




Article

Grindstone Chemistry: Design, One-Pot Synthesis, and Promising Anticancer Activity of Spiro[acridine-9,2'-indoline]-1,3,8-trione Derivatives against the MCF-7 Cancer Cell Line

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Abstract: In this study, the synthesis of one-pot 10-phenyl-3,4,6,7-tetrahydro-1*H*-spiro [acridine-9,2'-indoline]-1,3,8-trione derivatives was achieved via a four-component cyclocondensation reaction, which was carried out in solvent-free conditions, and using *p*-toluenesulfonic acid (*p*-TSA) as a catalyst. The product was confirmed by FT-IR, ¹H-NMR, ¹³C-NMR, mass spectra, and elemental analysis. Furthermore, the anticancer activity was screened for all compounds. Among these compounds, compound **1c** was more effective (GI₅₀ 0.01 μm) against MCF-7 cancer cell lines than standard and other compounds. Therefore, the objective of this study was achieved with a few promising molecules having been demonstrated to be potential anticancer agents.

Keywords: isatin; indole; solvent-free conditions; cyclocondensation; grinding; *p*-TSA catalyst; anticancer activity

1. Introduction

The advantages of acridine as a helpful nucleus in medicinal chemistry has consequently led to new designs, and the growth of its bi- and tri-analogues for delivering superior effects in targeted therapy compared to mono-analogues. Additionally, at present isatin and its derivatives may also be the most helpful beginning resources or ancestors within the synthesis of a good variety of spirocyclic indoles [1]. The spiro oxindole may be an advantageous heterocyclic core present in a sizable number of novel inhibitors with microtubule assembly [2], whereas pteropodines act as positive modulators of muscarinic M2 and 5-HT2 receptors [3]. Moreover, the spiro oxindole system is also a nucleus scaffold of many non-natural pharmaceutical elements with a wide assortment of biological uses, such as inhibitors of the human NK-1 receptor [4], antimicrobials [5], antineoplastics [6], and antibiotics [7]. Primarily, anticancer potency, as well as a number of other factors such as topoisomerase and telomerase inhibition, initiation of ROS mediated oxidative stress, cell cycle arrest, and interaction with P-glycoprotein, also come into play which makes the acridine/acridone moiety a privileged scaffold for anticancer chemotherapy [8]. The acridines exhibit antiprotozoal [9], antihelmintic [10] antineoplastic [11] and antiviral [12] activities. The 'Grindstone Chemistry' technique has been used as an inexperienced and speedy methodology for the synthesis of organic compounds [13,14]. Grindstone Chemistry may involve a small alteration and has established that several reactions are often carried out in high

yields by grinding two or more solids [15]. The formation of 10-phenyl-3,4,6,7-tetrahydro-1*H*-spiro [acridine-9,2'-indoline]-1,3,8-trione as a by-product is a part of our program aimed at the preparation of heterocyclic compounds [16–24], particularly spirooxindoles [25–29]. Some spiroindoles exhibit medicinally important activity, as shown in Figure 1. In Grindstone Chemistry, reactions are often performed by grinding the reactants for many minutes, without using any organic solvent. Apparently, this methodology is very effective for endothermic reactions. Based on the above results, we prepared new 10-phenyl-3,4,6,7-tetrahydro-1*H*-spiro [acridine-9,2'-indoline]-1,3,8-trione derivatives via Grindstone Chemistry and the new compounds were screened for anticancer activity.

