Synthesis and reactions of indeno[1,2-c]chromene-6,11-dione derivatives

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Indeno[1,2-c]chromene-6,11-dione was prepared using the readily obtainable starting materials via the condensation of dimethyl homophthalate with 2,6-dichlorobenzaldehyde in the presence of sodium hydride in dry benzene followed by saponification and cyclisation with concentrated sulfuric acid at 0°C. The tendency of indeno[1,2-c]chromene-6,11-dione for undergoing nucleophilic addition has been tested by reaction with nitrogen nucleophiles such as hydrazine hydrate, hydroxylamine hydrochloride, ethyl carbazate, cyanoacetic acid hydrazide, thiosemicarbazide and 4-methylbenzenesulfonohydrazide. The IR, ^{1}H NMR, ^{13}C NMR and mass spectra of the synthesised compounds are discussed.

Keywords: fused chromene and 1-substituted aminoquinazolin-2(1*H*)-one derivatives

The condensation of dimethyl homophthalate with aldehydes and ketones has been reported previously.[1-10] Those studies were also intended to explore the factors influencing the formation of the stereoisomeric half-esters produced. Note that the formation of one stereoisomer or the other (*E* or *Z*) is affected by the non-bonded interactions (which are both steric and/or polar in origin) involved in the formation of the diastereomeric condensate anions. This leads to the formation of the corresponding diastereomeric δ-lactones. This work deals with the exploitation of the above condensation using 2,6-dichlorobenzaldehyde and aiming for the synthesis of new heterocyclic systems. Thus, 2,6-dichlorobenzaldehyde was condensed with dimethyl homophthalate in the presence of sodium hydride as condensing agent in dry benzene and afforded the *Z*-isomer which further cyclised to give the desired methyl 2-[5-chloro-2-oxo-2*H*-chromen-3-yl]benzoate **1**.

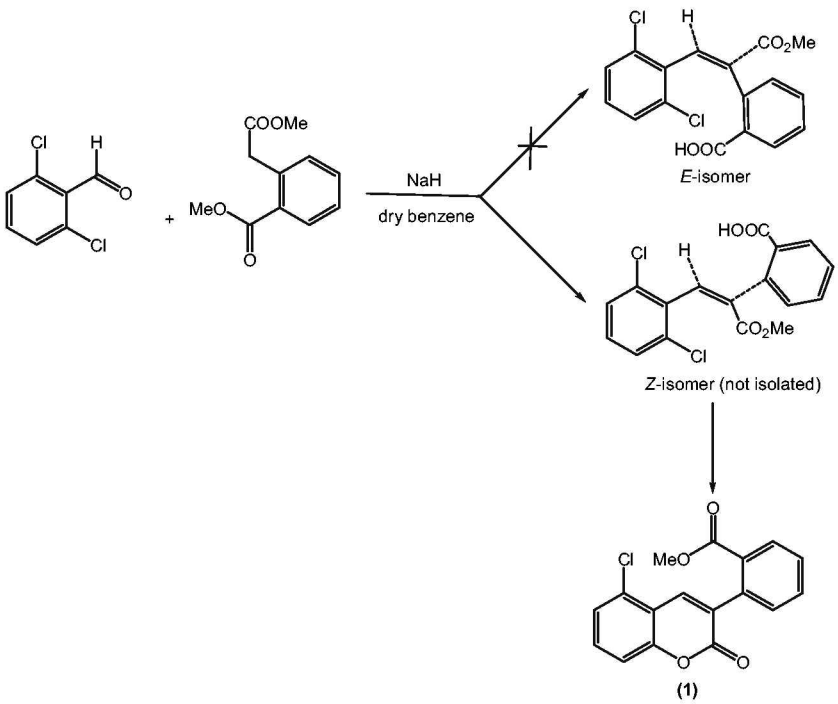
The preferential formation of the *Z*-isomer may be interpreted by considering the stability of the final product. By constructing space models for these isomers, it was found that the E-configuration is highly strained due to the steric interference between the *o*-carbomethoxy phenyl and the bulky substituted aryl group (Scheme 1).

