Synthesis and Biological Applications of Some Novel Spiro Heterocycles Containing 1,3,4-Thiadiazine, Thiazole, and Oxazole Derivatives

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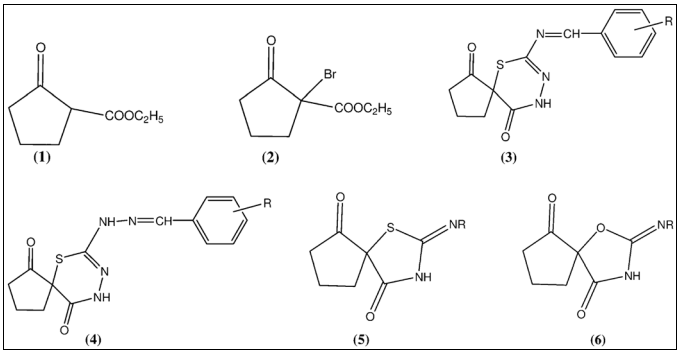

2-Ethoxy carbonylcyclopentanone **(1)** has been brominated to yield 2-bromo-2-ethoxy carbonylcyclopentanone **(2)** which on further reaction with substituted thiosemicarbazones, thiocarbohydrazones, thiocarbamides and carbamides has furnished 1-thia-3,4-diaza-5,7-dioxo-2-[(substituted benzylidine)-amino] spiro[*4.5*]dec-2-ene **(3a–e)**, 1-thia-3,4-diaza-5,7-dioxo-2-[(substituted benzylidine)-hydrazino] spiro[*4.5*] dec-2-ene **(4a–e)**, 1-thia-3-aza-2-(substituted imino)-4,6-dioxo-spiro[*4.4*]nonane **(5a–f)** and 1-oxa-3-aza-2-(substituted imino)-4,6-dioxo-spiro[*4.4*]nonane **(6a–g)** respectively. The structures of the compounds have been elucidated on the basis of spectral analysis.

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INTRODUCTION

In recent years, interest in 1,3,4-thiadiazines has increased in connection with a high biological activity and broad spectral action of their derivatives. New methods have been developed for the synthesis of 1,3,4-thiadiazines and condensed heterosystems based on these compounds. Thiadiazines display biological activities, such as antimicrobial [1, 2], antiirradiation [3, 4], and antiparasitic [5]. The compounds bearing thiadiazine nucleus are a versatile pharmacophore, which exhibits a wide variety of biological activities.

1,3,4-Thiadiazines represent the most widely studied class of compounds among the six theoretically possible thiadiazine isomers, they are of interest in a chemical sense because they are labile compounds which are capable of undergoing intramolecular rearrangements to give thiazole and pyrazole derivatives.

The five-membered heterocycles, oxazoles, and thiazoles have gained importance because of their varied physiological activities. Fused oxazoles [6] and thiazoles [7, 8] have been found to exhibit antihelmintic, insecticidal, sedative, tranquilizer, antiepileptic, antitubercular, and parasiticidal activities.

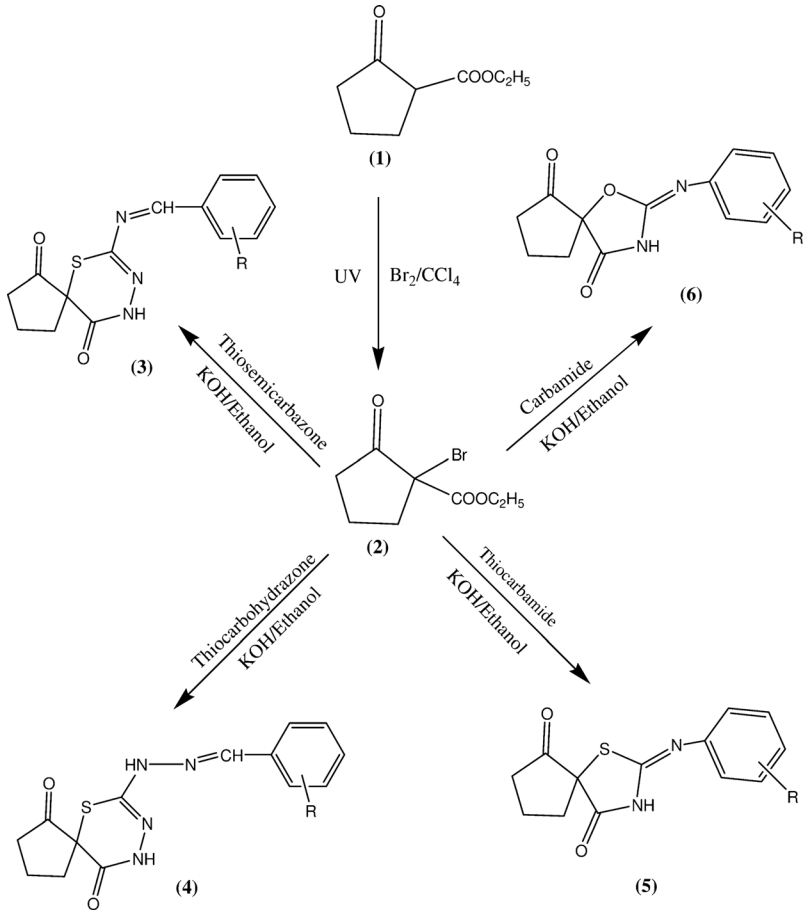
Spiro compounds containing sulfur and nitrogen are of great interest due to their physiological and biological activities [9, 10]. Spiro compounds are also known to possess various biological activities e.g., anti-inflammatory [11], fungistatic [12], and bacteriostatic [13].

