

A Facile Synthesis of Some Spirooxindole Derivatives via One-Pot Three-Component Reactions

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Tetrahydrospiro[chromene-4,3'-indole]-2-ones (**5a-c**) and spiro[indole-3,4'-pyrano(3',2'-d)pyrazole]-2-ones (**6a-b**) have been synthesized based on the one-pot three-component cyclocondensation reaction of 5-(un)substituted isatins (**1a-c**) with ethyl cyanoacetate (**2**) and 5,5-dimethylcyclohexane-1,3-dione (**3**) or 5-methyl-2-phenyl-2,4-dihydro-pyrazol-3-one (**4**) in absolute ethanol containing a catalytic amount of Et₃N carried out under both conventional heating and environmentally benign procedures. The structures of the resulting compounds were confirmed by spectral {IR, ¹H NMR, ¹³C NMR, 2D NMR [¹H-¹H COSY, ¹H-¹³C COSY (HETCOR)] and electrospray ionization tandem mass [(±) ESI-MS/MS]} analysis.

Key Words: Isatin, Spirooxindole, Ultrasound irradiation, Microwave irradiation, Retro diels-alder fragmentation.

INTRODUCTION

Five-membered nitrogen heterocycles, especially highly substituted pyrrolidines feature widely in pharmaceuticals, natural alkaloids, organocatalysts and are also useful building blocks in organic synthesis¹. The indole moiety is probably the most well-known heterocyclic compound, a common and important feature of a variety of natural products and medicinal agents². Compounds carrying the indole residue, such as isatin (1*H*-indole-2,3-dione) and its derivatives exhibiting antimicrobial,³⁻¹⁸ antiviral¹⁹⁻²³ antiparasitic²⁴ antitubercular²⁵⁻²⁷ anticancer²⁸⁻³⁵ anticonvulsant³⁶⁻⁴¹ antioxidant^{42,43} activities. Due to the above mentioned diverse properties of isatins, we report herein the synthesis of some spirooxindole compounds using simple, convenient and an efficient one-pot three-component reactions.

EXPERIMENTAL

All commercially available chemicals and reagents were used without further purification. Melting points were acquired in open capillary tubes and were measured on an electro thermal digital melting point apparatus. Infrared data were obtained using Perkin-Elmer, FT-IR spectrometer, as KBr pellets. ¹H, ¹³C and the 2D NMR spectra were recorded using a JEOL-NMR spectrometer at 300 MHz and 75 MHz, on solutions in DMSO-*d*₆ using TMS as an internal standard. Chemical shifts are given in ppm (δ-scale) and the coupling

constants are given in Hertz. Results of DEPT-135 experiment is shown in parentheses where relative to DMSO-*d*₆, (+) denotes CH₃ or CH and (-) denotes CH₂. Follow up of the reactions and checking the purity of the compounds were made by TLC on silica gel-protected glass sheets (Type Si250F, 'BAKER' of 0.2 mm thickness) using ethanol-chloroform (1:9) as eluant. The spots were detected by exposure to UV-lamp at λ 254 nm for few seconds. Mass spectra were obtained using a quattro premier triple quadrupole mass spectrometer (UPLC-MS/MS) equipped with electrospray ion source using both positive and negative ion mode. Ultrasonication was performed in a J.P. Selecta ultrasound cleaner with a frequency of 60 Hz and an output power of, 770 W. The reaction flask was located in the maximum energy area in the cleaner, where the surface of reaction (reaction vessel) is slightly lower than the level of the water. The temperature of the water bath was controlled by the addition or removal of circulated water. Microwave irradiated reactions were carried out on a Galanz microwave oven, operating at 1000 W, generating 60 Hz frequency.

Synthesis of spirooxindoles (5a-c and 6a-b): They were synthesized by following different methods.

Method A (conventional method): To a solution of 5-(un) substituted isatins (**1a-c**) (1 mmol), ethyl cyanoacetate (**2**) (0.13 g, 1 mmol) and triethylamine (3-4 drops) in absolute ethanol (25 mL), 5,5-dimethyl-cyclohexane-1,3-dione (**3**) (0.14 g, 1 mmol) or 5-methyl-2-phenyl-2,4-dihydro-pyrazole-3-one (**4**) (0.17 g, 1 mmol) was added and heated under

refluxed for about 2 h. The progress of the reaction was followed by TLC. After complication, the solvent was removed under reduced pressure and the residue was then washed well with ethanol, dried and recrystallized from methanol to afford pure products in cases (**5a-c**), while in cases (**6a,b**) the solid was treated with ether or petroleum ether (60-80 °C) and recrystallized from water/methanol.

Method B (ultrasound irradiation method): A mixture of 5-(un)substituted isatins (**1a-c**) (1 mmol), ethyl cyanoacetate (**2**) (0.13 g, 1 mmol), **3** or **4** (1 mmol) and triethylamine (3-4 drops) in absolute ethanol (25 mL) was irradiated in an ultrasonic bath for 1 h. After completion of the reaction (as indicated by TLC), the solvent was removed under reduced pressure and the resulting solid was then washed well with ethanol, dried and recrystallized from methanol or water/methanol to afford pure products in most cases (**5a-c**, **6a**), while in case (**6b**) the solid was treated with petroleum ether (60-80 °C) and recrystallized from water/methanol.