Compelling evidence for the structure of the ester **1** derived from the *Z*-half ester was gained from its ^{1}H NMR spectrum, which shows chemical shifts characteristic for carbomethoxy, olefinic and aromatic protons beside the mass spectrum.

The above cyclisation reaction can be portrayed by assuming that an intramolecular ester exchange took place, which has been enhanced by the suitably situated carboxyl and carbmethoxyl group for ring formation. This can be succinctly explained by the possible formation of the hypothetical pseudo-ester **A** as an intermediate, which undergoes cyclodehydrohalogenation to the lactone **B** which in turn rearranges to give **1** (Scheme 2).

Saponification of compound **1** yielded the corresponding carboxylic acid **2**. The IR spectrum of **2** show two carbonyl stretching absorption bands, which can be assigned both to α,β-unsaturated δ-lactone and aromatic acid. The ^{1}H NMR spectrum of **2** indicates the presence of the olefinic and aromatic protons together with carboxylic acid proton (out of scale).

The above acid was easily converted to the corresponding cyclic ketone 1-chloroindeno[1,2-*c*]chromene-6,11-dione **3** by the action of concentrated sulfuric acid at 0°C or acetyl



Scheme 1

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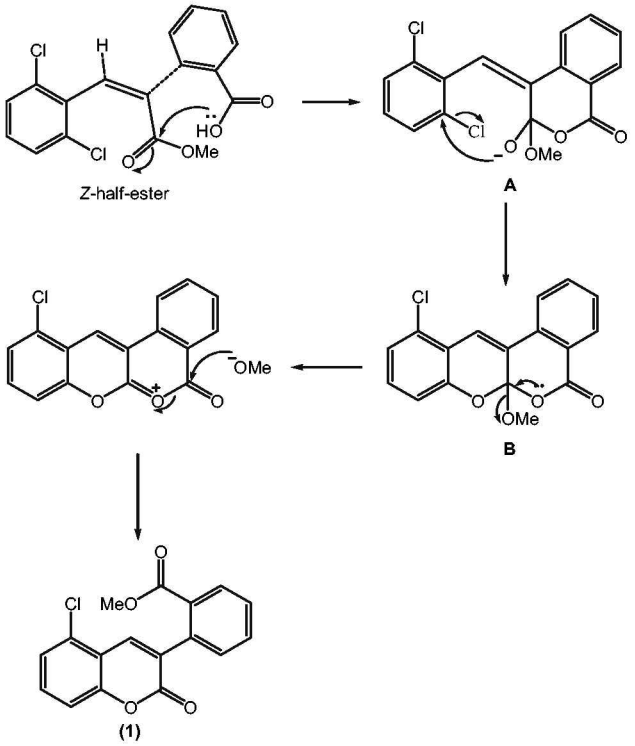
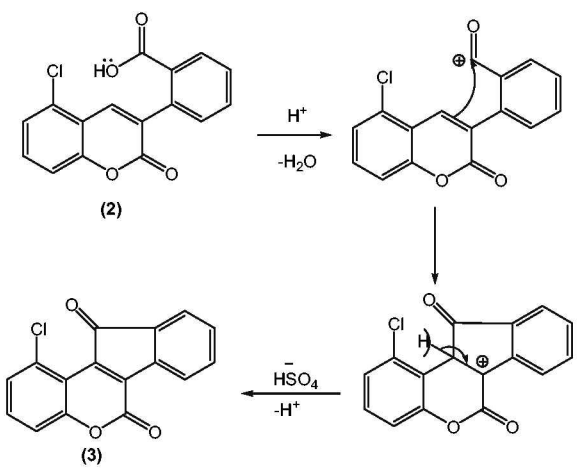


Scheme 2

chloride. Supporting evidence for the structure **3** is forthcoming from the spectral and analytical data. The IR spectrum of **3** show two carbonyl absorption bands characteristic for five membered ringed ketone condensed to aromatic system and α,β-unsaturated δ-lactone.[11] The formation of the above cyclic ketone can be attributable to the formation of a carbonium ion that results from the addition of a proton to the hydroxyl group of the carboxylic acid. The carbonium ion formed has a built-in nucleophile which attack the positive centre followed by deprotonation to form the cyclic ketone **3** (Scheme 3).