Thus, keeping in view the chemistry of 1,3,4-thiadiazines, oxazoles, and thiazoles, their derivatives have been synthesized by conventional methods.

RESULTS AND DISCUSSION

The synthesis of 2-bromo-2-ethoxy carbonylcyclopentanone (**2**) was achieved from 2-ethoxy carbonylcyclopentanone (**1**) which was synthesized using reported procedure [14]. The title compounds 2-amino-6-cyclopentanone-1,3,4-thiadiazine (**3a–e**) and 2-hydrazino-6-cyclopentanone-1,3,4-thiadiazine (**4a–e**), 1-thia-3-aza-2-imino-4,6-dioxo-spiro[4.4] nonane (**5a–f**) and 1-oxa-3-aza-2-imino-4,6-dioxo-spiro [4.4] nonane (**6a–g**) were synthesized by reacting bromo compound (**2**) with substituted thiosemicarbohydrazones [15], thiocarbohydrazones [16], thiocarbamides, and carbamides, respectively, in the presence of potassium hydroxide using ethanol as a solvent (Scheme 1).

Scheme 1. Pathway of synthesis of compound **3**, **4**, **5**, and **6**.



Further, the newly synthesized representative compounds were screened for their antimicrobial activity, which shows a significant activity against gram-positive as well as gram-negative bacteria. The activity data of these compounds are given in Table 2.

EXPERIMENTAL

Melting points of all the compounds were determined in open-ended capillary tubes on an electro thermal apparatus and were uncorrected. The progress of the reaction was monitored by thin layer chromatography (TLC) on silica gel coated aluminium plates (Merck) as adsorbent and UV light as visualizing agent. IR spectra (KBr) were recorded on Perkin-Elmer spectrometer in the spectral range of 4000–400 cm^{-1}. ^{1}H-NMR spectra were recorded on Varian 500 MHz NMR spectrometer using $CDCl_3$/DMSO-d_6 as solvent and TMS as an internal standard (chemical shifts in δ ppm).

2-Bromo-2-ethoxy carbonylcyclopentanone (2). 2-Ethoxy carbonylcyclopentanone (0.01 mol) was dissolved in a minimum quantity of carbon tetrachloride (10 mL). A solution of bromine (0.01 mol) in carbon tetrachloride was added drop wise with continuous stirring in the presence of UV light. The progress of reaction was monitored by TLC. The reaction mixture was washed with water and the product was separated by separating funnel, and purified by distillation to give 2-bromo-2-ethoxy carbonylcyclopentanone, yield 86%. Boiling point is 108–110°C.

1-Thia-3,4-diaza-5,7-dioxo-2-[(substituted benzylidine)-amino] spiro[4.5]dec-2-ene (3a–e). A mixture of bromo compound **2** (0.01 mol), substituted thiosemicarbazone (0.01 mol), and a KOH (0.02 mol) in ethanol (20 mL) were refluxed for about 4–5 h. Progress of the reaction was monitored by TLC. After completion of reaction, the contents were poured into crushed ice. The solid obtained was filtered off, washed with water and purified by recrystallization from ethanol to get **3a–e**.

