SYNTHESIS OF PYRANO[2,3-*h*]QUINOLINES AS TRICYCLIC ACRONYCINE ANALOGUES

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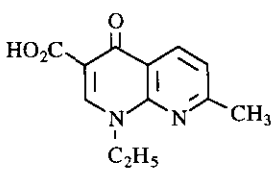
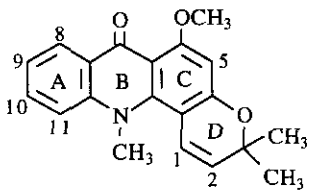
Abstract - Preparation of pyrano[2,3-*h*]quinolines containing either a carboxylic acid function or an aminated chain on various positions was achieved. In the course of this investigation, an unusual behaviour of the 4-functionalized chloro- and methoxypyrano[2,3-*h*]quinoline derivatives towards nucleophiles has been characterized.

Since the synthesis of nalidixic acid [1] in 1962, various new quinolonecarboxylic acids have been synthesized and studied as antibacterial [2] and chemotherapeutic agents.[3] In the search of new analogues of acronycine (**1**) [4] and in order to assess the importance of the A aromatic ring of this poorly water soluble compound, we have prepared pyrano[2,3-*h*]quinoline derivatives containing either a carboxylic acid function or an aminated side chain on their 3,4- or/and 5-position (Figure 1).
Such salifiable functional groups fixed on this ring system were supposed to improve the water solubility of corresponding compounds and hence their bioavailability.



Nalidixic Acid



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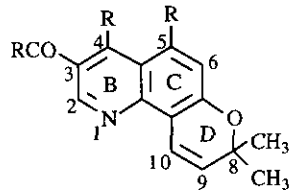
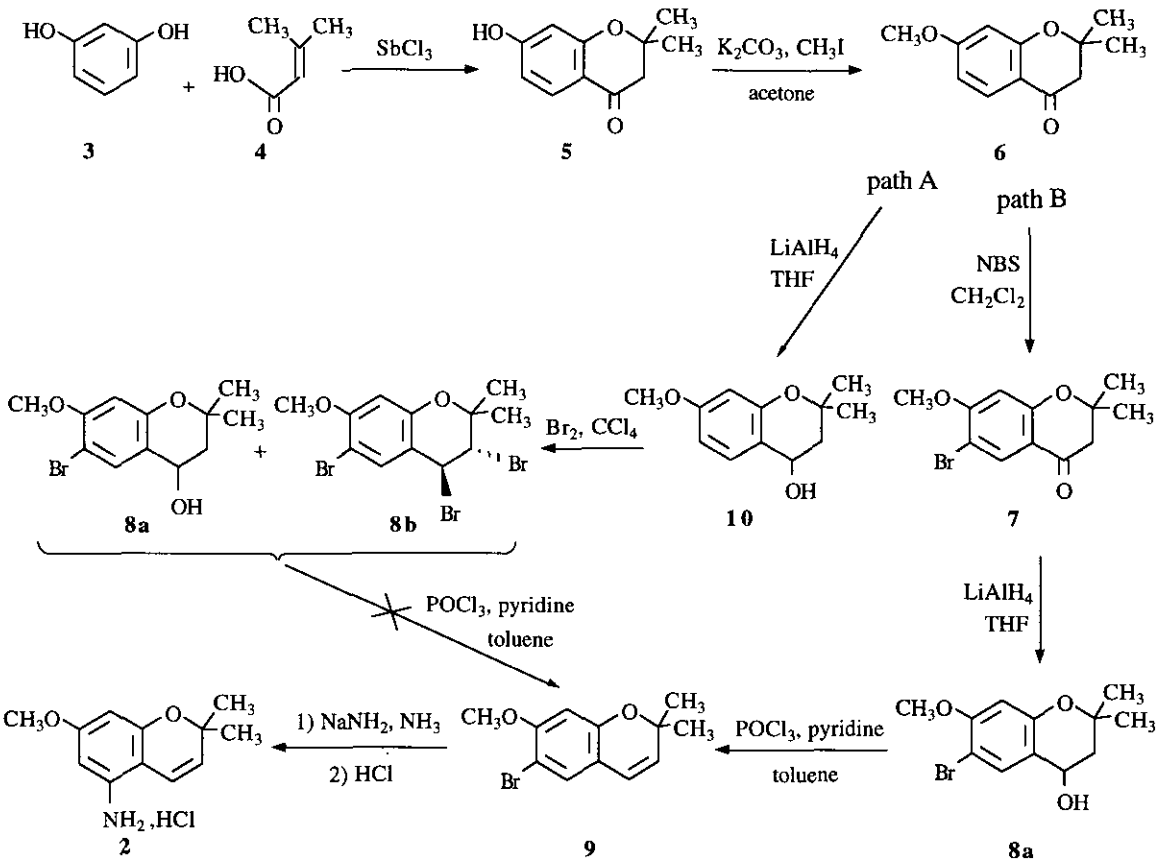


Pyrano[2,3-*h*]quinoline

Figure 1

RESULTS AND DISCUSSION

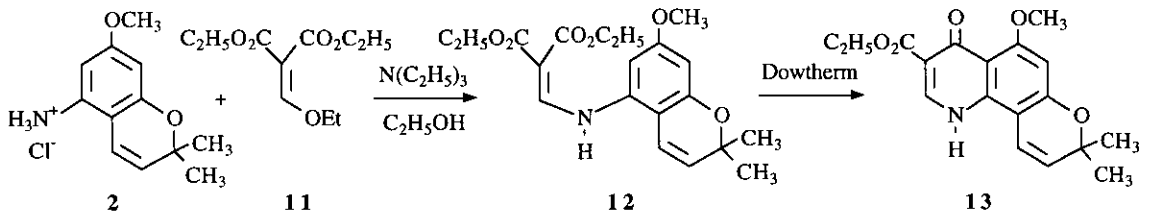
Synthesis of the pyrano[2,3-*h*]quinoline ring system required an access to aminochromene (**2**). Following a reported procedure,[5] we prepared (Scheme 1) chromanone (**6**) from resorcinol (**3**) and 3,3-dimethylacrylic acid (**4**). Reduction of **6** led to compound (**10**) in good yields but contrary to what it was described,[5] in our hands, bromination of **10** with bromine in carbon tetrachloride gave a mixture of mono and tribrominated compounds (**8a**) and (**8b**). Several attempts to separate these two compounds, either at this stage or after an elimination reaction, failed (Scheme 1, path A).



