Available online at www.joac.info

ISSN: 2278-1862

Journal of Applicable Chemistry

2014, 3 (2): 572-576

(International Peer Reviewed Journal)

Synthesis And Screening of Some Novel Indole Based 5-Sulfanyl-[1, 3, 4]-Oxadiazole

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Accepted on 26th February 2014

ABSTRACT

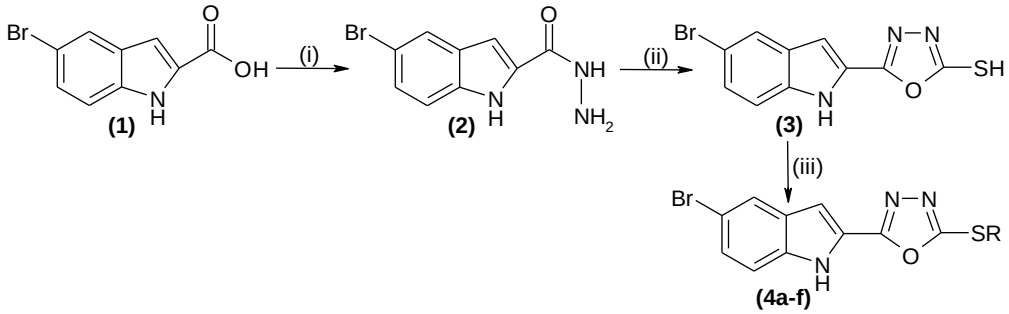
A series of novel 5-bromo-2-(5-substitutedsulfanyl-[1,3,4]-oxadiazol-2-yl)-1H-indoles ***(4a-f)*** *were synthesized in good yields from starting material, 5-bromo-1H-indole-2-carbxylic acid* ***(1)*** *and by involving 5-bromo-1H-indole-2-carbxylic acid hydrazide* ***(2)*** *and 5-(5-bromo-1H-indol-2-yl)-[1,3,4]oxadiazol-2-thiol* ***(3)*** *as intermediates. The chemical structures of the newly synthesized compounds were elucidated by their IR,* ^{1}H *&* ^{13}C *NMR and mass spectral data. Further, all the title compounds were screened for their antibacterial and anti-fungal activity.*

Keywords: [1,3,4]-Oxadiazols, Antibacterial activity, Antifungal activity.

INTRODUCTION

The oxadiazole chemistry has been developed extensively and is still developing. Presently there are a number of drugs used clinically, which comprise oxadiazole moiety in association with various heterocyclic rings. 1, 3, 4-Oxadiazoles are biologically active, synthetically useful and important heterocyclic compounds. The synthesis of novel oxadiazole derivatives and investigation of their chemical and biological behavior have gained more importance in recent decades for biological, medicinal and agricultural reasons. Different classes of oxadiazole compounds possess an extensive spectrum of pharmacological activities. Differently substituted oxadiazole moiety has also been found to have other important activities such as antibacterial [1], antimalarial [2], anti-inflammatory [3], antifungal [4], anticonvulsant [5], analgesic [6], antimicrobial [7], antimycobacterial [8], anticonvulsant [9], antitumor [10], antimalarial [11], herbicidal [12], vasodialatory [13], cytotoxic [14], hypolipidemic [15], ulcerogenic [16] and antiedema [17].

Inspired by the biological profile of 1,3,4-oxadiazoles and their increasing importance in pharmaceutical and biological fields, it was thought worthwhile to undertake the synthesis of 5-bromo-2-(5-substitutedsulfanyl-[1,3,4]-oxadiazol-2-yl)-1*H*-indoles **(4a-f)** with the view to obtain certain new chemical entities with two active pharmacophores in a single molecular frame work for the intensified biological activities. The synthetic route leading to the title compounds is summarized in Scheme 1.



Scheme 1. Synthesis of indole based 5-Sulfanyl-[1,3,4]-oxadiazole

Experimental conditions: (i) $NH_2NH_2.H_2O$, EtOH, reflux, 7 h; (ii) CS_2, alco. KOH, reflux, 8 h; (iii) R-Cl, alco. KOH, DMS, reflux, 5-6 h; **4R** (a) = CH_3, (b) = $PhCH_2$, (c) = *o*-CH_3-$PhCH_2$, (d) = *p*-CH_3-$PhCH_2$, (e) = *o*-Cl-$PhCH_2$, (f) = *p*-Cl-$PhCH_2$

MATERIALS AND METHODS

All reagents and solvents were used as purchased without further purification. Melting points were determined on a Fisher–Johns melting point apparatus and are uncorrected. Crude products were purified by column chromatography on silica gel of 60–120 mesh. IR spectra were obtained on a PerkinElmer BX serried FTIR 5000 spectrometer using KBr pellet. ^1H & ^{13}C NMR spectra were recorded on a Varian 300 and 100 MHz spectrometer. The chemical shifts were reported as ppm down field using TMS as an internal standard. Mass spectra were recorded on a VG-Micromass 7070H spectrometer operating at 70 eV.

