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Synthesis and antibacterial activity of some 5-(4-biphenylyl)-7-Aryl [3,4-d]-1,2,3-benzoselenadiazoles

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Abstract

A new series of 5-(4-biphenylyl)-7-aryl[3,4-d]-1,2,3-benzoselenadiazoles were prepared, characterized by elemental analysis, ^{1}H NMR and ^{13}C NMR spectral studies, and tested for antibacterial activities. The compounds were very effective against the tested Gram-positive bacteria; 7b was the most effective compound.

Keywords: *1,2,3-Selenadiazoles, synthesis, antibacterial activity*

Introduction

Recently, the synthesis of heterocyclic compounds containing selenium and the utilization of these compounds in organic synthesis has been steadily increasing[1–4]. Among selenium-containing heterocyclic compounds, the 1,2,3-selenadiazoles are of interest as versatile intermediates for the preparation of alkynes[5] and they undergo a wide variety of reactions as 1,3-dipoles or as a source of selenium[6,7].

Heterocyclic molecules with potential phamacophoric properties have attracted the attention of scientific communities as feasible alternatives to conventional drugs. The importance of the 1,2,3-selenadiazole nucleus is also well established in pharmaceutical chemistry and a considerable number of 1,2,3-selenadiazoles are well known as antibacterial and antifungal agents[8,9]. Their synthetic diversity and easy in manipulating skeletons has made these molecules as one of the foremost in medicinal chemistry and synthetic organic chemistry. We have recently reported the synthesis and antibacterial activity of a series of biphenyl substituted 1,2,3-thiadiazoles derivatives[10]. Based on the above reports and in continuation of our research on the synthesis of biologically active heterocyclic molecules, the synthesis and antibacterial evaluation of the title compounds are reported.

Materials and methods

Melting points were determined in open capillaries and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer (FT-IR-8300) in KBr pellets. ^{1}H NMR and ^{13}C NMR spectra were recorded in a Brucker instrument and Mass Spectra on Gass-5000 instrument at 70 eV. The purity of the compounds was checked by thin layer chromatography.

Synthesis of 6-ethoxycarbonyl-3-(4-biphenylyl)-5-substituted arylcyclohex- 2-en-1-one 4(a-j)

A mixture of sodium ethoxide (2 g sodium in 100 mL ethanol), distilled ethyl acetoacetate (0.01 mole) and styryl biphenyl ketone (0.01 mole) was dissolved in absolute ethanol (20 mL) and refluxed for 2 h on a steam bath and then cooled. The separated solid was filtered, washed with water and recrystallized from ethanol.

Spectral data: Comp. **4a**: ^{1}H NMR: ($CDCl_3$): δ 1.05 (t, 3H, $COOCH_2C\mathbf{H_3}$), 4.07 (q, 2H, $COO\mathbf{H_2}CH_3$),

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6.63 (s, 1H, C2-1H), 3.00–3.05 (m, 2H C4-2H), δ 3.84 (d, 1H, C6-1H, 3.13–3.17 (m, 1H, C5-1H), 7.25–7.64 (m, 14H, Ar-H). ^{13}C NMR: ($CDCl_3$): δ 60.8 ($COO\mathbf{C}H_2CH_3$), 13.8 ($COOCH_2\mathbf{C}H_3$), 169.1 ($\mathbf{C}OOCH_2CH_3$), 193.8 (C=O), 123.8 (C-2), 157.8 (C-3), 35.9 (C-4), 44.1 (C-5), 59.6 (C-6), 143.3, 141.0, 139.8 and 136.4 (*ipso* carbons) and 126.6–128.8 (Ar-C).

Synthesis of 3-(4-biphenylyl)-5-substituted arylcyclohex-2-en-1-one 5(a-j)

A mixture of the appropriate ketone (0.01 mole), glacial acetic acid (25 mL) and concentrated hydrochloric acid (12 mL) was refluxed for 10 h on a water bath. The reaction mixture was then poured into crushed ice and stirred well. The separated product was recrystallized from aqueous ethanol.

