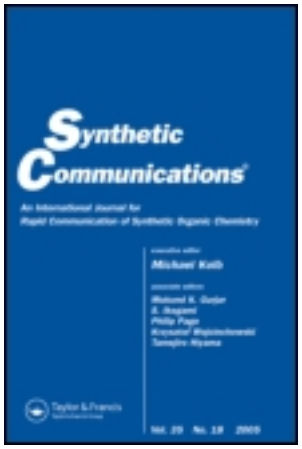

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SYNTHESIS OF NOVEL INDENO[1,2-c]ISOQUINOLINE DERIVATIVES

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Indeno[1,2-c]isochromene was prepared using the readily obtainable starting materials via the condensation of dimethyl homophthalate with 3,4-dimethoxybenzaldehyde in the presence of sodium methoxide in absolute methanol followed by saponification and cyclization with concentrated sulfuric acid at 0°C. The proclivity of cyclized product for undergoing nucleophilic addition has been tested by reaction with nitrogen nucleophiles. Structural assignments are based on spectroscopic data (infrared, ^{1}H NMR, ^{13}C NMR, and mass spectra) and confirmed by the single-crystal x-ray molecular structure (2 and 3).

Keywords: Indeno[1,2-c]isochromene; isoquinoline derivatives; nitrogen nucleophiles

INTRODUCTION

Isoquinolinones[1] are important compounds from both synthetic and applied points of view. Their structures are incorporated in several alkaloids[2] and other pharmacologically important compounds.[3] In particular, 1,2-dihydroisoquinoline derivatives[4] act as delivery systems that transport drugs through the otherwise highly impermeable blood–brain barrier.[5] These compounds also exhibit sedative,[6] antidepressant,[7] antitumor, and antimicrobial activities.[8] Isoquinolines are used in the manufacture of dyes, paints, insecticides, antifungal agents; as a solvent for the extraction of resins and terpenes; and as a corrosion inhibitor.[9,10]

Isoquinolinones have already been employed as useful intermediates in the synthesis of indenoisoquinolines,[11] protoberberines,[12,13] and dibenzoquinolizines[13] and are also of interest in medicinal chemistry.[14] Because of their biological and pharmacological importance, several methods have been reported for the synthesis of isoquinolinones. Most of these methods involve the use of either a preformed isoquinoline or homophthalic acid, which is in turn obtained by a multistep sequence.[15] Homophthalic acids are transformed into isoquinolinones via isocoumarins,[16,17] isoquinolone-4-carboxylic acid,[15] or homophthalimide.[15f]

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DISCUSSION

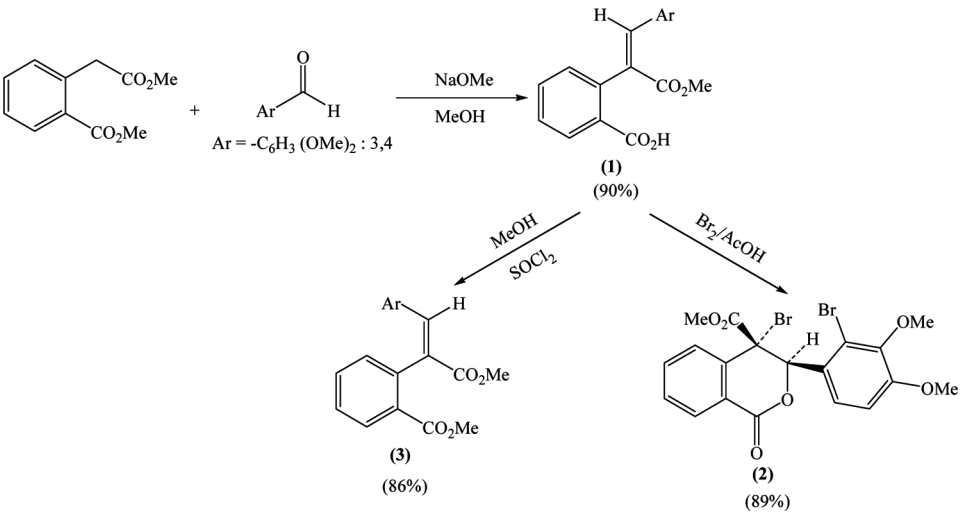
3,4-Dimethoxybenzaldehyde was condensed with dimethyl homophthalate in the presence of sodium methoxide in absolute methanol, which afforded the *Z*-isomer **1**. The preferential formation of the *Z*-isomer may be interpreted by considering the stability of the final product. By constructing space models for these isomers, it was found that the E-configuration is highly strained because of the steric interference between the o-carbmethoxy phenyl and the bulky substituted aryl group. Ample evidence for the Z-configuration of the half ester **1** is derived from its conversion to the iso-chromene derivative **2** (Scheme 1).

