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$KAl(SO_4)_2.12H_2O$ (Alum) as an efficacious and reusable heterogeneous catalyst for the one-pot synthesis of some novel spiro[imidazo[1,2-a]pyridine-7,3'-indole] 2',5(1'*H*,6*H*)dione derivatives

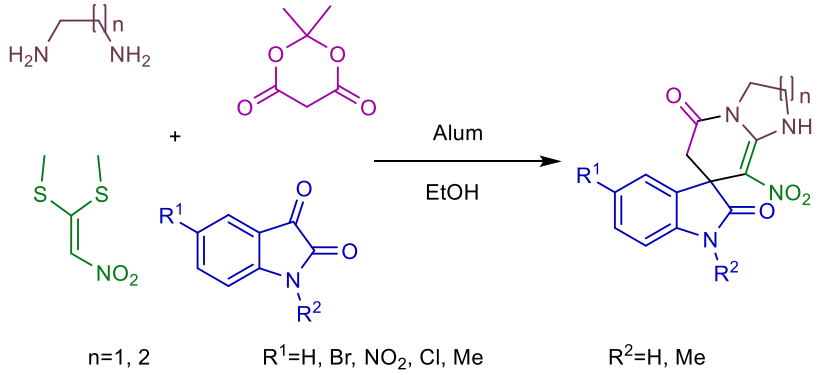
Leila Khatibshad,[a] Javad Azizian,[a] and Ali Asghar Mohammadi *[b]

[a]*Department of Chemistry, Science and Research Branch, Islamic Azad University, Tehran, Iran*
[b]*Chemistry and Chemical Engineering Research Center of Iran (CCERCI), 14335-186, Tehran, Iran*
Email: aliamohammadi@ccerci.ac.ir

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Abstract

A simple, efficient, and environmentally benign one-pot protocol has been developed for the synthesis of some novel spiro[imidazo[1,2-a]pyridine-7,3'-indole]-2',5(1'*H*,6*H*)-dione derivatives using potassium aluminum sulfate ($KAl(SO_4)_2{\cdot}12H_2O$, alum) as a reusable heterogeneous catalyst. The multicomponent reaction proceeds efficiently under mild reaction conditions to afford the desired spiro-fused heterocyclic compounds in yields of 88 to 93%. The present methodology features operational simplicity, easy work-up, high atom economy, and the use of an inexpensive, readily available, reusable catalyst, providing a practical approach for the construction of biologically-relevant spiro-heterocyclic frameworks.



Keywords: Alum, heterogeneous catalysis, one-pot synthesis, spirocyclic heterocycles, imidazo[1,2-a]pyridine, green chemistry.

Introduction

Spirocyclic compounds represent an important class of three-dimensional heterocyclic scaffolds that have attracted considerable attention in medicinal chemistry, owing to their unique structural features and diverse biological activities. The rigid spiro framework provides a well-defined spatial arrangement that can enhance molecular interactions with biological targets and, therefore, has been frequently incorporated into the design of biologically-active molecules. Among various spiro-fused heterocycles, compounds containing imidazo[1,2-a]pyridine and indole-based frameworks have received particular interest due to their valuable pharmacological properties. [1-3]

The imidazo[1,2-a]pyridine nucleus is recognized as a privileged heterocyclic scaffold which is found in numerous biologically-active compounds and marketed drugs,[4-8] including antitumor,[9,20] antiproliferative agents,[10] antitubercular agents,[11] phosphatidylinositol-3-kinase inhibitors,[12] anti-helmintic drugs,[13] anti-tubercular,[14] anti-tubulin agents,[15] anti-bacterial,[16] anti-mutagenic,[17] anti-psychotic,[18] anti-tumor,[19] and anti-protozoal agents.[20] Similarly, indole-2,5-dione derivatives have attracted significant attention because of their versatile biological properties and synthetic importance. Therefore, the development of efficient and straightforward methods for the construction of spiro-fused imidazo[1,2-a]pyridine indole derivatives remain an attractive objective in heterocyclic chemistry.