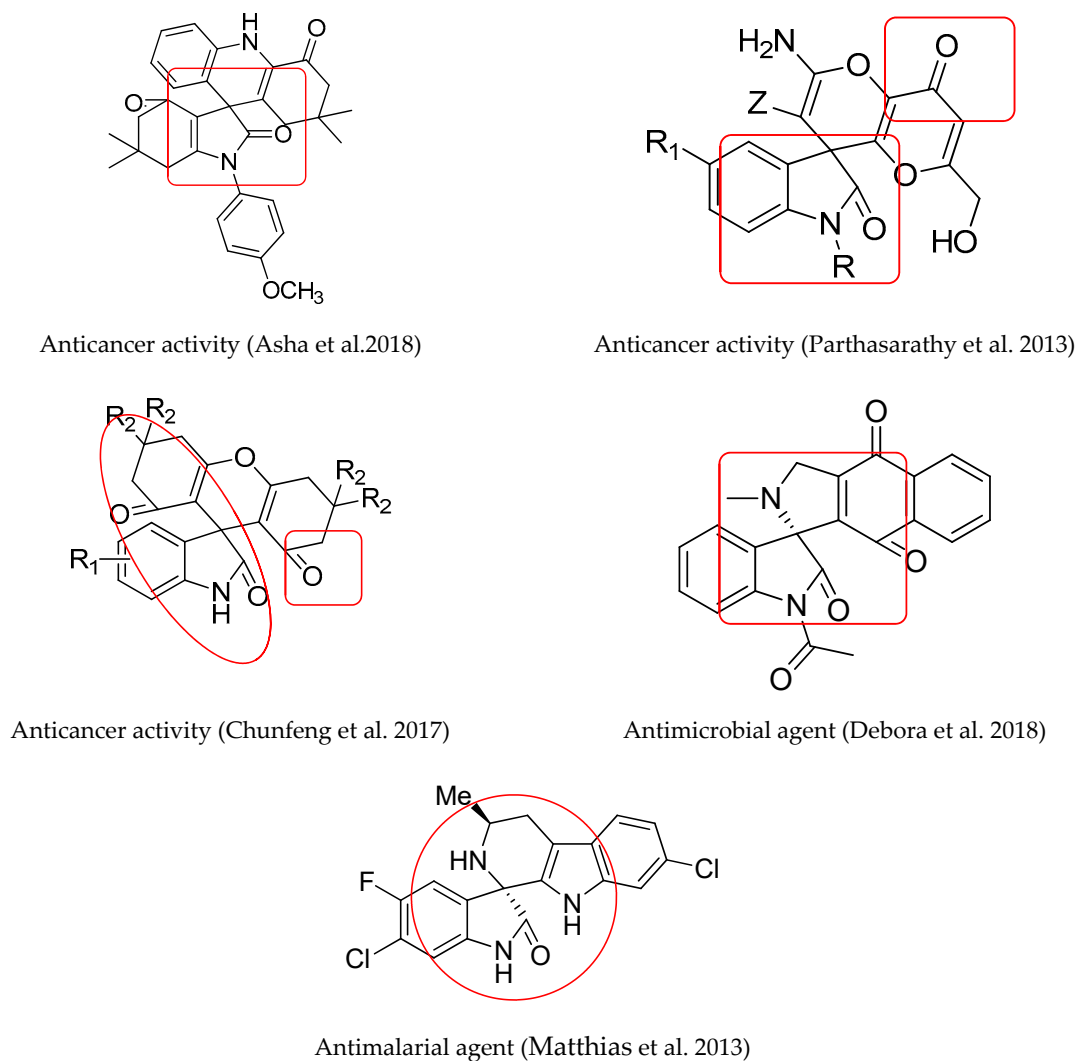


Figure 1. Some medicinally important compounds with spiroindole acridine derivatives [30–34].

