Indian Journal of Chemistry
Vol. 49B, January 2010, pp. 107-111

## Note

# A chemical strategy for the construction of quinoline isoquinoline core units

V K Pandey*, S Tusi, R Misra & R Shukla

Chemistry Department, University of Lucknow, Lucknow 226 007, India

Email: vinodkumarpandey@rediffmail.com

*Received 26 August 2008; accepted (revised) 7 September 2009*

A series of quinolino-isoquinolines **6** have been synthesized involving six synthetic steps and bioevaluated for their possible antimicrobial activity against *K. pneumoniae, E. coli, P. aeruginosa, S. aureus, C. albicans, C. neoformans, S. schenkii, T. mentagrophyte, A. flavus* and *C. paraplosis.*

**Keywords**: Antimicrobial activity, chromen-2-one, polyphosphoric acid

Quinolines and isoquinolines have attracted great attention of medicinal and synthetic chemists because of their presence in several natural products and numerous biological activities. An important role played by quinoline compounds was that of providing the first photographic film sensitizers, such as the cyanine dye, 'ethyl red'. Most of them possess a wide therapeutic activities *viz*. antiseptic, analgesic, trypanocidal, germicidal, antitubercular, anthelmintic and antiserotonic[1-6]. 8-Hydroxyquinoline derivatives and 4-substituted-7-chloroqui-nolines have been extensively used as powerful antiamoebic drugs[7,8]. Several quinoline derivatives as antimalarial agents are in clinical use since a long time[9-13]. In addition isoquinoline is the basic nucleus of drug prototypes such as emetine, papaverine, morphine and tubocurarine which are associated with amoebicidal, anti-hypertensive, analgesic and curareform activities[14]. Isoquinoline derivatives namely 1-isoquinoline carboxaldehyde thiosemicarbazone have been observed with antileukemic activity[15]. These valid observations prompted the authors to undertake the synthesis of 2-{7-hydroxy-4-methyl-2-oxo-1-[2-(1-oxo-3,4-diphenyl-2-aryl-1,2-dihydro-isoquinolin-7-yl)ethyl]-1,2-dihydroquinolin-8-yl-alkyl}-aryl-amides/imides to evaluate their antimicrobial activity.

## Results and Discussion

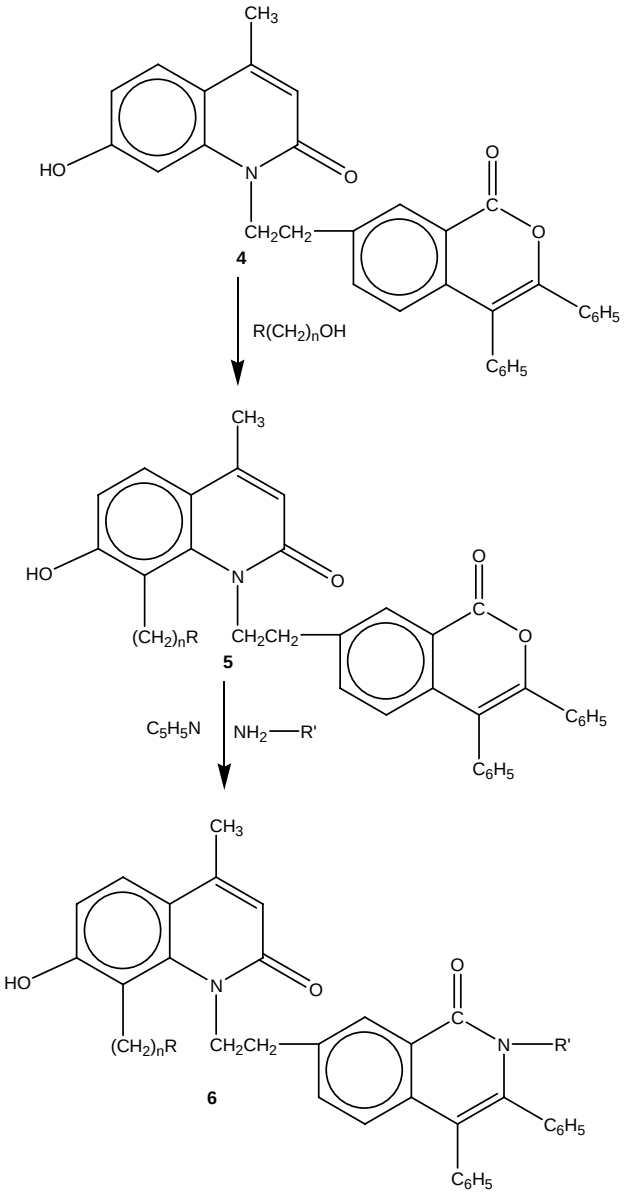
2-{7-Hydroxy-4-methyl-2-oxo-1-[2-(1-oxo-3,4-diphenyl-2-aryl-1,2-dihydro isoquinolin-7-yl) ethyl]-1,2-dihydroquinolin-8-yl)alkyl}-aryl-amides/imides **6** were obtained by heating under reflux a mixture of 2-{7-hydroxy-4-methyl-2-oxo-1-[2-(1-oxo-3,4-diphenyl-1*H*-isochromen-7-yl) ethyl]-1,2-dihydroquinolin-8-yl-alkyl]-aryl amides/imides **5** and primary aromatic amines in dry pyridine (**Scheme I**). These compounds **6** were characterized with the help of elemental analysis, $^{1}$H NMR, $^{13}$C NMR and mass spectral data (**Table I**).