The tendency of the cyclic ketone **3** for undergoing nucleophilic addition has been tested, by refluxing it with hydrazine hydrate, ethyl carbazate and/or cyanoacetic acid hydrazide. Thus, the reaction of compound **3** with hydrazine hydrate in refluxing dioxane afforded (*E*)-5-amino-1-chloro-11-hydrazono-5*H*-indeno[1,2-*c*]quinolin-6(11*H*)-one **4**. Ample evidence for the structure of compound **4** is derivable from the IR spectrum which show the disappearance of carbonyl absorption bands corresponding to the five-membered ringed



Scheme 3

ketone and the δ-lactone and retained new absorption band for the cyclic amide. Furthermore, the highest recorded peak in the mass spectrum at *m/z* = 311 (69.5) which in a good accordance with the proposed structure. In contrast, the reaction of **3** with hydroxylamine hydrochloride in boiling pyridine afforded the condensation product **5** with the ringed ketone as the sole product.

Ethyl [1-chloro-6,11-dioxo-6H-indeno[1,2-*c*]quinolin-5(11*H*)-yl]carbamate **6** was obtained in a moderate yield upon treatment of compound **3** with ethyl carbazate in boiling dioxane. However, refluxing **3** with cyanoacetic acid hydrazide yielded *N*-[1-chloro-6,11-dioxo-6*H*-indeno [1,2-*c*]quinolin-5(11*H*)-yl]-2-cyanoacetamide **7**. Spectroscopic evidence has been adduced in favour of the structure of the above products. Furthermore, treatment of compound **3** with thiosemicarbazide in boiling dioxane yielded 1-(1-chloro-6,11-dioxo-6*H*-indeno[1,2-*c*]quinolin-5(11*H*)-yl) thiourea **8**. Similarly, when compound **3** reacted with 4-methylbenzenesulfonohydrazide in refluxing dioxane afforded *N*-(1-chloro-6,11-dioxo-6*H*-indeno[1,2-*c*]quinolin-5 (11*H*)-yl)-4-methylbenzene sulfonamide **9**. (Scheme 4)

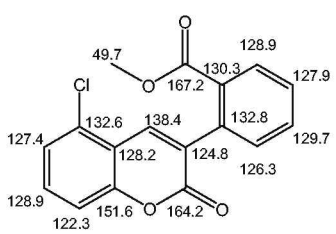
Full analysis of the spectroscopic data (IR ^{1}H NMR, ^{13}C NMR and mass spectra) were completely in accord with the proposed structures.

