Synthesis of Novel Fused Tricyclic Quinolones: 4*a*,5-Dihydro-1*H*-[1,2,4]triazino[1,6-*a*]quinoline-2,4,6(3*H*)-triones

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A versatile methodology to build the 1*H*-[1,2,4]triazino[1,6-*a*]quinoline-2,4,6(3*H*)-trione structure from methyl 6-fluoro4-oxo-1,4-dihydro-2-quinolinecarboxylate was developed. The method involves an *N*-amination followed by condensation of an aroyl isocyanate to form an alpha semicarbazidocarboxylate that readily cyclizes to the fused [1,2,4]triazino ring under ammonia/ethanol condition. Also, the reactivity of the [1,2,4]triazino ring thus obtained was studied.

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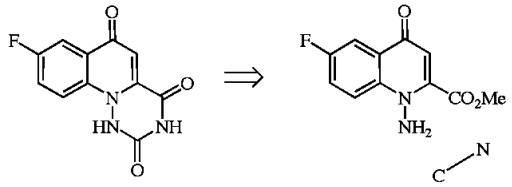
Among the different quinolones carboxylic families of antibacterial agents there is a series of potent tricyclic and tetracyclic compounds containing a three- or four-atom bridge connecting the N1-C8 vicinal positions of quinolones [1]. These series include oxolinic acid [2], tioxacin [3], flumequin [4], ofloxacin [5], and other different tricyclic quinolones, which contain a three-atom bridge connecting the C2 to either the N1 [6a-c] or the C3 [6d].

So, we are interested in preparing novel fused tricyclic quinolones that are non carboxylic at the C3 position, and contain a four-atom bridge connecting the N1 with the C2 incorporated into the [1,2,4]triazino ring. In this paper, we report first the synthesis of the 8-fluoro-1*H*-[1,2,4]-triazino[1,6-*a*]quinoline-2,4,6(3*H*)-trione, followed by the study of the reactivity of the [1,2,4]triazino-3,5-dione ring obtained.

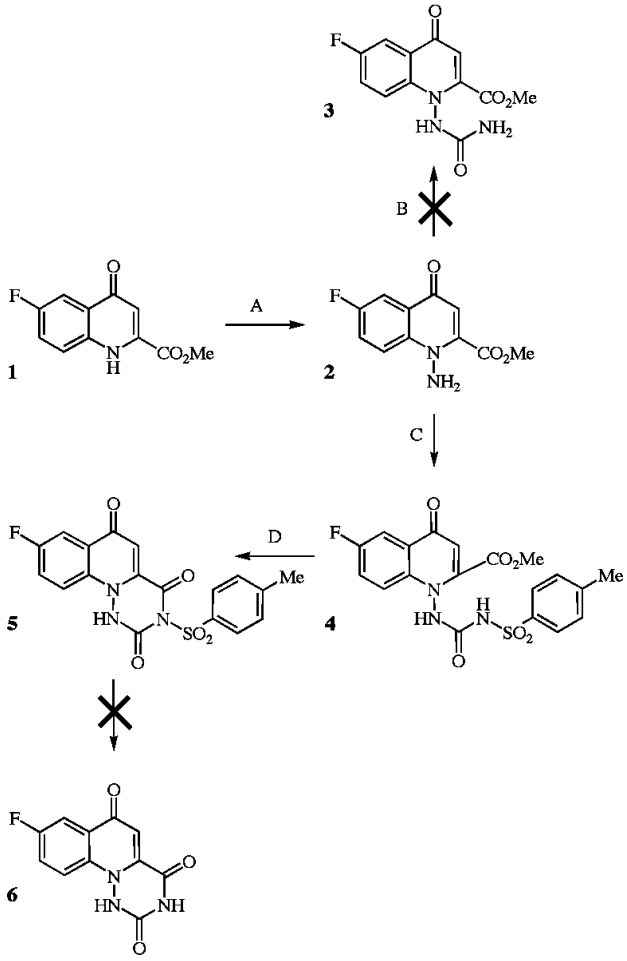
Historically, the [1,2,4]triazino-3,5-dione ring has been obtained from a [4+2] combination [7] between alpha hydrazino carboxylates and imidates [8], or by cyclization of alpha semicarbazido carboxylic acids derivatives [9]. Therefore, we chose to use methyl 1-amino-6-fluoro-4-oxo-1,4-dihydro-2-quinolinecarboxylate as the starting material. Our approach [4+2] is shown in Scheme 1, where the C-N moiety, we envisaged the synthesis of a semicarbazide, allows for an intramolecular cyclization to generate the triazino ring.