Multi-component reactions (MCRs) and one-pot synthetic strategies have emerged as powerful approaches for the rapid assembly of structurally complex molecules from simple starting materials. These methodologies offer several advantages, including operational simplicity, reduced reaction steps, improved atom economy, and minimized waste generation. Consequently, the development of environmentally friendly catalytic systems for multi-component syntheses has become an important research area.[21-26]

Several ameliorated procedures for the preparation of imidazo [1, 2-a] pyridines and their derivatives[16, 27-30] have been reported. Recently, various catalytic systems, including Lewis acids,[31, 32] the protic-acid trifluoroacetic acid (TFA),[33] inorganic bases, such as $NaHCO_3$,[34] piperidine-mediated multicomponent reactions (three-component reaction[35], 4 h, and four-component reactions[36] 12–14 h) have been developed for the synthesis of imidazo[1,2-*a*]pyridine frameworks. The preparations of some corresponding spiro[imidazo[1,2-a]pyridine-7,3′-indole]-2′,5(1′*H*,6*H*)-dione derivatives, however, have not yet been reported, and remain unexplored.

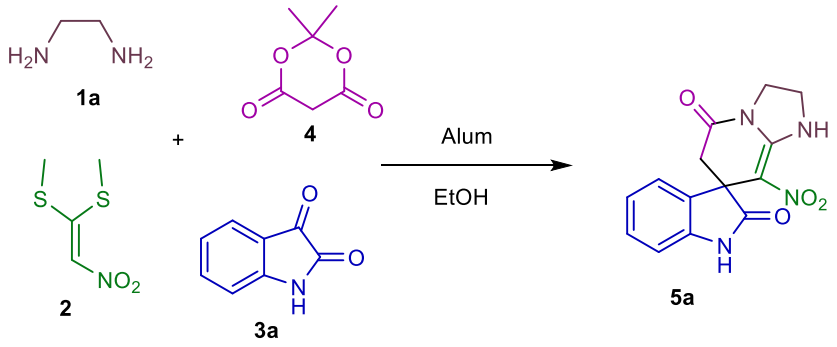
In recent years, heterogeneous catalysts have gained considerable attention due to their easy separation, recyclability, and potential application in sustainable chemical processes.[37-39] Potassium aluminum sulfate dodecahydrate ($KAl(SO_4)_2{\cdot}12H_2O$, alum) [40, 41] is an inexpensive, readily available, and environmentally benign inorganic salt that has been successfully employed as a catalyst in various organic transformations. Its Lewis acidic character, water tolerance, and recyclability make it an attractive candidate for environmentally friendly, green synthetic methodologies.

In continuation of our interest in the development of efficient catalytic approaches for the synthesis of biologically relevant heterocyclic compounds,[42-44] herein, we report a simple and practical, one-pot, synthesis of novel spiro[imidazo[1,2-*a*]pyridine-7,3′-indole]-2′,5(1′*H*,6*H*)-dione derivatives using alum as a reusable heterogeneous catalyst. The present protocol provides the target spiro heterocycles under mild conditions with good-to-excellent yields (88-93%) and highlights the potential of alum as an efficient catalyst for the construction of complex heterocyclic architectures.

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Results and Discussion

When a mixture of ethylene diamine **1a**, nitro ketene dithioacetal **2**, isatin **3a**, Meldrum's acid (2,2-dimethyl-1.3-dioxane-4,6-dione) **4**, and a catalytic quantity of $KAl(SO_4)_2.12H_2O$ (alum) was reacted in ethanol under reflux conditions, spiro[imidazo[1,2-*a*]pyridine-7,3'-indole]-2',5(1'*H*,6*H*)-dione **5a** was produced in 90% yield. The reaction was completed within 2 h (monitored by TLC, n-hexane/ethylacetate, 1:1) (Scheme 1).



Scheme 1. Synthesis of spiro[imidazo[1,2-*a*]pyridine-7,3'-indole]-2',5(1'*H*,6*H*)-dione product **5a**.

To establish the optimal reaction conditions, the model reaction of the appropriate starting materials was initially investigated in the presence of different catalysts (Alum, CH_3CO_2H, $NaHCO_3$, Et_3N), and under various reaction-condition parameters. The effects of catalyst loading (0.00, 0.10, 0.15, 0.20, 0.25 and 0.30 g), solvent (CH_3CN, $CHCl_3$, H_2O, a mixture of H_2O and ethanol, and methanol), temperature (RT, 50°C, 70°C, and reflux), and reaction time (30-200 min) were systematically examined.

In the absence of a catalyst, the desired spiro product was not obtained, indicating the important role of the catalyst in promoting the transformation. Several Lewis acids and heterogeneous catalytic ($AlCl_3$, $ZnCl_2$, $FeCl_3$) systems were subsequently evaluated. Among the investigated catalysts, potassium aluminum sulfate dodecahydrate [$KAl(SO_4)_2{\cdot}12H_2O$, alum] exhibited superior catalytic activity, and provided the desired product in an improved yield. Further optimization revealed that the amount of alum had a significant effect on the reaction efficiency. The optimum catalyst loading afforded the target product in the highest yield in a shorter reaction time.