Spectral Data: Comp. **5a**: ^{1}H NMR: ($CDCl_3$): δ 6.58 (d, 1H, C2-1H), 3.45–3.53 (m, 1H, C5-1H), 2.71–2.83 (m, 2H, C4-2H), 2.92–3.14, 3.45–3.53, (dd, dd, C6-2H), 7.25–7.65 (m, 14H, Ar-H). ^{13}C NMR: ($CDCl_3$): δ 198.9 (C-1), 124.9 (C-2), 157.9 (C-3), 36.1 (C-4), 41.2 (C-5), 43.4 (C-6), 143.2, 142.9, 139.9 and 137.1 (*ipso* carbons) and 126.6–128.8 (Ar-C).

Synthesis of 3-(4-biphenylyl)-5-substituted arylcyclohex-2-en-1-one semicarbazone 6(a-j)

A mixture of arylcyclohexanone (0.01 mole), semicarbazide hydrochloride (0.01 mole) and sodium acetate (0.015 mole) in ethanol (40 mL) was refluxed for 2 h on a steam bath and cooled. The separated solid was filtered, washed with water and recrystallized from ethanol.

Spectral Data: Comp. **6a**: ^{1}H NMR: ($CDCl_3$): δ 7.64 (s, 1H, N–H), 6.00 (s, 1H, C2-H), 2.04–2.40 (m, 2H, C6-2H), 2.73–2.80 (m, 2H, C4-2H), 2.97–3.08 (m, 1H, C5-1H) and δ 7.17–7.34 (m, 13H, Ar-H. ^{13}C NMR: ($CDCl_3$): δ 149.3 (C-1), 123.4 (C-2), 145.3 (C-3), 38.3 (C-4), 39.6 (C-5), 30.7 (C-6), 158.5 (C=O), 144.5 and 147.2 (*ipso* carbons) and 127.2–129.1 (Ar-C).

Synthesis of 5-(4-biphenylyl)-7-substituted aryl[3,4-d]-[1,2,3]-benzoselenadiazole 7(a-j)

Semicarbazone (0.001 mole) was treated with selenium dioxide powder (0.001 mole) in glacial acetic acid (30 mL) and the mixture was gently heated (50–60° C) with stirring until the evolution of gases ended. The reaction mixture was cooled, filtered and then poured into crushed ice. The product obtained was filtered, dried and purified on a column chromatography using silica gel as absorbent and benzene (CARE-carcinogenic) as the eluent. The elemental composition, yield and melting point are given in Table I. The Table II shows the ^{1}H and ^{13}C NMR spectral data of the compounds.

Antibacterial activity[11]

A two-fold serial dilution of the compounds and reference drug were prepared in Muller–Hinton agar. Drugs were dissolved in dimethylsulfoxide (DMSO; 1 mL) and the solution was diluted with water (9 mL). Further progressive double dilution with melted Muller–Hinton agar was performed to obtain the required concentrations. Petri dishes were incubated at 35 °C for 24 h. The minimum inhibitory concentration (MIC) was the lowest concentration of the tested compound that resulted in no visible growth on the plate. To ensure that the solvent had no effect on bacterial growth, a control test was also performed with test medium supplemented with DMSO at the same dilutions as used in the experiment.

Results and discussion

Chemistry

The 4-acetylbiphenyl **2** was obtained from acetylation of biphenyl **1** in the presence of anhydrous aluminium

Table I. Physical and analytical data for **7(a–j)**.