Scheme 1

Thus, we devised a new and selective access to the target chromene (**9**) starting from chromanone (**6**). Bromination reaction using *N*-bromosuccinimide in methylene chloride at room temperature turned out to give the monobrominated compound (**7**) in almost quantitative yield. From this intermediate, reduction and dehydration, followed by the amination reaction yielded the required and pure aminochromene (**2**) with improved yields with respect to those reported [5] (Scheme 1, path B). Moreover, it can be pointed out that although compounds (**8a**) and (**9**) have been described as oils,[5] samples obtained according to the new procedure are solids and melt at 94°C and 59-60°C respectively.

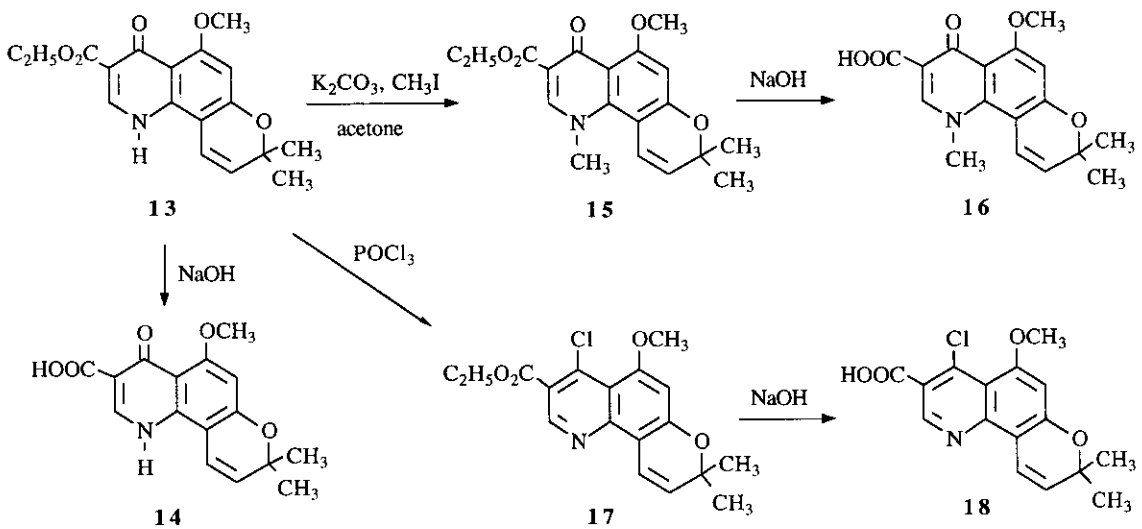
Aminochromene (**2**) was then condensed with diethyl ethoxymethylenemalonate (**11**) to afford chromene (**12**). Thermal cyclisation of **12** in boiling Dowtherm A (diphenyl / diphenyl ether 26.5:73.5) yielded ethyl (5-methoxy-8,8-dimethyl-4-oxo-4,8-dihydro-*1H*-pyrano[2,3-*h*]quinolin-3-yl)carboxylate (**13**) (Scheme 2).



Scheme 2

Further transformations of this ester (**13**) were performed in order to obtain various pyranoquinolinecarboxylic acid derivatives. Thus :

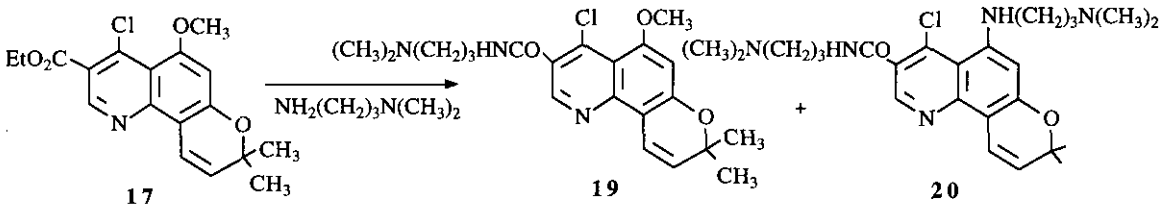
- Saponification by 1M sodium hydroxide gave the desired carboxylic acid (**14**).
- Methylation using the K_2CO_3/CH_3I/acetone mixture mainly yielded the *N*-methylated derivative (**15**) which was saponified with 1M sodium hydroxide to give *N*-methylpyrano[2,3-*h*]quinolonecarboxylic acid (**16**).
- Chlorination using boiling $POCl_3$ led to the chlorinated ethyl ester (**17**) which was also hydrolysed with 1M sodium hydroxide to give the corresponding carboxylic acid (**18**) (Scheme 3).



Scheme 3

In order to prepare more watersoluble derivatives, we decided to introduce an aminoalkylamino chain at the 4 position of pyrano[2,3-*h*]quinolines. Pyranoquinoline (**17**) was then treated with 3-dimethylaminopropylamine at various temperatures. Surprisingly, substitution which took place did not concern the 4-chlorine atom but other functions of this molecule (Scheme 4).

Moreover, according to the reaction temperature, products (**19**) and (**20**) were obtained in various proportions. They were both substituted on their carboxylic acid function and in the case of **20**, the methoxy group at the 5-position was replaced too. The higher the reaction temperature was set, the higher the yield of **20** was. This reactivity of the 3- and 5-positions of compound (**17**) was unexpected.