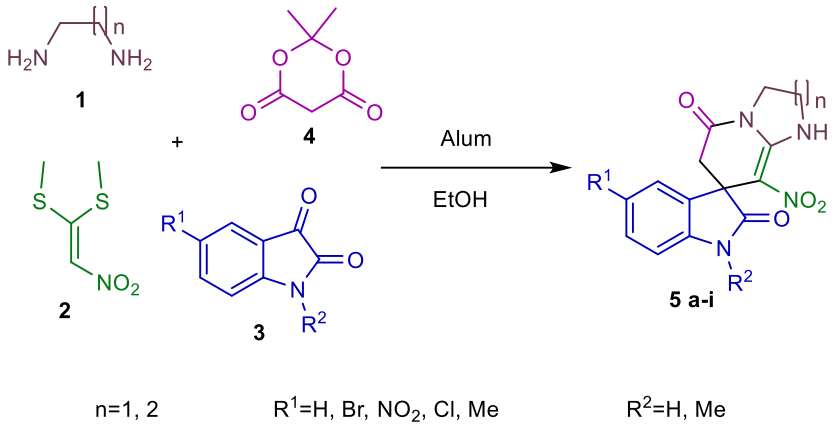
The influence of solvent was also examined. Polar protic solvents were found to be more suitable for this transformation; other solvents resulted in lower conversions. Further optimization revealed that the amount of alum had a significant effect on the reaction efficiency. The optimum catalyst loading afforded the target product in the highest yield within a shorter reaction time.

Under the optimized conditions (ethanol solvent, 0.2 g catalyst for a 1 mmol scale reaction, and reflux conditions), the reaction proceeded smoothly to provide the desired spiro-fused heterocyclic compound in good yield. The results demonstrated that alum acts as an efficient catalyst for this one-pot, multi-component transformation.

Following the optimization of the reaction conditions, the generality and scope of the developed methodology were investigated using a variety of substituted starting materials under the optimized reaction

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conditions. As illustrated in Scheme 2, a series of novel spiro[imidazo[1,2-a]pyridine-7,3′-indole]-2′,5(1′*H*,6*H*)-dione derivatives were successfully synthesized in moderate-to-excellent yields.



Scheme 2. Synthesis of spiro[imidazo[1,2-*a*]pyridine-7,3'-indole]-2',5(1'*H*,6*H*)-dione products **5a-i**.

Most of the synthesized compounds were obtained in good-to-excellent isolated yields (88–93%, Table 1). The substituent effect on the reaction efficiency was investigated using methyl, halogen, and nitro-substituted isatin derivatives. Among the examined substrates, nitro-substituted derivatives generally afforded higher yields, which may be attributed to the strong electron-withdrawing nature of the nitro group which enhances the electrophilicity of the Knoevenagel-derived intermediate, and facilitates the subsequent Michael addition step with the heterocyclic ketene aminal. Halogen-substituted substrates also showed good reactivity, while methyl-substituted derivatives provided slightly lower yields, possibly due to the electron-donating effect of the methyl group and reduced activation of the conjugated system.

The reaction tolerated a wide range of substituents on the aromatic ring, including electron-donating and electron-withdrawing groups. Substrates bearing methyl, halogen, and nitro substituents underwent the transformation efficiently to afford the corresponding spiro products. In general, electron-withdrawing substituents showed slightly more enhanced reactivity compared with electron-donating groups, although all investigated substrates provided the desired products in satisfactory yields.