2. Results and Discussion

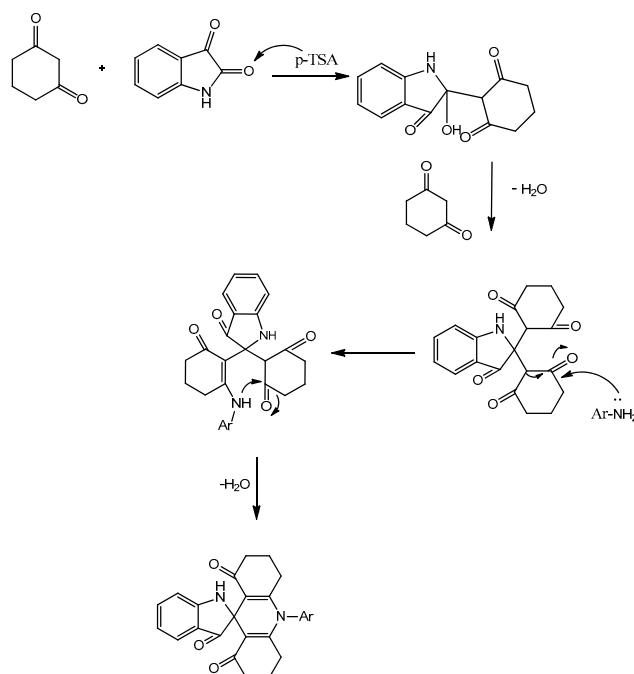
2.1. Chemistry

The synthetic methodology was evaluated with isatins, substituted anilines, and 1,3-cyclohexanedione, and the procedure followed that of [35]. All synthesized compounds were characterized by IR, ^1H and ^{13}C -NMR analysis. The IR spectrum of the compounds (**1a–1j**) showed an absorption band at 3258 to 3500 cm^{-1} due to N–H stretching, an absorption band at 2922 to 3234 cm^{-1} due to Ar–H stretching, an absorption band at 1664 to 1716 cm^{-1} due to C=O stretching, and another absorption band at 1276 to 1516 cm^{-1} due to C–N stretching. Compound **1h** exhibited an absorption band for the Cl–C group at 799 cm^{-1} and compounds **1b**, **1f** and **1i** displayed an absorption band for the NO_2 –C group

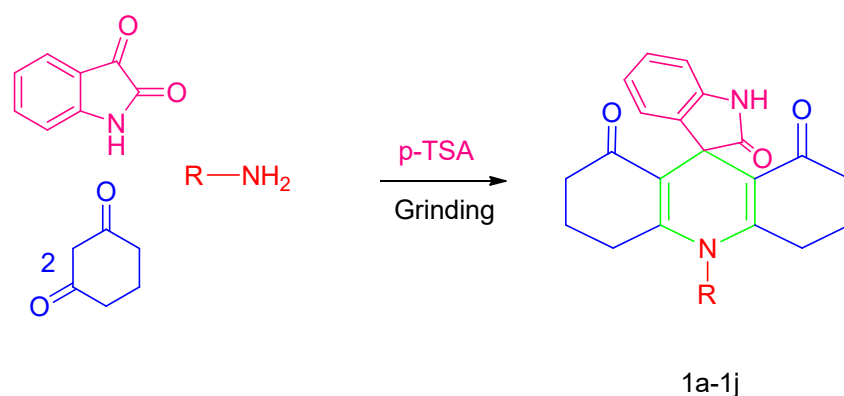
at 1504–1523 cm^{-1} . The ^1H NMR spectrum of compounds **1a–1j** showed a singlet at δ 10.10 to 10.26, attributable to N–H protons present in the isatin ring. The ^{13}C -NMR spectrum of compounds **1a–1j** exhibited peaks at δ 126.9 to 127.8, corresponding to the 2- position of C in the isatin ring. The corresponding spiro-[acridine-9,2'-indoline]-1,3,8-trione **1a–1j** was obtained in smart yields in similar conditions, which are shown in Table 1. We have not established an exact mechanism for the formation of spiro[acridine-9,2'-indoline]-1,3,8-trione derivatives, however, a sensible possibility is shown in Scheme 1. This scheme supposes that the initial addition of 1,3-cyclohexanedione to the isatin yielded the intermediate, which then reacted with an extra molecule of 1,3-cyclohexanedione. Finally, adding the substituted aniline to the intermediate, followed by cyclization, afforded the product **1a–1j**. Scheme 2 indicates the synthesis of spiro acridine derivatives of **1a–1j**.

Table 1. Optimization of the reaction conditions for compounds (**1a–1j**).

Compounds	R	Time (Min)	Yield (%)
1a	Ph	10	92
1b	-4-NO ₂ -C ₆ H ₄	10	91
1c	-4-OCH ₃ -C ₆ H ₄	10	88
1d	-2-OCH ₃ -C ₆ H ₄	10	87
1e	-3-CH ₃ -C ₆ H ₄	10	95
1f	-2-NO ₂ -C ₆ H ₄	10	82
1g	-4-CH ₃ -C ₆ H ₄	10	94
1h	-2-Cl-C ₆ H ₄	10	87
1i	-2,4-NO ₂ -C ₆ H ₄	10	78
1j	-4-Br-C ₆ H ₄	10	91



Scheme 1. Proposed mechanism for the synthesis of spiro [acridine-9,2'-indoline]-1,3,8-trione.