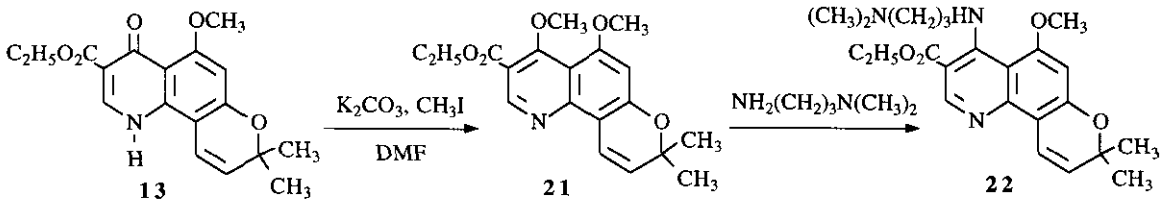


20°C, 2 days	62%	28%
40°C, 43 h	25%	44%
70°C, 23 h	-	69%

Scheme 4

Calculations using the Mopac software (Sybill-Tripos, AM1 method) were then performed with the aim to better understand this problem. Results show that partial charge on the 4- position bearing a chlorine atom was located to 0.073, whereas the partial charges on 5-position and on the ester carbon atom were at 0.1678 and 0.3612 respectively (Table 1), thus providing evidence that there is a good agreement between theoretical and experimental results.

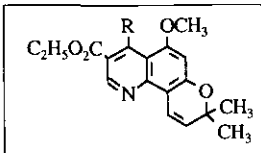
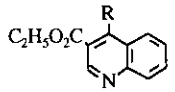
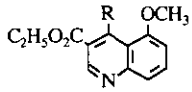
Following these results and in order to prepare the 4-aminosubstituted derivative (**22**), we decided to change the substituent on the 4-position. Methylation of ester (**13**) in new experimental conditions using the K_2CO_3/CH_3I mixture in DMF as solvent gave a separable mixture of the *O*-methylated compound (**21**) (63%) beside the *N*-methyl derivative (**15**) already described (11%). Then amination of compound (**21**) with 3-dimethylaminopropylamine at only 0°C gave 90% of the 4-substituted compound (**22**) (Scheme 5).



Scheme 5

Once again, this difference of reactivity was confirmed by the calculation of partial charges of compound (**21**) which appeared to be 0.2004 on the 4-position for **21** markedly more important than for **17** (0.0073) and approximately the same than for the 5-position (0.1699) and the ester carbon atom (0.3587) (Table 1). Partial charges of compounds (**17**) and (**21**) and quinoline derivatives as well, were also calculated. It appears that a methoxy group on the 5-position of the quinoline ring is crucial for the effect on the partial charge repartition (Table 1).

This research was performed in order to prepare simplified tricyclic analogues of acronycine (**1**) designed by removing of the A ring of this naturally occurring compound. Such new derivatives with various

R	**17** Cl	**21** OCH_3	Cl	OCH_3	Cl	OCH_3
CO	0.3612	0.3587	0.3577	0.3563	0.3599	0.3573
C4	0.073	0.2004	0.0439	0.1686	0.0630	0.1909
C5	0.1678	0.1699	-0.1017	-0.0982	0.1368	0.1384

Table 1. Partial charges of pyranoquinoline and quinoline derivatives

hydrophilic functions were actually obtained and studied.

Whereas all compounds were tested *in vitro* against L1210 murine lymphocytic leukemia cells, only compounds (**16**, **17**, **20** and **22**) displayed a moderate cytotoxicity with IC_{50} of 24, 19, 3 and 4 μM respectively. Compared to the IC_{50} of acronycine which is 22 μM, these values were promising.

However, the most surprising but interesting results concern the differentiation of the electronic effects of a chlorine atom and a methoxy group at the 4-position. Thus, the nucleophilic displacement of a chlorine atom on this 4-position can not be achieved whereas a methoxy group on the same position was easily substituted. Partial charge calculation are fully in agreement with these experimental results and suggest an enhancement effect of the neighboring methoxy group.

EXPERIMENTAL

Melting points were measured with an electrothermal apparatus using capillary tubes and are uncorrected. ^1H Nmr spectra were obtained in $CDCl_3$ or DMSO-d_6 using an AC-200 MHz Bruker spectrometer and ^{13}C nmr spectra were obtained in $CDCl_3$ or DMSO-d_6 using an AC-300 MHz Bruker apparatus. Chemical shifts are reported in ppm relative to deuteriated solvent as internal standard (^1H: 7.27 for $CDCl_3$ and 2.54 for DMSO-d_6;^{13}C: 77.2 for $CDCl_3$ and 39.7 for DMSO-d_6) and all coupling constants (*J*) are given in Hz. The mass spectra were recorded on AEI.MS-50 (MS-EI) or AEI.MS-9 (MS-CI) spectrometers and, as elemental analyses, they were performed in ICSN/CNRS, Gif sur Yvette, France.

5-Amino-7-methoxy-2,2-dimethyl-*2H*-chromene hydrochloride (2)

To a mixture containing sodium amide (6.7 g, 172 mmol) in liq. ammonia (220 ml) at -78° C, bromochromene (**9**) (20 g, 74.3 mmol) was added gradually. This solid had to be added by small fractions by means of a plastic tube connected to an Erlenmeyer flask. The complete dispersion of **9** allowed thus a significant increase of yield. The mixture was stirred at -78° C for 20 h and then ammonium chloride (13.7 g, 256 mmol) was added. After evaporation of ammonia at room temperature, the solid was taken up in toluene and water.The organic layer was dried ($MgSO_4$) and concentrated. The residue was then solubilized

in ether (120 ml) and poured gently to a solution of ether (300ml) saturated by gaseous hydrochloric acid. The hydrochloride (**2**) (11.7 g, 65%) was obtained as nonhygroscopic crystals, mp > 280°C ; ^{1}H nmr (DMSO-d_6) δ 6.56 (d, 1H, *J*=9.9 Hz, H-4), 6.37 (d, 1H, *J*=2.4 Hz, H-6), 6.24 (d, 1H, *J*=2.4 Hz, H-8), 5.69 (d, 1H, *J*= 9.9 Hz, H-3), 3.74 (s, 3H, OCH_3), 1.39 (s, 6H, 2-$(CH_3)_2$); Anal. Calcd for $C_{12}H_{16}NO_2Cl$: C, 59.65; H, 6.67; N, 5.79. Found : C, 60.04; H, 6.74; N, 5.63.