Method C (microwave irradiation method): An equimolar mixture of 5-(un)substituted isatins (**1a-c**) (1 mmol), ethyl cyanoacetate (0.13 g, 1 mmol), **3** or **4** (1 mmol) and triethylamine (3-4 drops) in the minimum quantity of ethanol 96 % required to form a slurry was irradiated inside a microwave oven at 300 W for 5 min. After completion, the excess solvent was removed under reduced pressure and the activated solid was then recrystallized from methanol to afford pure products in cases (**5a-c**), while in cases (**6a,b**) the solid was treated with petroleum ether (60-80 °C) and recrystallized from water/methanol.

Ethyl 2-amino-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indole]-2'-one-3-carboxylate (5a**) (Table-1, entry 1):** Pale orange fine cubes, m.p. 264 °C (from methanol); yield 59 %^A, 70 %^B, 95 %^C; IR (KBr, $\nu_{\max}$, cm⁻¹): 3369, 3235, 3179 (NH₂, NH), 1714 (C=O ester), 1687 (C=O ketone), 1671 (C=O γ -lactam); ¹H NMR (300 MHz, DMSO-*d*₆): δ_{H} (ppm) 0.79 (3H, t, *J* = 5.7, OCH₂CH₃), 0.94 (3H, s, 7-CH₃), 1.01 (3H, s, 7-CH₃), 2.01 (1H, d, ²*J* = 15.8, H_{ax}-8), 2.15 (1H, d, ²*J* = 15.8, H_{eq}-8), 2.55 (2H, s, 6-CH₂), 3.70 (2H, q, *J* = 5.7, OCH₂CH₃), 6.67 (1H, d, ³*J* = 7.1, H-7'), 6.74 (1H, td, ³*J* = 7.1, ⁴*J* = 1.1, H-5'), 6.83 (1H, d, ³*J* = 7.1, H-4'), 7.01 (1H, td, ³*J* = 7.1, ⁴*J* = 1.1, H-6'), 7.86 (2H, br. s, NH₂, D₂O exchangeable), 10.14 (1H, br. s, NH, D₂O exchangeable); ¹³C NMR, (75 MHz, DMSO-*d*₆) and DEPT-135: δ_{C} (ppm) 12.5 (OCH₂CH₃), 26.1, 27.2 [7-(CH₃)₂], 30.9 (C-7), 39.5 (C-6, overlapped with solvent signals), 46.1, 50.1 (C-8), 58.2 (OCH₂CH₃), 75.7 (spiro C), 107.5 (C-7'), 112.5, 119.9 (C-5'), 121.6 (C-4'), 126.6 (C-6'), 135.4, 143.4, 158.5, 161.8 (*sp*² carbons), 167.1 (CO ester)⁴⁴, 179.2 (CO 2'-oxindole)⁴⁴, 194.1 (CO chromene)⁴⁴; MS (+) ESI, *m/z* (%): 383 (2) [M+H]⁺ (C₂₁H₂₂N₂O₅+H)⁺, 367 (2) [383-NH₂]⁺, 338 (7) [383-OC₂H₅]⁺, 328 (67) [383-C₂H₂-C₂H₅]⁺, 309 (29) [383-CO₂C₂H₅-H]⁺, 293 (100) [383-NH₂-CO₂C₂H₅-H]⁺, 139 (22) [C₈H₁₁O₂]⁺, 115 (98) [C₅H₉NO₂]⁺.

Ethyl 2-amino-5'-bromo-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indole]-2'-one-3-carboxylate (5b**) (Table-1, entry 2):** White powder, m.p. 288 °C (from methanol); yield 62 %^A, 87 %^B, 95 %^C; IR (KBr, $\nu_{\max}$, cm⁻¹): 3387, 3276, 3213 (NH₂, NH), 1726 (C=O ester), 1687 (C=O ketone), 1653 (C=O γ -lactam); ¹H NMR (300 MHz, DMSO-