Scheme 2. One-pot synthesis of spiro[acridine-9,2'-indoline]-1,3,8-trione derivatives.

Anticancer Activity

The compounds (**1a–1j**) were evaluated for anticancer activity. The MCF-7 cancer cell line was used to test all compounds at a cytotoxic assay dose of 100 μM at 48 h (MTT anticancer assay measuring the functionality of animal and human cells) Table 2 indicates the results of each test compound with the growth inhibitor concentration (GI_{50}), total growth of inhibition (TGI), and lethal concentration (LC_{50}) values. The cytotoxic effect of **1c** ($\text{GI}_{50} = 0.01 \mu\text{M}$) was highly active, while **1b** ($\text{GI}_{50} = 0.02 \mu\text{M}$) was substantially active, and **1i** ($\text{GI}_{50} = 0.03 \mu\text{M}$) and **1j** ($\text{GI}_{50} = 0.04 \mu\text{M}$) were reasonably active in the MCF-7 cell line. Other compounds also exhibited significant activity. The cytotoxicity values are presented in Table 2.

Table 2. Anticancer activity of compounds (**1a–1j**).

Compounds	MCF-7 Cell Line		
	GI_{50} (μM)	TGI (μM)	LC_{50} (μM)
1a	02.7 ± 0.11	06.5 ± 1.06	08.1 ± 0.02
1b	0.02 ± 0.29	0.41 ± 2.32	0.87 ± 0.24
1c	0.01 ± 0.34	0.02 ± 1.19	0.71 ± 1.21
1d	0.09 ± 0.61	0.55 ± 0.38	1.40 ± 1.15
1e	0.19 ± 0.93	0.20 ± 1.32	0.70 ± 1.17
1f	0.52 ± 0.09	10.1 ± 2.22	22.1 ± 0.12
1g	0.35 ± 0.83	0.66 ± 1.12	14.2 ± 0.82
1h	0.26 ± 0.14	04.4 ± 1.09	09.7 ± 0.28
1i	0.03 ± 0.49	0.69 ± 0.61	2.12 ± 0.21
1j	0.04 ± 0.34	0.34 ± 0.55	1.01 ± 0.18
Doxorubicin	0.02 ± 0.70	0.21 ± 0.19	0.74 ± 0.35

3. Experimental

All of the chemicals were synthetic grade and commercially purchased from Merck. The melting point was determined by an open capillary tube and it was uncorrected. The IR spectra were recorded in KBr on a Shimadzu 8201pc ($4000\text{--}400 \text{ cm}^{-1}$). ^1H and ^{13}C -NMR spectra were recorded on a Bruker Avance II NMR spectrometer 300 MHz with DMSO-d_6 as the solvent, using tetramethylsilane (TMS) as an internal standard. Mass spectra (Perkin Elmer) and the elemental analysis (C, H, and N) were recorded using an elemental analyzer model (Varian EL III).

3.1. Synthesis of Compounds **1a–1j**

A mixture of isatin (10 mmol), phenylamine (10 mmol), and 1,3-cyclohexanedione (20 mmol), as well as p-toluenesulfonic acid (p-TSA) as a catalyst, were ground for 3–4 min, leading to a red color of 10-phenyl-3,4,6,7-tetrahydro-1*H*-spiro[acridine-9,2'-indoline]-1,3,8-trione. The final product was

washed with water and recrystallized with ethanol. The purity of the compound was checked by TLC. Hexane was used as eluting solvent in TLC. The product was separated by column chromatography. All the compounds were recrystallized by ethanol (see Supplementary Materials).

