



## Synthesis and characterization of novel (Z)-5-((1H-1, 2, 4-triazol-1-yl)methyl)-3-arylideneindolin-2-ones

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### ABSTRACT

Eight compounds of novel (Z)-5-((1H-1, 2, 4-triazol-1-yl)methyl)-3-arylideneindolin-2-ones(5a-h) have been synthesized by the Knoevenagel condensation of 5-((1H-1,2,4-triazol-1-ylmethyl)indolin-2-one(3) with 4-substituted aromatic aldehydes(4a-h). © 2015 Trade Science Inc. - INDIA

### KEYWORDS

Knoevenagel condensation;  
5-((1h-1,2,4-triazol-1-ylmethyl)indolin-2-one(3);  
4-substituted aromatic aldehydes(4a-h).

### INTRODUCTION

1H-Indol-2,3-dione and their derivatives are an important class of heterocyclic compounds in synthetic and medicinal chemistry with broad spectrum of biological activity like antibacterial (1), anti-inflammatory (2), analgesic (3), anti-viral (4), antifungal (5), anti-tubercular (6), anti-depressant (7). The marked biological importance and therapeutic activity of 1 H-Indol-2,3-dione and their derivatives prompted us to design the synthesis of novel (Z)-5-((1H-1, 2, 4-triazol-1-yl)methyl)-3-arylideneindolin-2-ones(5a-h).

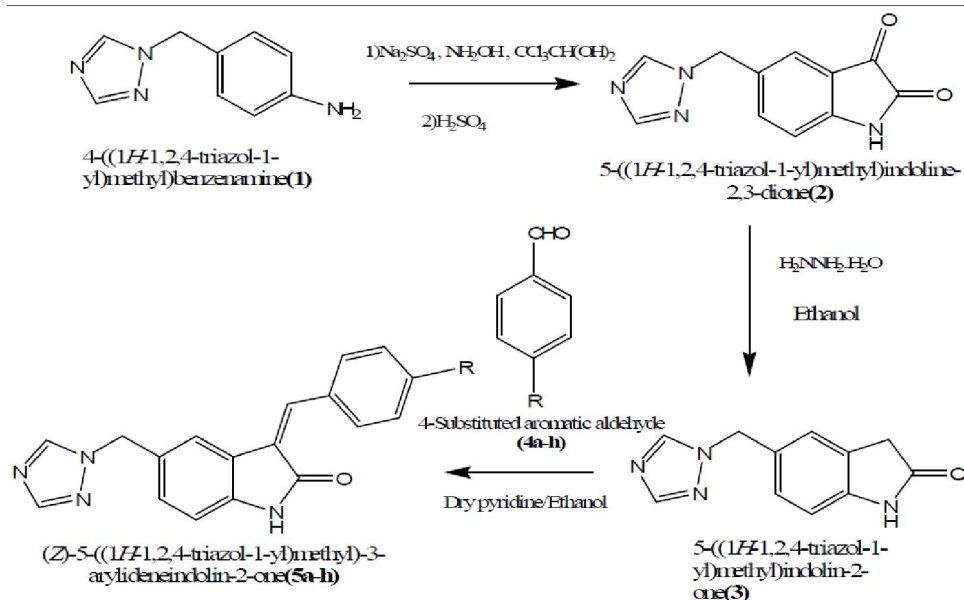
### RESULTS AND DISCUSSION

1H-Indol-2, 3-dione (isatin) is normally synthesized from Sandmeyer method, wherein the reaction of aniline with chloral hydrate and hydroxylamine hydrochloride in aqueous sulfate forms an isonitrosoacetanilide. Subsequent cyclisation to the isatin is accomplished after treating isonitrosoacetanilide with concentrated sulphuric acid.<sup>[8]</sup>

An important alternative to the Sandmeyer method is the method of Stolle. In this approach, N-substituted anilines are reacted with oxalyl chloride to form an intermediate chlorooxalylanilide which can be cyclized in the presence of Lewis acids such as anhydrous aluminum chloride,<sup>[9]</sup> BF<sub>3</sub>·Et<sub>2</sub>O,<sup>[10]</sup> or TiCl<sub>4</sub><sup>[11]</sup> to form 1-aryl isatin derivatives or polycyclic isatin derivatives.