## Pharmacological activity

Compounds **6** were evaluated for their antimicrobial activity involving four bacterial strains and six fungal strains following the broth micro dilution method as recommended by National Committee on clinical laboratory standards (NCCLS). The compounds **6f** and **6g** were found active against three bacterial strains *viz., Klebsiella pneumoniae, Escherichia coli* and *Pseudomonas aeruginosa*. However these two compounds could not exhibit any measurable degree of antibacterial activity against *Staphylococcus aureus*. In addition, compound **6i** showed moderate order of antibacterial activity only against *Pseudomonas aeruginosa*. The compounds **6e**, **6f**, and **6g** showed high to moderate level of antifungal activity against three fungi *viz*. *Candida albicans, Cryptococcus neoformans* and *Sporothrix schenkii*. These three compounds also showed antifungal activity of lower order against *Trichophyton mentagrophyte*. None of these compounds was found to show any measurable degree of antifungal activity against *Aspergillus flavus* and *Candida paraplosis*. The antimicrobial activity data has been incorporated in **Table II**.

## Experimental Section

Melting points were determined in open capillaries using a Toshniwal melting point apparatus and are uncorrected. IR spectra in KBr were recorded on a Perkin-Elmer spectrophotometer model 337 (USA) and $^{1}$H NMR spectra were recorded on a Bruker DRX 200 MHz spectrometer using TMS as an internal standard. (Chemical shifts in δ, ppm). The FAB mass spectra were recorded on JEOL SX 102/DA-600 mass spectrometer/Data System using Argon/Xenon (6 KV, 10 mA) as the FAB gas. The accelerating voltage was




**Scheme I**

10 kV and the spectra were recorded at RT. *m*-Nitrobenzyl alcohol (NBA) was used as the matrix when specified otherwise. The matrix peaks may have appeared at *m/z* 136, 137, 154, 289, 307 in the absence of any metal ions.

**7-Hydroxy-4-methyl-chromen-2-one, 1**

A mixture of resorcinol (0.1 mole) and ethyl-acetoacetate (EAA) (0.1 mole) with 75% sulphuric acid (50 mL) was heated at 100°C for 0.5 hr. The resulting dark-green solution was cooled and stirred into crushed ice (250 g). The crude product was filtered off and washed with cold water (100 mL). It was recrystallized from methanol as pale yellow plates, m.p. 184°C [185-86°C][16], yield 80%.