1.0-phenyl-3,4,6,7-tetrahydro-spiro[acridine-9,3-indoline]-1,2,8-trione (1a): Brown powder; mp 108–110 °C; IR: 3334 (NH), 3234 (Ar-H), 1716 (C=O), 1448 (C-N); ¹H NMR (CDCl₃, 500 MHz): δ = 10.06 (s, 1H, NH), 7.34–6.81 (m, 4H, N-Ph), 7.30–7.07 (m, 4H, Ph-isatin), 3.16 (m, 4H, CHD), 2.82 (m, 4H, CHD), 1.67 (dd, 4H, J = 7.5, 1.5 Hz, CHD); ¹³C-NMR (CDCl₃, 125 MHz): 168.2, 153.3, 141.2, 141.1, 129.6, 129.5, 127.8, 124.8, 122.8, 122.4, 115.2, 108.2, 51.3, 36.0, 21.3, 18.7; EI-MS: 411 (M⁺, 29.7%); Analysis calculated for C₂₆H₂₂N₂O₃: C, 76.08; H, 5.40; Found: C, 76.06; H, 5.39.

10-(4-nitrophenyl)-3,4,6,7-tetrahydro-1H-spiro[acridine-9,3'-indoline]1,2',8(2H,5H,10H)-trione (1b): Yellow needles; mp 108–110 °C; IR: 3350 (NH), 2920 (Ar-H), 1680 (C=O), 1516 (C-N), 1523 (NO₂); ¹H NMR (CDCl₃, 500 MHz): δ = 10.11 (s, 1H, NH), 8.01–6.62 (m, 4H, N-Ph), 7.31–7.09 (m, 4H, Ph (isatin)), 3.18 (m, 4H, CHD), 2.83 (m, 4H, CHD), 1.68 (dd, 4H, J = 7.5, 1.5 Hz, CHD); ¹³C-NMR (CDCl₃, 125 MHz): 168.3, 153.4, 147.3, 141.2, 137.9, 129.7, 127.9, 124.7, 123.9, 115.3, 108.3, 51.4, 36.1, 21.4, 18.8; EI-MS: 455 (M⁺, 29.7%); Analysis calculated for C₂₆H₂₁N₃O₅: C, 68.56; H, 4.56; Found: C, 68.54; H, 4.53.

10-(4-methoxyphenyl)-3,4,6,7-tetrahydro-1H-spiro[acridine-9,3'-indoline]-1,2',8(2H,5H, 10H)-trione (1c): Yellow needles; mp 108–110 °C; IR: 3425 (NH), 2922 (Ar-H), 1664 (C=O), 1452 (C-N); ¹H NMR (CDCl₃, 500 MHz): δ = 10.12 (s, 1H, NH), 7.32–7.10 (m, 4H, Ph (isatin)), 6.74–6.00 (m, 4H, N-Ph), 3.83 (s, 3H, -OCH₃), 3.19 (m, 4H, CHD), 2.84 (dd, 4H, J = 7.5, 1.5 Hz, CHD); ¹³C-NMR (CDCl₃, 125 MHz): 168.4, 153.3, 141.3, 133.5, 129.8, 127.6, 123.5, 115.4, 115.1, 108.4, 55.8, 51.5, 36.2, 21.5, 18.8; EI-MS: 441 (M⁺, 30.4%); Elemental analysis calculated value for C₂₇H₂₄N₂O₄: C, 73.62; H, 5.49; Found: C, 73.61; H, 5.48.

10-(2-methoxyphenyl)-3,4,6,7-tetrahydro-1H-spiro[acridine-9,3'-indoline]-1,2',8(2H,5H, 10H)-trione (1d): Yellow needles; mp 108–110 °C; IR: 3456 (NH), 3112 (Ar-H), 1709 (C=O), 1336 (C-N); ¹H NMR (CDCl₃, 500 MHz): δ = 10.14 (s, 1H, NH), 7.33–7.12 (m, 4H, Ph (isatin)), 6.85–6.12 (m, 4H, N-Ph), 3.83 (s, 3H, -OCH₃), 3.20 (m, 4H, CHD), 2.85 (dd, 4H, J = 7.5, 1.5 Hz, CHD); ¹³C-NMR (CDCl₃, 125 MHz): 168.5, 153.5, 148.9, 141.0, 129.5, 128.2, 127.8, 127.5, 125.2, 122.6, 115.2, 110.1, 108.3, 55.8, 51.6, 36.3, 21.6, 18.9; EI-MS: 441 (M⁺, 30.4%); Analysis calculated value for C₂₇H₂₄N₂O₄: C, 73.62; H, 5.49; Found: C, 73.61; H, 5.48.