1-Thia-3,4-diaza-5,7-dioxo-2-[(2′hydroxy-benzylidine)-amino] spiro [4.5]dec-2-ene (3b). Yield: 58%; mp = 104–109°C: Anal. Calcd. for $C_{14}H_{13}N_3O_3S$: C, 55.45; H, 4.29; N, 13.86. Found C, 55.35; H, 4.32; N, 13.95%. IR (cm^{-1}): 3408 (OH), 2205 (C═N), 2185 (C═N), 1725 (C═O), 1628 (C═O), ^{1}H-NMR (DMSO-d6, δ/ppm): 1.16 (t, 2H, CH_2), 1.50 (m, 2H, CH_2), 2.26 (t, 2H, CH_2), 4.04 (s, 1H, OH), 6.86–8.08 (m, 4H, Ar–H), 8.35 (s, 1H, CH), 11.36 (s, 1H, NH). ^{13}C-NMR (DMSO-d6, δ/ppm): 39.78–40.33 (CH_2 × 3), 116.04 (Spiro-C), 119.24–131.07 (Ar–C), 139.62 (HC═N), 156.43 (C═N), 170.42 (C═O), 173.40 (C═O).

1-Thia-3,4-diaza-5,7-dioxo-2-[(4′methoxy-benzylidine)-amino] spiro [4.5]dec-2-ene (3e). Yield: 64%; mp = 88–89°C: Anal. Calcd. for $C_{15}H_{15}N_3O_3S$: C, 56.78; H, 4.73; N, 13.25. Found C, 56.82; H, 4.69; N, 13.28%. IR (cm^{-1}): 2198 (C═N), 2156 (C═N), 1730 (C═O), 1635 (C═O), ^{1}H-NMR (DMSO-d6, δ/ppm): 1.16 (t, 2H,

Table 1

Physical data of synthesized compounds (**3a–e**), (**4a–e**), (**5a–f**), and (**6a–g**).

Compds	R	Mol. formula	Yield (%)	mp (°C)
3a	H	$C_{14}H_{13}N_3O_2S$	61	103–105
3b	o-OH	$C_{14}H_{13}N_3O_3S$	58	104–109
3c	p-Cl	$C_{14}H_{12}N_3O_2SC$	l72	96–98
3d	p-OCH_3-m-OH	$C_{15}H_{15}N3O_4S$	74	84–87
3e	p-OCH_3	$C_{15}H_{15}N_3O_3S$	64	88–91
4a	H	$C_{14}H_{14}N_4O_2S$	78	107–110
4b	o-OH	$C_{14}H_{14}N_4O_3S$	76	93–97
4c	p-Cl	$C_{14}H_{13}N_4O_2SCl$	81	106–109
4d	m-OCH_3-p-OH	$C_{15}H_{16}N_4O_4S$	64	92–95
4e	p-OCH_3	$C_{15}H_{16}N_4O_3S$	65	85–89
5a	p-OCH_3-C_6H_4	$C_{14}H_{14}N_2O_3S$	72	116–121
5b	p-CH_3-C_6H_4	$C_{14}H_{14}N_2O_2S$	60	105–111
5c	p-Cl-C_6H_4	$C_{13}H_{11}N_2O_2SCl$	68	106–110
5d	m-Cl-C_6H_4	$C_{13}H_{11}N_2O_2SCl$	54	91–92
5e	H	$C_7H_8N_2O_2S$	78	88–91
5f	C_6H_5	$C_{13}H_{12}N_2O_2S$	81	74–77
6a	p-OCH_3-C_6H_4	$C_{14}H_{14}N_2O_4$	58	105–107
6b	p-CH_3-C_6H_4	$C_{14}H_{14}N_2O_3$	55	63–65
6c	o-OCH_3-C_6H_4	$C_{14}H_{14}N_2O_4$	67	101–103
6d	o-NO_2-C_6H_4	$C_{13}H_{11}N_3O_5$	72	84–87
6e	o-Cl-C_6H_4	$C_{13}H_{11}N_2O_3Cl$	51	72–75
6f	H	$C_7H_8N_2O_3$	81	72–76
6g	C_6H_5	$C_{13}H_{12}N_2O_3$	84	84–87

CH_2), 1.49 (m, 2H, CH_2), 2.23 (t, 2H, CH_2), 3.77 (s, 3H, OCH_3), 6.95–8.09 (m, 4H, Ar–H), 8.35 (s, 1H, CH), 11.29 (s, 1H, NH). ^{13}C-NMR (DMSO-d6, δ/ppm): 39.78–40.33 (CH_2 × 3), 55.31 (OCH_3), 100.12 (Spiro-C), 114.19–147.42 (Ar–C), 142.27 (HC═N), 160.71 (C═N), 177.60 (C═O), 180.16 (C═O). The physical data of the compounds **3a–e** is given in Table 1.