Experimental

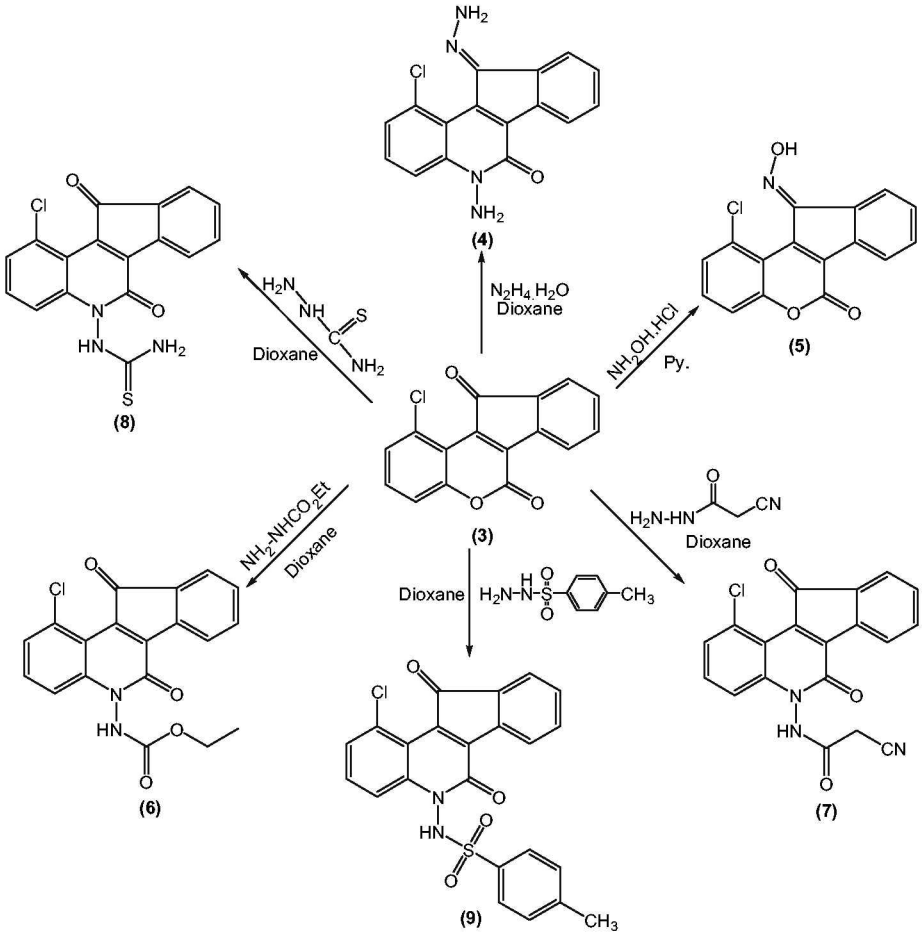
All melting points were taken on Griffin and Geory melting point apparatus and are uncorrected. IR spectra were recorded on Pye Unicam SP 1200 spectrophotometer using KBr Wafer technique. ^{1}H NMR spectra were determined on a Varian Gemini 200 MHz using TMS as internal standard (chemical shifts in δ). EI-MS were measured on a Schimadzu-GC-MS, QP 1000 EX instrument operating at 70 eV. ^{13}C NMR spectra were measured on JOEL 75 MHz. Elemental analyses were carried out at the microanalytical unit, faculty of science, Ain Shams University by using Perkin-Elmer 2400 CHN elemental analyser and satisfactory analytical data (± 0.4) were obtained for all compounds. The homogeneity of the synthesised compounds was controlled by TLC [using TLC aluminum sheets silica gel F_{254} (Merck)].

Methyl 2-[5-chloro-2-oxo-2H-chromen-3-yl]benzoate (**1**): A mixture of dimethyl homophthalate (2.08 g, 0.01 mole) and 2,6-dichlorobenzaldehyde (1.75 g, 0.01 mole) was stirred in dry benzene (30 ml) in the presence of sodium hydride (0.5 g, 0.02 mole) and two drops of absolute methanol. The whole mixture was stirred at room temperature for 10 min. (TLC). After slow evaporation of the solvent, the separated solid was dissolved in cold water then acidified with cold dilute hydrochloric acid. The deposited solid was filtered off, washed several times with cold water, dried and then recrystallised from ethanol to give **1** as white crystals; m.p. 177–179 °C, yield 89%. IR (ν): 1744 cm^{-1} ($C{=}O_{\alpha,\beta\text{-unsaturated }\delta\text{-lactone}}$) and 1686 cm^{-1} ($C{=}O_{\text{aryl conjugated ester}}$). ^{1}H NMR ($CDCl_3$) δ 8.17–7.19 (m, $7H_{arom.}$), 6.8 (s, 1H, C_4-H), 3.5 (s, 3H, COOMe). MS: 283 (100) [M–OMe], 255 (39.1), 176 (2.3). Anal. Calcd for $C_{17}H_{11}ClO_4$ (314.72): C, 64.87; H, 3.52; Cl, 11.26. Found: C, 65.07; H, 3.41; Cl, 11.10%.

^{13}C NMR for compound **1**.