Scheme 1



The key to the successful synthesis lies in the preparation of the methyl 1-amino-6-fluoro-4-oxo-1,4-dihydro-2-quinoline carboxylate. The starting synthon **1** was obtained by condensation dimethyl acetylenedicarboxylate with 4-fluoro aniline, followed by a cyclization in diphenylether at reflux, as previously described [10]. The intermediate, methyl 1-amino-6-fluoro-4-oxo-1,4-dihydro-2-quinolinecarboxylate **2**, was obtained through a high yield *N*-amination reaction at low temperature *via* the use of *O*-mesitylenesulfonylhydroxylamine (MSH) [11].

Scheme 2



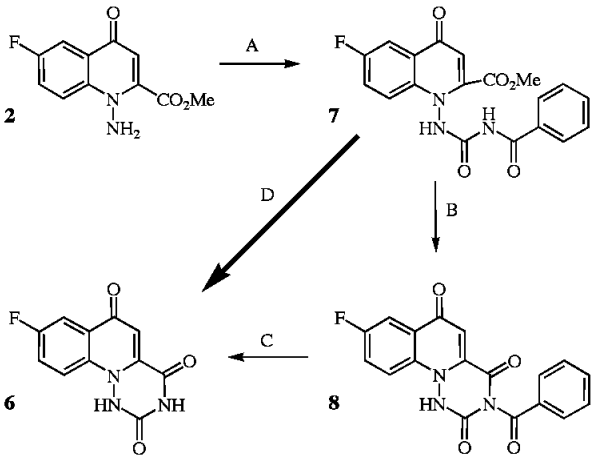
A) DMF, K_2CO_3, MSH, -10/0°C, 73%; B) KNCO, H_2O, 8 *N* HCl; C) $MeC_6H_4SO_2NCO$, DMF, 25°C, 73%; D) DMF, MeONa, 65°C, 76%.

Our initial attempts to obtain the semicarbazide moiety using potassium isocyanate under aqueous acidic conditions [12] resulted in failure, the starting material **2** being recovered unchanged (Scheme 2). As an alternative route, we envisaged the formation of an *N*-protected semicarbazide by a nucleophilic addition of the *N*-amino compound **2** onto an isocyanate, the last step of the synthesis being a *N*-deprotection. As the *para*-toluene sulfonyl isocyanate is commercially available, we expected that the sulfonamide bond would be easy to deprotect. Thus, compound **2**, when treated with the *para*-toluene sulfonyl isocyanate in DMF readily gave **4** in 73% yield. This reaction is exothermic. The triazino ring of **5** was formed by intramolecular cyclization using commercially available sodium methoxide in DMF (Scheme 2).

However, all our attempts to effect *N*-desulfonylation [13] did not take place: as example, heating in solvents such as ethanol or 1-butanol resulted in degradation. Reductive conditions such as tributyltin hydride [14] or naphthalene-sodium complex [15] result in deprotection but also bring about the nitrogen-nitrogen bond.

Another protective group was envisaged: the benzoyl moiety. To this end the synthesis of the benzoyl isocyanate was achieved from benzamide using oxalyl chloride [16].

Scheme 3



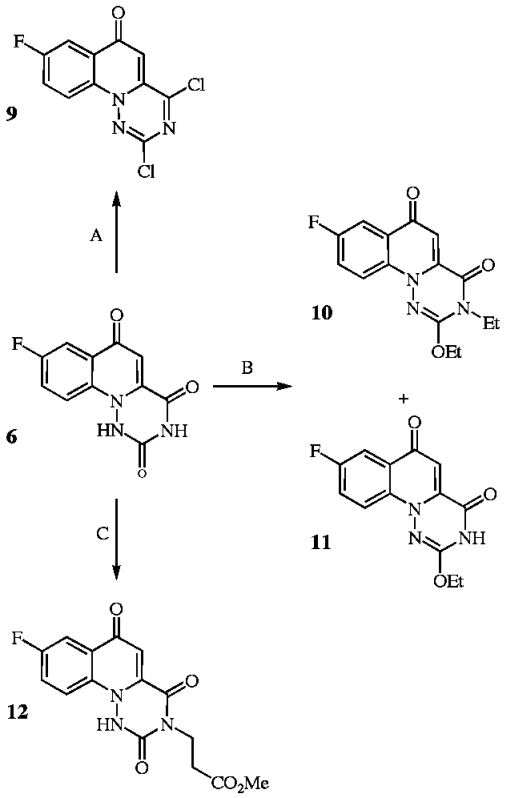
A) benzoyl isocyanate, DMF, 25°C, 71%; B) DMF, MeONa, 65°C, 61%; C) EtOH, 16 *N* NH_4OH, 25°C, 37%; D) EtOH, 16 *N* NH_4OH, 25°C, 77%.