In continuation of our interest in the development of efficient and simple procedures for the synthesis of novel (Z)-5-((1H-1, 2, 4-triazol-1-yl)methyl)-3-arylideneindolin-2-ones(5a-h) by the reaction of 5-((1H-1,2,4-triazol-1-ylmethyl) indolin-2-one(3) with 4-substituedaromatic aldehyde (4a-h) in presence of ethanol under reflux. Thus it has been found that 4-((1H-1,2,4-triazol-1yl)mehyl)-benzenamine (1) reacted with chloral hydrate,inpresence of hydroxyl amine and sodium sulphate followed by reaction with concentrated sulphuric acid to give 5-((1H-1,2,4-triazol-1-yl)methyl)indoline-2,3-dione(2). Later these were treated with hydrazine hydrate in ethanol under reflux yielding the corresponding 5-((1H-1,2,4-triazol-1-ylmethyl)indolin-2-one(3) in good yields. Treatment of

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Scheme

Compound	R
5a	H
5b	F
5c	OCH <sub>3</sub>
5d	NO <sub>2</sub>
5e	CH(CH <sub>3</sub> ) <sub>2</sub>
5f	Cl
5g	CH <sub>3</sub>
5h	CN

3 with varies 4-substituted aromatic aldehydes(4a-h) in ethanol under reflux 6-8hours gave the title compounds (5a-h).

The structures of compounds (5a)-hwere established on the basis of their elemental and spectral data (IR,Mass, <sup>1</sup>HNMR, <sup>13</sup>CNMR).

The IR spectrum of all final compounds exhibit a sharp band in the region of 1690-1700 cm<sup>-1</sup> due to –C=O stretching vibrations. <sup>1</sup>H NMR spectra of all the compounds (5a-h) having NH group at first position exhibits a broad singlet at δ10.5 to 11.0. And a doublet is observed at 7.20-7.30 is due vinylic proton. In mass spectra of all the compounds (5a-h) molecular ion peaks are all in accordance with their molecular weights.

## EXPERIMENTAL PROCEDURE

All the melting point are uncorrected. The purity was checked by thin layer chromatography with silica gel 60 GF254 E.Merck precoated plates (0.25 mm) was visualized using UV. 0.1 for flash chromatography on silica gel (particle size 100-200 mesh). and characterized by spectral studies. The IR spectra were recorded on shimadzu FTIR model 8010 spectrophotometer and are given in cm<sup>-1</sup> in KBr. The <sup>1</sup>HNMR & <sup>13</sup>CNMR spectra were recorded on Bruker AM-400 NMR spectrometers in deuterated chloroform and deuterated DMSO. The chemical shifts are reported in δ (ppm) relative to tetramethylsilane as internal standard. Mass spectra analyses performed with an Agilent 6400 Series equipped with an electrospray ionization source (capillary voltage at 4000V, nebulizing gas temperature at 300 °C, nebulizing gas flow at 12 L/ min).

## 5-((1H-1,2,4-triazol-1-yl)methyl)indoline-2,3-dione

4-((1H-1,2,4-triazol-1-yl)methyl)-benzenamine (0.03mol) into 500 mL round bottom flask with 250 mL water. Dried over anhydrous sodium sulfate (0.25 mol) and hydroxylamine hydrochloride (0.11 mol) were added under stirring, then add 2 mol / L hydrochloric acid solution 5 mL, stir at room temperature for 5 min, finally add chloral hydrate (0.035 mol). The reaction mixture was stirred at room temperature for 15 min,

and then reacted at 90 °C for 2 h. The reaction was monitored by TLC after 2 h to confirm whether the starting material was disappeared, then cooled to room temperature, filtered, dried in vacuum to give a yellow solid 6.96g.

20 mL concentrated sulfuric acid into 100 mL round bottom flask. The yellow solid 6.96 g was slowly added to concentrated sulfuric acid at 50°C, and then reacted for 30 minutes at 65°C. The reaction mass was cooled to room temperature then poured into ice-water mixture, stirred for 30 minutes. Filter the solid and dried under vacuum oven to give 6.12g of 5-[1,2,4]triazol-1-ylmethyl-1H-indole-2,3-dione(2).