*d*₆): δ_{H} (ppm) 0.82 (3H, t, *J* = 5.5, OCH₂CH₃), 0.96 (3H, s, 7-CH₃), 1.01 (3H, s, 7-CH₃), 2.07 (1H, d, ²*J* = 15.9, H_{ax}-8), 2.14 (1H, d, ²*J* = 15.9, H_{eq}-8), 2.53 (2H, s, 6-CH₂), 3.73 (2H, q, *J* = 5.5, OCH₂CH₃), 6.65 (1H, d, ³*J* = 8.5, H-7'), 7.01 (1H, d, ⁴*J* = 1.8, H-4'), 7.22 (1H, dd, ³*J* = 8.5, ⁴*J* = 1.8, H-6'), 7.93 (2H, br. s, NH₂, D₂O exchangeable), 10.32 (1H, br. s, NH, D₂O exchangeable); ¹³C NMR (75 MHz, DMSO-*d*₆) and DEPT-135: δ_{C} (ppm) 12.9 (OCH₂CH₃), 26.9, 27.2 [7-(CH₃)₂], 30.8 (C-7), 39.9 (C-6, overlapped with solvent signals) 46.1, 50.3 (C-8), 58.7 (OCH₂CH₃), 74.9 (spiro C), 109.3 (C-7'), 111.3, 111.7, 124.3 (C-4'), 129.1 (C-6'), 137.8, 142.8, 158.4, 162.2 (*sp*² carbons), 166.7 (CO ester)⁴⁴, 178.7 (CO 2'-oxindole)⁴⁴, 194.2 (CO chromene)⁴⁴; MS (+) ESI, *m/z* (%): 461 (50) [M+H]⁺ (C₂₁H₂₁⁷⁹BrN₂O₅+H)⁺, 463 (54) [461+2]⁺ (C₂₁H₂₁⁸¹BrN₂O₅+H)⁺, 443 (6) [461-H₂O]⁺, 433 (12) [461-CO]⁺, 416 (6) [461-OC₂H₅]⁺, 389 (96) [461-CO₂C₂H₅+H]⁺, 371 (4) [461-NH₂-CO₂C₂H₅-H]⁺, 347 (4) [461-C₅H₇NO₂-H, RDA fragmentation]⁺, 311 (5) [389-Br+H]⁺, 295 (28) [416-C₈H₁₀O+H, RDA fragmentation]⁺, 279 (54) [295-NH₂]⁺, 259 (11) [461-C₈H₁₀O-HBr, RDA fragmentation]⁺, 229 (24) [259-NH-NH₂+H]⁺, 217 (100) [295-Br+H]⁺, 213 (74) [259-OC₂H₅-H]⁺, 201 (26) [229-CO]⁺, 199 (31) [259-NH₂-OC₂H₅+H]⁺, 169 (18) [C₆H₅BrN-H]⁺, 157 (21) [229-CO₂C₂H₅+H]⁺.

Ethyl 2-amino-5'-chloro-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indole]-2'-one-3-carboxylate (5c**) (Table-1, entry 3):** White powder, m.p. 278 °C (from methanol); yield 70 %^A, 70 %^B, 62 %^C; IR (KBr, $\nu_{\max}$, cm⁻¹): 3384, 3276, 3215 (NH₂, NH), 1725 (C=O ester), 1688 (C=O ketone), 1650 (C=O γ -lactam); ¹H NMR (300 MHz, DMSO-*d*₆): δ_{H} (ppm) 0.82 (3H, t, *J* = 5.5, OCH₂CH₃), 0.96 (3H, s, 7-CH₃), 1.01 (3H, s, 7-CH₃), 2.07 (1H, d, ²*J* = 15.7, H_{ax}-8), 2.14 (1H, d, ²*J* = 15.7, H_{eq}-8), 2.53 (2H, s, 6-CH₂), 3.73 (2H, q, *J* = 5.5, OCH₂CH₃), 6.68 (1H, d, ³*J* = 8.3, H-7'), 6.90 (1H, d, ⁴*J* = 1.9, H-4'), 7.09 (1H, dd, ³*J* = 8.3, ⁴*J* = 1.9, H-6'), 7.93 (2H, br. s, NH₂, D₂O exchangeable), 10.31 (1H, br. s, NH, D₂O exchangeable); ¹³C NMR (75 MHz, DMSO-*d*₆) and DEPT-135: δ_{C} (ppm) 12.4 (OCH₂CH₃), 26.3, 26.7 [7-(CH₃)₂], 30.9 (C-7), 39.3 (C-6, overlapped with solvent signals), 43.1, 49.8 (C-8), 58.2 (OCH₂CH₃), 75.1 (spiro C), 108.7 (C-7'), 111.8, 121.7 (C-4'), 123.7, 126.3 (C-6'), 137.5, 142.5, 158.5, 162.2 (*sp*² carbons), 166.8 (CO ester)⁴⁴, 178.9 (CO 2'-oxindole)⁴⁴, 194.2 (CO chromene)⁴⁴; MS (-) ESI, *m/z* (%): 415 (36) [M-H]⁻ (C₂₁H₂₁³⁵ClN₂O₅-H)⁻, 417 (14) [415+2]⁻ (C₂₁H₂₁³⁷ClN₂O₅-H)⁻, 401 (4) [415-CH₃+H]⁻, 387 (8) [415-CO]⁻, 370 (6) [415-OC₂H₅]⁻, 369 (28) [387-H₂O]⁻, 362 (100) [415-H₂O-Cl]⁻, 360 (10) [415-C₂H₂-C₂H₅]⁻, 343 (32) [415-CO₂C₂H₅+H]⁻, 325 (12) [415-NH₂-CO₂C₂H₅-H]⁻, 309 (52) [343-Cl+H]⁻, 302 (3) [415-C₅H₇NO₂, RDA fragmentation]⁻, 293 (22) [415-C₈H₁₀O, RDA fragmentation]⁻.