(3R,4S)-Methyl-4-bromo-3-(2-bromo-4,5-dimethoxyphenyl)-1-oxo-3,4-dihydro-1H-isochromene-4-carboxylate **2** was formed as the sole product in fairly good yield via the stirring of compound **1** with a mixture of bromine and acetic acid at room temperature for 1 h. The structure **2** was substantiated from the micro-analytical and spectroscopic data beside the x-ray crystallographic analysis (Fig. 1).

This cyclization reaction can be envisioned by assuming that acid-catalyzed electrophilic addition of bromine to the activated double bond took place, followed by intramolecular 1,6-exo-tet cyclization (Scheme 2).

Esterification of **1** using absolute methanol in the presence of thionyl chloride under reflux yielded the isomeric diester (E)-methyl 2-[3-(3,4-dimethoxyphenyl)-1-methoxy-1-oxo-prop-2-en-2-yl]benzoate **3**, which indicates the occurrence of *cis*/*trans*-isomerization under acidic conditions (Scheme 1). The structure assigned for the E-configuration of the diester **3** is established from analytical and spectral data. Furthermore, x-ray crystallographic analysis (Fig. 2) confirms the proposed structure.

Adequate evidence for the Z-configuration of **1** is forthcoming from saponification and cyclization of the corresponding diacid. Thus, mild saponification of **1** yields the Z-dibasic acid **4**. Cyclization of **4** using concentrated sulfuric acid at 0°C afforded 9,10-dimethoxyindeno[1,2-c]isochromene-5,11(6aH, 11aH)dione **5** (Scheme 3).



Scheme 1. Lactonization and esterification of Z-half ester **1**.

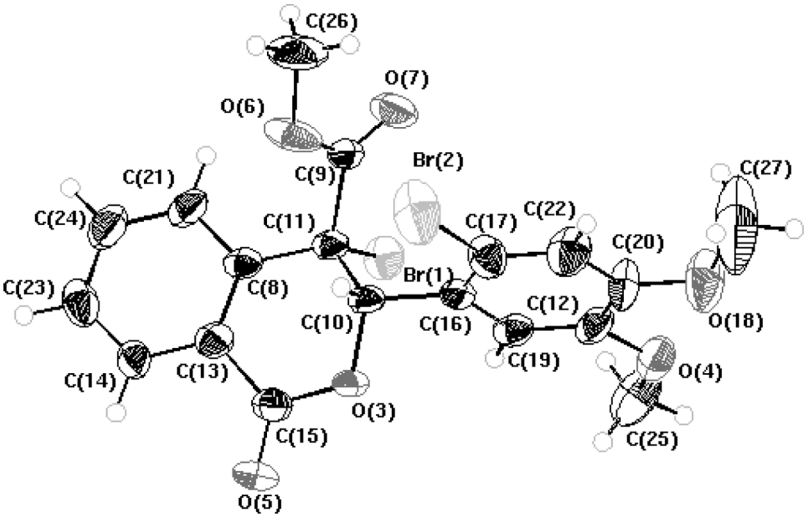
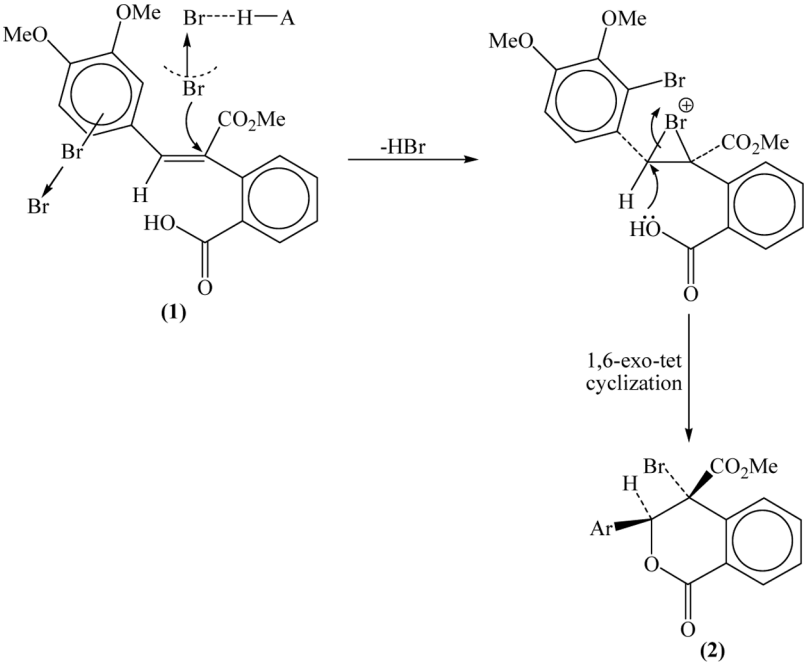