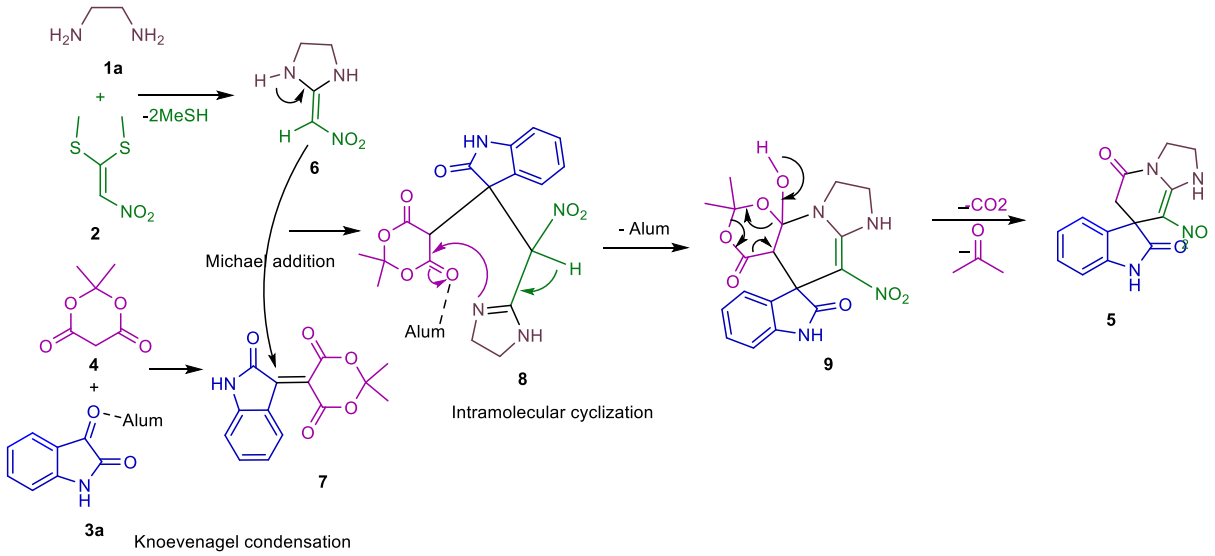
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The successful formation of these spiro-fused heterocycles demonstrates the efficiency and versatility of the alum-catalyzed, one-pot protocol. The mild reaction conditions, simple experimental procedure, and broad substrate compatibility make this methodology a valuable approach for the construction of structurally complex heterocyclic frameworks.

Table 1: Preparation of compounds **5a-i** by condensation of alkylene diamine **1a-b**, 1,1-bis(methylthio)-2-nitro ethylene **2**, isatin **3a-e**, and Meldrum's acid **4**. [a]Yields based on isatin

Products	R_1	R_2	n	Time (min)	Yield (%)[a]
5a	H	H	1	110	90[30]
5b	Br	H	1	70	93
5c	NO_2	H	1	60	93
5d	Cl	H	1	80	92
5e	Me	H	1	100	88
5f	H	Me	1	110	90[30]
5g	H	H	2	100	90[30]
5h	Br	H	2	60	91
5i	NO_2	H	2	70	92

A plausible mechanism for the formation of spiro[imidazo[1,2-*a*]pyridine-7,3′-indole]-2′,5(1′*H*,6*H*)-dione derivatives **5a** is proposed in Scheme 3. Initially, the Knoevenagel condensation of isatin **3a** with Meldrum's acid **4** may generate the corresponding alkylidene-Meldrum's acid intermediate **7**. Meanwhile, the heterocyclic ketene aminal (HKA) **6** is formed through the condensation of ethylenediamine **1** with 1,1-bis(methylthio)-2-nitroethylene **2**. Subsequently, the nucleophilic addition of HKA **6** to intermediate **7** via a Michael addition affords intermediate **8**. The resulting intermediate undergoes intramolecular cyclization through nucleophilic attack of the nitrogen atom on the carbonyl group, leading to intermediate **9**. Finally, the desired spiro-fused imidazo[1,2-a]pyridine derivative **5** is formed through the decomposition of the Meldrum's acid moiety with the elimination of acetone and carbon dioxide.



Scheme 3. Suggested mechanism for the synthesis of products **5a-i**.

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The recyclability of alum was investigated using the model reaction under the optimized reaction conditions. After completion of the reaction, the reaction mixture was cooled and filtered to remove the solid organic product. Water was then added to the precipitate to dissolve and separate the alum catalyst into the aqueous phase. The aqueous phase was concentrated by evaporation of water to recover alum, which was further washed with a small amount of hot acetone (or ethanol), dried, and reused in subsequent reaction cycles without significant loss of catalytic activity. As shown in Figure 1, alum could be efficiently recovered and reused for several consecutive cycles without significant loss of catalytic activity. The isolated yield of the desired spiro product remained almost unchanged after repeated uses, demonstrating the stability and practical utility of alum as a recyclable heterogeneous catalyst.