7-Hydroxy-2,2-dimethylchroman-4-one (5)

This compound was prepared according to a described procedure [6] and recrystallized from ethanol-water as orange crystals, mp 170°C (lit.,[6] mp 169°C).

7-Methoxy-2,2-dimethylchroman-4-one (6)

This compound was prepared as described [5] and recrystallized from hexane as orange crystals, mp 79°C (lit.,[5] mp 81-82°C).

6-Bromo-7-methoxy-2,2-dimethylchroman-4-one (7)

To a solution containing chromanone (**6**) (16.4 g, 7.9 mmol) in methylene chloride (150 ml), *N*-bromosuccinimide (16.5 g, 9.3 mmol) was added gradually. The mixture was stirred at room temperature for 24 h and then washed with water. The organic layer was dried ($MgSO_4$) and concentrated. The expected product was recrystallized from hexane to obtain compound (**7**) (22.1 g, 98 %) as white needles, mp 111-112 °C; ^{1}H nmr ($CDCl_3$) δ 8.01 (s, 1H, H-5), 6.39 (s, 1H, H-8), 3.89 (s, 3H, OCH_3), 2.65 (s, 2H, CH_2), 1.43 (s, 6H, 2-$(CH_3)_2$); Anal. Calcd for $C_{12}H_{13}O_3Br$: C, 50.55; H, 4.60; Br, 28.02. Found : C, 50.55; H, 4.83; Br, 27.95.

6-Bromo-4-hydroxy-7-methoxy-2,2-dimethylchromane (8a)

To a mixture containing $LiAlH_4$ (1.72 g, 45.3 mmol) in THF (40 ml), a solution of **7** (10 g, 35 mmol) in THF (50 ml) was added dropwise. After complete addition, the mixture was refluxed for 1 h, cooled and then ethyl acetate (8 ml) and water (2 ml) were added. The solids were filtered, the organic layer was dried ($MgSO_4$) and evaporated to dryness under reduced pressure. After recrystallization from hexane, the expected product (**8a**) (10.1 g, 95 %) was obtained as white crystals, mp 94 °C (lit.,[5] oil); ^{1}H nmr ($CDCl_3$) δ 7.57 (s, 1H, H-5), 6.34 (s, 1H, H-8), 4.77 (dd, 1H, *J*=8.4, 6 Hz, H-4), 3.82 (s, 3H, OCH_3), 2.14 (dd, 1H, *J*=13.5, 6 Hz, H-3 eq), 1.81 (dd, 1H, *J*=13.5, 8.4 Hz, H-3 ax), 1.42 (s, 3H, CH_3), 1.30 (s, 3H, CH_3).

6-Bromo-7-methoxy-2,2-dimethyl-*2H*-chromene (9)

To a solution containing toluene (2.1 ml) and dry pyridine (1.3 ml, 16.8mmol), $POCl_3$ (0.24 ml, 2.6 mmol) and the preceding pure alcohol (**8**) (600 mg, 2.09 mmol) were added. After being refluxed for 2 h, the mixture was poured onto ice-water (10 ml) and extracted with ether. The organic layer was washed successively with 1M aqueous hydrochloric acid, a saturated aqueous sodium hydrogen carbonate solution and brine, and then dried ($MgSO_4$) and concentrated. The expected product was recrystallized from methanol to obtain product (**9**) (540 mg, 96 %) as white needles, mp 59-60 °C (lit.,[5] oil); ^{1}H nmr ($CDCl_3$) δ 7.10 (s, 1H, H-5), 6.38 (s, 1H, H-8), 6.18 (d, 1H, *J*=10 Hz, H-4), 5.46 (d, 1H, *J*=10 Hz, H-3), 3.82 (s, 3H, OCH_3), 1.40 (s, 6H, 2-$(CH_3)_2$); Anal. Calcd for $C_{12}H_{13}O_2Br$: C, 53.55; H, 4.87; Br, 29.69. Found : C, 53.56; H, 4.88; Br, 29.76.

4-Hydroxy-7-methoxy-2,2-dimethylchromane (10)

To a mixture containing $LiAlH_4$ (17.4 g, 0.46 mol) in dry THF (395 ml), a solution of **6** (72.6 g, 0.35 mol) in 395 ml of dry THF was added dropwise. After complete addition, the mixture was refluxed for 15 min, cooled and then ethyl acetate (80 ml) and water (20 ml) were added. The solids were filtered, the organic layer was dried ($MgSO_4$) and evaporated on a rotatory evaporator. The expected product (**10**) (71 g, 97 %) was obtained as a white oil; ^1H nmr ($CDCl_3$) δ 7.27 (d, 1H, *J*=8.5 Hz, H-5), 6.46 (dd, 1H, *J*=8.5, 2.5 Hz, H-6), 6.29 (d, 1H, *J*=2.5 Hz, H-8), 4.70 (dd, 1H, *J*=8.4, 6.1 Hz, H-4), 3.70 (s, 3H, OCH_3), 2.48 (br s, 1H, OH), 2.04 (dd, 1H, *J*=13.4, 6.1 Hz, H-3 eq), 1.75 (dd, 1H, *J*=13.4, 8.4 Hz, H-3 ax), 1.38 (s, 3H, CH_3), 1.25 (s, 3H, CH_3); Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found : C, 69.02; H, 7.84.