2-(5-Chloro-2-oxo-2H-chromene-3-yl)benzoic acid (**2**): The ester **1** (3.15 g, 0.01 mole) was heated under reflux with (10%) sodium hydroxide (30 ml) for 1 h (TLC). The reaction mixture was allowed to cool and then acidified with cold dilute hydrochloric acid. The deposited solid was filtered off, washed several times with cold water, dried and then recrystallised from ethanol to give **2** as white crystals; m.p. 219–221 °C, yield 85%. IR (ν): br. 3560–2562 cm^{-1} (acidic OH group), 1701 ($C{=}O_{\text{aromatic acid}}$). ^{1}H NMR ($CDCl_3$) δ 11.44 (s, 1H, COOH),

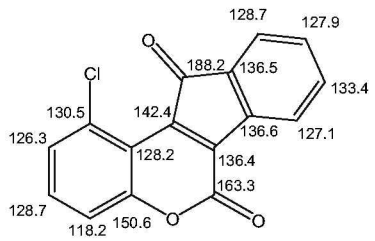


Scheme 4

8.3–7.08 (m, $8H_{arom.}$ + C_4–H). MS: 303 (M + 2, 8.1), 301 (24.4), 283 (100), 255 (13.3), 176 (32.7). Anal. Calcd for $C_{16}H_9ClO_4$ (300.70): C, 63.91; H, 3.01; Cl, 11.79. Found: C, 64.23; H, 3.19; Cl, 11.61%.

1-Chloroindeno[1,2-c]chromene-6,11-dione (**3**): The acid **2** (3 g, 0.01 mole) was stirred at 0°C with concentrated sulfuric acid (30 ml) for 30 min, then cooling overnight in refrigerator. The reaction mixture was poured onto ice cold water and the deposited solid was filtered off, washed several times with cold water, dried and then recrystallised from benzene to give **3** as buff crystals; m.p. 159–161°C, yield 83%. IR (ν): 1784 cm^{-1} ($C{=}O_{\text{five membered ringed ketone}}$), 1734 cm^{-1} ($C{=}O_{\alpha,\beta\text{-unsaturated }\delta\text{-lactone}}$). ^1H NMR ($CDCl_3$) δ 8.3–7.2 (m, $7H_{arom.}$). MS: 285 (33.6) [M + 2], 283 (100). Anal. Calcd for $C_{16}H_7ClO_3$ (282.68): C, 67.98; H, 2.49; Cl, 12.54. Found: C, 68.27; H, 2.33; Cl, 12.29%.

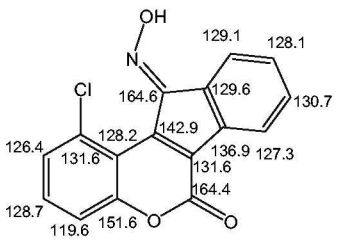
^{13}C NMR for compound **3**.



(E)-5-Amino-1-chloro-11-hydrazono-5H-indeno[1,2-c]quinolin-6(11H)-one (**4**): A mixture of **3** (2.83 g, 0.01 mole) and hydrazine hydrate (1 ml, 0.02 mole) in 15 ml dioxane was refluxed for 6 h (TLC). After evaporation of solvent left a yellow solid product which collected by filtration and recrystallised from benzene to give **4** as pale yellow crystals; m.p. 106–108°C, yield 80%. IR (ν): br. 3376–3271 cm^{-1} (NH_2), 1718 cm^{-1} ($C{=}O_{\text{cyclic amide}}$). ^1H NMR ($CDCl_3$) δ 8.2–7.1 (m, $7H_{arom.}$), 5.85 (br.s, 4H, $2NH_2$ exchangeable with D_2O). MS: 313 (M + 2, 19.2), 311 (69.6), 176 (34.5), 123 (100). Anal. Calcd for $C_{16}H_{11}ClN_4O$ (310.74): C, 61.84; H, 3.56; Cl, 11.4; N, 18.02. Found: C, 62.18; H, 3.47; Cl, 11.20; N, 17.88%.