Nucleophilic addition of **2**, with this isocyanate, followed by intramolecular cyclization of the resulting adduct readily afforded the *N*-protected tricyclic compound **8**, with an overall yield of 43% (Scheme 3). Debenzoylation of **8** with aqueous 16 *N* ammonia and ethanol afforded the desired compound **6** but in only poor yields (37%). After optimization of this step we achieving the cyclization and the deprotection in one pot from **7** using the same conditions (aqueous 16 *N* ammonia and ethanol) in excellent yield (77%) (Scheme 3).

In order to assess the reactivity of the [1,2,4]triazino moiety, different reactions were envisaged. Chloration [17] using phosphorus oxychloride as reactant and solvent, readily gave the dichloro compound **9** in 95% yield (Scheme 4). In the proton magnetic resonance spectrum, we observed a chemical shift of the H5 signal at low field (6.61 ppm to 8.54 ppm), and the mass spectrum confirmed the presence of two chloro atoms with peaks m/z 284 $[M]^+$ (100%), m/z 286 $[M+2]^+$ (64%) and m/z 288 $[M+4]^+$ (10%).

Standard alkylation of **6** in the presence of sodium hydride and iodoethane gave a mixture of *N*- and *O*-alkylated products **10** and **11** in 19% and 78% yield, respectively. This reaction revealed that a competitive alkylation takes place due to the prototropic equilibrium shown in Scheme 5.

Scheme 4

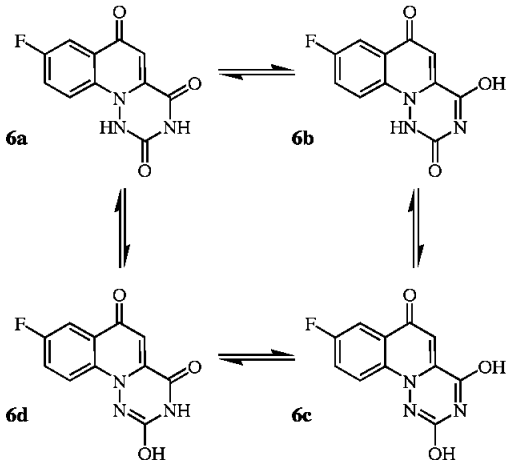


A) $POCl_3$, reflux, 30 min, 95%; B) (**7**), DMF, NaH, EtI, 25°C, 19 and 78%; C) DMF, triton B, methyl acrylate, 100°C, 67%.

On the other hand, a Michaël addition with methyl acrylate in presence of triton B at 100 °C led to the selective introduction of the methyl propanoate group onto the nitrogen atom N3. Different magnetic resonance experiments

such as proton, carbon, NOESy and HMQC, confirmed the three structures **10**, **11** and **12**.

Scheme 5



At the same time, a molecular modeling study was performed. The four prototropic forms were modeled and optimized with SYBYL (v.6.4) [18] *via* MOPAC [19], using AM1. Two other methods, *ab initio*, were also used in order to find the stability of each form (Spartan and Games). The results in Table 1 showed, without ambiguity, that **6a** and **6d** are the most stable forms from an energetic standpoint and that the nitrogen atom N3 is more electronegative than N1 in both forms.

Table 1

	MOPAC (AM1)		3-21G*	Spartan 3-21G*	Games
	Energie (Kcal)	Charge N_1	Charge N_3	Energie (Hartree)	Energie (Hartree)
6a	-45.47	-0.22	-0.36	-902.3705	-902.3680
6b	-29.05	-0.27	-0.26	-902.3330	-902.3322
6c	-32.40	-0.19	-0.21	-902.3374	-902.3373
6d	-46.07	-0.15	-0.33	-902.3656	-902.3654

So this molecular modeling study corroborated the reactivity that we observed for the alkylation of compound **6**.

In summary, we have synthesized a new class of fused tricyclic quinolone that contain a four-atom bridge connecting the N1 with the C2 incorporated into the triazino ring. The route required 5 steps from commercially available arylamines with an overall yield of 33%. We have selectively alkylated the nitrogen atom N3 by a Michaël addition whereas a standard alkylation gave a mixture of *N*- and *O*-alkylated product and *O*-alkylated product. This reactivity offers routes to a wide variety of analogues in order to perform some structural modifications within the framework of our SAR studies. Further work including biological activity and other reactions are under way in our laboratory.