5-Bromo-1*H*-indole-2-carbxylic acid hydrazide 2: A mixture of compound 5-bromo-1*H*-indole-2-carbxylic acid **1** (0.01 mol) and hydrazine hydrate (0.025 mol) in ethanol (20 ml) was refluxed for 7 h, cooled to room temperature and filtered. The crude product was recrystallized from ethanol to give **5**-bromo-1*H*-indole-2-carbxylic acid hydrazide **2**. Yellow solid, yield: 70%, mp: 120-122 °C; IR (KBr): 3149 (N-H), 3032 (C-H, Ar), 1642 (C=O), 1578 (C=C, Ar) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 10.58 (s, 1H, NH), 7.70 (s, 1H, CONH), 7.62 (s, 1H, Ar-H), 7.54 (d, 1H, J = 7.0 Hz, Ar-H), 7.42 (d, 1H, J = 7.0 Hz, Ar-H), 7.39 (s, 1H, Ar-H), 5.30 (s, 2H, NH_2); MS: 254 *m/z* (M^+).

5-(5-Bromo-1*H*-indol-2-yl)-[1,3,4]oxadiazol-2-thiol 3: To an alcoholic solution of potassium hydroxide (5% 0.015 mol), 5-bromo-1*H*-indole-2-carbxylic acid hydrazide **2** and carbon disulphide (10 ml) were added. The reaction mixture was heated under reflux for 8 hrs, cooled and triturated with cold water, and then it was filtered to get a clear solution and neutralized carefully with dil. hydrochloric acid. The product 5-(5-bromo-1*H*-indol-2-yl)-[1,3,4]oxadiazol-2-thiol **3**, thus separated was filtered, washed thoroughly with cold water, dried and purified. Pale solid, yield: 73%, mp: 146-148 °C; IR (KBr): 3145 (N-H), 3030 (C-H, Ar), 1570 (C=C, Ar), 1438 (C=N), 1226 (C-S), 1132 (C-O) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 10.40 (s, 1H, NH), 7.75 (s, 1H, Ar-H), 7.64 (d, 1H, J = 7.2 Hz, Ar-H), 7.50 (d, 1H, J = 7.2 Hz, Ar-H), 7.41 (s, 1H, Ar-H), 3.82 (s, 1H, SH); MS: 296 *m/z* (M^+).

General Experimental Procedure For the synthesis of 5-Bromo-2-(5-substitutedsulfanyl-[1,3,4]-oxadiazol-2-yl)-1*H*-indoles (4a - 4f) : The mixture of compound 5-(5-bromo-1*H*-indol-2-yl)-[1,3,4]oxadiazol-2-thiol **3** (0.01 mol), dimethyl sulfate and aliphatic or aromatic chloride (0.01 mol) in alcoholic potassium hydroxide (5% 150 ml) was stirred well, refluxed on water bath for 5-6 hrs, then cooled and poured on to ice cold water. The mixture was neutralized with dilute hydrochloric acid. The product thus separated was filtered, washed with small portions of ice cold water, dried and recrystallized from suitable solvent.

5-Bromo-2-(5-methylsulfanyl-[1,3,4]oxadiazol-2-yl)1H-indole (4a): *Brown* solid, yield: 71%, mp: 130-132 °C; IR (KBr): 3165 (N-H), 3028 (C-H, Ar), 2945 (C-H, CH_3), 1572 (C=C, Ar), 1442 (C=N), 1232 (C-S), 1140 (C-O) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 10.40 (s, 1H, NH), 7.58 (d, 1H, J = 7.3 Hz, Ar-H), 7.50 (d, 1H, J = 7.3 Hz, Ar-H), 7.48 (s, 1H, Ar-H), 7.35 (s, 1H, Ar-H), 1.23 (s, 3H, CH_3); MS: 310 *m/z* (M^+).