**7-Hydroxy-1-(2-hydroxyethyl)-4-methyl-1*H*-quinolin-2-one, 2**

A mixture of 7-hydroxy-4-methyl-chromen-2-one **1** (0.05 mole) and 2-aminoethanol (0.05 mole) in dry pyridine (100 mL) was heated for 6 hr under anhydrous reaction conditions. The resultant solution was allowed to cool at RT. Subsequently, the solution was poured into 75 mL of ice-cold water containing 25 mL of diluted hydrochloric acid slowly with constant shaking. Solidification occurred which was allowed to be completed. The white solid thus separated out was filtered off and washed with water repeatedly. It was dried at 100°C and recrystallized from ethanol as white crystalline solid, m.p. 174°C [174-75°C][17], yield 65%.

**3-[2-(7-Hydroxy-1-methyl-2-oxo-2*H*-quinolin-1-yl) ethyl] benzoic acid, 3**

Synthesis of the titled compound **3** was achieved following the method of Tscherniac[18]. Thus, a mixture of 7-hydroxy -1-(2-hydroxy-ethyl)-4-methyl-1*H*-quinolin-2-one **2** (0.02 mole) and benzoic acid (0.02 mole) was dissolved in a mixture of Conc. sulphuric acid and gl. acetic acid (100 mL; 1:1) by stirring cautiously. While dissolving, the contents were occasionally cooled. A clear solution dark in colour was obtained which was further stirred mechanically for one hr. The acidic solution thus obtained, was left under refrigeration overnight and poured into crushed-ice (250 g) in instalments with stirring. A white coloured solid separated out which was filtered off and washed successively with water in order to remove the sulphonated product. Recrystallization from acetone afforded analytically pure sample which was white crystalline in appearance. It melted at 134°C [134°C][17], yield 60%.

**7-Hydroxy-4-methyl-1-[2-(1-oxo-3,4-diphenyl-1*H*-isochromen-7-yl)ethyl]-1*H*-quinolin-2-one, 4**

A mixture of 3-[2-(7-hydroxy-1-methyl-2-oxo-2*H*-quinolin-1-yl) ethyl] benzoic acid 3 (0.01 mole), benzoin (0.01 mole) and polyphosphoric acid (20 mL) was heated at 100°C for 4 hr. Subsequently, the contents were cooled and 50 mL water was added to the reaction-mixture which was then boiled for an hr and filtered hot. The residue was washed with a solution of 10% sodium bicarbonate and water. It was dried *in vacuo* and recrystallized from gl.acetic acid,

