Int. J. Chem. Sci.: 11(1), 2013, 539-545
ISSN 0972-768X
www.sadgurupublications.com

SYNTHESIS, CHARACTERIZATION AND PHARMACOLOGICAL EVALUATION OF SOME NOVEL 2,5-DISUBSTITUTED-1,3,4-THIxADIAZOLE DERIVATIVES

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ABSTRACT

2,5-disubstituted-1,3,4-thiadiazole derivatives have been synthesized with different substituted aromatic acid. Esterification of aromatic acid with ethanol followed by hydrazination, salt formation and cyclization to formed 5-(2-chlorophenyl)-1,3,4-thiadiazole-2-thiol, 5-(3-chlorophenyl)-1,3,4-thiadiazole-2-thiol, 5-(2-nitrophenyl)-1,3,4-thiadiazole-2-thiol and 5-(4-nitrophenyl)-1,3,4-thiadiazole-2-thiol. All the new compounds were confirmed by IR, NMR and mass spectral analysis. These compounds were evaluated for their antibacterial and anti-inflammatory activity.

Key words: 1, 3, 4-thiadiazole, Anti-inflammatory, Antibacterial.

INTRODUCTION

Several number of five membered hetrocycles containing nitrogen and sulphur atom, have been studied because of their interesting biological importance. The pharmacological profile of 1,3,4-thiadiazole is very extensive like antimicrobial[1-6], antifungal[7-9], antitubercular[10-12], anti-inflammatory[13-15] and analgesic[16,17]. A considerable No. of 1,3,4-thiadiazole derivatives repoted diuretic[18], anthelmenintic[19], anticancer[20-22], anticonvulsant[23-24] and antiplatelet[25] activity.

EXPERIMENTAL

Melting points were determined by open capillary tube method. Purity of the compounds were checked by column chromatography and TLC (Thin layer chromatography) on silica gel G (60-120 mess) and silica gel GF_{254} (4 : 1) in various solvent systems plates. Spots were visualized under iodine vapours and UV light chamber. IR spectra were recorded on Bruker alpha (α) FTIR-Spectrometer. ^{1}H NMR spectra were noted on Brucker DRX-400

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MHz using TMS as internal reference (chemical shift δ ppm) in DMSO/$CDCl_3$. Mass spectra (m/z %) were recorded on a Jeol-JMS-D-300 Mass spectrometer.

Materials and methods

General procedure of synthesis of compounds (2a-2d)

Benzoic acid (0.05 mol) and its derivatives **(1a-1d)** and anhydrous ethanol (100 mL) were taken in RBF fitted with dropping funnel and magnetic stirring bar. To this solution concentrated sulfuric acid (15-20 mL) was added dropwise through a dropping funnel. Then solution was refluxed for 6 h at 50^{o}C, cooled to room temperature and poured into an equal volume of water. The organic phase was washed with saturated aqueous sodium bicarbonate solution (10 mL). These crude products **(2a-2d)** were dried over magnesium sulfate.

General procedure of synthesis of compounds (3a-3d)

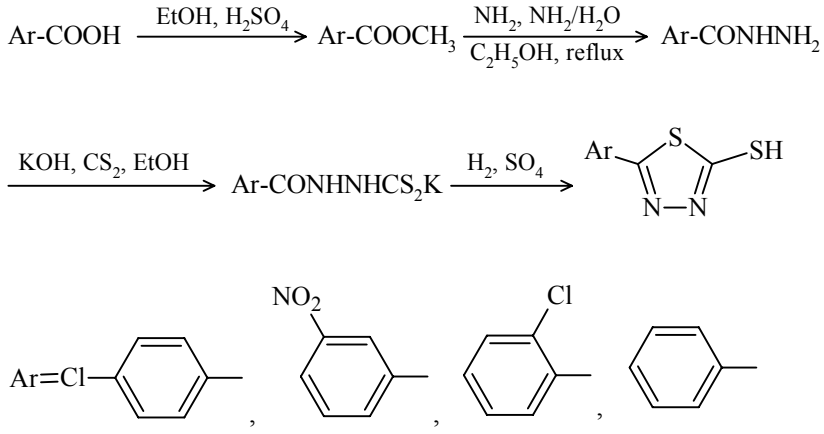
Ethyl benzoate and its derivatives (**2a-2d)** is hydrazinated using anhydrous ethanol (80 mL) and hydrazine hydrate (40 mL, 80%). Then solution was refluxed for 8 h at 40-60^{o}C. The reaction mixture was cooled to 20^{o}C, solid precipitate of substituted benzohydrazide **(3a-3d)** were obtained. These products were recrystallized with ethanol.