Figure 1. Molecular structure of (3R,4S)-methyl-4-bromo-3-(2-bromo-4,5-dimethoxyphenyl)-1-oxo-3,4-dihydro-1H-isochromene-4-carboxylate **2**.

The synthetic route for the target compound **5** is shown in Scheme 4.

The indeno[1,2-c]isochromene **5** was used as the key starting material for synthesis of indeno[1,2-c]isoquinoline derivatives.[11] Thus, refluxing **5** with hydrazine



Scheme 2. Acid-catalyzed electrophilic addition of bromine to **1** followed by intramolecular cyclization.

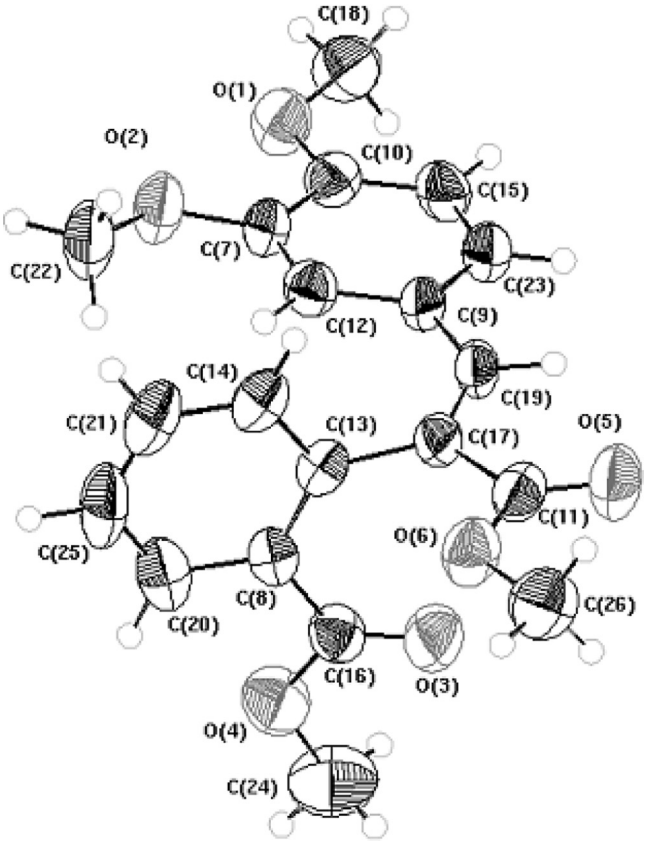


Figure 2. X-ray crystal structure of compound **3**.