**Table I** — Characterization data of compounds **5a-6i**

| Compd | R | n | R' | m.p. (°C) | Yield (%) | Found (Calcd) (%) C | H | N | Mass (*m/z*) | $^1$H NMR ($CDCl_3$,δ, ppm) | $^{13}$C NMR ($CDCl_3$,δ, ppm) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **5a** | Phthali-mido | 1 | | 128 | 58 | 76.57 (76.59 | 4.56 4.55 | 4.23 4.25) | | | |
| **5b** | Phthali-mido | 2 | | 136 | 55 | 76.75 (76.78 | 4.79 4.76 | 4.13 4.16) | | | |
| **5c** | Salicyla-mido | 1 | | 140 | 50 | 75.90 (75.92 | 4.95 4.93 | 4.30 4.32) | | | |
| **5d** | Benza-mido | 1 | | 120 | 55 | 77.83 (77.84 | 5.08 5.06 | 4.41 4.43) | | | |
| **6a** | Phthali-mido | 1 | *p*-methyl-phenyl | 100-01 | 60 | 78.69 (78.71 | 4.99 4.95 | 5.59 5.62) | 747 ($M^+$), 732, 730, 719, 656, 587, 568, 414, 399, 239, 160, 91 | 7.15-7.80 (m,14H,ArH), 2.20 (s, 6H, $CH_3$), 4.41 (s, 2H, N–$CH_2$CH–C), 4.43 (t, 2H, N–$CH_2$–$CH_2$, *J* = 7.40 Hz), 3.90 (t, 2H, C–$CH_2$–$CH_2$, *J* = 7.40 Hz), 5.66 (s, H, Ar–OH) | |
| **6b** | Phthali-mido | 1 | Phenyl | 130 | 55 | 78.55 (78.58 | 4.78 4.77 | 5.70 5.72) | | | |
| **6c** | Phthali-mido | 1 | *p*-methoxy-phenyl | 116-17 | 45 | 77.03 (77.06 | 4.88 4.84 | 5.47 5.50) | 763($M^+$), 708, 603, 602, 582, 472, 441, 401, 160, 105 | 7.26-7.98 (m, 3H, ArH), 2.48 (s, 3H, Ar-$CH_3$), 3.79 (s, 3H, $OCH_3$), 3.89 (s, 2H, N-$CH_2$-C), 4.79 (t, 2H, N-$CH_2$, *J* = 7.50 Hz), 4.29 (t, 2H, C-$CH_2$-C, *J* = 7.50 Hz), 5.10 (s, 1H, ArOH), 5.14 (s, 1H, C=CH) | 20.19, 28.44, 38.31, 38.52. 38.73, 38.94, 39.57. 77.01, 77.33, 111.26, 112.78, 114.54, 116.27, 118.32, 119.32, 120.10, 121.64, 122.18, 125.21, 127.25, 129.47, 131.86, 135.51, 142.80, 168.72 |
| **6d** | Phthali-mido | 2 | Phenyl | 82-83 | 47 | 78.68 (78.71 | 4.96 4.95 | 5.59 5.62) | | 6.75-6.85 (m, 24H, ArH), 2.25 (s, 3H, $ArCH_3$), 2.65 (s, 3H, Ar-O-$CH_3$), 4.45 (t, 4H, N-$CH_2$-$CH_2$ *J*=7.25 Hz), 3.95 (t, 4H, C-$CH_2$-$CH_2$,-N, *J*=7.25 Hz), 5.10 (s, 1H, ArOH) | |
| **6e** | Phthali-mido | 2 | *p*-methoxy-phenyl | 90 | 50 | 77.21 (77.22 | 5.05 5.01 | 5.38 5.40) | 778 ($M^+$+1), 777 ($M^+$), 749, 746, 617, 599, 441, 174, 146, 105 | 7.15-7-90 (m, 26H, ArH), 2.21 (s, 3H, $ArCH_3$), 4.40 (s, 2H, NH-$CH_2$), 4.43 (t, 2H, N-$CH_2$-$CH_2$, *J*=7.45 Hz), 3.96 (t,2H, C-$CH_2$-$CH_2$, *J*=7.45 Hz), 4.95 (s, 1H, ArOH), 8.85 (brs, 1H, CONH) | |
| **6f** | Salicyla-mido | 1 | *p*-methyl-phenyl | 80 | 54 | 78.12 (78.15 | 5.32 5.29 | 5.66 5.69) | | | |
| **6g** | Salicyla-mido | 1 | Phenyl | 90 | 51 | 77.98 (78.00 | 5.14 5.11 | 5.79 5.80) | | | |

—*Contd*

**Table I** — Characterization data of compounds **5a-6i—***Contd*

| Compd | R | n | R' | m.p. (°C) | Yield (%) | Found (Calcd) (%) C | H | N | Mass (*m/z*) | $^1$H NMR ($CDCl_3$,δ, ppm) | $^{13}$C NMR ($CDCl_3$,δ, ppm) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **6h** | Benza-mido | 1 | Phenyl | 88-89 | 55 | 79.73 (79.77 | 5.24 5.23 | 5.91 5.94) | 707 (M+), 692, 690, 630, 573, 59, 335, 307, 279, 134, 120, 105 | | 18.50, 78.50, 80.21, 115.34, 117.00, 118.68, 119.20, 124.64, 125.36, 129.41, 131.87, 133.61, 134.51, 143.85, 161.32, 168.50 |
| **6i** | Benza-mido | 1 | *p*-methyl-phenyl | 110 | 47 | 79.84 (79.88 | 5.42 5.40 | 5.80 5.82) | | | |