EXPERIMENTAL

Melting points (uncorrected) were determined on a Köfler apparatus. Infrared (ir) spectra were recorded on a Perkin-Elmer Paragon FT-IR 1000 spectrophotometer with 4 cm^{-1} resolution, only the most significant ir absorptions are given. ^1H nmr spectra were recorded at 250 MHz and ^{13}C nmr spectra were recorded at 62.89 MHz on a Brucker AM-250 MHz instrument. Chemical shifts are expressed in parts per million (ppm). Mass spectra were recorded on a Perkin-Elmer SCIEZ API 3000 spectrometer (ion spray).

Methyl 1-Amino-6-fluoro-4-oxo-1,4-dihydro-2-quinolinecarboxylate (**2**).

To a solution of **1** (3 g, 14 mmol) dissolved in 27 ml of DMF with 4.7 g (35 mmol) of potassium carbonate, 1 g of MSH was added every quarter of an hour, until all of the precursor disappeared. The temperature was maintained between –10/0 °C. The mixture was poured into 500 ml of ice cold water. The precipitate so formed was then collected by filtration, washed and dried in a steam room at 100 °C to give **2** as a white solid (73%), mp 224 °C; ir (KBr): 3351 (NH_2), 1735, 1608 (C=O) cm^{-1}; ^1H nmr (250 MHz, DMSO-d_6): δ 3.88 (s, 3, OCH_3), 6.13 (s, 1, H3), 6.39 (s, 2, N*H*$_2$), 7.73-7.8 (m, 2, H5, H7), 7.93 (dd, 1, $J_{8,F}$ = 4.0 Hz, $J_{8,7}$ = 10.0 Hz, H8); ^{13}C nmr (62.89 MHz, DMSO-d_6): δ 55.70 (OCH_3), 108.06 (C3), 111.93 (d, $J_{C,F}$ = 22.64 Hz, C5), 122.79 (d, $J_{C,F}$ = 8.17 Hz, C8), 123.66 (d, $J_{C,F}$ = 25.15 Hz, C7), 129.84 (Cq), 141.64 (Cq), 50.65 (Cq), 161.53 (d, $J_{C,F}$ = 243.38 Hz, C6), 165.55 (C=O), 177.65 (C=O); HRMS (EI^+) 236.0455 (M^+; calc. for $C_{11}H_9FN_2O_3$, 236.0219).

Anal. Calcd. for $C_{11}H_9FN_2O_3$: C, 55.94; H, 3.84; N, 11.86. Found: C, 55.82; H, 3.86; N, 11.71.

Methyl 6-Fluoro-1-[({[(4-methylphenyl) sulfonyl]amino}-carbonyl)amino]-4-oxo-1,4-dihydro-2-quinolinecarboxylate (**4**).

Under nitrogen, to a solution of **2** (3 g, 12.71 mmol) in 25 ml of freshly distilled DMF, was added dropwise 2.6 ml (16.52 mmol) of *para*-toluene sulfonyl isocyanate. After 6 hours at room temperature, the reaction mixture was evaporated and the crude product was purified by column chromatography eluting with 9:1 CH_2Cl_2/MeOH to afford a pale yellow solid (73%), mp 208-210 °C; ir (KBr): 3230 (NH), 1737, 1698, 1633 (C=O) cm^{-1}; ^1H nmr (250 MHz, DMSO-d_6): δ 2.47 (s, 3, C*H*$_3$), 3.70 (s, 3, OC*H*$_3$), 6.47 (s, 1, H3), 7.38-7.42 (m, 3, H7, phenyl), 7.66-7.78 (m, 4, H5, H8, phenyl), 10.52 (s, 1, NH), 12.06 (s, 1, NH); ^{13}C nmr (62.89 MHz, DMSO-d_6): δ 19.48 (CH_3), 51.81 (OCH_3), 108.13 (d, $J_{C,F}$ = 20.12 Hz, C5), 108.29 (C3), 117.45 (d, $J_{C,F}$ = 7.79 Hz, C8), 120.63 (d, $J_{C,F}$ = 25.15 Hz, C7), 125.81 (2C, phenyl), 127.73 (2C, phenyl), 127.97 (Cq), 135.24 (Cq), 136.89 (Cq), 142.54 (Cq), 142.76 (Cq), 149.63 (C=O), 157.54 (d, $J_{C,F}$ = 244.64 Hz, C6), 159.76 (C=O), 173.99 (C=O); HRMS (EI^+) 433.1730 (M^+; calc. for $C_{19}H_{16}FN_3O_6S$, 433.2163).

8-Fluoro-3-[(4-methylphenyl)sulfonyl]-1*H*-[1,2,4]triazino[1,6-*a*]-quinoline-2,4,6(3*H*)-trione (**5**).