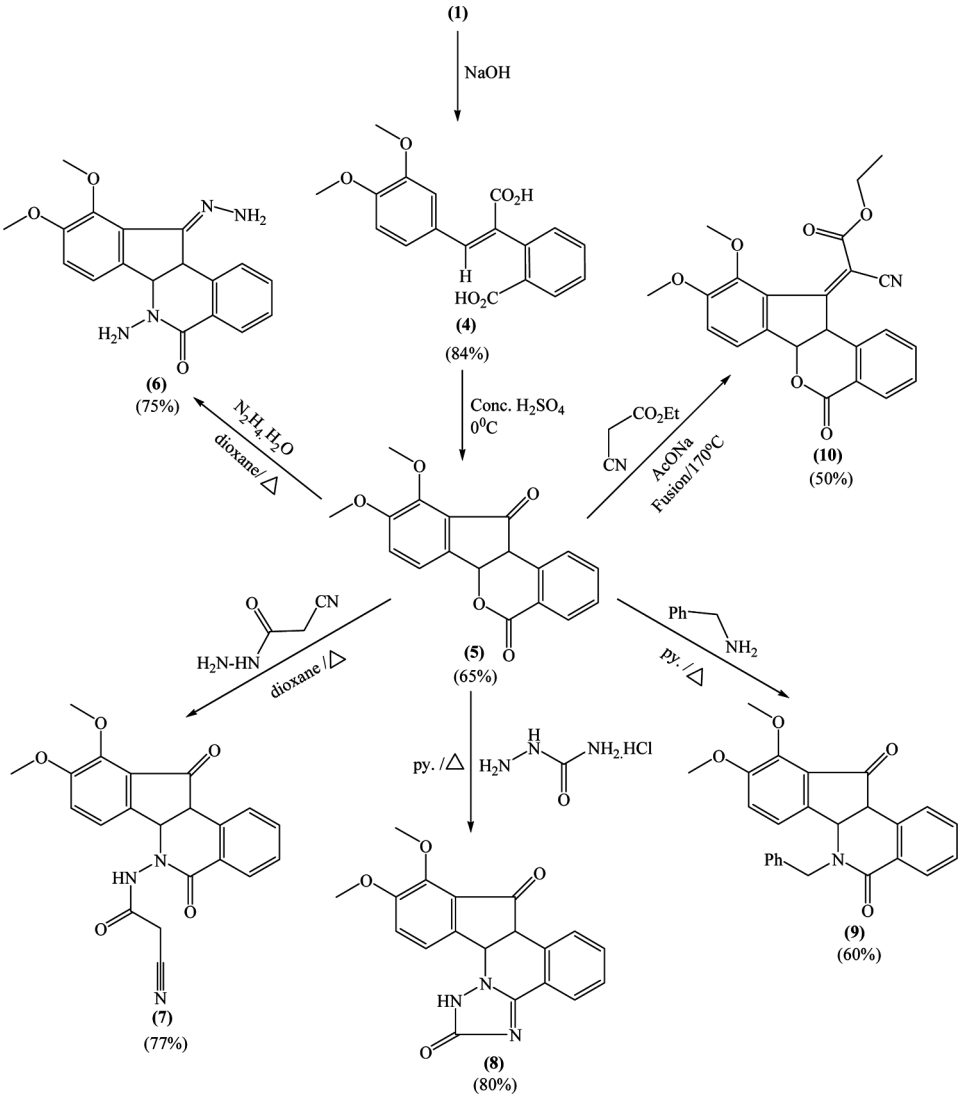
hydrate (80%) in dioxane afforded the (E)-6-amino-11-hydrazono-9,10-dimethoxy-6,6a,11,11a-tetra-hydroindeno[1,2-c]isoquinolin-5-one **6** (Scheme 3).

Treatment of the ketolactone **5** with cyanoethanoic hydrazide in boiling dioxane yielded the 2-cyano-N-(9,10-dimethoxy-5,11-dioxo-11,11a-dihydro-5H-indeno[1,2-c]isoquinolin-6(6aH)-yl) acetamide **7** (Scheme 3).

[1,2,4]Triazolo[2,3-a]isoquinoline derivative **8** was obtained as the sole product in fairly good yield upon treatment of compound **5** with semicarbazide hydrochloride in refluxing pyridine (Scheme 3). The reaction involves nucleophilic ring opening via nitrogen attack at the carbonyl group of the δ-lactone (tetrahedral mechanism) followed by 1,5-exo-trig cyclization with elimination of 2 mol water.

Refluxing the ketolactone **5** with benzylamine in pyridine afforded the 6-benzyl-9,10-dimethoxy-6,6a-dihydro-11aH-indeno[1,2-c]isoquinolin-5,11-dione **9** (Scheme 3).