Ethyl 6'-amino-3'-methyl-1'-phenylspiro[indole-3,4'-pyrano(3',2'-d)pyrazole]-2-one-5'-carboxylate (6a**) (Table-1, entry 4):** Pale brown powder, m.p. 190 °C (from water/methanol); yield 50 %^A, 95 %^B, 95 %^C; IR (KBr, $\nu_{\max}$, cm⁻¹): 3352, 3254, 3211 (NH₂, NH), 1697 (C=O ester), 1640 (C=O γ -lactam); ¹H NMR (300 MHz, DMSO-*d*₆): δ_{H} (ppm) 0.75 (3H, t, *J* = 6.9, OCH₂CH₃), 1.57 (3H, s, 3'-CH₃), 3.75 (2H, q, *J* = 6.9, OCH₂CH₃), 6.85-6.91 (2H, m, H-5,7), 6.97 (1H, d, ³*J* = 7.3, H-4), 7.17 (1H, t, ³*J* = 7.3, H-6), 7.34 (1H, t, ³*J* = 7.3, H-4''), 7.51 (2H, t, ³*J* = 8.1, H-3',5'), 7.81 (2H, d, ³*J* = 8.1, H-2'',6''),

TABLE-1
 SYNTHESIS OF **5a-c** AND **6a,b** via CLASSICAL HEATING, ULTRASOUND AND MICROWAVE IRRADIATION CONDITIONS

Entry	Products	R	Method A ^a		Method B ^b		Method C ^c	
			Time (min)	Yield (%)	Time (min)	Yield (%)	Time (min)	Yield (%)
1	5a	H	120	59	60	70	5	95
2	5b	Br	120	62	60	87	5	95
3	5c	Cl	120	70	60	70	5	70
4	6a	H	120	50	60	95	5	95
5	6b	Cl	120	73	60	95	5	95

^aMethod A: Refluxing in abs. ethanol; ^bMethod B: Ultrasound irradiation at 25-30 °C in abs. ethanol; ^cMethod C: Microwave irradiation at 300 W (in the minimum quantity of ethanol 96 %)

8.21 (2H, br. s, NH₂, D₂O exchangeable), 10.51 (1H, br. s, NH, D₂O exchangeable); ¹³C NMR (75 MHz, DMSO-*d*₆) and DEPT-135: δ_c (ppm) 10.9 (3'-CH₃), 12.3 (OCH₂CH₃), 46.7, 58.2 (OCH₂CH₃), 73.8 (spiro C), 97.4, 108.1 (C-7), 119.2 (C-2'',6''), 120.9 (C-5), 122.4 (C-4), 125.6 (C-6), 126.9 (C-4''), 128.6 (C-3'',5''), 135.1, 136.6, 141.4, 143.2 (C-1''), 143.5, 160.6 (*sp*² carbons), 167.1 (CO ester), 178.5 (CO 2-oxoindole); MS (-) ESI, *m/z* (%): 415 (54) [M-H]⁻ (C₂₃H₂₀N₄O₄-H)⁻, 400 (2) [415-CH₃]⁺, 395 (100) [415-NH₂-4H]⁺, 384 (43) [415-C₂H₅-2H]⁺, 369 (28) [415-OC₂H₅-H]⁺, 348 (400-2x C₂H₂)⁺, 302 (39) [415-C₅H₇NO₂, RDA fragmentation]⁻, 259 (23) [415-C₁₀H₈N₂, RDA fragmentation]⁻.

Ethyl 6'-amino-5-chloro-3'-methyl-1'-phenylspiro[indole-3,4'-pyrano(3',2'-d)pyrazole]-2-one-5'-carboxylate (6b**) (Table-1, entry 5):** Dark brown powder, m.p. 200 °C (from water/methanol); yield 73 %^A, 95 %^B, 95 %^C; IR (KBr, $\lambda_{\max}$, cm⁻¹): 3355, 3254, 3194 (NH₂, NH), 1701 (C=O ester), 1640 (C=O γ -lactam); ¹H NMR (300 MHz, DMSO-*d*₆): δ_H (ppm) 0.79 (3H, t, *J* = 7.3, OCH₂CH₃), 1.63 (3H, s, 3'-CH₃), 3.78 (2H, q, *J* = 7.3, OCH₂CH₃), 6.87 (1H, d, ³*J* = 8.1, H-7), 7.12 (1H, br. s, H-4, there is ⁴*J* coupling but not resolved), 7.22 (1H, d, ³*J* = 8.1, H-6, there is ⁴*J* coupling but not resolved), 7.35 (1H, t, ³*J* = 8.1, H-4''), 7.52 (2H, t, ³*J* = 8.1, H-3'',5''), 7.81 (2H, d, ³*J* = 8.1, H-2'',6''), 8.27 (2H, br. s, NH₂, D₂O exchangeable), 10.66 (1H, br. s, NH, D₂O exchangeable); ¹³C NMR (75 MHz, DMSO-*d*₆) and DEPT-135: δ_c (ppm) 11.5 (3'-CH₃), 12.9 (OCH₂CH₃), 47.5, 58.8 (OCH₂CH₃), 73.7 (spiro C), 97.2, 109.9 (C-7), 119.7 (C-2'',6''), 123.2 (C-4), 125.5, 126.1 (C-4''), 127.4 (C-6), 129.1 (C-3'',5''), 137.1, 137.6, 140.8, 143.7 (C-1''), 143.8, 161.1 (*sp*² carbons) 167.4 (CO ester), 178.8 (CO 2-oxoindole); MS (-) ESI, *m/z* (%): 449 (76) [M-H]⁻ (C₂₃H₁₉³⁵ClN₄O₄-H)⁻, 451 (16) [449+2]⁻ (C₂₃H₁₉³⁷ClN₄O₄-H)⁻, 435 (2) [449-CH₃+H]⁻, 421 (4) [449-CO]⁻, 403 (6) [449-OC₂H₅-H]⁻, 395 (9) [421-C₂H₂]⁻, 382 (42) [435-2x C₂H₂-H]⁺, 336 (100) [449-C₅H₇NO₂, RDA fragmentation]⁻, 293 (9) [449-C₁₀H₈N₂, RDA fragmentation]⁻, 245 (8) [293-CH₃-Cl+2H]⁻, 219 (6) [245-C₂H₂]⁻, 205 (8) [293-CONH-OC₂H₅]⁺, 191 (16) [219-CO]⁻, 159 (12) [205-CONH₂-2H]⁻, 117 (65) [205-C₂H₂-CO-Cl+H]⁺, 76 (14) [C₆H₄]⁺.