Under nitrogen, to a solution of **4** (4.5 g, 10 mmol) in 20 ml of freshly distilled DMF, was added 1.43 g (25 mmol) of sodium

methoxide. After 4 hours of heating at 76 °C, the reaction mixture was added to 50 ml of cold water. Some traces of **4** were removed by filtration under millipore. The filtrate was acidified with cold aqueous 3 *N* HCl. The precipitate was collected by filtration, washed with cold water, diethyl ether and dried under vacuum to give **5** as a pale yellow solid (76%), mp > 264 °C. The compound can be recrystallised from water; ir (KBr): 3293 (NH), 1723, 1614 (C=O) cm^{-1}; ^1H nmr (250 MHz, DMSO-d_6): δ 2.27 (s, 3, CH_3), 6.12 (s, 1, H5), 7.26 (s, 1, NH), 7.33 (d, 2, J = 8.0 Hz, phenyl), 7.67 (d, 2, J = 8.0 Hz, phenyl), 7.69-7.75 (m, 2, H7, H9), 7.98 (dd, 1, $J_{10,F}$ = 4.26 Hz, $J_{10,9}$ = 9.44 Hz, H10); ^{13}C nmr (62.89 MHz, DMSO-d_6): δ 21.84 (CH_3), 106.25 (C5), 110.16 (d, $J_{C,F}$ = 22.64 Hz, C7), 121.16 (d, $J_{C,F}$ = 8.17 Hz, C10), 121.94 (d, $J_{C,F}$ = 25.15 Hz, C9), 126.38 (Cq), 126.56 (2C, phenyl), 127.97 (Cq), 130.24 (2C, phenyl), 139.93 (Cq), 142,36 (Cq), 142.80 (Cq), 149.76 (C=O), 159.83 (d, $J_{C,F}$ = 243.38 Hz, C8), 164.73 (C=O), 175.80 (C=O); HRMS (EI^+) 401.2144 (M^+; calc. for $C_{18}H_{12}FN_3O_5S$, 401.1743).

Anal. Calcd. for $C_{18}H_{12}FN_3O_5S$: C, 53.86; H, 3.01; N, 10.47. Found: C, 53.91; H, 2.92; N, 10.51.

Methyl 1-{[(Benzoylamino)carbonyl]amino}-6-fluoro-4-oxo-1,4-dihydro-2-quinolinecarboxylate (**7**).

Under nitrogen, to a solution of **2** (10 g, 42.37 mmol) in 85 ml of freshly distilled DMF, was added dropwise 8 g (55.08 mmol) of benzoyl isocyanate. After 6 hours at room temperature, the reaction mixture was evaporated and the crude product was purified by column chromatography eluting with 9:1 CH_2Cl_2/MeOH to afford a pale yellow solid (71 %), mp 108-110 °C; ir (KBr): 3240 (NH), 1739, 1721, 1681, 1618 (C=O) cm^{-1}; ^1H nmr (250 MHz, DMSO-d_6): δ 3.81 (s, 3, OCH_3), 6.51 (s, 1, H3), 7.50-7.56 (m, 3, phenyl), 7.65 (ddd, 1, $J_{7,F}$ = 9.5 Hz, $J_{7,5}$ = 3.0 Hz, $J_{7,8}$ = 9.0 Hz, H7), 7.77 (dd, 1, $J_{5,F}$ = 9.0 Hz, $J_{5,7}$ = 3.0 Hz, H5), 7.8 (dd, 1, $J_{8,7}$ = 9.0 Hz, $J_{8,F}$ = 5.0 Hz, H8), 8.01-8.05 (m, 2, phenyl), 11.35 (s, 1, NH), 11.46 (s, 1, NH); ^{13}C nmr (62.89 MHz, DMSO-d_6): δ 54.38 (OCH_3), 110.3 (d, $J_{C,F}$ = 22.64 Hz, C5), 111.15 (C3), 122.37 (d, $J_{C,F}$ = 8.17 Hz, C8), 124.62 (d, $J_{C,F}$ = 25.15 Hz, C7), 129.29 (Cq), 130.91 (2C, phenyl), 131.07 (2C, phenyl), 134.31 (phenyl), 135.67 (Cq), 141.10 (Cq), 145.94 (Cq), 155.77 (C=O), 161.56 (d, $J_{C,F}$ = 244.64 Hz, C6), 163.87 (C=O), 169.97 (C=O), 178.16 (C=O); HRMS (EI^+) 383.1735 (M^+; calc. for $C_{19}H_{14}FN_3O_5$, 383.1352).