1-Thia-3,4-diaza-5,7-dioxo-2-[(substituted benzyl dine)-hydrazine]spiro[4.5]dec-2-ene (4a–e). The 2-bromo-2-ethoxy carbonylcyclopentanone **2** (0.01 mol), was dissolved in a minimum quantity of ethanol (20 mL) containing KOH (0.02 mol) as a catalyst. An equimolar quantity of substituted thiocarbohydrazone (0.01 mol) was added to it and the reaction mixture was refluxed for about 4–5 h. Progress of the reaction was monitored by TLC. After completion of reaction, the contents were poured into crushed ice. The solid obtained was filtered off, washed with water and purified by recrystallization from ethanol to get **4a–e**.

1-Thia-3,4-diaza-5,7-dioxo-2-[(2′-hydroxy-benzyl dine)-hydrazine]spiro[4.5]dec-2-ene (4b). Yield: 76%; mp = 93–97°C: Anal. Calcd for $C_{14}H_{14}N_4O_3S$: C, 52.83; H, 4.40; N, 17.61. Found C, 52.89; H, 4.42; N,17.58%. IR (cm^{-1}): 3395 (OH), 1721 (C═O), 1622 (C═O), 1533 (C═N).^{1}H-NMR (DMSO-d6, δ/ppm): 0.66 (t, 2H, CH_2), 0.97 (m, 2H, CH_2), 1.57 (t, 2H, CH_2), 4.96 (s, 1H, OH), 6.00–6.8 (m, 4H, Ar–H), 8.58 (s, 1H, CH), 9.28 (s, 1H, NH), 10.52 (s, 1H, NH). ^{13}C-NMR (DMSO-d6, δ/ppm): 38.66–40.32 (CH_2 × 3), 53.68 (N═CH), 105.59 (Spiro-C), 114.19–147.42 (Ar–C and HC═N), 154.39 (C═N), 170.42 (C═O), 173.43 (C═O).

1-Thia-3,4-diaza-5,7-dioxo-2-[(4′-hydroxy-3′methoxy-benzyldine)-hydrazine]spiro[4.5]dec-2-ene (4d). Yield: 64%; mp = 92–95°C: Anal. Calcd. for $C_{15}H_{16}N_4O_4S$: C, 51.72; H, 4.60; N, 16.09. Found C, 51.62; H, 4.62; N, 16.14%. IR (cm^{-1}): 3422 (OH), 1625 (C═O), 1548 (C═N). ^{1}H-NMR (DMSO-d6, δ/ppm): 1.16 (t, 2H, CH_2), 1.50 (m, 2H, CH_2), 2.26 (t, 2H, CH_2), 3.81 (s, 3H, OCH_3), 4.02 (s, 1H, OH), 6.90–7.90 (m, 3H, Ar–H), 8.58 (s, 1H, CH), 9.28 (s, 1H, NH), 10.4 (s, 1H, NH). ^{13}C-NMR (DMSO-d6, δ/ppm): 35.14–40.32 (CH_2 × 3), 56.45 (N═CH), 98.60 (Spiro-C), 115.10–131.72 (Ar–C and HC═N), 152.67 (C═N), 179.55 (C═O), 195.10 (C═O). The physical data of the compounds **4a–e** are given in Table 1.

Table 2

Antimicrobial activities of some newly synthesized compounds.

	Inhibition zone (mm)						
	Gram-negative		Gram-positive		Fungi		Yeast
Compounds	*E. coli*	*P. putide*	*B. subtilis*	*S. lactis*	*A. niger*	*P.* sp.	*C. albicans*
3a	17	15	18	21	12	10	5
3c	16	16	17	21	10	10	5
4b	15	14	18	19	8	8	5
4c	18	19	19	20	8	8	5
5a	19	17	16	19	11	10	4
5b	18	16	17	18	13	9	4
6d	19	18	16	20	0	0	0
6f	20	19	18	19	7	8	5
Ampicilin®	24	20	19	22	24	14	14

E. coli = *Escherichia coli*; *P. putide* = *Pseudomonas putide*; *B. subtilis* = *Bacillus subtilis*; *S. lactis* = *Sterptococcus lactis*; *A. niger* = *Aspergillus niger*; *P.* sp. = *Penicillium* sp.; *C. albicans* = *Candida albicans*. The sensitivity of microorganisms to the tested compounds is identified in the following manner[a]: Highly sensitive = inhibition zone: 15–20 mm; moderately sensitive = inhibition zone: 10–15 mm; slightly sensitive = inhibition zone: 5–10 mm; not sensitive = inhibition zone: 0 mm.