RESULTS AND DISCUSSION

In our initial endeavor, we have investigated a three-component reaction of 5-(un)substituted isatins (**1a-c**) with ethyl cyanoacetate (**2**), 5,5-dimethylcyclohexane-1,3-dione (**3**) and Et₃N in absolute ethanol by using several methods such as thermal heating (Method A), ultrasound irradiation (method B) and microwave irradiation (method C) conditions to afford

functionalized spirooxindole derivatives (**5a-c**) (Scheme-I, Table-1). In comparison, the reaction realized under ultrasound and microwave irradiation had higher yields than those performed under classical conditions for less time and temperature. However, each of them gave the desired **5** and **6** as the single products. Proposed mechanism for the synthesis of **5** was described in (Scheme-II)⁴⁵. The process represent a typical cascade reaction in which the isatin **1** first condenses with ethyl cyanoacetate (**2**) to produce non-isolated isatylidene derivative **7** in absolute ethanol in the presence of Et₃N. This step was regarded as a fast knoevenagel condensation. Then, **7** is attacked via Michael addition of **3** to give the intermediate **8** followed by the cycloaddition of hydroxyl group to the cyano moiety to form the desired product **5**. Structural elucidation of spiro[chromene-4,3'-indole]-2-ones (**5a-c**) was accomplished using 1D and 2D NMR spectrometric studies as described for **5b** (Fig. 1).

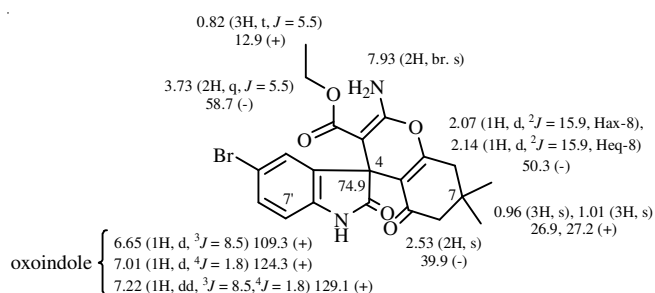
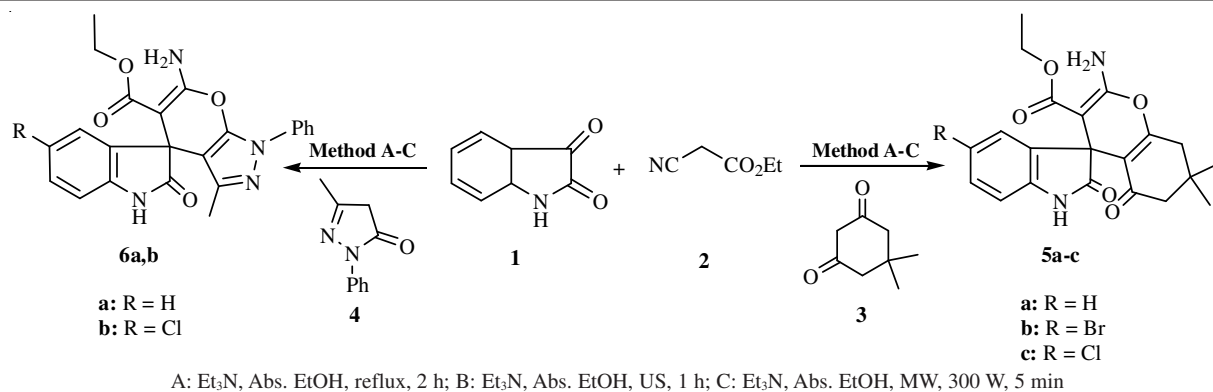
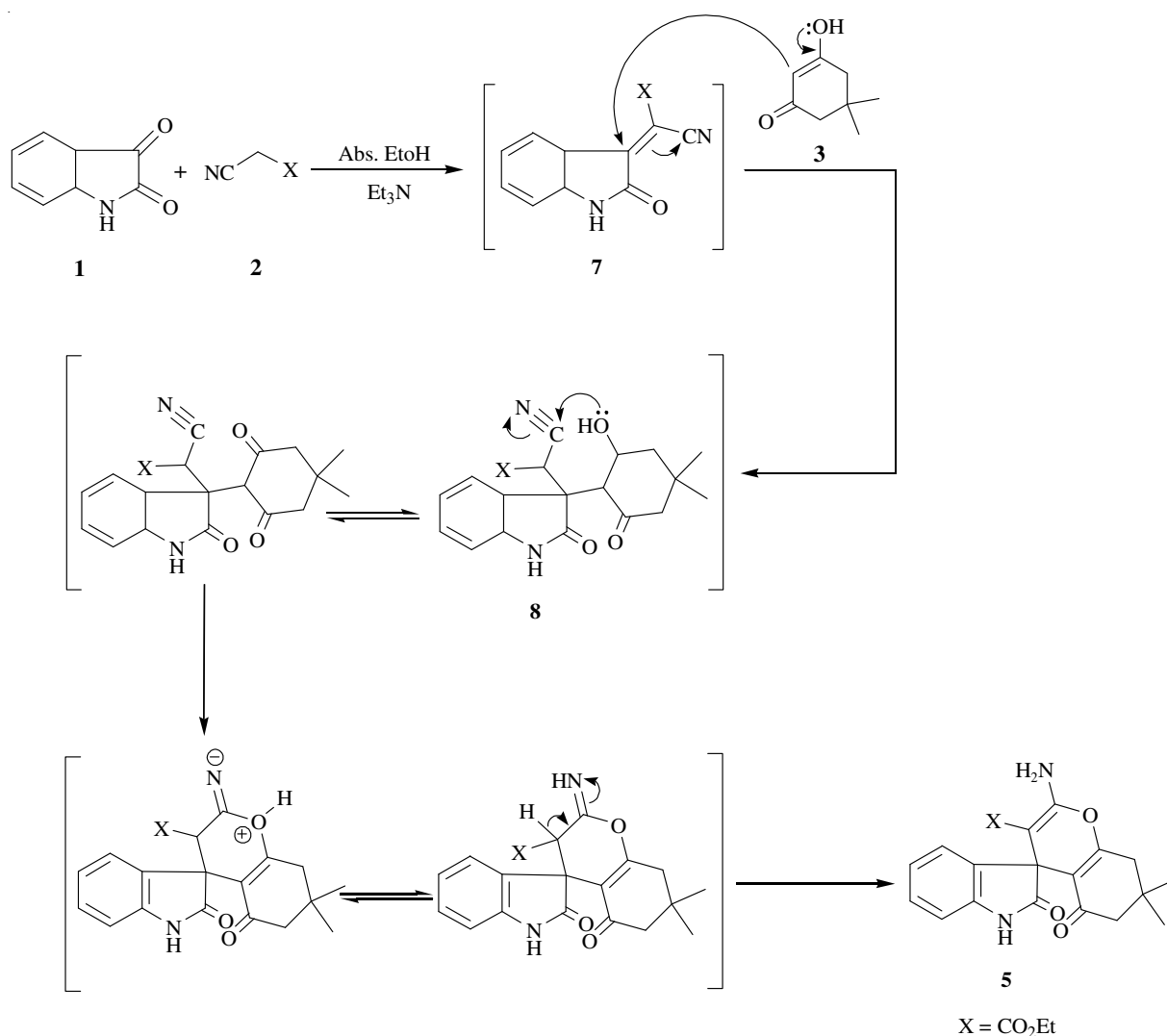