#### 5-((1H-1,2,4-triazol-1-ylmethyl)indolin-2-one

5-((1H-1,2,4-triazol-1-yl)methyl)indoline-2,3-dione (0.01 mol) was put into 50 mL round bottom flask with 15 mL anhydrous ethanol and 0.62 g (0.01 mol) 85%hydrazine hydrate to reflux for 3 h. The reaction was cooled to room temperature and added 0.30 g sodium hydroxide to reflux for another 3 h., When the reaction was complete, the reaction mixture was poured into ice-water mixture, then the precipitate was collected by filtration and dried under vacuum to give 5-((1H-1,2,4-triazol-1-ylmethyl)indolin-2-one (2.08 g).

#### General experimental procedure for (Z)-5-((1H-1,2,4-triazol-1-yl)methyl)-3-arylideneindolin-2-ones(5a-h)

5-((1H-1,2,4-triazol-1-yl)methyl)indolin-2-one (0.005 mol) into 50 mL round bottom flask with 10 mL ethanol, 0.5 mL dry pyridine, and (0.0053 mol) 4-substituted aromatic aldehydes(4a-h). The reaction mixture was refluxed for 6-8 h. The reaction was cooled to room temperature, added 20 mL anhydrous ethanol under reduced pressure to remove the solvent. Using petroleum ether: ethyl acetate = 15:1, 200-300 mesh silica gel column to give (Z)-5-((1H-1,2,4-triazol-1-yl)methyl)-3-arylideneindolin-2-ones(5a-h) (0.78-0.80 g).

#### 5a: (Z)-5-((1H-1,2,4-triazol-1-yl)methyl)-3-benzylideneindolin-2-one

Yield: 51.7%, MP:272-274°C, IR (KBr in cm<sup>-1</sup>): 3193 (NH), 1690 (C=O), 1613 (C=C). <sup>1</sup>HNMR(DMSO-d<sub>6</sub>) δ/ppm, 10.86(s, 1H), 8.49(d, 2H, triazol protons), 7.62(d,1H), 7.54-7.56(dd, 2H),

7.05-7.11(m, 2H), 7.36-7.38(dd,2H), 7.30(s,1H, Vinyl-H),6.98(m,1H), 5.40(s,2H). <sup>13</sup>CNMR(DMSO-d<sub>6</sub>, 60MHz), 170.5, 153.3, 143.2, 141.3, 139.5, 135.8, 131.9, 129.5, 128.7, 127.1, 125.8, 125.4, 122.8, 122.2, 120.8, 60.2. ESI-MS : 303.3(M+H<sup>+</sup>), Anal.calcd. for C<sub>18</sub>H<sub>14</sub>N<sub>4</sub>O: C,71.51; H, 4.67; N, 18.53. Found: C, 71.41, H, 4.71, N, 18.55.

#### 5b: (Z)-5-((1H-1,2,4-triazol-1-yl)methyl)-3-(4-fluorobenzylidene)indolin-2-one

Yield: 49.3%, MP:255-258°C, IR(KBr in cm<sup>-1</sup>): 3185(NH Stretching),1685(C=O Stretching), 1328(C-F Stretching),1613(C=C Stretching), <sup>1</sup>HNMR(DMSO-d<sub>6</sub>) δ/ppm: 10.70(brs, 1H), 8.46(s,1H), 8.40(s,1H), 7.62-7.63(d, 1H), 7.50-7.54(dd, 2H), 7.28(s 1H), 7.19(s,1H), 6.90-6.96(m, 3H), 5.42(s,2H); <sup>13</sup>CNMR(DMSO-d<sub>6</sub>) 169.1, 162.3, 160.5, 152.8, 148.4, 142, 140.8, 132, 131, 129.2, 128, 127.2, 123, 122.3, 121.3, 118.5, 58.2. ESI Mass : 321.3(M+H<sup>+</sup>). Anal.calcd for C<sub>18</sub>H<sub>13</sub>FN<sub>4</sub>O: C, 67.49; H,4.09; N, 17.49. Found: C, 67.37; H, 4.15, N,17.43.