General procedure of Synthesis of compounds (4a-4d)

Substituted benzohydrazide **(3a-3d)** stirred with KOH (0.2 mol) and anhydrous ethanol (100 mL), when homogenous mixture was obtained CS_2 (0.1 mol) added to reaction mixture. The reaction system was stirred at room temperature for an additional 6 h, filtered, and the resulting solids were used for the next step without further purification.

General procedure of synthesis of 5-substituted-1,3,4-thiadiazole-2-thiol (C1 –C4)

Magnetic stirring bar was first charged with sulfuric acid (80 mL, 98%) and then cooled on an ice bath with vigorous stirring. When the temperature reached below −2°C, **(4a-4d)** (22.9 g, 0.08 mol) was slowly added into it. After completion of the addition, the reaction mixture was kept below 0°C and stirred for another 5 h. The mixture was poured into ice water (200 mL) a large amount of white solid precipitated, which was separated by suction filtration. The solids were washed with water to a pH value of 6, the cake was dissolved in 10% aqueous NaOH and the insoluble part was removed through filtration. The filtrate was acidified by HCl (36%) to a pH of 2. The resulting white solid was filtered, washed with water and recrystallized from EtOH.



Scheme

RESULTS AND DISCUSSION

Antimicrobial activity

The synthesized compounds were evaluated for their antibacterial activity against gram positive and gram negative bacteria by Disc- diffusion method. Ofloxacine were used as standard drugs for antibacterial activity.

Anti-inflammatory activity

The synthesized compounds were evaluated for their anti-inflammatory activity in Wister albino rats by Carrageenan induced paw edema method using Ibuprofen as standard drug.

Table 1: Physical properties of compounds (C_1 –C_4)

Compounds	Yield (%)	R_f	MP (^oC)	Mol. formula	Mol. wt.
C_1	72	0.62	202	$C_8H_5N_2S_2Cl$	228.5
C_2	68	0.66	198	$C_8H_5O_2N_3S_2$	239
C_3	71	0.59	200	$C_8H_5N_2S_2Cl$	228.5
C_4	65	0.58	201	$C_8H_6N_2S_2$	194

Table 2: Anti-inflammatory activities of compounds (C_1 –C_4)

Compounds	Dose (mg/Kg)	Inhibition of paw oedema after 3 hrs (%)	Inhibition of paw oedema after 6 hrs (%)
C_1	90	32.34	59.26
C_2	90	30.52	60.72
C_3	90	29.89	57.48
C_4	90	31.46	61.16
Control	-	-	-
Ibuprofen	40	40.29	66.44
Dose of Standard drug: 40 mg/Kg			

Table 3: Anti-bacterial activities of compounds (C_1 –C_4)

Compds.	Zone of inhibition in mm (Concentration: 25 µg/disc)							
	S. aureus	**% inhibition**	***B. subtilis***	**% inhibition**	***E. coli***	**% inhibition**	***P. aeruginosa***	**% *inhibition***
C_1	13	81.25	13	76.47	13	81.25	15	83.33
C_2	14	87.50	14	82.35	14	87.50	14	77.38
C_3	13	81.50	12	70.59	12	75.00	14	77.38
C_4	14	87.50	14	82.35	14	87.50	16	88.89
Ofloxacine	16	100.00	17	100.00	16	100.00	18	100.00

Compound (C1): 5-(4-Chloro phenyl)-1,3,4-thiadiazole-2-thiol

^{1}H-NMR (DMSO d_6, 300 MHz): δ 8.00 (1H, s, J = 7.998), 7.97 (1H, s, J = 7.969), 7.915 (J = 7.914), 7.89 (1H, s, 7.885), 7.578 (J = 7.577), 7.55 (1H, s, J = 7.548), 7.485 (J = 7.486), 7.46 (J = 7.457), 1.3 (J = 1.274).

