Efficient Synthesis and Characterization Of 4-Thiazolidinone derivatives by 3-Formylindole and 2-Naphthylamine

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Abstract- A series of 4-Thiazolidinone derivatives were synthesized by reaction of 3-formyl-2-arylidnole derivatives, 2-aminonaphthaline and mercaptoacetic acid. The structures of the new compounds were assigned on the basis of their analytical and spectral data.

Index terms- Heterocycles, 3-formylindole, 4-Thiazolidinone, 2-Aminonaphthaline, One pot synthesis

I. INTRODUCTION

Sulfur containing heterocycles have been under investigation for a long time because of their important medicinal properties[1]. Among these type of molecules, 4-thiazolidinones have been shown to have various important biological activities such as antimicrobial[2], antifungal[3], antiviral[4], antituberculostatic[5], anti-HIV[6], cardioprotective[7], anticancer[8], anticonvulsant[9], anti-inflammatory[10] and analgesic properties[11]. In the same way, Indole is another nitrogen containing bicyclic heterocyclic compound and belongs to the privileged structure in modern medicinal chemistry[12]. Indole derivatives represent many important classes of therapeutical agents in medicinal chemistry such as anticancer[13], antioxidant[14], anti-inflammatory[15], anticonvulsant[16], antimalarial[17], antipyretic[18], antimicrobial[19], antifungal[20], analgesic[21], antitubercular[22] and so on. Furthermore, some indole derivatives, such as melatonin and serotonin, influence many important biochemical processes. They act as antioxidant and play an important role in the immune system [23]. The aforementioned compounds have inspired us to attach substituted indole to the 4-thiazolidinone scaffold, and the combination of two privileged structures in one molecule leads to drug-like molecules. Therefore, in continuation of our research program on indole derivatives[24-25], a series of novel 4-thiazolidinone derivatives have been designed and synthesized by simple and practical approach. In this study we report the rapid and efficient method for the synthesis of novel 3-Naphthalen-2-yl-2-(2-phenyl-1H-indol-3-yl)-thiazolidin-4-one derivative via one-pot three-component condensation with quantitative yield.

II. MATERIALS AND METHOD

General procedure for the synthesis of 3-Naphthalen-2-yl-2-(2-phenyl-1H-indol-3-yl)-thiazolidin-4-one (4a-g)

The starting compound 3-formyl-2-aryl-indole derivatives (1a-g) were prepared by literature method[26-27] and thus obtained final compound was recrystallized with acetone. A mixture of corresponding 3-formyl-2-arylidnole (1a-g) (1 mmol), 2-aminonaphthaline (2) (1 mmol), and acetic acid (10 drops) in toluene (30 mL) was heated at 110°C with a Dean–Stark trap for 3h. Afterward, the mercaptoacetic acid (3) (2 mmol) was added and the mixture was heated until the reaction was complete, as shown by TLC. The organic layer was washed with a saturated solution of NaHCO₃ (3 x 30 mL), dried with MgSO₄ and concentrated to give the products. When necessary, the compounds were washed with a hot solution of hexane:ethyl acetate (9:1) to furnish the pure products. The purity of the compounds were checked by TLC using silica gel-G as adsorbent, UV light or iodine to accomplish visualization. IR spectra were recorded on a Shimadzu FT IR– 8400S spectrophotometer as KBr pellets. The ¹H NMR and ¹³C spectra were obtained in DMSO-d₆ using TMS as an internal standard on a Bruker spectrophotometer at 300 MHz and 75MHz respectively. The Mass spectra of compounds were determined on a Waters Xevo Q-Tof spectrometer at 70 eV. All the Melting points were determined using the open-ended capillary tube method and are uncorrected.

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The chemistry using amine, aldehyde and mercaptoacetic acid proceeded uneventfully and the product was isolated in quantitative yield after work up. In a typical experiment, 3-formyl-2-phenylindole derivatives and 2-aminonaphthalamine were heated in toluene for 3 h, followed by addition of mercaptoacetic acid. We have observed that presence of electron withdrawing group gives better yields as compared with electron donating group. Our mechanistic investigations using spectral studies gave proof to the cyclized products. The IR spectra of compounds 4a-g showed two absorption band in the region 1660-1690 cm⁻¹ this can be attributed to the cyclic C=O vibration. The N-H is observed at 3320-3350 cm⁻¹. The compounds was further assigned by NMR spectra of compounds 4a-g the aromatic signals were observed as a multiplet in the region δ 6.48-7.77. A singlet due to –NH was observed at δ10.34-1126. The methyl group in compound 4f and 4e were observed as a singlet at δ2.34 and 3.64 respectively.

Table 1 Physical data of compounds 4a-g.