Bromination of 4-hydroxy-7-methoxy-2,2-dimethylchromane (10)

To a cooled solution containing **10** (69.9 g, 0.34 mol) in carbon tetrachloride (415 ml) at -20°C, bromine (55.8 g, 0.35 mol) was added dropwise. The mixture was stirred at room temperature for 1 h and then washed twice with saturated aqueous sodium hydrogen carbonate solution. The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure. In our hands and contrary to what it was described, the resulting oil corresponded to a mixture of products (**8b**) and (**8a**) (97 g); ^1H nmr (**8b**, $CDCl_3$) δ 7.07 (s, 1H, H-5), 6.40 (s, 1H, H-8), 5.44 (d, 1H, *J*=7.4 Hz, H-4), 3.83 (d, 1H, *J*=7.4 Hz, H-3), 3.74 (s, 3H, OCH_3), 1.40 (s, 6H, 2-$(CH_3)_2$).

Diethyl *N*-[(7-methoxy-2,2-dimethyl-*2H*-chromen)-5-yl]aminomethylenemalonate (12)

A solution of aminochromene (**2**) (1 g, 4.1 mmol) in absolute ethanol (10 ml), triethylamine (0.9 ml, 6.4 mmol) and diethyl ethoxymethylenemalonate (EMME) (1 ml, 5.9 mmol) was refluxed for 24 h. The mixture was cooled, ether was added and the mixture was filtered. The solvent was evaporated under reduced pressure and the crude product was recrystallized from hexane to obtain title compound (**12**) (950 mg, 61 %) as white crystals, mp 91-92 °C; ^1H nmr (DMSO-d_6) δ 11.18 (d, 1H, *J*=13.1 Hz, NH), 8.41 (d, 1H, *J*=13.1 Hz, vinyl-H), 6.43 (d, 1H, *J*=10 Hz, H-4), 6.28 (d, 1H, *J*=2.2 Hz, H-6), 6.21 (d, 1H, *J*=2.2 Hz, H-8), 5.59 (d, 1H, *J*=10 Hz, H-3), 4.30 (q, 2H, *J*=7 Hz, OCH_2), 4.22 (q, 2H, *J*=7 Hz, OCH_2), 3.78 (s, 3H, OCH_3), 1.41 (s, 6H, 2-$(CH_3)_2$), 1.36 (t, 3H, *J*=7 Hz, CH_3), 1.30 (t, 3H, *J*=7 Hz, CH_3); EIms (m/z) : 375 (M^+, 15%), 314 (M-61, 100%); Anal. Calcd for $C_{20}H_{25}NO_6$: C, 63.99; H, 6.71; N, 3.73. Found : C, 63.96; H, 6.71; N, 3.67.

Ethyl (5-methoxy-8,8-dimethyl-4-oxo-4,8-dihydro-*1H*-pyrano[2,3-*h*]quinolin-3-yl)carboxylate (13)

Compound (**12**) (500 mg, 1.33 mmol) was added in boiling Dowtherm A (5 ml, 250°C) (purchased from Fluka). After 10 min at reflux, Dowtherm was evaporated under reduced pressure. The expected product was recrystallized from acetonitrile to yield the expected product (**13**) (342 mg, 78 %) as white crystals, mp 208 °C; ^1H nmr (DMSO-d_6) δ 12.80 (s, 1H, NH), 9.02 (s, 1H, H-2), 7.35 (d, 1H, *J*=10 Hz, H-10), 6.47 (s, 1H, H-6), 5.60 (d, 1H, *J*=10 Hz, H-9), 4.44 (q, 2H, *J*=7 Hz, OCH_2), 3.98 (s, 3H, OCH_3), 1.48 (s, 6H, 8-$(CH_3)_2$), 1.42 (t, 3H, *J*=7 Hz, CH_3); ^{13}C nmr ($CDCl_3$) δ 14.3 (CH_3), 28.3 (8-$(CH_3)_2$), 56.4 (OCH_3), 61.6 (OCH_2), 78.0 (C8), 98.6 (C6), 102.7, 109.5, 118.3 (C10), 126.4 (C9), 149.2, 150.8 (C2), 157.6, 159.4, 168.2 (CO ester), 170.5 (CO); CIms (m/z) : 358 (M+29, 28%), 344 (41, M+15), 330 (100, MH^+); Anal. Calcd for $C_{18}H_{19}NO_5$: C, 65.64; H, 5.81; N, 4.25. Found : C, 65.49; H, 5.88; N, 4.23.

(5-Methoxy-8,8-dimethyl-4,8-dihydro-4-oxo-*1H*-pyrano[2,3-*h*]quinolin-3-yl)carboxylic acid (14)

A mixture of 1M sodium hydroxide (4 ml, 4mmol) containing quinoline (**13**) (65 mg, 0.2 mmol) was refluxed for 4 h and the precipitate was filtered. The mixture was cooled, acidified with acetic acid,filtered and recrystallized from ethanol to obtain the expected product (**14**) (45 mg, 71 %) as brown crystals, mp 140-150 °C; ^{1}H nmr ($CDCl_3$) δ8.79 (s, 1H, H-2), 6.75 (br d, 1H, *J*=10 Hz, H-10), 6.64 (s, 1H, H-6), 5.78 (br d, 1H, *J*=10 Hz, H-9), 3.87 (s, 3H, OCH_3), 1.70 (s, 6H, 8-$(CH_3)_2$); EIms (m/z) : 301 (M^+, 62%), 286 (47, M-15), 255 (50, M-46), 242 (100, M-59); Anal. Calcd for $C_{16}H_{15}NO_5 \cdot H_2O$: C, 60.18; H, 5.37; N, 4.39. Found : C, 59.82; H, 5.45; N, 4.19.