Compound. No.	m.p°C	Yield* %	Molecular formula	Elemental analysis %		
				Carbon found/calcd.	Hydrogen found/calcd.	Nitrogen found/calcd.
7a	118–120	38	$C_{24}H_{16}N_2Se$	70.26 / 70.07	3.98 / 3.89	7.02 / 6.81
7b	151–159	49	$C_{24}H_{15}N_2BrSe$	67.86 / 67.13	3.65 / 3.49	5.99 / 5.39
7c	176–177	44	$C_{24}H_{15}N_2SeCl$	64.99 / 64.71	3.70 / 3.37	6.51 / 6.29
7d	164–165	37	$C_{24}H_{15}N_2ClSe$	63.82 / 64.71	3.49 / 3.37	6.73 / 6.29
7e	128–129	35	$C_{24}H_{15}N_2FSe$	58.51 / 58.77	3.22 / 3.06	5.28 / 5.71
7f	179–181	40	$C_{24}H_{15}N_3O_2Se$	62.97 / 63.15	3.51 / 3.28	9.45 / 9.21
7 g	122–124	50	$C_{24}H_{15}N_3O_4Se$	63.71 / 63.15	3.74 / 3.28	9.71 / 9.21
7 h	177–179	36	$C_{24}H_{18}N_2OSe$	68.69 / 68.02	4.59 / 4.08	6.56 / 6.34
7i	160–161	41	$C_{25}H_{18}N_2Ose$	69.07 / 68.02	4.39 / 4.08	6.92 / 6.34
7j	163–165	52	$C_{30}H_{20}N_2O_2Se$	70.27 / 69.36	3.38 / 3.85	6.56 / 6.34

*Isolated yield of purified product

Table II. ^{1}H and ^{13}C NMR spectral data for **7(a–j)**.

Compound No.	^{1}H NMR (δ, ppm)					^{13}C NMR (δ, ppm)						
	CH_3	H-4	H-6	Ar-H	CH_3	C-9	C-8	C-7	C-5	C-4	*ipso* carbons	Aromatic carbons and C-6
7a	–	8.90 (d)	8.00 (d)	7.26–7.85 (m)	–	162.9	144.1	141.1	142.6	123.0	140.4, 138.3	127.1–129.3
7b	–	8.90 (d)	7.95 (d)	7.19–7.84 (m)	–	161.7	144.1	140.2	141.1	123.0	137.2, 138.0, 138.7	125.7–130.7
7c	–	8.94–8.95 (d)	7.95 (d)	7.23–7.85 (m)	–	162.2	145.7	140.4	141.2	123.4	138.1, 137.7, 135.6	127.0–130.3
7d	–	8.90 (d)	7.95–7.96 (d)	7.25–7.84 (m)	–	162.9	141.3	140.3	141.1	123.3	138.1, 137.1, 135.0	127.1–129.5
7e	–	8.91 (d)	8.00 (d)	7.26–7.86 (m)	–	160.1	145.4	138.2	144.6	122.0	134.9, 136.6, 137.0	127.0–130.5
7f	–	8.97 (d)	8.03–8.04 (d)	7.25–7.86 (m)	–	163.1	144.2	140.3	141.6	124.1	137.7, 135.9, 132.8	127.1–130.3
7g	–	8.97 (d)	8.03 (d)	7.25–7.88 (m)	–	163.1	148.1	141.5	143.9	124.5	140.2, 137.6, 136.0	127.1–128.9
7h	3.82 (s)	8.91 (d)	7.97–7.98 (d)	7.04–7.85 (m)	55.3	162.2	141.0	140.3	140.5	122.7	156.2, 138.5, 135.3	111.5–130.9
7i	3.89 (s)	8.86 (d)	7.95 (d)	7.03–7.77 (m)	55.3	162.7	143.9	140.3	141.0	122.4	160.1, 138.3, 138.0, 135.0	114.6–128.8
7j	–	8.89 (d)	7.98 (d)	7.01–7.83 (m)	–	163.5	144.9	141.8	144.6	120.1	159.0, 141.0, 138.8, 138.3	117.6–131.3