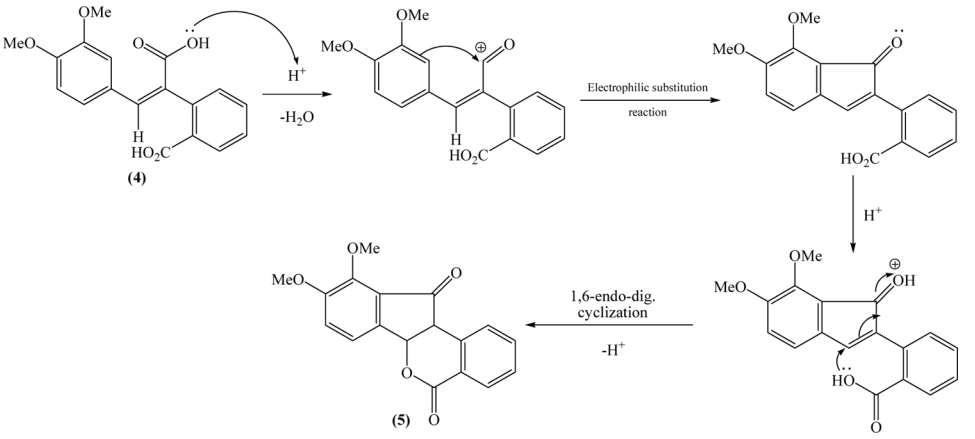
However, fusion of **5** with an active methylene compound such as ethyl cyanoacetate in the presence of anhydrous sodium acetate on an oil bath at 170°C afforded (Z)-ethyl2-cyano-2-(9,10-dimethoxy-5-oxo-indeno[1,2-c]isochromene-11(5H,6aH,11aH)ylidene)acetate **10** (Scheme 3).



Scheme 3. Reactions of indeno[1,2-c]isochromene **5** with nitrogen and carbon nucleophiles.

EXPERIMENTAL

All melting points were taken on a Griffin and Geory melting-point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Pye Unicam SP 1200 spectrophotometer using the KBr wafer technique. ^{1}H NMR spectra were determined on a Varian Gemini 300-MHz instrument using tetramethylsilane (TMS) as internal standard (chemical shifts in δ). ^{13}C NMR spectra were measured on a Jeol 75-MHz instrument. Electron impact–mass spectrometry (EI-MS) was measured on a Schimadzu GC-MS, QP 1000 EX instrument operating at 70 eV. Elemental analyses



Scheme 4. Cyclization of the dibasic acid **4** using conc. H_2SO_4 at 0°C.

were carried out at the Microanalytical Unit, Faculty of Science, Ain Shams University using a Perkin-Elmer 2400 CHN elemental analyzer, and satisfactory analytical data (±0.4) were obtained for all compounds. The homogeneity of the synthesized compounds was controlled by thin-layer chromatography (TLC) using TLC aluminum sheets with silica gel F_{254} (Merck).

(Z)-2-(3-(3,4-Dimethoxyphenyl)-1-methoxy-1-oxoprop-2-en-2-yl)benzoic Acid 1

A mixture of dimethyl homophthalate (2.08 g, 0.01 mol) and 3,4-dimethoxybenzaldehyde (1.66 g, 0.01 mol) was stirred in absolute methanol (50 ml) in the presence of sodium methoxide (0.5 g Na in 50 ml MeOH). The whole mixture was stirred at room temperature for 1 h (TLC). The precipitated solid was filtered off, dissolved in cold water, and acidified with cold, dilute hydrochloric acid. The deposited solid was filtered off, washed several times with cold water, dried, and then recrystallized from ethanol to give **1** as white crystals; mp 177–179°C, yield 90%. IR (ν): br 3396–2436 cm^{-1} (acidic OH group), 1722 cm^{-1} ($C{=}O_{\alpha,\beta\text{-unsaturated ester}}$), 1685 cm^{-1} ($C{=}O_{\text{aromatic acid}}$). MS: 342 (100), 265 (34.1), 151 (38.8), 91 (3.0), 65 (7.5). Anal. calcd. for $C_{19}H_{18}O_6$ (342.35): C, 66.6; H, 5.3. Found: C, 66.3; H, 5.4.