Ethyl (5-methoxy-1,8,8-trimethyl-4-oxo-4,8-dihydro-*1H*-pyrano[2,3-*h*]quinolin-3-yl)-carboxylate (15)

To compound (**13**) (333 mg, 1.01 mmol) dissolved in acetone (16 ml), potassium carbonate (168 mg, 1.2 mmol) and iodomethane (0.075 ml, 1.2 mmol) were added. The mixture was stirred 3 days at 60°C with addition of one equivalent of each reagent every 24 h. It was then cooled, filtered and evaporated under reduced pressure. The crude product was dissolved in methylene chloride and washed with water. The organic layer was then dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified on a silica gel column with methylene chloride-ethanol (95:5) to obtain the pyranoquinoline (**21**) (see below) (37 mg, 11%) and the expected product (**15**) which was recrystallized from ethyl acetate (146 mg, 42 %) as white crystals, mp 155 °C; ^{1}H nmr ($CDCl_3$) δ8.17 (s, 1H, H-2), 6.54 (d, 1H, *J*=9.7 Hz, H-10), 6.36 (s, 1H, H-6), 5.49 (d, 1H, *J*=9.7 Hz, H-9), 4.33 (q, 2H, *J*=7.1 Hz, OCH_2), 3.88 (s, 3H, OCH_3), 3.83 (s, 3H, NCH_3), 1.48 (s, 6H, 8-$(CH_3)_2$), 1.35 (t, 3H, *J*=7.1 Hz, CH_3); ^{13}C nmr ($CDCl_3$) δ14.2 (CH_3), 26.4 (8-$(CH_3)_2$), 46.2 (NCH_3), 56.0 (OCH_3), 60.4 (OCH_2), 75.8 (C8), 96.7 (C6), 102.5, 113.6, 114.8, 120.4 (C10), 124.0 (C9), 142.5, 149.3 (C2), 149.4, 158.0, 162.4, 165.5 (CO ester), 173.7 (CO); EIms (m/z) : 343 (M^+, 100%), 328 (63, M-15), 314 (37, M-29); Anal. Calcd for $C_{19}H_{21}NO_5$: C, 66.46; H, 6.16; N, 4.08. Found : C, 66.07; H, 5.94; N, 4.13.

(5-Methoxy-1,8,8-trimethyl-4,8-dihydro-4-oxo-*1H*-pyrano[2,3-*h*]quinolin-3-yl)carboxylic acid (16)

A solution of 1M sodium hydroxide (5 ml, 5 mmol) containing pyranoquinoline (**15**) (84 mg, 0.24 mmol) was refluxed for 1 h. The mixture was cooled and acidified with acetic acid. The precipitate was then filtered and recrystallized from acetonitrile to obtain compound (**16**) (66 mg, 86 %), as brown crystals, mp 240 °C; ^{1}H nmr ($CDCl_3$) δ8.55 (s, 1H, H-2), 6.61 (br d, 1H, *J*=9.7 Hz, H-10), 6.49 (s, 1H, H-6), 5.59 (br d, 1H, *J*=9.7 Hz, H-9), 3.97 (s, 6H, OCH_3, NCH_3), 1.52 (s, 6H, 8-$(CH_3)_2$); ^{13}C nmr ($CDCl_3$) δ 27.2 (8-$(CH_3)_2$), 48.2 (NCH_3), 57.0 (OCH_3), 98.4 (C6), 103.6, 110.3, 112.8, 120.6 (C10), 125.6 (C9), 143.5, 150.5 (C2), 160.5, 162.9, 167.6 (CO), 178.7 (CO); Anal. Calcd for $C_{17}H_{17}NO_5$: C, 64.75; H, 5.43; N, 4.44. Found : C, 64.52; H, 5.17; N, 4.50.

Ethyl (4-chloro-5-methoxy-8,8-dimethyl-*8H*-pyrano[2,3-*h*]quinolin-3-yl)carboxylate (17)

Compound (**13**) (325 mg, 0.99 mmol) was dissolved in $POCl_3$ (10 ml, 40mmol) and the mixture was refluxed for 2 h. The excess of $POCl_3$ was then evaporated under reduced pressure and ice was added onto the residue. After stirring, the aqueous layer was basified with ammonia and extracted with methylene

chloride. The organic layer was then dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified on a silica gel column with initially heptane-ethyl acetate (1:1) and then finally heptane-ethyl acetate-triethylamine (47.5:47.5:5) as eluent. Recrystallization from cyclohexane gave the expected product (**17**) (187 mg, 55 %) as white crystals, mp 178 °C; ^{1}H nmr ($CDCl_3$) δ 8.50 (s, 1H, H-2), 6.83 (d, 1H, *J*=10 Hz, H-10), 6.73 (s, 1H, H-6), 5.69 (d, 1H, *J*=10 Hz, H-9), 4.37 (q, 2H, *J*=7.1 Hz, OCH_2), 3.93 (s, 3H, OCH_3), 1.66 (s, 6H, 8-$(CH_3)_2$), 1.38 (t, 3H, J=7.1 Hz, CH_3); ^{13}C nmr ($CDCl_3$) δ 13.6 (CH_3), 30.5 (8-$(CH_3)_2$), 55.7 (OCH_3), 60.1 (OCH_2), 60.6 (C8), 106.6 (C6), 112.3, 114.6, 116.9, 117.2 (C10), 129.0 (C9), 134.4, 137.9, 142.5 (C2), 159.7, 165.1, 172.4 (CO ester); EIms (m/z) : 349 and 347 (M^+), 334 and 332 (M-15); Anal. Calcd for $C_{18}H_{18}NO_4Cl$: C, 62.16; H, 5.22; N, 4.03; Cl, 10.19. Found : C, 62.24; H, 5.15; N, 3.98; Cl, 10.30.