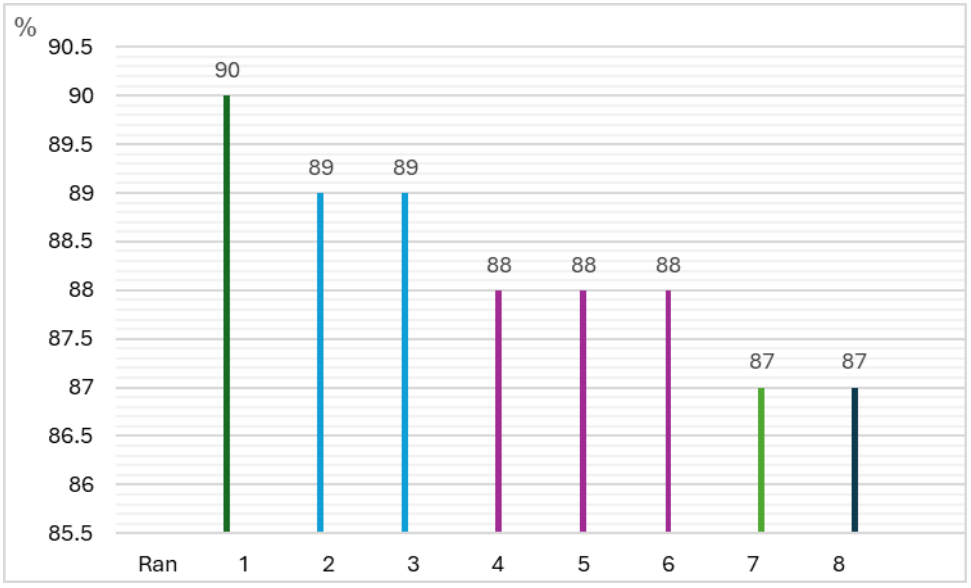


Figure 1: The same alum ($KAl(SO_4)_2 \cdot 12H_2O$) catalyst was used for each of the eight runs for **5a**

The excellent recyclability of alum can be attributed to its heterogeneous nature, facile recovery, and structural stability under the reaction conditions. These features, together with its low cost and commercial availability, make alum an attractive catalyst for sustainable organic synthesis.

Overall, this work describes an efficient and straightforward one-pot, four-component, cyclo-condensation strategy for the synthesis of spiro[imidazo[1,2-*a*]pyridine-7,3′-indole]-2′,5(1′*H*,6*H*)-dione derivatives from ethylenediamine, nitro ketene dithioacetal, isatin derivatives, and Meldrum's acid. The methodology features operational simplicity, broad substrate tolerance, and high product yields, highlighting the potential of this approach for the construction of complex spiro-fused heterocyclic frameworks.

Conclusions

We have developed a practical one-pot, four-component, strategy for the synthesis of novel spiro[imidazo[1,2-*a*]pyridine-7,3′-indole]-2′,5(1′*H*,6*H*)-dione derivatives using potassium aluminum sulfate dodecahydrate (alum) as a readily available, and recyclable, heterogeneous catalyst. The present protocol enables the construction of diverse spiro-fused heterocyclic frameworks under mild reaction conditions in good-to-excellent yields. This

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methodology offers several advantages, including the use of an inexpensive catalyst, operational simplicity, facile product isolation, and efficient recovery and reuse of the catalyst. This alum-catalyzed multi-component approach provides a convenient and sustainable route toward the syntheses of biologically relevant spiro heterocycles.

Experimental Section

General. All reagents and solvents are commercially available and were purchased from the Fluka, Merck and Aldrich chemical companies and used without further purification. The progress of the reactions was monitored by thin layer chromatography (TLC) using Merck silica gel plates, and visualization was performed under ultraviolet light or by appropriate staining methods. Melting points were obtained in open capillary tubes on an Electro-thermal 9200 apparatus. Infrared (IR) spectra were recorded using KBr pellets on a Shimadzu IR 470 spectrophotometer. ^{1}H NMR (300, MHz) and ^{13}C NMR (75 MHz) spectra were determined on a Bruker DRX Avance instrument. Chemical shifts are reported in ppm (δ) relative to tetramethylsilane (TMS) as an internal standard and coupling constants (*J*) are reported in Hz. Elemental analyses for C, H and N were performed using a Heraus CHN rapid analyzer. Mass spectra were recorded on an Agilent Technologies G7081B (Analyzer: Quadrupole) mass spectrometer.

