *21*, 61.
4. Nakanishi, T.; Suzuki, M.; Siamoto, A.; Kabasawa, T. *J. Nat. Prod*. **1999**, *621*, 864.
5. Sripada, L.; Teske, J. A.; Deiters, A. *Org. Biomol. Chem*. **2008**, *6*, 263.
6. Phillips, S. D.; Castle, R. N. *J. Heterocycl. Chem*. **1981**, *18*, 223.
7. Denny, W. A. *Curr. Med. Chem*. **2002**, *9*, 1655.
8. Lynch, M. A.; Duval, O.; Sukhanova, A.; Devy, J.; Mackay, S. P.; Waigh, R. D.; Nabiev, I. *Bioorg. Med. Chem. Lett***. 2001**, *11*, 2643.
9. Janin, Y. L.; Croisy, A.; Riou, J. F.; Bisagni, E. *J. Med. Chem*. **1993**, *36*, 3686.
10. Atwell, G. L.; Baguley, B. C.; Denny, W. A. *J. Med. Chem*. **1998**, *31*, 774.
11. Luedtke, N. W.; Liu, Q.; Tor, Y. *Bioorg. Med. Chem*. **2003**, *11*, 5235.
12. Nishiwaki, H.; Miura, M.; Imai, K.; Ohno, R.; Kawashima, K. *Cancer. Res*. **1974**, *34*, 2699.
13. Guntaka, R. V.; Mahy, B. W.; Bishop, J. M.; Varmus, H. E. *Nature*. **1975**, *253*, 507.
14. Nakanishi, T.; Suzuki, M.; Mashiba, A.; Ishikawa, K.; Yokotsuka, T. *J. Org. Chem*. **1998**, *63*, 4235.
15. Stermitz, F. R.; Larson, K. A.; Kim, D. K. *J. Med. Chem*. **1973**, *16*, 939.
16. Osornio, Y. M.; Miranda, L. D. *Rev. Soc. Quim. Mex*. **2004**, *48*, 288.
17. Pettit, G. R.; Gaddamidi, V.; Goswami, A.; Cragg, G. M. *J. Nat. Prod*. **1984**, *47*, 796.
18. 18.Harayama, T.; Akamatsu, H.; Okamura, K.; Miyagoe, T.; Akiyama, T.; Abe, H.; Takeuchi, Y. *J. Chem. Soc., Perkin Trans. 1* **2001**, 523.
19. Vavreckova, C.; Gawlik, I.; Muller, K. *Planta. Med*. **1996**, *62*, 397.

20. Schmeller, T.; Latz-Bruning, B.; Wink, M. *Phytochemistry* **1997**, *44*, 257.
21. 21.Vrba, J.; Hrbac, J.; Ulrichova, J.; Modriansky, M. *Chemico-Biological Interaction* **2004**, *147*, 35.
22. 22. Whittaker, J.; Mcfadyen, W. D.; Baguley, B. C.; Murray, V. *Anticancer Drug Des*. **2001**, *16*, 81.
23. 23. Alba, F. J.; Bermudez, A.; Daban, J. R. *Electrophoresis* **2001**, *22*, 399.
24. 24. Mullins, S. T.; Sammes, P. G.; West, R. M. Yahioglu, G. *J. Chem. Soc., Perkin Trans*. *1* **1996**, 75.
25. 25. Ewing, J.; Hughes, G.; Ritchie, E.; Taylor, W. C. *Nature* **1952**, *169*, 618.
26. 26. Yadav, J. S.; Subba Reddy, B. V.; Yadav, N. N.; Gupta, M. K. *Tetrahedron Lett*. **2008**, *49*, 2815.
27. 27. Yavari, I.; Ghazanfarpour-Darijani, M.; Sabbaghan, M.; Hossaini, Z. *Tetrahedron Lett*. **2007**, *48*, 3749.
28. Hadda, T. B.; Rahima, B.; Kerbal, A.; Bennani, B.; Al Houari, G.; Baba, B. F.; Akkurt, M.; Demailly, G.; Benazza, M. *Arkivoc*. **2008**, *(ii)*, 1.
29. Orito, K.; Harada, R.; Uchiito, S.; Tokuda, M. *Org. Lett*. **2000**, *2*, 1799.
30. Yavari, I.; Hossaini, Z.; Sabbaghan, M. Ghazanfarpour-Darijani, M. *Monatsh. Chem*. **2007**, *138*, 677.
31. Alizadeh, A.; Zohreh, N. *Synthesis* **2008**, 429.
32. Terzidis, M. A.; Tsoleridis, C. A.; Stephanidou-Stephanatou, J. *Synlett* **2009**, *2*, 229.
33. Diaz, J. L.; Miguel. M.; Lavilla, R. *J. Org. Chem*. **2004**, *69*, 3550.
34. Nassiri, M.; Maghsoodlou, M. T.; Heydari, R.; Habibi-Khorassani, S. M. *Mol. Divers*. **2008**, *12*, 111.
35. Anderson. W. K.; Heider, A. R.; Raju, N.; Yucht, J. A. *J. Med. Chem*. **1988**, *31*, 2097.
36. Goldbrunner, M.; Loidl, G.; Polossek, T.; Mannschreck, A.; Von Angerer, E. *J. Med. Chem*. **1997**, *40*, 3524.
37. Ambros, R.; Von Angerer, S.; Wiegrebe, W. *Arch. Pharm*. **1988**, *321*, 481.
38. Acheson, R. M.; Elmore, N. F. *Adv. Heterocycl. Chem*. **1978**, *23*, 263.
39. Kalantari, M.; Islami, M. R.; Hasani, Z.; Saidi, K. *Arkivoc* **2006**, (*x*), 55.
40. Islami, M. R.; Mollazehi, F.; Sheibani, H. *Arkivoc* **2005**, (*x*), 25.
41. Hassani, Z.; Islami, M. R.; Sheibani, H.; Kalantari, M.; Saidi, K. *Arkivoc* **2006**, (*i*), 89.
42. Maghsoodlou, M. T.; Habibi-Khorassani, S. M.; Rofouei, M. K.; Adhamdoust, S. R.; Nassiri, M. *Arkivoc* **2006**, (*xii*), 138.
43. Nair, V.; Pattoorpadi Babu, B.; Varghese, V.; Sinu, C. R.; Rajan Paul, R.; Anabha, E. R.; Suresh, E. *Tetrahedron Lett*. **2009**, *50*, 3716.
44. Nair, V.; Ramachandran Sreekanth, A.; Pillai Abhilash, N.; Thankappan Nair Biju, A.; Varma, L.; Viji, S, Mathew, S. *Arkivoc* **2005**, *(xi)*, 178.
45. Terzidis, M. A.; Tsoleridis, C. A.; Stephanidou-Stephanatou, J. *Synlett* **2009**, *2*, 229.
46. Kazemian, M. A.; Nassiri, M.; Maghsoodlou, M. T.; Habibi-Khorassani, S. M.; Vasheghani-Farahani, F. *Arkivoc* **2008**, (*xvii*), 173.

47. Eliel, E.; Wilen, S. H. *Stereochemistry of Organic Compounds*. Wiley: New York, p 570.
48. Yavari, I.; Nasiri, F.; Djahaniani, H. *Phosphorus, Sulfur and Silicon* **2003**, *178*, 2627.
49. Silverstein, R. M.; Webester, F. X.; Kiemle, D. J. *Spectrometric Identification of Organic Compounds*. John Wiley and Sons, Editor, Rebbic Brennan, pp 141-143, 2006, Seventh Edition.