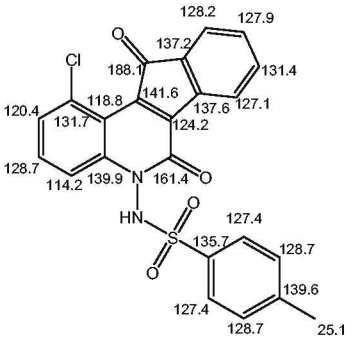
(E)-1-Chloro-11-(hydroxyimino)indeno[1,2-c]chromen-6(11H)-one (**5**): A mixture of **3** (2.83 g, 0.01 mole) and hydroxylamine hydrochloride (0.7 g, 0.01 mole) in 15 ml pyridine was refluxed for 3 h (TLC). The reaction mixture was allowed to cool and then acidified with cold dilute hydrochloric acid. A brown oil was formed which was solidify by trituration with ether. This solid which collected by filtration was then recrystallised from benzene to give **5** as pale yellow crystals; m.p. 178–180°C, yield 55%. IR (ν): 3266 cm^{-1} (OH), 1729 cm^{-1} ($C{=}O_{\alpha,\beta\text{-unsaturated }\delta\text{-lactone}}$), 1656 cm^{-1} (C=N). ^1H NMR ($CDCl_3$) δ 7.6–6.95 (m, $7H_{arom.}$), 2.1 (br.s, 1H, exchangeable with D_2O). MS: 300 (M + 2, 20.2), 298 (70.5), 282 (100), 255 (9.0), 176 (19.1). Anal. Calcd for $C_{16}H_8ClNO_3$ (297.69): C, 64.55; H,2.70; Cl, 11.90; N, 4.70. Found: C, 64.92; H, 2.53; Cl, 11.60; N, 4.66%.

^{13}C NMR for compound **5**.



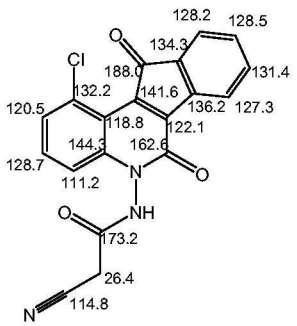
Ethyl [1-chloro-6,11-dioxo-6H-indeno[1,2-c]quinolin-5(11H)-yl] carbamate (**6**): A mixture of **3** (2.83 g, 0.01 mole) and ethyl carbazate (1 g, 0.01 mole) in 15 ml dioxane was refluxed for 6 h (TLC). After evaporation of solvent, a white solid was deposited which was recrystallised from ethanol to give **6** as white crystals; m.p. 118–120°C, yield 75%. IR (ν): 1745 cm^{-1} ($C{=}O_{\text{5-membered ringed ketone}}$), 1720 cm^{-1} ($C{=}O_{\text{ester}}$), 1693 cm^{-1} ($C{=}O_{\text{cyclic amide}}$). ^1H NMR ($CDCl_3$) δ 8.3–7.23 (m, $7H_{arom.}$), 7.2 (br.s, 1H, NH), 4.2–4.1 (q, 2H), 1.25–1.2 (t, 2H). MS: 371 (M + 2, 30.3), 369 (100), 297 (35.7), 176 (33.1). Anal. Calcd for $C_{19}H_{13}ClN_2O_4$ (368.77): C, 61.88; H, 3.55; Cl, 9.61; N, 7.59. Found: C, 62.31; H, 3.37; Cl, 9.39; N, 7.51%.

^{13}C NMR for compound **6**.



N-[1-Chloro-6,11-dioxo-6H-indeno[1,2-c]quinolin-5(11H)yl]-2-cyanoacetamide (**7**): A mixture of **3** (2.83 g, 0.01 mole) and cyanoacetic acid hydrazide (1 g, 0.01 mole) in 15 ml dioxane was refluxed for 6 h (TLC). After concentration, a white solid was deposited which collected by filtration and recrystallised from ethanol to give **7** as colourless crystals; m.p. 96–98 °C, yield 82%. IR (ν): br. 3526, 3451, 3178 cm^{-1} (NH), 1740, 1702 cm^{-1} (C=O). ^{1}H NMR ($CDCl_3$) δ 8.8 (s, 1H, NH), 8.2–7.2 (m, 7H$_{arom.}$), 3.7–3.5 (d,d, 2H, $COCH_2CN$). MS: 366 (M + 2, 30.7), 364 (100), 323 (21.9), 282 (32.7), 176 (34.8). Anal. Calcd for $C_{19}H_{10}ClN_3O_3$ (363.76): C, 62.73; H, 2.77; Cl, 9.74; N, 11.55. Found: C, 63.00; H, 2.66; Cl, 9.62; N, 11.37%.