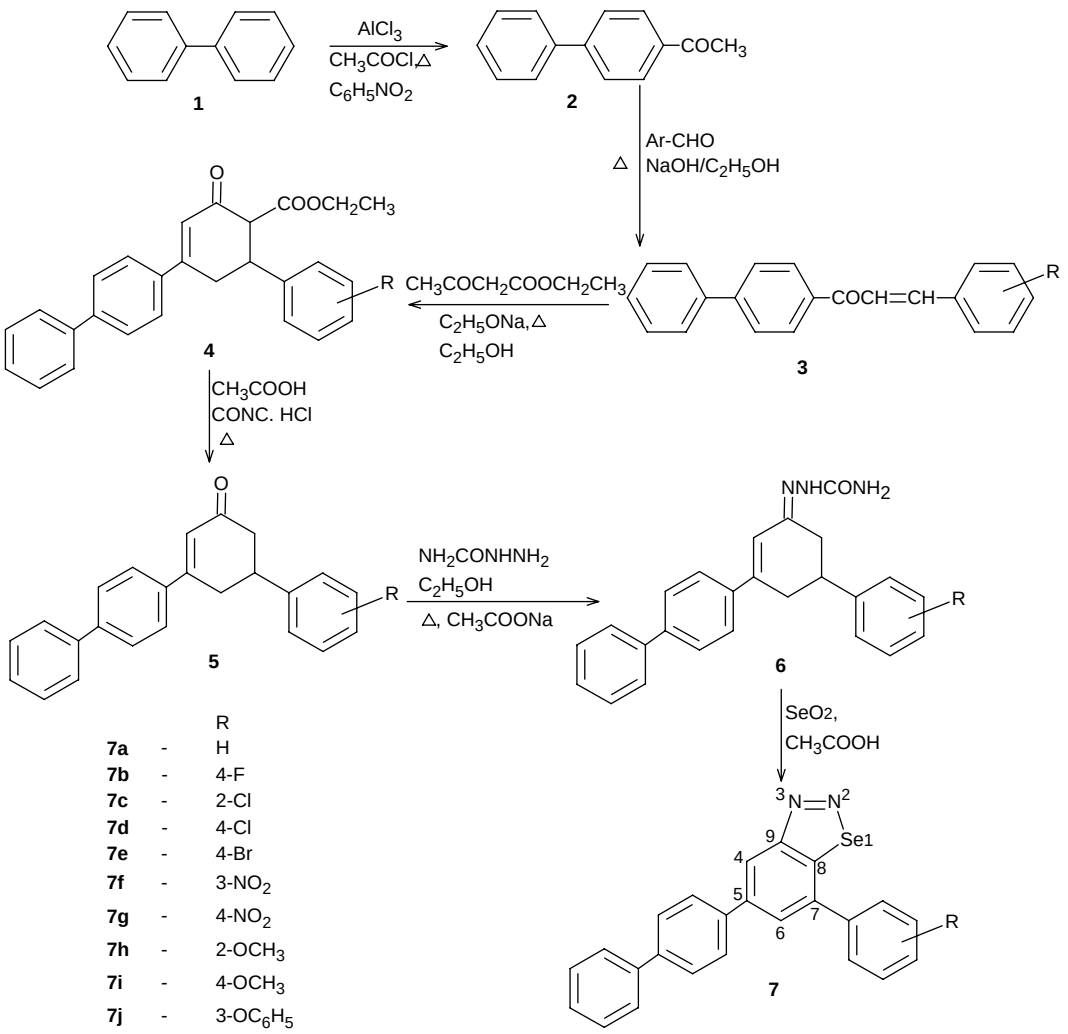
chloride. The 4-acetylbiphenyl on treatment with different aromatic aldehydes in the presence of base gave the styryl biphenyl ketones **3a–j**. These ketones on treatment with ethyl acetoacetate in presence of sodium ethoxide, gave the 6-ethoxycarbonyl-3-(4-biphenylyl)-5-substituted arylcyclohex-2-en-1-ones **4a–j**. Compounds **4a–j** were subjected to decarboxylation; to give the 3-(4-biphenylyl)-5-substituted arylcyclohex-2-en-1-ones **5a–j**. Compounds **5a–j** were converted into their semicarbazones **6a–j**, which on further treatment with selenium dioxide in acetic acid, gave the 5-(4-biphenylyl)-7-aryl[3,4-d][1,2,3]-benzoselenadiazoles **7a–j** (Scheme 1).