<table>
<thead>
<tr>
<th>S. No.</th>
<th>compound</th>
<th>Ph</th>
<th>M.P. (⁰C)</th>
<th>Yield (%)</th>
<th>Molecular Formula</th>
</tr>
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<tr>
<td>1</td>
<td>4a</td>
<td>C₆H₅</td>
<td>188-190</td>
<td>56</td>
<td>C₂₇H₂₀N₂OS</td>
</tr>
<tr>
<td>2</td>
<td>4b</td>
<td>4-ClC₆H₄</td>
<td>240-242</td>
<td>63</td>
<td>C₂₇H₁₉ClN₂OS</td>
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<tr>
<td>3</td>
<td>4c</td>
<td>4-FC₆H₄</td>
<td>185-187</td>
<td>68</td>
<td>C₂₇H₁₉FN₂OS</td>
</tr>
<tr>
<td>4</td>
<td>4d</td>
<td>4-BrC₆H₄</td>
<td>210-212</td>
<td>60</td>
<td>C₂₇H₁₉BrN₂OS</td>
</tr>
<tr>
<td>5</td>
<td>4e</td>
<td>4-OCH₃C₆H₄</td>
<td>192-195</td>
<td>65</td>
<td>C₂₈H₂₂N₂O₂S</td>
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<tr>
<td>6</td>
<td>4f</td>
<td>4-CH₃C₆H₄</td>
<td>234-236</td>
<td>59</td>
<td>C₂₈H₂₂N₂OS</td>
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<tr>
<td>7</td>
<td>4g</td>
<td>3-NO₂C₆H₄</td>
<td>216-218</td>
<td>60</td>
<td>C₂₇H₁₉N₃O₃S</td>
</tr>
</tbody>
</table>

Spectral data:
3-Naphthalen-2-yl-2-(2-phenyl-1H-indol-3-yl)-thiazolidin-4-one (4a): C₂₇H₂₀N₂OS, Mol. Wt 420.53 ; IR (KBr) ν max in cm⁻¹ 3340, 3030,1685 ; ¹H NMR (DMSO-d₆) δ in ppm 10.34(s, 1H, NH), 6.75-7.61(m, 16H, Ar-H), 5.91(s, 1H, CH), 3.38(s, 2H, CH₂) ; ¹³C NMR (DMSO-d₆) 167.21, 145.35, 139.64, 138.37, 135.63, 134.23, 131.24, 129.27, 128.42, 125.41, 124.67, 122.68, 121.43, 120.36, 119.13, 113.28, 108.25, 51.53, 37.41 ; Anal. Calcd. C: 77.12, H: 4.79, N: 6.66. Found: C: 77.16, H: 4.81, N: 6.62 ; MS: m/z 421.53
2-[2-(4-Chloro-phenyl)-1H-indol-3-yl]-3-naphthalen-2-yl-thiazolidin-4-one (4b) C₂₇H₁₉ClN₂OS, Mol. Wt 454.97 ; IR (KBr) ν max in cm⁻¹ 3345, 3037,1660 ; ¹H NMR (DMSO-d₆) δ in ppm 10.54(s, 1H, NH), 6.52-7.63(m, 15H, Ar-H), 5.94(s, 1H, CH), 3.41(s, 2H, CH₂) ; ¹³C NMR (DMSO-d₆) 167.43, 143.97, 138.53, 136.65, 135.21, 134.23, 132.61, 131.93, 129.73, 128.68, 126.84, 125.23,
2-[2-(4-Fluoro-phenyl)-1H-indol-3-yl]-3-naphthalen-2-yl-thiazolidin-4-one (4c) C$_{27}$H$_{19}$FN$_2$OS, Mol. Wt 438.52 ; IR (KBr) $v_{max}$ in cm$^{-1}$ 3350, 3025,1665 ; $^1$H NMR (DMSO-d$_6$) $\delta$ in ppm 10.44(s, 1H, NH), 6.48-7.77(m, 15H, Ar-H), 5.95(s, 1H, CH), 3.36(s, 2H, CH$_2$) ; $^{13}$C NMR (DMSO-d$_6$) 167.49, 163.19, 143.17, 138.43, 136.65, 134.33, 132.11, 129.93, 127.68, 126.84, 125.73, 124.48, 122.32, 121.56, 120.61, 117.39, 114.29, 113.76, 109.18, 51.23, 37.88 ; Anal. Calcd. C: 73.95, H: 4.37, N: 6.39. Found: C: 73.93, H: 4.39, N: 6.37 ; MS: m/z 439.52