**Table II** — Antimicrobial activity of compounds **6a-6i**

| Compd | Antibacterial activity MIC in μg/mL | | | | Antifungal activity MIC in μg/mL | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | *K. pneumoniae* | *E. coli* | *P. aeruginosa* | *S. aureus* | *C. albicans* | *C. neoformans* | *S. schenkii* | *T. mentagrophyte* | *A. flavus* | *C. paraplosis* |
| **6a** | >50 | >50 | 25 | >50 | >50 | 25 | 25 | 12.50 | >50 | >50 |
| **6b** | >50 | >50 | 12.50 | >50 | >50 | >50 | >50 | >50 | >50 | >50 |
| **6c** | >50 | >50 | 50 | >50 | >50 | >50 | >50 | 50 | >50 | >50 |
| **6d** | 50 | 50 | 25 | >50 | 25 | 25 | 25 | 50 | >50 | >50 |
| **6e** | >50 | >50 | 50 | 50 | 12.50 | 6.25 | 25 | 50 | >50 | >50 |
| **6f** | 25 | 25 | 6.25 | 50 | 6.25 | 3.12 | 12.50 | 25 | >50 | >50 |
| **6g** | 12.50 | 25 | 3.12 | >50 | 3.12 | 1.56 | 25 | 25 | 50 | >50 |
| **6h** | >50 | 50 | 25 | >50 | >50 | 50 | >50 | >50 | >50 | >50 |
| **6i** | >50 | >50 | 12.50 | 50 | >50 | 50 | >50 | >50 | 50 | >50 |

as light yellow crystals. m.p. 145- 46°C, yield 55%. Anal for $C_{33}H_{25}NO_4$: Found (Calcd) (%), C 89.47(89.50), H 5.04(5.01),N 2.56(2.80). IR (KBr): 1745 (lactone C=O), 1685 (tert.amide C=O), 3605 $cm^{-1}$ (Ar-OH). $^1$H NMR ($CDCl_3$): δ 2.25 (s, 3H, $ArCH_3$), 5.15 (s, 1H, ArOH), 4.15 (t, 2H, *N*-$CH_2$-$CH_2$, *J* = 7.10 Hz), 3.85 (t, 2H, *N*-$CH_2CH_2$, *J* = 7.10 Hz), 7.15-7.77 (m, 17H, Ar-H).

### 2-{7-Hydroxy-4-methyl-2-oxo-1-[2-(1-oxo-3,4-diphenyl-1*H*-isochromen-7-yl)ethyl]-1,2-dihydro-quinolin-8-yl-alkyl} arylamides/imides, 5

A finely powdered mixture of 7-hydroxy-4-methyl-1-[2-(1-oxo-3,4-diphenyl-1*H*-isochromen-7-yl)ethyl]-1*H*-quinolin-2-one 4 (0.005 mole) and an arylamido/imido alkanol (0.005 mole) was dissolved in 50 mL of Conc. sulphuric acid by stirring carefully. When a clear solution was obtained, it was mechanically stirred for 1 hr and subsequently refrigerated overnight. It was poured into 200 mL of ice-cold water. The solid so obtained was filtered off and was washed repeatedly with cold water. It was dried *in vacuo* and recrystallization was done from ethanol. The compounds of this category are presented in **Table I** along with their characterization data.

### 2-{7-Hydroxy-4-methyl-2-oxo-1-[2-(1-oxo-3,4-diphenyl-2-aryl-1,2-dihydro-isoquinolin-7-yl)ethyl]-1,2-dihydro-quinolin-8-yl-alkyl}-arylamides/imides, 6

To a solution of 2-{7-hydroxy-4-methyl-2-oxo-1-[2-(1-oxo-3,4-diphenyl-1*H*-isochromen-7-yl)ethyl]-1,2-dihydro-quino-lin-8-yl-alkyl}-aryl-amide/imide, **5** (0.007 mole) in dry pyridine (15 mL) was added a solution of a primary amine (0.007 mole) in anhydrous pyridine (15 mL) slowly with vigorous stirring. After the addition was completed, the solution was heated under reflux for 6 hr. The hot solution was allowed to cool and subsequently poured into 250 g crushed ice containing 25 mL of diluted hydrochloric acid. On complete addition the emerging solid was allowed to settle down. It was filtered off

and washed with dilute ethanol. The compounds of this category are presented in **Table I** along with their characterization data.

**Acknowledgements**

The authors are thankful to the Head of the Department of Chemistry, University of Lucknow, Lucknow for providing necessary laboratory facilities and to the Director of CDRI, Lucknow for providing elemental, spectral and biological activity data.

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