Typical procedure for the preparation of spiro[imidazo[1,2-a]pyridine-7,3′-indole]-2′,5(1′*H*,6*H*)-dione derivatives. A mixture of ethylenediamine **1a** (1 mmol, 0.0600 g) and 1,1-bis(methylthio)-2-nitroethylene **2** (1 mmol, 0.165 g) in ethanol (10 mL) was stirred under reflux conditions for 4 h in a 25 mL round-bottom flask. The formation of the corresponding heterocyclic ketene aminal (HKA) **6** was monitored by TLC (EtOAc/n-hexane, 4:1). Subsequently, alum ($KAl(SO_4)_2{\cdot}12H_2O$, 0.2 g), isatin **3a** (1 mmol), and Meldrum's acid **4** (1 mmol) were added to the reaction mixture, and the resulting mixture was refluxed for the appropriate time reported in Table 1. After completion of the reaction, as monitored by TLC, the reaction mixture was cooled to room temperature and filtered through a sintered funnel. Water (20 mL) was added to the obtained solid mixture to dissolve the alum catalyst, and the remaining solid product was collected by filtration. The crude product was purified by recrystallization from ethanol to afford the corresponding pure spiro[imidazo[1,2-a]pyridine-7,3′-indole]-2′,5(1′H,6H)-dione **5a**.

For catalyst recovery, the aqueous phase containing alum was concentrated by evaporation of water. The recovered alum was washed with a small amount of hot acetone (or ethanol), dried, and reused in subsequent reaction cycles.

Experimental Results

8-Nitro-2,3-dihydro-1*H*-spiro[imidazo[1,2-*a*]pyridine-7,3'-indole]-2',5(1'*H*,6*H*)-dione (5a). White solid, yield: 90%, MP: 318-320 °C, IR (KBr) (ν_{max}/cm^{-1}) 3331 (NH), 3329 (NH),3128, 1725 (C=O), 1683 (C=O), 1632; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H (ppm) 2.35 (d, 1H, *J*=15.9 Hz, CH_2), 3.02 (d,1H, *J*=15.9 Hz, CH_2), 3.79-3.85 (m, 2H, CH_2), 3.92-4.05 (m, 2H, CH_2), 6.82-6.91 (m, 2H, Ar-H), 7.13-7.21 (m, 2H, Ar-H), 9.83 (s, 1H, NH), 10.57 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ_C (ppm) 42, 43, 44, 50, 110, 122, 123, 129, 132, 142, 152, 154, 166, 178. MS (EI, 70 eV) *m/z*: 300.26 (M^+, 65%). Anal. calcd for $C_{14}H_{12}N_4O_4$: C, 56.00; H, 4.03; N, 18.66 %. Found: C, 56.88; H, 3.86; N, 18.50 %.

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5'-Bromo-8-nitro-2,3-dihydro-1*H*-spiro [imidazo [1,2-*a*]pyridine-7,3'-indole]-2',5(1'*H*,6*H*)-dione (5b). White solid, yield: 93%, MP: 253-255 °C, IR (KBr) (ν_{max}/cm^{-1}) 3361 (NH), 3279 (NH),3024, 1730 (C=O), 1679 (C=O), 1645; ^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ_H (ppm) 2.43 (d, 1H, *J*=16.2 Hz, CH_2), 3.00 (d,1H, *J*=16.2 Hz, CH_2), 3.79-3.84 (m, 2H, CH_2), 3.92-4.10 (m, 2H, CH_2), 6.79 (d, 1H, *J*=9 Hz, Ar-H), 7.35-7.39 (m, 1H, Ar-H), 7.42 (s, 1H, Ar-H), 9.87 (s, 1H, NH), 10.72 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO- *d*$_6$) δ_C (ppm) 41, 43, 44, 50.3, 105, 112, 114, 126, 132, 134, 142, 154, 165, 177. MS (EI, 70 eV) *m/z*: 379.16 (M^{++}, 55%), 377.15 (M^{++}, 55%). Anal. calcd for $C_{14}H_{11}BrN_4O_4$: C, 44.35; H, 2.92; N, 14.78 %. Found: C, 44.24; H, 2.81; N, 14.65 %.

5',8-Dinitro-2,3-dihydro-1*H*-spiro [imidazo [1,2-*a*]pyridine-7,3'-indole]-2',5(1'*H*,6*H*)-dione (5c). White solid, yield: 93%, MP: 310-312 °C, IR (KBr) (ν_{max}/cm^{-1}) 3355 (NH), 3258 (NH),2925, 1735 (C=O), 1682 (C=O), 1645; ^{1}H NMR (300 MHz, DMSO- *d*$_6$) δ_H (ppm) 2.62 (d, 1H, *J*=16.5 Hz, CH_2), 3.00 (d,1H, *J*=16.5 Hz, CH_2), 3.84-3.87 (m, 2H, CH_2), 3.91-4.08 (m, 2H, CH_2), 7.04 (d, 1H, *J*=7.8 Hz, Ar-H), 8.10 (s, 1H, Ar-H)8.17 (d, 1H, *J*=8.4 Hz, Ar-H), 9.95 (s, 1H, NH), 11.33 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO- *d*$_6$) δ_C (ppm) 41, 43, 44, 50, 110, 119, 125, 131, 133, 140., 143, 154, 165, 193. MS (EI, 70 eV) *m/z*: 345.26 (M^{++}, 68%). Anal. calcd for $C_{14}H_{11}N_5O_6$: C, 48.70; H, 3.21; N, 20.28 %. Found: C, 48.57; H, 3.10; N, 20.17 %.