(4-Chloro-5-methoxy-8,8-dimethyl-*8H*-pyrano[2,3-*h*]quinolin-3-yl)carboxylic acid (18)

The pyranoquinoline (**17**) (100 mg, 0.29 mmol) was stirred at room temperature for 3 h in 1M sodium hydroxide (5 ml, 5 mmol). The mixture was filtered, acidified with acetic acid and extracted with methylene chloride. The organic layer was then dried ($MgSO_4$) and evaporated under reduced pressure. Recristallization from ethanol gave the expected product (**18**) (60 mg, 65 %) as yellow crystals, mp 294 °C; ^{1}H nmr (DMSO-d_6) δ 15.71 (s, 1H, OH), 8.90 (s, 1H, H-2), 7.22 (s, 1H, H-6), 6.88 (d, 1H, *J*=9.3 Hz, H-10), 6.13 (d, 1H, *J*=9.3 Hz, H-9), 3.96 (s, 3H, OCH_3), 1.75 (s, 6H, 8-$(CH_3)_2$); EIms (m/z) : 321 and 319 (M^+), 306 and 304 (M-15), 275 and 273 (M-46), 262 and 260 (M-59).

(4-Chloro-5-methoxy-8,8-dimethyl-*8H*-pyrano[2,3-*h*]quinolin-3-yl)-*N*-(3-dimethylaminopropyl)carboxamide (19)

Under nitrogen, a solution containing pyranoquinoline (**17**) (85 mg, 0.24 mmol) in 3-dimethylaminopropylamine (1 ml, 12 mmol) was stirred at room temperature for 2 days. The excess of amine was then removed by evaporation, water was added to the residue and the mixture extracted with methylene chloride. The organic layer was then dried ($MgSO_4$) and evaporated to dryness under reduced pressure. The residue was chromatographed on a silica gel column with heptane-ethyl acetate-triethylamine (20:75:5) as eluent to give compound (**20**) (33 mg, 28%) and **19**. After recrystallization from ethyl acetate, the expected product (**19**) was obtained (63 mg, 62 %) as white crystals, mp 86-88 °C; ^{1}H nmr (DMSO-d_6) δ 9.99 (t, 1H, *J*=7 Hz, NH), 8.80 (s, 1H, H-2), 7.05 (s, 1H, H-6), 6.84 (d, 1H, *J*=10.3 Hz, H-10), 6.07 (d, 1H, *J*=10.3 Hz, H-9), 3.91 (s, 3H, OCH_3), 3.86 (m, 2H, α-CH_2), 2.29 (t, 2H, *J*=7 Hz, γ-CH_2), 2.17 (s, 6H, N$(CH_3)_2$), 1.70 (m, 2H, β-CH_2), 1.69 (s, 6H, 8-$(CH_3)_2$); FABms (m/z) : 406 and 404 (M^+); Anal. Calcd for $C_{21}H_{26}N_3O_3Cl{\cdot}0.5\ H_2O$: C, 61.09, H, 6.59; N, 10.18; Cl, 8.59. Found : C, 61.16; H, 6.50; N, 10.00; Cl, 8.36.

(4-Chloro-8,8-dimethyl-5-(3-dimethylaminopropylamino)-*8H*-pyrano[2,3-*h*]quinolin-3-yl)-*N*-(3-dimethylaminopropyl)carboxamide (20)

A solution of 3-dimethylaminopropylamine (1 ml, 12 mmol) containing the pyranoquinoline (**17**) (102 mg, 0.29 mmol) was stirred at 70°C for 23 h. The amine in excess was then removed by evaporation, water was added to the residue and the precipitate was filtered. It was chromatographed on an alumina column with heptane-ethyl acetate-triethylamine (20:75:5) as eluent. After evaporation, the residue was taken up in ether to give the expected product (**20**) (99 mg, 69 %) as yellow crystals, mp 93-95 °C; ^{1}H nmr ($CDCl_3$) δ 10.24 (t, 1H, *J*= 6.9 Hz, NH), 9.93 (t, 1H, *J*= 6.9 Hz, NH), 8.81 (s, 1H, H-2), 6.70 (d, 1H, *J*=10.3 Hz, H-

10), 6.34 (s, 1H, H-6), 5.42 (d, 1H, *J*=10.3 Hz, H-9), 3.44 (q, 2H, *J*= 6.9 Hz, α-CH_2), 3.18 (q, 2H, *J*= 6.9 Hz, α-CH_2), 2.37 (m, 4H, 2xγ-CH_2), 2.21 (s, 12H, 2x$N(CH_3)_2$), 1.81 (m, 4H, 2xβ-CH_2), 1.62 (s, 6H, 8-$(CH_3)_2$); ^{13}C nmr ($CDCl_3$) δ 26.3 (β-CH_2), 27.1 (β-CH_2), 31.1 (8-$(CH_3)_2$), 36.9 (α-CH_2), 40.6 (α-CH_2), 44.8 ($N(CH_3)_2$), 45.0 ($N(CH_3)_2$), 56.7 (γ-CH_2), 56.8 (γ-CH_2), 61.8 (C8), 103.2, 105.9 (C6), 110.8, 113.5, 118.2 (C10), 125.1 (C9), 136.8, 138.7, 142.4 (C2), 151.0, 164.2, 178.7 (CO); FABms (m/z) : 476 and 474 (M^+); Anal. Calcd for $C_{25}H_{36}N_5O_2Cl \cdot 0.25\ (CH_3CH_2)O$: C, 63.40; H, 7.88; N, 14.22; Cl, 7.20. Found : C, 63.62; H, 7.49; N, 13.96; Cl, 7.76.