Fig. 1. Selected ¹H and ¹³C NMR/DEPT-135 chemical shifts of **5b**

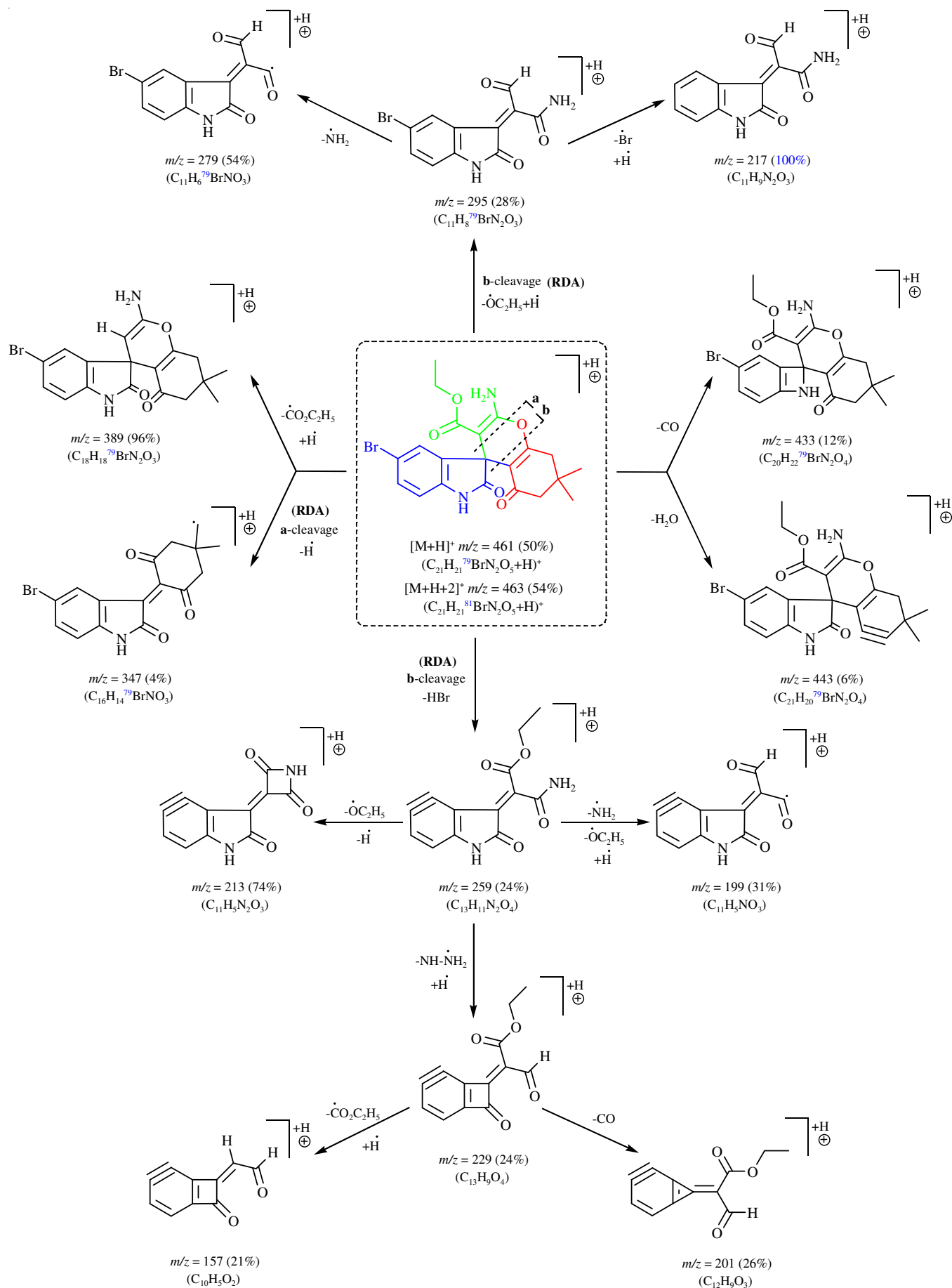
The IR spectra of **5** showed absorption bands at 3387-3179 cm⁻¹ corresponding to the NH₂ and N-H stretching, in addition to bands in the range 1726-1650 cm⁻¹, which are characteristic to C=O groups. In the ¹H NMR spectrum of **5b** demonstrated a triplet at 0.82 ppm (*J* = 5.5 Hz) due to 3-CH₃ protons of ester group. These protons showed ¹H-¹H COSY correlations with 3-CH₂ and ¹H-¹³C COSY correlations with carbon signal at 12.9 (+) ppm. The two singlet at 0.96 and 1.01 ppm were assigned to 7-(CH₃)₂ chromene protons from their ¹H-¹³C COSY correlations with C-7 at 26.9 (+) and 27.2 (+) ppm. The 8-CH₂ protons appeared as doublets at 2.07 and 2.14 ppm (²*J* = 15.9 Hz) and showed ¹H-¹³C COSY correlations with carbon signal at 50.3 (-) ppm. While, 6-CH₂ protons appeared as singlet at 2.53 ppm and showed ¹H-¹³C COSY correlations with C-6 at 39.9 (-) ppm. The quartet at 3.73 ppm (*J* = 5.5 Hz), related by ¹H-¹H COSY correlations with 3-CH₃ protons of ester group, due to 3-CH₂ showed ¹H-¹³C COSY correlations with carbon signal at 58.7 (-) ppm. The H-7', 4' and 6' of the oxindole ring occurred as two doublets at 6.65

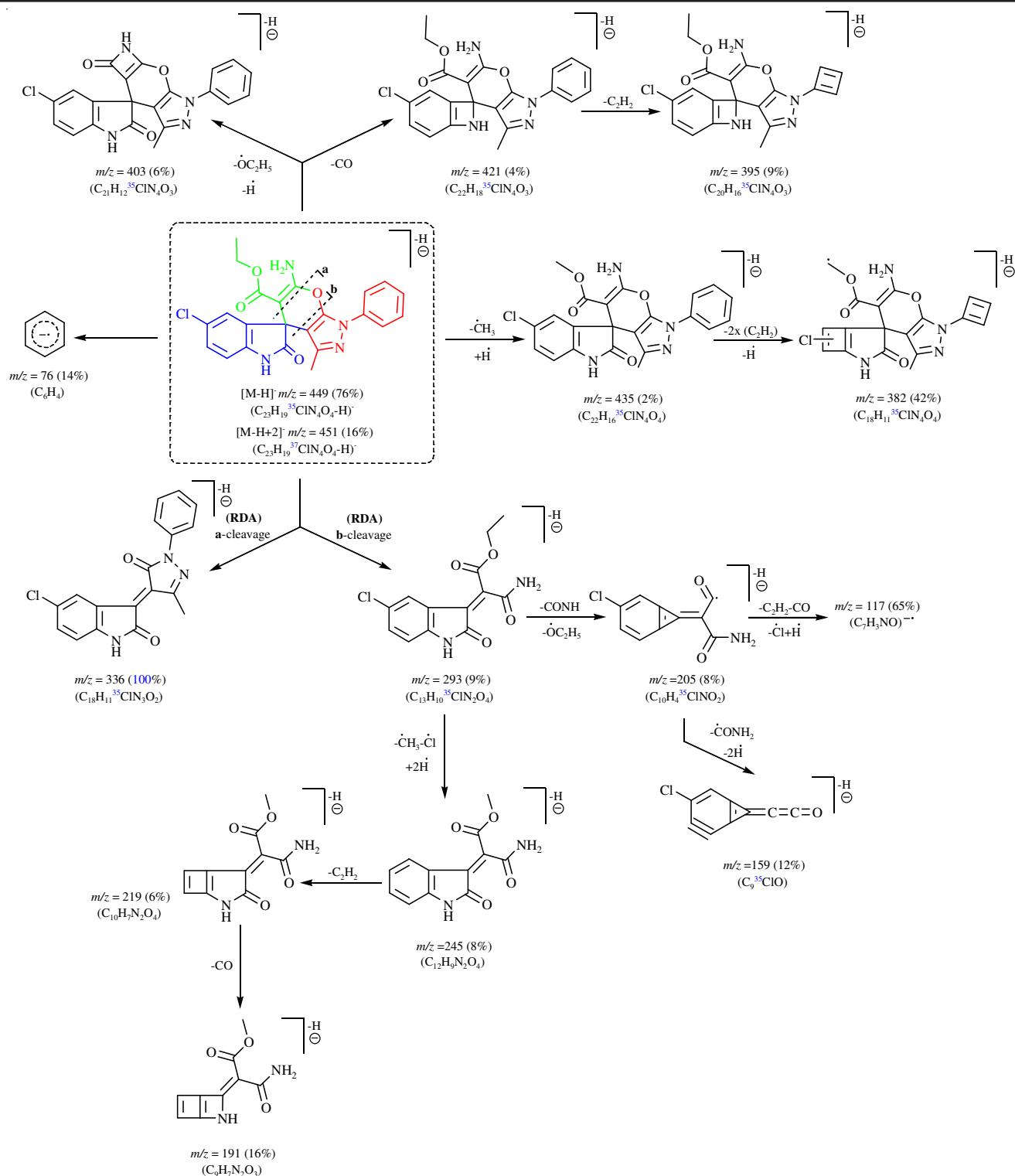
Scheme-I: Synthesis of spirooxindole derivatives **5** and **6**Scheme-II: Proposed mechanism for the formation of spiro[chromene-4,3'-indol]-2-ones **5**