10-(m-tolyl)-3,4,6,7-tetrahydro-1H-spiro[acridine-9,3'-indoline]-1,2',8(2H,5H,10H)-trione (1e): Yellow needles; mp 108–110 °C; IR: 3500 (NH), 3096 (Ar-H), 1695 (C=O), 1276 (C-N); ¹H NMR (CDCl₃, 500 MHz): δ = 10.16 (s, 1H, NH), 7.34–7.13 (m, 4H, Ph (isatin)), 7.08–5.70 (m, 4H, N-Ph), 3.21 (m, 4H, CHD), 2.88 (dd, 4H, J = 7.5, 1.5 Hz, CHD), 2.34 (s, 3H, CH₃); ¹³C-NMR (CDCl₃, 125 MHz): 168.6, 153.6, 141.1, 129.6, 129.4, 127.4, 124.2, 119.8, 119.0, 115.3, 108.4, 51.7, 36.4, 21.7, 19.0; EI-MS: 425 (M⁺, 30.3%); Elemental analysis calculated value for C₂₇H₂₄N₂O₃: C, 76.39; H, 5.70; Found: C, 76.37; H, 5.68.

10-(2-nitrophenyl)-3,4,6,7-tetrahydro-1H-spiro[acridine-9,3'-indoline]-1,2',8(2H,5H,10H)-trione (1f): Yellow needles; mp 108–110 °C; IR: 3425 (NH), 2922 (Ar-H), 1664 (C=O), 1452 (C-N), 1504 (NO₂); ¹H NMR (CDCl₃, 500 MHz): δ = 10.18 (s, 1H, NH), 8.01–6.89 (m, 4H, N-Ph), 7.35–7.14 (m, 4H, Ph (isatin)), 3.22 (m, 4H, CHD), 2.86 (dd, 4H, J = 7.5, 1.5 Hz, CHD); ¹³C-NMR (CDCl₃, 125 MHz): 168.7, 153.7, 147.8, 134.6, 130.5, 129.9, 129.3, 127.3, 126.6, 124.8, 115.4, 108.6, 51.8, 36.5, 21.8, 19.2; EI-MS: 456 (M⁺, 29.7%); Elemental analysis calculated value for C₂₆H₂₁N₃O₅: C, 68.56; H, 4.65; Found: C, 68.54; H, 4.64.

10-(p-tolyl)-3,4,6,7-tetrahydro-1H-spiro[acridine-9,3'-indoline]-1,2',8(2H,5H,10H)-trione (1g): Yellow needles; mp 108–110 °C; IR: 3221 (NH), 3029 (Ar-H), 1703 (C=O), 1276 (C-N); ¹H NMR (CDCl₃, 500 MHz): δ = 10.20 (s, 1H, NH), 7.36–7.15 (m, 4H, Ph (isatin)), 6.98–6.08 (m, 4H, N-Ph), 3.23 (m, 4H, CHD), 2.87 (dd, 4H, J = 7.5, 1.5 Hz, CHD), 2.34 (s, 3H, CH₃); ¹³C-NMR (CDCl₃, 125 MHz): 168.8, 153.8, 138.2, 131.2,

129.8, 129.2, 127.2, 123.2, 115.6, 108.7, 51.9, 36.6, 21.9, 19.3; EI-MS: 425 (M^+ , 30.3%); Elemental analysis calculated value for $C_{27}H_{24}N_2O_3$; C, 76.39; H, 5.70; Found: C, 76.37; H, 5.67.

10-(2-chlorophenyl)-3,4,6,7-tetrahydro-1H-spiro[acridine-9,3'-indoline]-1,2',8(2H,5H,10H)-trione (1h): Yellow needles; mp 108–110 °C; IR: 3258 (NH), 3012 (Ar-H), 1695 (C=O), 1452 (C-N), 799 (Cl); 1H NMR ($CDCl_3$, 500 MHz): δ = 10.22 (s, 1H, NH), 7.40–6.57 (m, 4H, N-Ph), 7.37–7.16 (m, 4H, Ph (isatin)), 3.24 (m, 4H, CHD), 2.88 (dd, 4H, J = 7.5, 1.5 Hz, CHD); ^{13}C -NMR ($CDCl_3$, 125 MHz): 168.9, 153.9, 144.2, 132.2, 130.7, 29.1, 127.1, 127.6, 125.4, 123.8, 115.7, 108.8, 52.0, 36.7, 22.0, 19.4; EI-MS: 446 (M^+ , 36.7%); Elemental analysis calculated value for $C_{26}H_{21}N_2O_3$; C, 70.19; H, 4.76; Found: C, 70.17; H, 4.74.