3-Benzoyl-8-fluoro-1*H*-[1,2,4]triazino[1,6-*a*]quinoline-2,4,6(3*H*)-trione (**8**).

Under nitrogen, to a solution of **7** (2.9 g, 7.57 mmol) in 20 ml of freshly distilled DMF, was added 1.1 g (18.92 mmol) of sodium methoxide. After 4 hours of heating at 76 °C, the reaction mixture was added to 50 ml of cold water. Some traces of **7** were removed by filtration under millipore. The filtrate was acidified with cold aqueous 3*N* HCl. The precipitate was collected by filtration, washed with cold water, diethyl ether and dried under vacuum to give **8** as a pale yellow solid (61%), mp 220 °C; ir (KBr): 3274 (NH), 1730, 1701, 1609, 1566 (C=O) cm^{-1}; ^1H nmr (250 MHz, DMSO-d_6): δ 6.48 (s, 1, H5), 7.53-7.63 (m, 3, phenyl), 7.69 (dd, 1, $J_{7,F}$ = 10.5 Hz, $J_{7,9}$ = 3.5 Hz, H7), 7.82 (ddd, 1, $J_{9,7}$ = 3.5 Hz, $J_{9,10}$ = 9.5 Hz, $J_{9,F}$ = 9.0 Hz, H9), 7.96 (dd, 1, $J_{10,9}$ = 9.5 Hz, $J_{10,F}$ = 5.0 Hz, H10), 8.03-8.10 (m, 2, phenyl), 11.37 (s, 1, NH); ^{13}C nmr (62.89 MHz, DMSO-d_6): δ 108.93 (d, $J_{C,F}$ = 25.15 Hz, C7), 109.36 (C5), 119.48 (d, $J_{C,F}$ = 8.17 Hz, C10), 121.68 (d, $J_{C,F}$ = 25.15 Hz, C9), 126.45 (Cq), 128.16 (4C, phenyl), 131.64 (phenyl), 132.96 (Cq), 138.41 (Cq), 144.79 (Cq), 153.11 (C=O), 154.97 (d, $J_{C,F}$ = 233.95 Hz, C8), 162.28 (C=O), 167.28 (C=O), 175.60 (C=O); HRMS (EI^+) 351.0580 (M^+; calc. for $C_{18}H_{10}FN_3O_4$, 351.0931).

Anal. Calcd. for $C_{18}H_{10}FN_3O_4$: C, 61.54; H, 2.87; N, 11.96. Found: C, 61.33; H, 2.91; N, 12.11.

8-Fluoro-1*H*-[1,2,4]triazino[1,6-*a*]quinoline-2,4,6(3*H*)-trione (**6**).

To a solution of **7** (23 g, 60.05 mmol) in 300 ml of absolute ethanol, was added 915 ml of aqueous 16 *N* ammonia. After 48 hours at room temperature, the precipitate was collected by filtration, washed with diethyl ether and dried under vacuum to afford a pale yellow solid (77%), mp >264 °C; The compound can be recrystallised from water; ir (KBr): 3125, 3079 (NH), 1675, 1598, 1566 (C=O) cm^{-1}; uv: (water): λ max 226 nm (ε 25118-31622); λ max 242 nm (ε 31622-39810); λ max 275 nm (ε 19952-25118); λ max 410 nm (ε 10000-12589); ^1H nmr (250 MHz, DMSO-d_6): δ 6.61 (s, 1, H5), 7.1 (s, 1, NH), 7.63 (ddd, 1, $J_{9,7}$ = 3.0 Hz, $J_{9,F}$ = 9.0 Hz, $J_{9,10}$ = 9.0 Hz, H9), 7.81 (dd, 1, $J_{7,9}$ = 3.0 Hz, $J_{7,F}$ = 9.0 Hz, H7), 8.70 (dd, 1, $J_{10,F}$ = 5.0 Hz, $J_{10,9}$ = 9.0 Hz, H10), 10.73 (s, 1, NH); ^{13}C nmr (62.89 MHz, DMSO-d_6): δ 103.96 (C5), 110.61 (d, $J_{C,F}$ = 22.64 Hz, C7), 121.91 (d, $J_{C,F}$ = 25.15 Hz, C9), 124.35 (d, $J_{C,F}$ = 7.54 Hz, C10), 131.86 (Cq), 136.03 (Cq), 137.11 (Cq), 153.63 (C=O), 161.47 (d, $J_{C,F}$ = 251.37 Hz, C8), 161.14 (C=O), 173.15 (C=O); HRMS (EI^+) 247.0404 (M^+; calc. for $C_{11}H_6FN_3O_3$, 247.0393).