Ethyl (4,5-dimethoxy-8,8-dimethyl-*8H*-pyrano[2,3-*h*]quinolin-3-yl)carboxylate (21)

To a solution containing **13** (334 mg, 1.01 mmol) in dry DMF (15 ml), potassium carbonate (170 mg, 1.23 mmol) and iodomethane (0.075 ml, 1.2 mmol) were added. After stirring at 70°C for 7 h, the mixture was cooled, poured onto ice-water and extracted with methylene chloride. The organic layer was then washed with water, dried ($MgSO_4$) and evaporated under reduced pressure. After purification on a silica gel column with heptane-ethyl acetate (2:1) as eluent, the pyranoquinoline (**21**) was obtained (222 mg, 63 %) as a yellow oil beside compound (**15**) (40 mg, 11%); ^1H nmr (**21**, $CDCl_3$) δ 9.08 (s, 1H, H-2), 7.34 (d, 1H, *J*=10 Hz, H-10), 6.51 (s, 1H, H-6), 5.57 (d, 1H, *J*=10 Hz, H-9), 4.40 (q, 2H, *J*=7.1 Hz, OCH_2), 3.96 (s, 6H, 2xOCH_3), 1.48 (s, 6H, 8-$(CH_3)_2$), 1.40 (t, 3H, *J*=7.1 Hz, CH_3); Anal. Calcd for $C_{19}H_{21}NO_5 \cdot 0.5\ H_2O$: C, 64.76; H, 6.29; N, 3.97. Found : C, 64.75; H, 5.95; N, 3.98.

Ethyl (5-methoxy-8,8-dimethyl-4-(3-dimethylaminopropylamino)-*8H*-pyrano[2,3-*h*]quinolin-3-yl)carboxylate (22)

The mixture of pyranoquinoline (**21**) (99 mg, 0.29 mmol) and 3-dimethylaminopropylamine (1 ml, 12 mmol) was stirred at 0°C for 19 h. The amine was then evaporated under reduced pressure, water was added and the aqueous layer was extracted with methylene chloride. The organic layer was washed with brine, water and dried ($MgSO_4$). After evaporation under reduced pressure, the expected product (**22**) was obtained (107 mg, 90 %) as a yellow oil; ^1H nmr (DMSO-d_6) δ 8.58 (s, 1H, H-2), 8.40 (t, 1H, *J*=6.6 Hz, NH), 7.24 (d, 1H, *J*=9.8 Hz, H-10), 6.61 (s, 1H, H-6), 5.65 (d, 1H, *J*=9.8 Hz, H-9), 4.30 (q, 2H, *J*=7.1 Hz, OCH_2), 4.02 (s, 3H, OCH_3), 3.09 (q, 2H, *J*=6.6 Hz, α-CH_2), 2.28 (t, 2H, *J*=6.6 Hz, γ-CH_2), 2.13 (s, 6H, $N(CH_3)_2$), 1.74 (qn, 2H, *J*=6.6 Hz, β-CH_2), 1.46 (s, 6H, 8-$(CH_3)_2$), 1.34 (t, 3H, *J*=7.1 Hz, CH_3); ^{13}C nmr ($CDCl_3$) δ 14.5 (CH_3), 28.1 (8-$(CH_3)_2$), 28.4 (β-CH_2), 45.4 ($N(CH_3)_2$), 47.2 (α-CH_2), 56.2 (OCH_3), 57.4 (γ-CH_2), 60.6 (OCH_2), 77.5 (C8), 97.3 (C6), 103.9, 106.1, 109.8, 118.7 (C10), 126.4 (C9), 152.6 (C2), 155.1, 156.1, 159.2, 167.5 (CO); Anal. Calcd for $C_{23}H_{31}N_3O_4$: C, 66.81; H, 7.56; N, 10.16. Found : C, 66.63; H, 7.47; N, 10.10.

REFERENCES

1. G. Y. Lesher, E. J. Froelich, M. D. Gruett, J. H. Bailey, and P. R. Brundage, *J. Med. Chem.*, 1962, **5**, 1063.

2. Y. Jinbo, H. Kondo, Y. Inoue, M. Taguchi, H. Tsujishita, Y. Kotera, F. Sakamoto, and G. Tsukamoto, *J. Med. Chem.*, 1993, **36**, 2621; Y. Todo, H. Takagi, F. Iino, Y. Fukuoka, Y. Ikeda, K. Tanaka, I. Saikawa, and H. Narita, *Chem. Pharm. Bull.*, 1994, **42**, 2049; Y. Todo, J. Nitta, M. Miyajima, Y. Fukuoka, Y. Ikeda, Y. Yamashiro, I. Saikawa, and H. Narita, *Chem. Pharm. Bull.*, 1994, **42**, 2055;Y. Todo, J. Nitta, M. Miyajima, Y. Fukuoka, Y. Yamashiro, N. Nishida, I.

Saikawa, and H. Narita, *Chem. Pharm. Bull.*, 1994, **42**, 2063; S. Radl and D. Bouzard, *Heterocycles*, 1992, **34**, 2143; V. Cecchetti, S. Clementi, G. Cruciani, A. Fravolini, P. G. Pagella, A. Savino, and O. Tabarrini, *J. Med. Chem.*, 1995, **38**, 973.

3. T. R. Burke Jr., B. Lim, V. E. Marquez, Z. H. Li, J. B. Bolen, I. Stefanova, and I. D. Horak, *J. Med. Chem.*, 1993, **36**, 425; C. Antonello, E. Uriarte, M. Palumbo, S. Valisena, C. Parolin, and G. Palù, *Eur. J. Med. Chem.*, 1993, **28**, 291; R. J. Ife, T. H. Brown, D. J. Keeling, C. A. Leach, M. L. Meeson, M. E. Parsons, D. R. Reavill, C. J. Theobald, and K. J. Wiggall, *J. Med. Chem.*, 1992, **35**, 3413; R. A. Bucsh, J. M. Domagala, E. Laborde, and J. C. Sesnie, *J. Med. Chem.*, 1993, **36**, 4139.
4. C. Jolivet, C. Rivalle, and E. Bisagni, *J. Chem. Soc., Perkin Trans .1*, 1995, 511; C. Jolivet, C. Rivalle, C. Huel, and E. Bisagni, *J. Chem. Soc., Perkin Trans .1*, 1995, 2333.
5. S. Blechert, K. E. Fichter, and E. Winterfeldt, *Chem. Ber.*, 1978, **111**, 439.
6. M. Miyano and M. Matsui, *Bull. Chem. Soc. Jpn*, 1958, **31**, 397.

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