2-[2-(4-Bromo-phenyl)-1H-indol-3-yl]-3-naphthalen-2-yl-thiazolidin-4-one (4d) C$_{27}$H$_{19}$BrN$_2$OS, Mol. Wt 499.42 ; IR (KBr) $v_{max}$ in cm$^{-1}$ 3340, 3030,1670 ; $^1$H NMR (DMSO-d$_6$) $\delta$ in ppm 11.26(s, 1H, NH), 6.75-7.67(m, 15H, Ar-H), 5.98(s, 1H, CH), 3.43(s, 2H, CH$_2$) ; $^{13}$C NMR (DMSO-d$_6$) 166.49, 145.37, 138.13, 136.15, 134.33, 133.31, 132.11, 130.93, 128.18, 126.64, 125.73, 124.48, 123.10, 122.82, 121.26, 120.42, 114.49, 113.46, 109.28, 50.13, 38.88 ; Anal. Calcd. C: 64.93, H: 3.83, N: 5.61. Found: C: 64.91, H: 3.85, N: 5.59 ; MS: m/z 500.42

2-[2-(4-Methoxy-phenyl)-1H-indol-3-yl]-3-naphthalen-2-yl-thiazolidin-4-one (4e) C$_{26}$H$_{25}$N$_2$OS, Mol. Wt 450.55 ; IR (KBr) $v_{max}$ in cm$^{-1}$ 3325, 3010,1690 ; $^1$H NMR (DMSO-d$_6$) $\delta$ in ppm 10.85(s, 1H, NH), 6.55-7.68(m, 15H, Ar-H), 5.73(s, 1H, CH), 3.64(s, 3H, CH$_3$) 3.33(s, 2H, CH$_2$) ; $^{13}$C NMR (DMSO-d$_6$) 167.59, 161.73, 145.77, 138.43, 134.94, 133.11, 130.61, 129.93, 128.67, 126.24, 125.60, 124.45, 123.44, 122.12, 121.16, 120.44, 116.08, 114.49, 113.22, 109.28, 51.53, 38.21 ; Anal. Calcd. C: 74.64, H: 4.92, N: 6.22. Found: C: 74.62, H: 4.94, N: 6.20 ; MS: m/z 451.55

2-[2-(4-Methyl-phenyl)-1H-indol-3-yl]-3-naphthalen-2-yl-thiazolidin-4-one (4f) C$_{26}$H$_{23}$N$_2$OS, Mol. Wt 434.55 ; IR (KBr) $v_{max}$ in cm$^{-1}$ 3320, 3030,1680 ; $^1$H NMR (DMSO-d$_6$) $\delta$ in ppm 10.57(s, 1H, NH), 6.80-7.61(m, 15H, Ar-H), 5.91(s, 1H, CH), 3.38(s, 2H, CH$_2$), 2.34(s, 3H, CH$_3$) ; $^{13}$C NMR (DMSO-d$_6$) 166.81, 142.42, 139.33, 138.11, 136.62, 135.51, 134.55, 132.11, 131.60, 129.53, 128.18, 126.34, 125.24, 124.68, 122.43, 121.91, 120.19, 114.55, 111.96, 107.64, 50.88, 37.96, 21.19 ; Anal. Calcd. C: 77.39, H: 5.10, N: 6.45. Found: C: 77.37, H: 5.12, N: 6.43 ; MS: m/z 435.55

2-[2-(3-Nitro-phenyl)-1H-indol-3-yl]-3-naphthalen-2-yl-thiazolidin-4-one (4g) C$_{27}$H$_{19}$N$_3$O$_3$S, Mol. Wt 465.52 ; IR (KBr) $v_{max}$ in cm$^{-1}$ 3330, 3035,1670 ; $^1$H NMR (DMSO-d$_6$) $\delta$ in ppm 10.34(s, 1H, NH), 6.85-7.71(m, 15H, Ar-H), 5.95(s, 1H, CH), 3.32(s, 2H, CH$_2$) ; $^{13}$C NMR (DMSO-d$_6$) 166.92, 151.28, 143.43, 139.21, 138.37, 134.62, 133.22, 132.47, 131.55, 128.51, 126.29, 125.65, 124.32, 122.74, 121.91, 120.30, 114.87, 113.39, 106.67, 51.59, 37.60 ; Anal. Calcd. C: 69.66, H: 4.11, N: 9.03. Found: C: 69.64, H: 4.13, N: 9.01 ; MS: m/z 466.52

IV. CONCLUSION

We applied one pot methodology to promote the synthesis of 4-Thiazolidinone derivatives by the reaction of 3-formyl-2-arylidene, 2-aminonaphthylamine and mercaptoacetic acid in good yield and good purities. Synthesized compounds were characterized by IR, $^1$H NMR, $^{13}$C NMR, and Mass spectra.

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