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-arylindole 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

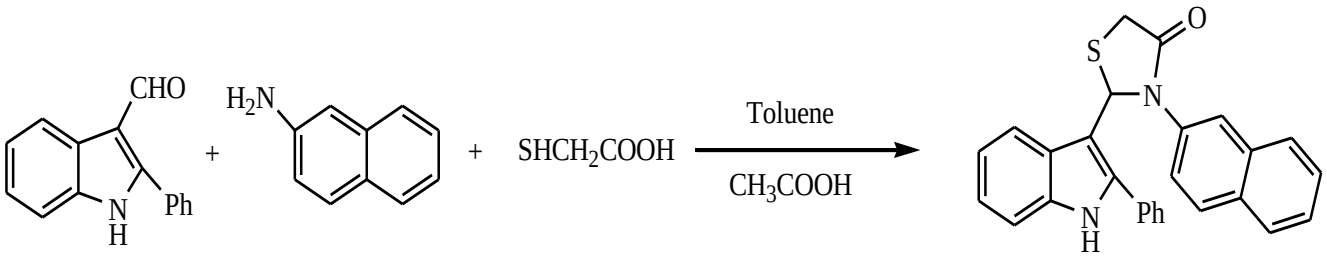
I. INTRODUCTION

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 an 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], antiinflammatory[15], anticonvulsant[16], antimalarial[17], antipyratic[18], antimicrobial[19], antifungal[20], analgesis[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 scafford, and the combination of two privileged structures in one molecule leads to drug-like molecules. Therefor, 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-1*H*-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 recrystalized with acetone. A mixture of corresponding 3-formyl-2-arylindole **(1a-g)** (1 mmol), 2-aminonaphthaline **(2)** (1 mmol), and acetic acid (10drops) in toluene (30 mL) was heated at 110 ^{0}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 $NaHCO_3$ (3 x 30 mL), dried with $MgSO_4$ and concentrated to give the products. When necessary, the compounds were washed with a hot solution of hexane:ethyl acetate (9:1) to furnished 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 ^{1}H NMR and ^{13}C spectra were obtained in DMSO-d_6 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.



(1) **(2)** **(3)** **(4a-g)**

Figure 1

III. RESULTS AND DISCUSION

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 **Table 1**. Our mechanistic investigations using spectral studies gave proof of 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.

S. No.	compound	Ph	M.P. (^{0}C)	Yield (%)	Molecular Formula
1	4a.	C_6H_5	188-190	56	$C_{27}H_{20}N_2OS$
2	4b.	4-ClC_6H_4	240-242	63	$C_{27}H_{19}ClN_2OS$
3	4c.	4-FC_6H_4	185-187	68	$C_{27}H_{19}FN_2OS$
4	4d.	4-BrC_6H_4	210-212	60	$C_{27}H_{19}BrN_2OS$
5	4e.	4-$OCH_3C_6H_4$	192-195	65	$C_{28}H_{22}N_2O_2S$
6	4f.	4-$CH_3C_6H_4$	234-236	59	$C_{28}H_{22}N_2OS$
7	4g.	3-$NO_2C_6H_4$	216-218	60	$C_{27}H_{19}N_3O_3S$

Spectral data:

3-Naphthalen-2-yl-2-(2-phenyl-1*H*-indol-3-yl)-thiazolidin-4-one (4a): $C_{27}H_{20}N_2OS$, Mol. Wt 420.53 ; IR (KBr) ν_{max} in cm^{-1} 3340, 3030,1685 ; ^{1}H NMR (DMSO-d_6) 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, CH_2) ; ^{13}C 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)-1*H*-indol-3-yl]-3-naphthalen-2-yl-thiazolidin-4-one (4b) $C_{27}H_{19}ClN_2OS$, Mol. Wt 454.97 ; IR (KBr) ν_{max} in cm^{-1} 3345, 3037,1660 ; ^{1}H NMR (DMSO-d_6) 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, CH_2) ; ^{13}C 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,

124.43, 122.32, 121.20, 120.11, 114.19, 113.48, 109.98, 51.33, 37.38 ; Anal. Calcd. C: 71.28, H: 4.21, N: 6.16 . Found: C: 71.30, H: 4.23, N: 6.14 ; MS: m/z 455.97

2-[2-(4-Fluoro-phenyl)-1*H*-indol-3-yl]-3-naphthalen-2-yl-thiazolidin-4-one (4c) $C_{27}H_{19}FN_2OS$, Mol. Wt 438.52 ; IR (KBr) ν_{max} in cm^{-1} 3350, 3025,1665 ; ^{1}H NMR (DMSO-d_6) δ 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-d6) 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)-1*H*-indol-3-yl]-3-naphthalen-2-yl-thiazolidin-4-one (4d) $C_{27}H_{19}BrN_2OS$, Mol. Wt 499.42 ; IR (KBr) ν_{max} in cm^{-1} 3340, 3030,1670 ; ^{1}H NMR (DMSO-d_6) δ 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-d6) 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)-1*H*-indol-3-yl]-3-naphthalen-2-yl-thiazolidin-4-one (4e) $C_{28}H_{22}N_2O_2S$, Mol. Wt 450.55 ; IR (KBr) ν_{max} in cm^{-1} 3325, 3010,1690 ; ^{1}H NMR (DMSO-d_6) δ 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-d6) 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)-1*H*-indol-3-yl]-3-naphthalen-2-yl-thiazolidin-4-one (4f) $C_{28}H_{22}N_2OS$, Mol. Wt 434.55 ; IR (KBr) ν_{max} in cm^{-1} 3320, 3030,1680 ; ^{1}H NMR (DMSO-d_6) δ 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-d6) 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)-1*H*-indol-3-yl]-3-naphthalen-2-yl-thiazolidin-4-one (4g) $C_{27}H_{19}N_3O_3S$, Mol. Wt 465.52 ; IR (KBr) ν_{max} in cm^{-1} 3330, 3035,1670 ; ^{1}H NMR (DMSO-d_6) δ 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-d6) 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-arylindole, 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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