Anal. Calcd. for $C_{11}H_6FN_30_3$: C, 53.45; H, 2.45; N, 17.00. Found: C, 53.68; H, 2.36; N, 16.92.

2,4-Dichloro-8-fluoro-6*H*-[1,2,4]triazino-[1,6-*a*]quinolin-6-one (**9**).

Compound **6** (1 g, 4.05 mmol) in 10 ml of phosphorus oxychloride was heated under reflux during half an hour. After evaporation, the crude product was poured into 500 ml of ice cold water. The precipitate formed was then collected by filtration, washed with water until pH 6, dried under vacuum to afford a yellow solid (95%), mp 218-220 °C. The compound can be recrystallised from DMF; ir (KBr): 1656 (C=N), 1620 (C=O) cm^{-1}; uv: (ethanol): λ max 256 nm (ε 39810); λ max 286 nm (ε 19952-25118); λ max 388 nm (ε = 12589-15848); m/z = 284 $[M]^+$ (100%); 286 $[M+2]^+$ (64%); 288 $[M+4]^+$ (10%); ^1H nmr (250 MHz, DMSO-d_6): δ 8.15 (ddd, 1, $J_{9,10}$ = 10.0 Hz, $J_{9,F}$ = 9.0 Hz, $J_{9,7}$ = 3.0 Hz, H9), 8,28 (dd, 1, $J_{7,9}$ = 3.0 Hz, $J_{7,F}$ = 9.0 Hz, H7), 8.54 (s, 1, H5), 9.10 (dd, 1, $J_{10,9}$ = 10.0 Hz, $J_{10,F}$ = 5.0 Hz, H10); ^{13}C nmr (62.89 MHz, DMSO-d_6): δ 111.20 (d, $J_{C,F}$ = 25.53 Hz, C7), 120.73 (C5), 124.22 (d, $J_{C,F}$ = 9.94 Hz, C10), 125.02 (d, $J_{C,F}$ = 25.97 Hz, C9), 126.27 (Cq), 129.89 (Cq), 134.50 (Cq), 135.74 (Cq), 143.29 (Cq), 162.79 (C=O), 163.79 (d, $J_{C,F}$ = 254.26 Hz, C8); HRMS (EI^+) 284.0481 (M^+; calc. for $C_{11}H_4Cl_2FN_3O$, 284.0765).

Anal. Calcd. for $C_{11}H_4Cl_2FN_3O$: C, 46.51; H, 1.42; N, 14.79. Found: C, 46.47; H, 1.36; N, 14.85.

Standard Alkylation Procedure.

To a solution of **6** (300 mg, 1.21 mmol) in 20 ml of freshly distilled DMF, was added 48 mg (1.21 mmol) of sodium hydride. When hydrogen emission ceased, 0.12 ml of ethyl iodide was added dropwise. After 24 hours at room temperature, the reaction mixture was neutralized with aqueous ammonium chloride and evaporated under vacuum. The residue was adsorbed onto silica gel and chromatographed by eluting with 9:1 and 8:2

CH_2Cl_2/MeOH to give two yellow solids **10** and **11**, respectively with 19% and 78% yields.

2-Ethoxy-3-ethyl-8-fluoro-3*H*-[1,2,4]-triazino[1,6-*a*]quinoline-4,6-dione (**10**).

This compound has mp 190-192 °C; R_f (9:1 CH_2Cl_2/MeOH) 0.87; ir (KBr): 1710, 1655 (C=O) cm^{-1}; ^1H nmr (250 MHz, DMSO-d_6): δ 1.19 (t, 3, J = 7.0 Hz, NCH_2CH_3), 1.42 (t, 3, J = 7.0 Hz, OCH_2CH_3), 3.92 (q, 2, J = 7.0 Hz, NCH_2CH_3), 4.53 (q, 2, J = 7.0 Hz, OCH_2CH_3), 6.66 (s, 1, H5), 7.77 (ddd, 1, $J_{9,10}$ = 10.0 Hz, $J_{9,F}$ = 8.0 Hz, $J_{9,7}$ = 3.0 Hz, H9), 7.83 (dd, 1, $J_{7,9}$ = 3.0 Hz, $J_{7,F}$ = 9.0 Hz, H7), 8.50 (dd, 1, $J_{10,9}$ = 10.0 Hz, $J_{10,F}$ = 5.0 Hz, H10); ^{13}C nmr (62.89 MHz, DMSO-d_6): δ 12.84 (NCH_2CH_3), 13.81 (OCH_2CH_3), 36.82 (NCH_2CH_3), 65.61 (OCH_2CH_3), 103.69 (C5), 109.70 (d, $J_{C,F}$ = 25.53 Hz, C7), 120.58 (Cq), 122.22 (d, $J_{C,F}$ = 25.97 Hz, C9), 127.65 (Cq), 133.45 (d, $J_{C,F}$ = 9.94 Hz, C10), 135.02 (Cq), 147.29 (Cq), 155.79 (C=O), 166.94 (d, $J_{C,F}$ = 245.26 Hz, C8), 173.34 (C=O); HRMS (EI^+) 303.0990 (M^+; calc. for $C_{15}H_{14}FN_3O_3$, 303.1019).