2-(5-Benzylsulfanyl-[1,3,4]oxadiazol-2-yl)-5-bromo-1H-indole (4b): Gray solid, yield: 76%, mp: 141-143 °C; IR (KBr): 3165 (N-H), 3038 (C-H, Ar), 2940 (C-H, CH_2), 1570 (C=C, Ar), 1448 (C=N), 1236 (C-S), 1128 (C-O) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 10.65 (s, 1H, NH), 7.70 (s, 1H, Ar-H), 7.68 (d, 1H, J = 6.9 Hz, Ar-H), 7.65-7.38 (m, 5H, Ar-H), 7.54 (d, 1H, J = 6.9 Hz, Ar-H), 7.43 (s, 1H, Ar-H), 1.62 (s, 2H, CH_2); MS: 386 *m/z* (M^+).

5-Bromo-2-[5-(2-methyl-benzylsulfanyl)-[1,3,4]oxadiazol-2-yl]1H-indole (4c): Yellow solid, yield: 78%, mp: 168-170 °C; IR (KBr): 3154 (N-H), 3026 (C-H, Ar), 1565 (C=C, Ar), 1438 (C=N), 1226 (C-S), 1138 (C-O) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 10.50 (s, 1H, NH), 7.74 (s, 1H, Ar-H), 7.62 (d, 1H, J = 7.0 Hz, Ar-H), 7.60-7.32 (m, 4H, Ar-H), 7.50 (d, 1H, J = 7.0 Hz, Ar-H), 7.39 (s, 1H, Ar-H), 1.68 (s, 2H, CH_2), 1.23 (s, 3H, CH_3); MS: 400 *m/z* (M^+).

5-Bromo-2-[5-(4-methyl-benzylsulfanyl)-[1,3,4]oxadiazol-2-yl]1H-indole (4d): Pale yellow solid, yield: 80%, mp: 150-152 °C; IR (KBr): 3178 (N-H), 3036 (C-H, Ar), 2945 (C-H, CH_2), 1578 (C=C, Ar), 1445 (C=N), 1238 (C-S), 1145 (C-O) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 10.48 (s, 1H, NH), 7.85 (s, 1H, Ar-H), 7.74 (d, 1H, J = 7.2 Hz, Ar-H), 7.72 (d, 2H, J = 6.8 Hz, Ar-H), 7.45 (d, 2H, J = 6.8 Hz, Ar-H), 7.42 (d, 1H, J = 7.2 Hz, Ar-H), 7.36 (s, 1H, Ar-H), 1.58 (s, 2H, CH_2), 1.26 (s, 3H, CH_3); MS: 400 *m/z* (M^+).

5-Bromo-2-[5-(2-chloro-benzylsulfanyl)-[1,3,4]oxadiazol-2-yl]1H-indole (4e): Brown solid, yield: 78%, mp: 139-141 °C; IR (KBr): 3154 (N-H), 3026 (C-H, Ar), 1565 (C=C, Ar), 1438 (C=N), 1226 (C-S), 1142 (C-O) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 10.38 (s, 1H, NH), 7.69 (s, 1H, Ar-H), 7.60 (d, 1H, J = 7.4 Hz, Ar-H), 7.58-7.38 (m, 4H, Ar-H), 7.48 (d, 1H, J = 7.4 Hz, Ar-H), 7.36 (s, 1H, Ar-H), 1.47 (s, 2H, CH_2); MS: 420 *m/z* (M^+).

5-Bromo-2-[5-(4-chloro-benzylsulfanyl)-[1,3,4]oxadiazol-2-yl]1H-indole (4f): Greenish gray solid, yield: 82%, mp: 160-162 °C; IR (KBr): 3178 (N-H), 3048 (C-H, Ar), 2948 (C-H, CH_2), 1580 (C=C, Ar), 1458 (C=N), 1234 (C-S), 1136 (C-O) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 10.69 (s, 1H, NH), 7.79 (s, 1H, Ar-H), 7.71 (d, 1H, J = 7.0 Hz, Ar-H), 7.69 (d, 2H, J = 6.9 Hz, Ar-H), 7.50 (d, 2H, J = 6.9 Hz, Ar-H), 7.48 (d, 1H, J = 7.0 Hz, Ar-H), 7.34 (s, 1H, Ar-H), 1.49 (s, 2H, CH_2); MS: 420 *m/z* (M^+).