(3R,4S)-Methyl-4-bromo-3-(2-bromo-4,5-dimethoxyphenyl)-1-oxo-3,4-dihydro-1H-iso-chromene-4-carboxylate 2

Bromine (3 ml in 15 ml AcOH) was added dropwise to a solution of the half ester **1** (3.42 g, 0.01 mol) in acetic acid (30 ml) with stirring at room temperature for 1 h. The whole mixture was then kept at room temperature overnight. The reaction mixture was then diluted with cold water. The precipitated solid was filtered off, dried, and then recrystallized from benzene to give **2** as buff crystals; mp 182–184°C, yield 89%. IR (ν): 1748 cm^{-1} ($C{=}O_{\delta\text{-lactone}}$), 1739 cm^{-1} ($C{=}O_{\text{ester}}$). ^1H NMR ($CDCl_3$) δ 8.5–7.2 (m, $6H_{\text{arom.}}$), 6.58 (s, 1H, C_3-H), 4.14 (s, 6H, Ar-OMe), 4.09 (s, 3H,

COOMe). MS: 500 (28.1), 420 (10.2), 333 (8.8), 256 (100). Anal. calcd. for $C_{19}H_{16}Br_2O_6$ (500.14): C, 45.6; H, 3.2; Br, 31.9. Found: C, 45.4; H, 3.1; Br, 31.6.

Single-Crystal X-Ray Diffraction Analysis of $C_{19}H_{16}O_6Br_2$

Intensities were collected on the Kappa CCD Enraf-Nonius FR 590 diffractometer[18] using the ω-2θ scan technique. $C_{19}H_{16}O_6Br_2$ crystallized in space group $P2_1/C$ with a = 20.1043 (7) Å, b = 8.7046 (2) Å, c = 11.0497 (3) Å, and β = 97.0923 (11)°, V = 1918.90 (10) A^{-3}, Z = 4. Of the 9619 unique reflections measured (Mo Kα radiation), 2273 were considered observed [$I > 3\sigma$ (I)]. The final refinement residuals were R = 0.068 (on F) and $wR_2 = 0.144$ (on F^2). The data was solved using SIR 92.[19] The radiation type is a graphite monochromatized[20] Mo Kα (λ = 0.71073 Å) operated at 50 kV and 20 mÅ. The data was refined using Maxus.

(E)-Methyl-2-(3-(3,4-dimethoxyphenyl)-1-methoxy-1-oxoprop-2-en-2-yl)benzoate 3

$SOCl_2$ (7 ml) was added dropwise with stirring to a solution of the half ester **1** (3.42 g, 0.01 mol) in absolute methanol (50 ml) at room temperature for 0.5 h. The whole mixture was then refluxed on a water bath for 8 h. The excess methanol was distilled off, and the reaction product then poured on sodium carbonate solution. The deposited solid was filtered off, dried, and recrystallized from ethanol to give **3** as colorless crystals; mp 110–112°C, yield 86%. IR (ν): 1720 cm^{-1} ($C{=}O_{ester}$). ^1H NMR ($CDCl_3$) δ 8.1–6.7 (m, $7H_{arom.}$), 6.2 (s, 1H, olefinic), 3.8 (s, 6H, Ar-OMe), 3.7 (s, 3H, COOMe), 3.36 (s, 3H, Ar-COOMe). MS: 356 (68.5), 297 (20.5), 151 (27.4), 79 (19.2), 59 (100). Anal. calcd. for $C_{20}H_{20}O_6$ (356.37): C, 67.4; H, 5.6. Found: C, 67.1; H, 5.3.

Single-Crystal X-Ray Diffraction Analysis of $C_{20}H_{20}O_6$

Intensities were collected on the Kappa CCD Enraf-Nonius FR 590 diffractometer[18] using the ω-2θ scan technique. $C_{20}H_{20}O_6$ crystallized in space group $P2_1$ with a = 7.8839 (4) Å, b = 8.1087 (4) Å, c = 14.4840 (10) Å, and β = 97.447 (2)°. Of the 2917 unique reflections measured (Mo Kα radiation), 844 were considered observed [$I > 3\sigma$ (I)]. The final refinement residuals were R = 0.041 (on F) and $wR_2 = 0.084$ (on F^2). The data was solved using SIR 92.[19] The radiation type is a graphite monochromatized[20] Mo Kα (λ = 0.71073 Å) operated at 50 kV and 20 mÅ. The data was refined using Maxus.