[a]Each result represents the average of triplicate readings.

1-Thia-3-aza-2-imino-4,6-dioxo-spiro[4.4]nonane (5a–f). A mixture of 2-bromo-2-ethoxy carbonylcyclopentanone **2** (0.01 mol) and substituted thiocarbamide (0.01 mol) was added to a solution of KOH (0.02 mol) in ethanol (20 mL). The reaction mixture was refluxed for about 7–8 h. Progress of the reaction was monitored by TLC. After completion of reaction, the contents were poured into ice-cold dilute HCl. The resulting solid obtained was filtered off, washed several times with water and purified by recrystallization from ethanol to get **5a–f**.

1-Thia-3-aza-2-(4′methylphenyl)-imino-4,6-dioxo-spiro [4.4]nonane (5b). Yield: 60%; mp = 105–111°C: Anal. Calcd. for $C_{14}H_{14}N_2O_2S$: C, 61.31; H, 5.11; N, 10.22. Found C, 61.22; H, 5.22; N, 10.26%. IR (cm^{-1}): 1732 (C═O), 1626 (C═O), 1533 (C═N). ^{1}H-NMR (DMSO-d6, δ/ppm): 1.18 (t, 2H, CH_2), 1.22 (m, 2H, CH_2), 1.86 (t, 2H, CH_2), 2.28 (s, 3H, CH_3), 4.09 (s, 1H, NH), 7.20–7.78 (m, 4H, Ar–H). ^{13}C-NMR (DMSO-d6, δ/ppm): 23.42 (CH_3) 35.14–40.32 ($CH_2 \times 3$), 101.62 (Spiro-C), 129.37–138.51 (Ar–C), 153.06 (C═N), 186.26 (C═O), 187.99 (C═O). The physical data of the compounds **5a–f** are given in Table 1.

1-Oxa-3-aza-2-imino-4,6-dioxo-spiro[4.4]nonane (6a–g). To a solution of 2-bromo-2-ethoxy carbonylcyclopentanone **2** (0.01 mol) and substituted carbamide (0.01 mol) in ethanol (20 mL), KOH (0.02 mol) was added as catalyst. The reaction mixture was refluxed for about 7–8 h. Progress of the reaction was monitored by TLC. After completion of reaction, the contents were poured into ice-cold dilute HCl. The resulting solid obtained was filtered off, washed several times with water, and purified by recrystallization from ethanol to get **6a–g**.

1-Oxa-3-aza-2-(4′-methoxyphenyl)-imino-4,6-dioxo-spiro [4.4]nonane (6a). Yield: 58%; mp = 105–107°C: Anal. Calcd. for $C_{14}H_{14}N_2O_4$: C, 61.31; H, 5.11; N, 10.22. Found C, 61.38; H, 5.18; N, 10.26%. IR (cm^{-1}): 1715 (C═O), 1626 (C═O), and 1551 (C═N). ^{1}H-NMR (DMSO-d6, δ/ppm): 1.16 (t, 2H, CH_2), 1.31 (m, 2H, CH_2), 1.88 (t, 2H, CH_2), 3.67 (s, 3H, OCH_3), 5.69 (s, 1H, NH), and 6.71–7.20 (m, 4H, Ar–H). ^{13}C-NMR (DMSO-d6, δ/ppm): 35.14–40.32 ($CH_2 \times 3$), 55.34 (OCH_3), 104.14 (Spiro-C), 125.41–141.08 (Ar–C), 155.66 (C═N), 185.04 (C═O), and 195.78(C═O). The physical data of the compounds **6a–g** are given in Table 1.

ANTIMICROBIAL EVALUATION

The newly synthesized representative compounds were tested for their antimicrobial activity against the following microorganisms: (a) gram-negative – *Escherichia coli*, *Pseudomonas putide*; (b) Gram-positive – *Bacillus subtilis*, *Streptococcus lactis*; (c) Fungi: *Aspergillus niger*, *Penicillium* sp.; (d) Yeast – *Candida albicans*. The preliminary screening of the investigated compounds was performed using the filter paper disc-diffusion method [17]. The compounds were tested at a concentration of 100 μg/mL. The zone of inhibition was measured in mm and compared with reference standard ampicillin trihydrate (100 μg/mL). The compounds tested displayed good activity towards gram-positive bacteria, but were less active against gram-negative bacteria. The results of antibacterial screening studies are reported in Table 2.

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