RESULTS AND DISCUSSION

Synthesis: The synthesis of the target compound **4a-f** commenced from commercially available 5-bromo-1*H*-indole-2-carbxylic acid **(1)**. The initial intermediate 5-bromo-1*H*-indole-2-carbxylic acid hydrazide **(2)** has been prepared on condensation of compound **1** with hydrazine hydrate in ethanol under reflux for 7 h. The key intermediate 5-(5-bromo-1*H*-indol-2-yl)-[1,3,4]oxadiazol-2-thiol **(3)** for the synthesis of the title compounds was prepared under reflux of compound **2** with CS_2 in presence of alcoholic KOH for 8 h. Finally compound **3** on reaction with different halides in presence of alcoholic KOH and DMS at reflux temperature for 5-6 h afforded the title compounds 5-bromo-2-(5-substitutedsulfanyl-[1,3,4]-oxadiazol-2-yl)-1*H*-indoles **(4a-f)** in good to excellent yields. The chemical structures of all the newly synthesized compounds were confirmed by their IR, ^1H & ^{13}C NMR and mass spectral data and further these compounds were screened for their antibacterial and antifungal activities and have been found that most of them showed promising activity.

Biological activity: The disc diffusion method [18] was used for the screening of anti microbial activity. The *in vitro* antibacterial activity of 5-bromo-2-(5-substitutedsulfanyl-[1,3,4]-oxadiazol-2-yl)-1*H*-indoles **(4a-f)** was tested against three Gram-positive bacteria *i.e. Staphylococcus aureus, Staphylococcus albus, Streptococcus faecalis* and against three Gram-negative bacteria *i.e., Escherichia coli, Proteus mirabilis, Salmonella typhi*. The antifungal activity of the compounds was screened against two representative fungal organisms namely *Candia albicans* and *Aspergillus fumigatus*. Amicacin and Fluconazole were used in antibacterial and antifungal activity studies as reference compounds. The lowest concentration (highest dilution) of the compounds at which, there was no visually detectable bacterial growth was taken as minimum inhibitory concentration (MIC) and it was determined for the compounds **4a-f**. The zone of inhibition caused by the various compounds on the micro organisms was measured and the activity rated on the basis of the size of the inhibition zone. The observed zone of inhibition in mm is presented in **table 1**.

Table 1. Antimicrobial activity of compounds **4a-f** (Zone of inhibition in mm)

Compound	Antibacterial activity						Antifungal activity	
	S.aureus	*S.albus*	*S.faecalis*	*E coli*	*P. mirabilis*	*S.typhi*	*C.albicans*	*A.fumigatus*
4a	11	13	13	12	0	10	10	12
4b	21	19	18	16	17	15	21	22
4c	18	19	20	14	15	15	21	23
4d	22	20	24	14	14	15	21	23
4e	8	9	10	11	11	10	12	10
4f	14	12	13	12	1	13	12	10
Amicacin	24	22	26	20	21	18	-	-
Fluconazole	-	-	-	-	-	-	23	25

The results of the antimicrobial screening of the tested compounds revealed that, all the tested compounds exhibited antimicrobial activity comparable with that of reference compounds. Most of the compounds showed significant and high activity against both bacteria and fungi. Both compounds 4b and 4c exhibited highest antifungal activity against *C. albicans* and *A. fumigatus* as compared to the standard drug. Highest antimicrobial activity was observed in the product 4d against *S. aureus, S. albus* and *S. faecalis* but shows only moderate activity against *E. coli* and *P. mirabilis*. This compound also performed high activity against two fungal organisms. Compound 4a, compare with other molecules was found to be totally inactive against *P. mirabilis*. Compound 4e was good active only against *S. faecalis* and almost inactive towards *E. coli*. This compound exhibited moderate activity against the rest of organisms. It can be concluded that the antimicrobial activity of such compounds may change by introduction or elimination of a specific group.

APPLICATIONS

In the present study the derivatives which we have synthesized were screened for their antibacterial activity, which are promising as active pharmacophore. Further studies are undergoing to explore the scope of the various biological activities.

CONCLUSIONS

In conclusion, the present paper describes the synthesis of 5-bromo-2-(5-substitutedsulfanyl-[1,3,4]-oxadiazol-2-yl)-1*H*-indoles **(4a-f)**, from commercially available 5-bromo-1*H*-indole-2-carbxylic acid. These compounds were screened for their antibacterial and antifungal activities and have been found that most of them showed promising activity.

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