FT-IR: 3375.2369.96, 2334.75, 1638.28, 1543.69, 1425.43, 1267.98, 1085.36, 843.40, 749.45, 668.65.

Mass (m/z %): C (42.74%), H (2.22%), N (12.46%), S (28.50%), Cl (15.80%).

Compound (C2): 5-(3-Nitro phenyl)-1,3,4-thiadiazole-2-thiol:

^{1}H NMR (DMSO d_6, 300 MHz): δ 3.35 (J = 3.3) 0.8 (m, J = 0.932), 1.3 (m, J = 1.321).

IR: 3175.17, 3083.66, 2955.16, 2920.22, 2849.95, 2360.81, 2330.99, 1705.69, 1678.04, 1523.99, 1466.39, 1391.26, 1226.50, 1024.84, 1108.97, 806.42.

Mass (m/z %): C (39.18%), H (2.04%), O (13.06%), S (26.12%), N (17.14%).

Compound (C3): 5-(2-chloro phenyl)-1,3,4-thiadiazole-2-thiol

^{1}H NMR (DMSO d_6, 300 MHz): δ 8.38 (1H, s, J = 8.336), 7.94 (2H, d, J = 7.926), 7.885 (1H, s, J = 7.870), 7.86 (j = 7.856), 7.80 (J = 7.824), 7.63 (J = 7.608), 7.58 (3H, t, J = 7.575), 7.51 (m, J = 7.507), 7.4 (m, J = 7.422), 2.03 (s, J = 1.980), 1.28 (J = 1.2925), 0.9 (m, J = 0.9085).

IR: 3281.00, 2951.67, 2922.36, 2852.60, 1640.13, 1551.22, 1362.76, 1331.09, 1279.86, 1175.30, 1027.30, 959.46, 716.16, 681.55.

Mass (m/z %): C (41.92%), H (2.18%), N (12.23%), S (27.95%), Cl (15.50%).

Compound (C4): 5-Phenyl-1,3,4-thiadiazole-2-thiol

^{1}H NMR (DMSO d_6, 300 MHz): δ 7.915 (J = 7.905), 7.87 (J = 7.887), 7.81 (J = 7.822), 7.61 (J = 7.682), 7.58 (J = 7.579), 7.557 (J = 7.559), 7.525 (J = 7.523), 7.48 (J = 7.485), 1.99 (J = 1.984), 1.255 (J = 1.3685).

IR: 3351.82, 2923.91, 2852.88, 2754.77, 1640.85, 1503.84, 1444.66, 1340.55, 1272.11, 1178.09, 1059.61, 363.40, 763.40, 686.88.

Mass (m/z %): C (35.79%), H (2.98%), N (13.92%), S (31.81%).

All the synthetic compounds were obtained and further purified then characterization were carried out of all the compounds (C_1 to C_4) using IR, ^{1}H NMR, and Mass spectra. Antiinflammatory activity was carried out by using carrageenean induced paw oedema method. C_2 and C_4 have shown the significant anti-inflammatory activity against Ibuprofen as standard drug. Antimicrobial activity was carried out using gram positive and gram negative bacteria. All compounds have shown moderate antimicrobial activity against all the organism.

ACKNOWLEDGEMENT

I (TA) am heartly thankful to Mr. Arvind Kumar Singh, KNIMT Sultanpur (UP) for his kind support through my Project Work and also thankful to SAIF, CDRI Lucknow, India for providing technical support and facilities to carry out this work.

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Accepted : 25.01.2013