(Z)-2-(1-Carboxy-2-(3,4-dimethoxyphenyl)vinyl)benzoic Acid 4

The half-ester **1** (3.42 g, 0.01 mol) 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 recrystallized from ethanol to give **4** as white crystals; mp 193–195°C, yield 84%. IR (ν): br 3500–3100 cm^{-1} (acidic OH group), 1678 ($C{=}O_{\alpha,\beta\text{-unsaturated acid}}$). MS: 328 (61.3), 310 (23.2), 282

(16.0), 122 (6.1), 77 (52.5), 51 (100). Anal. calcd. for $C_{18}H_{16}O_6$ (328.32): C, 65.8; H, 4.9. Found: C, 65.7; H, 5.1.

9,10-Dimethoxyindeno[1,2-c]isochromene-5,11(6aH,11aH)-dione 5

The acid **4** (3.28 g, 0.01 mol) was stirred at 0°C with concentrated sulfuric acid (30 ml) for 30 min, then left 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 recrystallized from benzene to give **5** as pale yellow crystals; mp 186–188°C, yield 65%. IR (ν): 1737 cm^{-1} ($C{=}O_{\delta\text{-lactone}}$), 1710 cm^{-1} ($C{=}O_{\text{saturated five-membered ketone}}$). ^1H NMR ($CDCl_3$) δ 8.15–7.20 (m, $6H_{arom.}$), 6.26–6.24 (d, 1H, C_{6a}-H, $J = 6.9$ Hz), 4.17–4.15 (d, 1H, C_{11a}-H, $J = 6.9$ Hz), 3.92 (s, 6H, 2OMe). MS: 310 (100), 282 (39.5), 251 (99.1). Anal. calcd. for $C_{18}H_{14}O_5$ (310.30): C, 69.6; H, 4.5. Found: C, 69.3; H, 4.5.

(E)-6-Amino-11-hydrazono-9,10-dimethoxy-6,6a,11,11a-tetrahydroindeno[1,2-c]isoquinolin-5-one 6

A mixture of **5** (3.1 g, 0.01 mol) and hydrazine hydrate (1 ml, 0.02 mol) in 20 ml dioxane was refluxed for 6 h (TLC). After evaporation of solvent, the colorless solid product was collected by filtration and recrystallized from dioxane to give **6** as colorless crystals; mp 226–228°C, yield 75%. IR (ν): br. 3316, 3284 cm^{-1} (NH_2), 1649 cm^{-1} ($C{=}O_{\text{cyclic amide}}$). MS: 338 (42.8), 307 (100). Anal. calcd. for $C_{18}H_{18}N_4O_3$ (338.36): C, 63.9; H, 5.3; N, 16.5. Found: C, 63.8; H, 5.2; N, 16.2.

2-Cyano-N-(9,10-dimethoxy-5,11-dioxo-11,11a-dihydro-5H-indeno[1,2-c]isoquinolin-6(6aH)-yl)acetamide 7

A mixture of **5** (3.1 g, 0.01 mol) and cyanoethanoic hydrazide (1 g, 0.01 mol) in 20 ml dioxane was refluxed for 6 h (TLC). After evaporation of solvent, a yellow solid product was separated, collected by filtration, and recrystallized from dioxane to give **7** as yellow crystals; mp 254–256°C, yield 77%. IR (ν): 3285 cm^{-1} (NH), 2253 (w) cm^{-1} ($C{\equiv}N$), 1709 cm^{-1} ($C{=}O_{\text{saturated five-membered ketone}}$), 1666 cm^{-1} ($C{=}O_{\text{cyclic amide}}$). ^1H NMR (DMSO-d_6) δ 10.7 (s, 1H, NH, exchangeable with D_2O), 7.9–7.2 (m, $6H_{arom.}$), 5.57–5.55 (d, 1H, C_{11}-H, $J = 6$ Hz), 4.59–4.57 (d, 1H, C_{11a}-H, $J = 6$ Hz), 4.03 (d,d, 2H, CH_2), 3.82 (s, 6H, 2OMe). MS: 323 ([$M^{+\bullet}$ $-CH_2{=}C{=}O$, $-CN^{\bullet}$, 28.4), 307 (100), 293 (22.5), 264 (17.5), 165 (23.5), 77 (21.6). Anal. calcd. for $C_{21}H_{17}N_3O_5$ (391.38): C, 64.4; H, 4.4; N, 10.73. Found: C, 64.1; H, 4.3; N, 10.4.