(³*J* = 8.5 Hz) and 7.01 (⁴*J* = 1.8 Hz) and doublet of doublets at 7.22 ppm (³*J* = 8.5, ⁴*J* = 1.8 Hz), respectively, which showed ¹H-¹³C COSY correlations with C-7' at 109.3 (-), C-4' at 124.3 (-) and C-6' at 129.1 (-) ppm. The D₂O exchangeable protons at 7.93 and 10.32 ppm assigned to NH₂ and NH groups, respectively. Moreover, the ¹³C NMR exhibited signal at 74.9 for the spiro carbon atom beside three signals in the range of 166.7-194.2 for the carbonyl groups. All other carbons in this

spectrum appeared at their expected chemical shift. The mass spectrum of **5b** further confirmed its structure, which gave protonated (quasi-molecular) ion [M+H]⁺ peak at *m/z* 461 as well as at *m/z* 463 for bromine isotope. The plausible mass fragmentation pattern of **5b** was described in Scheme-III.

Furthermore, we have applied this reaction on 5-methyl-2-phenyl-2,4-dihydropyrazole-3-one (**4**) instead of **3** under similar conditions to furnish the respective spiro[indole-

Scheme-III: Proposed fragmentation pathways of protonated **5b**



Scheme-IV: Proposed fragmentation pathways of deprotonated **6b**

3,4'-pyrano(3',2'-*d*)pyrazole]-2-ones derivatives (**6a-b**) (**Scheme-II**, Table-1). The structure of cycloadducts **6a-b** was confirmed through 1D and 2D NMR spectroscopic data (Fig. 2).

The IR spectra of **6** showed absorption bands in the 3355-3194 and 1701-1640 cm^{-1} regions resulting from the NH_2 , NH and $\text{C}=\text{O}$ functions, respectively. ^1H NMR spectrum of **6b** exhibited a singlet at 1.63 ppm due to the 3'- CH_3 protons of pyrazole ring. Further, 3'- CH_3 showed ^1H - ^{13}C COSY corre-

lations with carbon signal at 11.5 (+) ppm. This spectrum also appeared signals in the range 7.35-7.81 for the phenyl protons. The chemical shifts of other proton absorptions in the latter spectrum of **6b** as well as the whole carbon signals in the ^{13}C NMR spectrum were in complete consistent with its structure (cf. Experimental). Finally, the mass spectrum displayed distinguishing peaks at $m/z = 449$ and 451, which further supported the formation of **6b** (**Scheme-IV**).

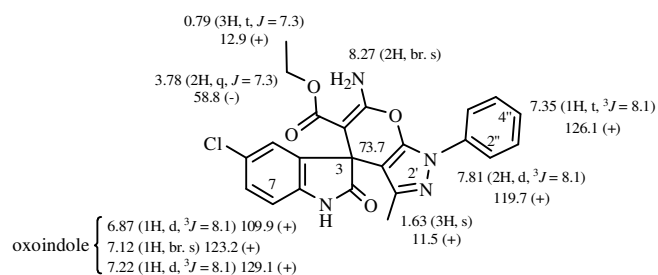


Fig. 2. Selected ^1H and ^{13}C NMR/DEPT-135 chemical shifts of **6b**

Conclusion

Herein we described an effective approach for constructing a class of spirooxindole derivatives with high selectivity under conventional heating, ultrasound and also by microwave irradiation methods. In general, improvement in rates and yields of the reactions were observed by carrying out them under environmentally benign procedures. The biological evaluations of these derivatives are ongoing in our laboratory and will be reported in due course.

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