#### 5c: (Z)-5-((1H-1,2,4-triazol-1-yl)methyl)-3-(4-methoxybenzylidene)indolin-2-one

Yield:48.2%, MP:189-192°C, IR(KBr in cm<sup>-1</sup>): 3192(NH Stretching),1696(C=O Stretching),1615(C=C Stretching),1020 (C-O Stretching); <sup>1</sup>HNMR(DMSO-d<sub>6</sub>, 400MHz) δ/ppm: 10.68(brs, 1H), 8.38(s,1H), 8.33 (s,1H), 7.70-7.73(m, 1H), 7.28-7.32(m, 3H), 7.22(s 1H), 6.80-6.89(m, 3H), 5.38(s,2H), 3.86 (s, 3H) ; <sup>13</sup>CNMR(DMSO-d<sub>6</sub>, 100MHz) 170.2, 160.9,151.6, 144.3, 141.2, 137.6, 132.3, 129.6, 127.3, 125.4, 122.8, 122, 121.3, 114.3, 114.0,110.5 60.2, 58.3. ESI Mass : 333.4(M+H<sup>+</sup>), Anal.calcd. for C<sub>19</sub>H<sub>16</sub>N<sub>4</sub>O<sub>2</sub>: C, 68.66; H, 4.85, N, 16.86 Found: C,68.54; H, 4.92; N,16.86.

#### 5d: (Z)-5-((1H-1,2,4-triazol-1-yl)methyl)-3-(4-nitrobenzylidene)indolin-2-one

Yield: 46.9%, MP:210-212°C, IR(KBr in cm<sup>-1</sup>): 3186(NH Stretching),1690(C=O Stretching),1615(C=C Stretching),1358&1537 (NO<sub>2</sub> group Stretching); <sup>1</sup>HNMR(DMSO-d<sub>6</sub>, 400MHz) δ/ppm: 10.70(brs, 1H), 8.40(s,1H), 8.36 (s,1H), 8.32-8.35(dd, 2H), 7.78-7.83(dd, 2H), 7.52-7.54(d, 1H),7.43(s,1H),7.20(s,1H), 6.90-6.93(d, 1H), 5.40(s,2H) ; <sup>13</sup>CNMR(DMSO-d<sub>6</sub>, 100MHz) 169.8,

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152.1, 148.2, 143.5, 142.3, 142.1, 140.7, 132.1, 129.3, 128.6, 127.4, 126.8, 122.1, 121.4, 120.9, 58.2. ESI Mass :348.1 (M+H<sup>+</sup>), Anal.calcd. for C<sub>18</sub>H<sub>13</sub>N<sub>5</sub>O<sub>3</sub>: C, 62.24; H, 3.77; N, 20.16. Found: C, 62.18, H, 3.82, N, 13.85.

### 5e: (Z)-5-((1H-1,2,4-triazol-1-yl)methyl)-3-(4-isopropylbenzylidene)indolin-2-one

Yield: 45.4%, MP:195-197°C, IR(KBr in cm<sup>-1</sup>): 3185(NH Streching), 1690(C=O Streching), 1615(C=C Streching), 1370, 1385 (isopropyl group splitting); <sup>1</sup>HNMR(DMSO-d<sub>6</sub>, 400MHz) δ/ppm: 10.80(brs, 1H), 8.36(s, 1H), 8.30(s, 1H), 7.70-7.72(d, 1H), 7.30-7.35(dd, 2H), 7.30(s, 1H), 7.23(s, 1H), 7.13-7.16(dd, 1H), 6.86-6.89(d, 1H), 5.36(s, 2H), 2.93-2.96(m, 1H), 1.20-1.22(d, 6H); <sup>13</sup>CNMR(DMSO-d<sub>6</sub>, 100MHz) 169.5, 153.2, 148.6, 143.8, 142.1, 141.4, 140.9, 133.1, 130.1, 128.4, 127.1, 126.9, 122.3, 121.0, 120.5, 58.5, 36.5, 23.2. ESI Mass : 344.4(M+H<sup>+</sup>), Anal.calcd. for C<sub>21</sub>H<sub>20</sub>N<sub>4</sub>O: C, 73.23; H, 5.85; N, 16.27. Found: C, 73.10, H, 5.92; N, 16.27.