Anal. Calcd. for $C_{13}H_{10}FN_3O_3$: C, 56.73; H, 3,66; N, 15.27. Found: C, 56.68; H, 3.52; N, 15.34.

2-Ethoxy-8-fluoro-3*H*-[1,2,4]triazino[1,6-*a*]quinoline-4,6-dione (**11**).

This compound has mp >264 °C; R_f (9:1 CH_2Cl_2/MeOH) 0.10; ir (KBr): 3400 (NH), 1721, 1650 (C=O) cm^{-1}; ^1H nmr (250 MHz, DMSO-d_6): δ 1.29 (t, 3, J = 7.0 Hz, OCH_2CH_3), 4.53 (q, 2, J = 7.0 Hz, OCH_2CH_3), 6.61 (s, 1, H5), 7.65 (ddd, 1, $J_{9,10}$ = 9.0 Hz, $J_{9,F}$ = 8.0 Hz, $J_{9,7}$ = 3.0 Hz, H9), 7.82 (dd, 1, $J_{7,9}$ = 3.0 Hz, $J_{7,F}$ = 9.0 Hz, H7), 8.57 (dd, 1, $J_{10,9}$ = 9.0 Hz, $J_{10,F}$ = 5.0 Hz, H10); ^{13}C nmr (62.89 MHz, DMSO-d_6): δ 14.37 (OCH_2CH_3), 62.01 (OCH_2CH_3), 101.69 (C5), 108.92 (d, $J_{C,F}$ = 22.07 Hz, C7), 120.24 (d, $J_{C,F}$ = 25.34 Hz, C9), 120.62 (Cq), 120.76 (Cq), 125.70 (Cq), 128.89 (Cq), 135.26 (d, $J_{C,F}$ = 12.82 Hz, C10), 150.04 (C=O), 158.80 (d, $J_{C,F}$ = 238.98 Hz, C8), 172.75 (C=O); HRMS (EI^+) 275.0705 (M^+; calc. for $C_{13}H_{10}FN_3O_3$, 275.0706).

Anal. Calcd. for $C_{13}H_{10}FN_3O_3$: C, 56.73; H, 3,66; N, 15.27. Found: C, 56.56; H, 3.70; N, 15.57.

Methyl 3-(8-Fluoro-2,4,6-trioxo-1,2,4,6-tetrahydro-3*H*-[1,2,4]triazino[1,6-*a*]-quinolin-3-yl)propanoate (**12**).

To a solution of **6** (214 mg, 0.87 mmol) in 20 ml of DMF and 20 ml of methyl acrylate heated at 100 °C, was added a catalytic amount of triton B. After 3 hours, the reaction mixture was evaporated under vacuum. The residue was poured into an ice cold aqueous 3 *N* HCl. The precipitate was collected by filtration, washed with water until pH 6, with diethyl ether then dried under vacuum. Purification by column chromatography (8:2 CH_2Cl_2/MeOH) gave a pale yellow solid (67%), mp >264 °C; ir (KBr): 3368 (NH), 1753, 1691, 1618 (C=O) cm^{-1}; ^1H nmr(250 MHz, DMSO-d_6): δ 2.65 (t, 2, J = 7.8 Hz, CH_2), 3.61 (s, 3, OCH_3), 4.18 (t, 2, J = 7.8 Hz, NCH_2), 7.46 (s, 1, H5), 7.92-8.02 (m, 2, H7, H9), 9.01 (dd, 1, $J_{10,F}$ = 4.4 Hz, $J_{10,9}$ = 9.4 Hz, H10); ^{13}C nmr, DEPT 135 (62.89 MHz, DMSO-d_6): δ 31.45 (CH_2), 36.06 (NCH_2), 51.45 (OCH_3); HRMS (EI^+) 333.0887 (M^+; calc. for $C_{15}H_{12}FN_3O_5$, 333.0872).

Anal. Calcd. for $C_{14}H_{10}FN_3O_5$: C, 52.67; H, 3.16; N, 13.16. Found: C, 52.73; H, 3.09; N, 12.98.

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