[1,2,4]Triazolo[2,3-a]isoquinoline Derivative 8

A mixture of **5** (3.1 g, 0.01 mol) and semicarbazide hydrochloride (1.11 g, 0.01 mol) in 20 ml pyridine was refluxed for 6 h (TLC). After evaporation of solvent, a buff solid product was deposited, collected by filtration, dried, and recrystallized from ethanol/dioxane to give **8** as buff crystals; mp > 330°C, yield 80%. IR (ν): 3432 cm^{-1} (NH), 1707 cm^{-1} ($C{=}O_{\text{saturated five-membered ketone}}$), 1682 cm^{-1}

($C{=}O_{cyclic\ imide}$), 1662 cm^{-1} (C=N). MS: 349 (43.1), 323 (58.5), 50 (100). Anal. calcd. for $C_{19}H_{15}N_3O_4$ (349.34): C, 65.3; H, 4.3; N, 12.0. Found: C, 65.1; H, 4.3; N, 11.7.

6-Benzyl-9,10-dimethoxy-6,6a-dihydro-11aH-Indeno[1,2-c]isoquinoline-5,11-dione 9

A mixture of **5** (3.1 g, 0.01 mol) and benzylamine (1 ml, 0.01 mole) in 15 ml pyridine was refluxed for 3 h (TLC). The reaction mixture was allowed to cool and acidified with cold dilute hydrochloric acid. The precipitate was collected by filtration and recrystallized from ethanol to give **9** as pink crystals; mp 169–171°C, yield 60%. IR (ν): 1707 cm^{-1} ($C{=}O_{saturated\ five\text{-}membered\ ketone}$), 1657 cm^{-1} ($C{=}O_{cyclic\ amide}$). ^1H NMR ($CDCl_3$) δ 8.20–6.71 (m, $11H_{arom.}$), 5.55–5.50 (d, 1H, C_{6a}-H, $J = 15$ Hz), 4.87–4.82 (d, 1H, C_{11a}-H, $J = 15$ Hz), 4.22 (s, 2H, CH_2), 3.85 (s, 6H, 2OMe). ^{13}C NMR ($CDCl_3$) δ (ppm): 198.71 (C_{11}), 163.08 (C_5), 155.77 (C_{10}), 150.71 (C_9), 147.63 (C_{1a}), 137.15 (C_{4a}), 133.35 (C'_1, benzyl ring), 132.36 (C_{7a}), 129.16 (C_2), 128.99 (C_1), 128.22 (C'_3, benzyl ring), 127.89 (C'_2, benzyl ring), 127.82 (C_4), 127.35 (C_3), 127.18 (C'_4, benzyl ring), 126.01 (C_{10a}), 106.44 (C_7), 104.48 (C_8), 57.16 (C_{11a}), 56.31 (OCH_3), 56.10 (OCH_3), 51.85 (C_{6a}), 50.64 (NCH_2). MS: 399 (13.3), 308 (24.4), 294 (40.1), 106 (58.4), 91 (100), 65 (38.6). Anal. calcd. for $C_{25}H_{21}NO_4$ (399.44): C, 75.2; H, 5.3; N, 3.5. Found: C, 75.1; H, 5.4; N, 3.2.

(Z)-Ethyl-2-cyano-2-(9,10-dimethoxy-5-oxoindeno[1,2-c]isochromen-11(5H,6aH,11aH)ylidene)acetate 10

A mixture of **5** (3.1 g, 0.01 mol), ethyl cyanoacetate (1.13 ml, 0.01 mol), and fused sodium acetate (0.82 g, 0.01 mol) was fused in an oil bath at 170°C for 15 min. The crude product was stirred with water for 15 min, filtered, dried, and then recrystallized from ethanol/dioxane to give **10** as white crystals; mp 204–207°C, yield 50%. IR (ν): 2249 cm^{-1} (C≡N), 1742 cm^{-1} ($C{=}O_{\delta\text{-lactone}}$), 1702 cm^{-1} ($C{=}O_{\alpha,\beta\text{-unsaturated ester}}$). MS: 405 (11.2), 293 (100). Anal. calcd. for $C_{23}H_{19}NO_6$ (405.40): C, 68.1; H, 4.7; N, 3.4. Found: C, 67.8; H, 5.1; N, 3.4.

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