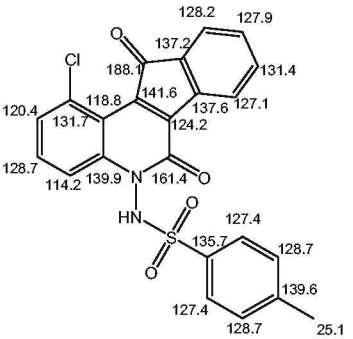
^{13}C NMR for compound **7**.



1-(1-Chloro-6,11-dioxo-6H-indeno[1,2-c]quinolin-5(11H)-yl) thiourea (**8**): A mixture of **3** (2.83 g, 0.01 mole) and thiosemicarbazide (0.9 g, 0.01 mole) in 15 ml dioxane was refluxed for 6 h (TLC). After evaporation of the solvent, a yellow solid was deposited which was recrystallised from ethanol/dioxane to give **8** as pale yellow crystals; m.p. 162–164 °C, yield 83%. IR (ν): br. 3450, 3321, 3187 cm^{-1} (NH, NH_2), 1726 cm^{-1} ($C=O_{5\text{-membered ringed ketone}}$), 1691 cm^{-1} ($C=O_{cyclic\ amide}$), 1173 cm^{-1} (C=S). ^{1}H NMR ($CDCl_3$) δ 7.8–6.5 (m, 7H$_{arom.}$), 4.1 (Hump, 3H, exchangeable with D_2O). MS: 338 (8.9) [M-H_2O], 297 (100), 283 (17.6), 176 (38.5). Anal. Calcd for $C_{17}H_{10}ClN_3O_2S$ (355.78): C, 57.39; H, 2.83; Cl, 9.96; N, 11.81; S, 9.00. Found: C, 57.60; H, 2.61; Cl, 10.10; N, 11.59; S, 8.83%.

N-(1-Chloro-6,11-dioxo-6H-indeno[1,2-c]quinolin-5(11H)-yl)-4-methylbenzene sulfonamide (**9**): A mixture of **3** (2.83 g, 0.01 mole) and 4-methylbenzenesulfonohydrazide (1.83 g, 0.01 mole) in 15 ml dioxane was refluxed for 4 h (TLC). After evaporation of the solvent, a pale yellow solid was deposited which was recrystallised from dioxane to give **9** as colourless crystals; m.p. 200–202 °C, yield 80%. IR (ν): 3260 cm^{-1} (NH), 1733 cm^{-1} ($C=O_{5\text{-membered ringed ketone}}$), 1693 cm^{-1} ($C=O_{cyclic\ amide}$). ^{1}H NMR (DMSO-$d_6$) δ 7.8–6.5 (m, 11H$_{arom.}$), 2.4 (br.s, 1H, NH, exchangeable with D_2O), 2.16 (s, 3H, ArMe). MS: 451 (21), 296 [M–$C_7H_7SO_2$, 100], 282 (32.4), 239 (44.7), 171 (66.2), 91 (30.1). Anal. Calcd for $C_{23}H_{15}ClN_2O_4S$ (450.87): C, 61.27; H, 3.35; Cl,7.86; N, 6.21; S, 7.10. Found: C, 61.39; H, 3.26; Cl, 7.47; N, 6.60; S, 7.21%.

^{13}C NMR for compound **9**.



Received 30 June 2008; accepted 18 August 2008
Paper 08/0025 *doi: 10.3184/030823408X360364373*
Published online: 10 November 2008

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