5'-Chloro-8-nitro-2,3-dihydro-1*H*-spiro[imidazo[1,2-*a*]pyridine-7,3'-indole]-2',5(1'H,6*H*)-dione (5d). White solid, yield: 92%, MP: 300-302 °C, IR (KBr) (ν_{max}/cm^{-1}) 3278 (NH), 3136 (NH),2931, 1753 (C=O), 1701 (C=O), 1659; ^{1}H NMR (300 MHz, DMSO- *d*$_6$) δ_H (ppm) 2.43 (d, 1H, *J*=16.2 Hz, CH_2), 3.01 (d,1H, *J*=16.2 Hz, CH_2), 3.79-3.84 (m, 2H, CH_2), 3.89-4.04 (m, 2H, CH_2), 6.84 (d, 1H, *J*=8.1 Hz, Ar-H), 7.22-7.26 (m, 1H, Ar-H), 7.32 (s, 1H, Ar-H), 9.86 (s, 1H, NH), 10.70 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO- *d*$_6$) δ_C (ppm) 41, 43, 44, 49, 103, 108, 114, 123, 128, 134, 142, 153, 163, 177. MS (EI, 70 eV) *m/z*: 334.71 (M^{++}, 45%). Anal. calcd for $C_{14}H_{11}ClN_4O_4$: C, 50.24; H, 3.31; N, 16.74 %. Found: C, 50.11; H, 3.18; N, 16.59 %.

5'-Methyl-8-nitro-2,3-dihydro-1*H*-spiro[imidazo[1,2-*a*]pyridine-7,3'-indole]-2',5(1'*H*,6*H*)-dione (5e). White solid, yield: 88%, MP: 318-320 °C, IR (KBr) (ν_{max}/cm^{-1}) 3354 (NH), 3291 (NH),2986, 1731 (C=O), 1672 (C=O), 1615; ^{1}H NMR (300 MHz, DMSO- *d*$_6$) δ_H (ppm) 2.33 (d, 1H, *J*=15.9 Hz, CH_2), 3.01 (d,1H, *J*=15.9 Hz, CH_2), 3.81-3.86 (m, 2H, CH_2), 3.93-4.07 (m, 2H, CH_2), 6.72 (d, 1H, *J*=7.8 Hz, Ar-H), 6.93 (s, 1H, Ar-H), 6.97 (d, 1H, *J*=7.8 Hz, Ar-H), 9.77 (s, 1H, NH), 10.41 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO- *d*$_6$) δ_C (ppm) 21, 42, 43, 44, 50, 106, 110, 123, 129, 131, 132, 140, 153, 166, 178. MS (EI, 70 eV) *m/z*: 314.29 (M^+, 50%). Anal. calcd for $C_{15}H_{14}N_4O_4$: C, 57.32; H, 4.49; N, 17.83 %. Found: C, 57.21; H, 4.35; N, 17.66 %.

1'-Methyl-8-nitro-2,3-dihydro-1*H*-spiro[imidazo[1,2-*a*]pyridine-7,3'-indole]-2',5(1'*H*,6*H*)-dione (5f). White solid, yield: 90%, MP: 286-288 °C, IR (KBr) (ν_{max}/cm^{-1}) 3321 (NH),3024, 1742 (C=O), 1707 (C=O), 1628; ^{1}H NMR (300 MHz, DMSO- *d*$_6$) δ_H (ppm) 2.36 (d, 1H, *J*=15.9 Hz, CH_2), 3.05 (d,1H, *J*=15.9 Hz, CH_2), 3.81-3.86 (m, 2H, CH_2), 3.97-4.06 (m, 2H, CH_2), 6.95-7.04 (m, 2H, Ar-H), 7.18 (d, 1H, *J*=7.2 Hz, Ar-H), 7.30 (t, 1H, *J*=7.5 Hz, Ar-H), 9.08 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-*d6*) δ_C (ppm) 27, 42, 43, 44, 49, 106, 109, 122, 122, 123, 129, 144, 154, 166, 176. MS (EI, 70 eV) *m/z*: 314.29 (M^{++}, 60%). Anal. calcd for $C_{15}H_{14}N_4O_4$: C, 57.32; H, 4.49; N, 17.83 %. Found: C, 57.17; H, 4.37; N, 17.70 %.