10-(2,4-dinitrophenyl)-3,4,6,7-tetrahydro-1H-spiro[acridine-9,3'-indoline]-1,2',8(2H,5H, 10H)-trione (1i): Yellow needles; mp 108–110 °C; IR: 3350 (NH), 3027 (Ar-H), 1664 (C=O), 1452 (C-N), 1516 (NO_2); 1H NMR ($CDCl_3$, 500 MHz): δ = 10.24 (s, 1H, NH), 8.85–7.15 (m, 4H, N-Ph), 7.38–7.17 (m, 4H, Ph (isatin)), 3.25 (m, 4H, CHD), 2.89 (dd, 4H, J = 7.5, 1.5 Hz, CHD); ^{13}C -NMR ($CDCl_3$, 125 MHz): 167.0, 154.0, 147.9, 138.8, 138.0, 130.8, 129.2, 127.0, 120.8, 118.1, 115.8, 108.9, 52.3, 36.8, 22.1, 19.5; EI-MS: 501 (M^+ , 30.1%); Elemental analysis calculated value for $C_{26}H_{20}N_4O_7$; C, 62.40; H, 4.03; Found: C, 62.38; H, 4.01.

10-(4-bromophenyl)-3,4,6,7-tetrahydro-1H-spiro[acridine-9,3'-indoline]-1,2',8(2H,5H,10H)-trione (1j): Yellow needles; mp 108–110 °C; IR: 3425 (NH), 2922 (Ar-H), 1664 (C=O), 1452 (C-N); 1H NMR ($CDCl_3$, 500 MHz): δ = 10.26 (s, 1H, NH), 7.54–7.35 (m, 4H, N-Ph), 7.39–7.18 (m, 4H, Ph (isatin)), 3.26 (m, 4H, CHD), 2.90 (dd, 4H, J = 7.5, 1.5 Hz, CHD); ^{13}C -NMR ($CDCl_3$, 125 MHz): 167.1, 154.2, 140.2, 130.1, 129.5, 125.4, 126.9, 116.7, 115.9, 109.1, 52.4, 36.9, 22.3, 19.6; EI-MS: 490 (M^+ , 28.6%); Elemental analysis calculated value for $C_{26}H_{21}N_2O_3$; C, 70.19; H, 4.76; Found: C, 70.17; H, 4.74.

3.2. Cytotoxic Activity

The newly synthesized compounds (**1a–1j**) were screened for their cytotoxic activity according to the procedure suggested in previous literature [36].

4. Conclusions

We have reported a one-pot, and four-component methodology for the synthesis of 10-phenyl-3,4,6,7-tetrahydro-1H-spiro[acridine-9,2-indolidine]-1,3,8-trione derivatives via Grindstone Chemistry. The cytotoxic activity was screened for all compounds, demonstrating that compound **1c** was highly active (GI_{50} 0.01 μ m) against MCF-7 cancer cell lines in comparison to doxorubicin and other compounds. In conclusion, the synthesized acridine-based indole derivatives can be considered as potential therapeutic lead molecules for anticancer activity.

Supplementary Materials: The following are available online, 1H -NMR and ^{13}C -NMR Spectrum of the compounds **1a–1j**.

Author Contributions: P.G.: organic compound preparation; P.P.: preparation of synthetic compound and chemical data analysis; A.D.: formal analysis; S.A.: financial support; A.I.: spectral analysis and S.R.: investigation of all part of this manuscript chemistry and biology. Original drafts were prepared and the manuscript was written through the contributions of all authors. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: There are no conflicts to declare.

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Sample Availability: Samples of the compounds are available from the authors.

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