### 5f: (Z)-5-((1H-1,2,4-triazol-1-yl)methyl)-3-(4-chlorobenzylidene)indolin-2-one

Yield: 47.6%, MP:185-187°C, IR(KBr in cm<sup>-1</sup>): 3193(NH Streching), 1690(C=O Streching), 1615(C=C Streching), 740 (C-Cl Streching); <sup>1</sup>HNMR(DMSO-d<sub>6</sub>, 400MHz) δ/ppm: 10.81(brs, 1H), 8.40(s, 1H), 8.36(s, 1H), 7.55-7.58(d, 1H), 7.38-7.42(dd, 2H), 7.35(s, 1H), 7.27-7.30(dd, 2H), 7.24(s, 1H), 6.88-6.91(d, 1H), 5.38(s, 2H); <sup>13</sup>CNMR(DMSO-d<sub>6</sub>, 100MHz) 169.8, 152.1, 148.3, 141.5, 140, 133.8, 133.4, 132, 129, 128.6, 128, 127.4, 123, 122.1, 58.5 ESI Mass : 337.1(M+H<sup>+</sup>). 339.2, Anal.calcd. for C<sub>18</sub>H<sub>13</sub>ClN<sub>4</sub>O: C, 64.19; H, 3.89; N, 16.64. Found: C, 64.10, H, 3.94, N, 16.64.

### 5g: (Z)-5-((1H-1,2,4-triazol-1-yl)methyl)-3-(4-methylbenzylidene)indolin-2-one

Yield: 49.6%, MP:203-205°C, IR(KBr in cm<sup>-1</sup>): 3190(NH Streching), 1690(C=O Streching), 1615(C=C Streching); <sup>1</sup>HNMR(DMSO-d<sub>6</sub>, 400MHz) δ/ppm: 10.86(brs, 1H), 8.36(s, 1H), 8.30(s, 1H), 7.50-7.52(d, 1H), 7.30-7.34(dd, 2H), 7.30(s, 1H), 7.22(s, 1H), 7.08-7.12(dd, 2H), 6.85-6.87(d, 1H), 5.42(s, 2H), 2.43(s, 3H); <sup>13</sup>CNMR(DMSO-d<sub>6</sub>,

100MHz) 170.2, 152.1, 148.3, 141.4, 140, 133.2, 132.3, 131.9, 130, 129, 127, 126.4, 123, 122, 121.3, 59.1, 25.1 ESI Mass :317.1 (M+H<sup>+</sup>). Anal.calcd. for C<sub>19</sub>H<sub>16</sub>N<sub>4</sub>O: C, 72.13; H, 5.10; N, 17.71. Found: C, 72.10, H, 4.95, N, 17.68.

### 5h: (Z)-5-((1H-1,2,4-triazol-1-yl)methyl)-3-(4-cyanobenzylidene)indolin-2-one

Yield:48.3% MP:260-262°C, IR(KBr in cm<sup>-1</sup>): 3195(NH Streching), 2245(CN Streching) 1700(C=O Streching), 1613(C=C Streching); <sup>1</sup>HNMR(DMSO-d<sub>6</sub>, 400MHz) δ/ppm: 10.86(brs, 1H), 8.43(s, 1H), 8.38(s, 1H), 7.60-7.64(dd, 2H), 7.48-7.51(m, 3H), 7.36(s, 1H), 7.19(s, 1H), 6.86-6.89(d, 1H), 5.42(s, 2H); <sup>13</sup>CNMR(DMSO-d<sub>6</sub>, 100MHz) 172.6, 152.3, 148.1, 141.1, 140, 137.6, 133.4, 133.0, 131.3, 129.4, 128, 127.2, 123.5, 123.2, 120, 116.4, 59.1 ESI Mass : 328.1(M+H<sup>+</sup>). Anal.calcd. for C<sub>19</sub>H<sub>13</sub>N<sub>5</sub>O: C, 69.71; H, 4.00; N, 21.39. Found: C, 69.60; H, 4.06; N, 21.42

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