9'-Nitro-1',2',3',4'-tetrahydrospiro[indole-3,8'-pyrido[1,2-*a*]pyrimidine]-2,6'(1*H*,7'*H*)-dione (5g). Orange solid, yield: 90%, MP: 290-292 °C, IR (KBr) (ν_{max}/cm^{-1}) 3321 (NH), 3263 (NH),2915, 1747 (C=O), 1698 (C=O), 1658; ^{1}H NMR (300 MHz, DMSO- *d*$_6$) δ_H (ppm) 1.90-2.05 (m, 2H, CH_2), 2.59 (d, 1H, *J*=15.9 Hz, CH_2), 3.27 (d,1H, *J*=15.9 Hz, CH_2), 3.41-3.61 (m, 4H, CH_2), 6.87-6.91 (m, 3H, Ar-H), 7.18-7.22 (m, 1H, Ar-H), 9.93 (s, 1H, NH), 10.21 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO- *d*$_6$) δ_C (ppm) 19, 35, 38, 39, 50, 106, 116, 120, 123, 126, 129, 139, 153, 168. 174. MS (EI, 70 eV) *m/z*: 314.29 (M^+, 70%). Anal. calcd for $C_{15}H_{14}N_4O_4$: C, 57.32; H, 4.49; N, 17.83 %. Found: C, 57.18; H, 4.36; N, 17.69 %.

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5-Bromo-9'-nitro-1',2',3',4'-tetrahydrospiro[indole-3,8'-pyrido[1,2-*a*]pyrimidine]-2,6'(1*H*,7'*H*)-dione (5h). White solid, yield: 91%, MP: 322-324 °C, IR (KBr) (ν_{max}/cm^{-1}) 3340 (NH), 3257 (NH),3069, 1752 (C=O), 1690 (C=O), 1656; ^{1}H NMR (300 MHz, DMSO- d_6) δ_H (ppm) 1.94-2.06 (m, 2H, CH_2), 2.61 (d, 1H, *J*=16.5 Hz, CH_2), 3.27 (d,1H, *J*=16.5 Hz, CH_2), 3.46-3.58 (m, 4H, CH_2), 6.86 (d, 1H, *J*=8.4 Hz, Ar-H), 7.04 (s, 1H, Ar-H), 7.38 (d, 1H, *J*=8.4 Hz, Ar-H), 9.96 (s, 1H, NH), 10.35 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO- d_6) δ_C (ppm) 19, 19, 35, 38, 50, 117, 121, 123, 130, 133, 142, 152, 154, 165, 179. MS (EI, 70 eV) *m/z*: 394.19 (M^{+2}, 50%), 392.16 (M^+, 50%). Anal. calcd for $C_{15}H_{13}BrN_4O_4$: C, 45.82; H, 3.33; Br, 20.32; N, 14.25 %. Found: C, 45.68; H, 3.15; Br, 20.15; N, 14.12 %.

5,9'-Di-nitro-1',2',3',4'-tetrahydrospiro[indole-3,8'-pyrido[1,2-*a*]pyrimidine]-2,6'(1*H*,7'*H*)-dione (5i). Orange solid, yield: 92%, MP: 296-298 °C, IR (KBr) (ν_{max}/cm^{-1}) 3488 (NH), 3244 (NH),3095, 1754 (C=O), 1706 (C=O), 1657; ^{1}H NMR (300 MHz, DMSO- d_6) δ_H (ppm) 1.93-2.01 (m, 2H, CH_2), 2.73 (d,1H, *J*=16.5 Hz, CH_2), 3.47-3.54 (m, 5H, CH_2), 7.09 (d, 1H, *J*=8.7 Hz, Ar-H), 7.74 (s, 1H, Ar-H), 8.13 (d, 1H, *J*=8.7 Hz, Ar-H), 10.04 (s, 1H, NH), 10.91 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO- d_6) δ_C (ppm) 19, 34, 36, 38, 50, 105, 117, 121, 123, 126, 142, 146, 154, 168, 173. MS (EI, 70 eV) *m/z*: 359.29 (M^{++}, 55%). Anal. calcd for $C_{15}H_{13}N_5O_6$: C, 50.14; H, 3.65; N, 19.49 %. Found: C, 50.02; H, 3.51; N, 19.36 %.

Supplementary Material

^{1}H and ^{13}C NMR spectra for compounds **5 a-i** are reported in the Supplementary Material associated with this paper.

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