The yield, melting point, molecular formula and elemental compositions of compounds **7a–j** are given in Table I. The IR spectra of **6** displayed primary bands at 3442, 3240 (—NHCO, —$CONH_2$), 1720 (–$CONH_2$) and 1426 cm^{-1} (—C═N), while in **7** the IR spectra exhibited bands at 1585 (N═N) and 682 cm^{-1} (C-Se). The absence of bands in the regions 3442, 3240 and 1426 cm^{-1} and the presence of bands in the region 1585 and 682 cm^{-1} is regarded as positive evidence for the formation of **7**.

In the ^{1}H NMR spectra of **7** two doublets were observed in the region of 8.9 and 8.0 ppm due to the H-4 and H-6 protons. In the ^{13}C NMR spectra the up field signal at 122.4 ppm is assigned to C-4. The ^{13}C chemical shifts values of the two carbons C-8 and C-9 are observed at 162.4 and 144.1 ppm. In distinguishing between the two carbons C-8 and C-9, C-9 is expected to appear downfield due to the electronegativity of nitrogen. Hence, the signals at 162.9 and 141.1 ppm are assigned to C-9 and C-8 respectively. The signal of C-6 is merged with the aromatic carbon signals as confirmed from HETCOR-NMR. The doublet at 8.9 ppm (H-4) has a cross peak with the ^{13}C NMR signal at 122.4 ppm. Similarly H-6 has a cross peak with the ^{13}C NMR signal at the aromatic region in HETCOR. The ^{1}H and ^{13}C chemical shift values for all the compounds **7a–j** are given in Table II.

Pharmacology

The antibacterial activity of compounds **7a**–**j** was assessed in comparison with norfloxacin against some Gram-positive (*Staphylococcus aureus*, and *Bacillus subtilis*) and Gram-negative (*Escherichia coli* and *Klebsiella pneumoniae*) bacteria and the results are summarized in Table III. The antibacterial data indicated that compounds **7a**–**j** had a better activity against the Gram-positive organisms tested. However, all the compounds were nearly inactive against the Gram-negative bacteria tested. The antibacterial data revealed that the 1,2,3-selenadiazoles **7a**–**j** possess almost similar antibacterial profiles. The selective antibacterial activity against Gram-positive bacteria was in contrast to the good antibacterial activity of



Scheme 1. Synthetic pathway to compounds **7a–j**.

norfloxacin against both Gram-positive and Gram-negative bacteria. Compounds **7b** and **7e** were more active than the rest of the compounds tested. Among the halogenated compounds the 4-fluoro **7b** is more effective than the 4-bromo **7e** and 4-chloro **7d** compounds. Thus, the nature and position of the substituent influences the extent of antibacterial activity.

Table III. *In vitro* antibacterial activity of **7a–j** and standard (MIC μg ml^{-1}).

Compounds	*S. aureus*	*B. subtilis*	*E. coli*	*K.* pneumoniae
7a	0.64	0.50	>60	>60
7b	0.20	0.16	11	45
7c	0.43	0.41	>60	>60
7d	0.32	0.29	26	55
7e	0.25	0.22	18	48
7f	0.55	0.51	>60	>60
7g	0.41	0.38	37	51
7h	0.55	0.45	44	>60
7i	0.68	0.58	>60	>60
7j	0.58	0.52	49	>60
Norfloxacin	0.51	0.018	0.15	0.05

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References

[1] Ando W, Kumamoto Y, Ishizuka H, Tokitoh N. Tetrahedron Lett 1987;28:4707.
[2] Arsenyan P, Oberte K, Rubina K, Belyakov S. Tetrahedron Lett 2005;46:1001.
[3] Arsenyan P, Pudova O, Lukevics E. Tetrahedron Lett 2002;43:4817.
[4] Lalezari I, Shafiee A, Yalpani M. Tetrahedron Lett 1969;10:5105.

[5] Nishiyama Y, Hada Y, Anjiki M, Miyake K, Hanita S, Sonoda N. J Org Chem 2002;67:1520.
[6] Morley CP, Ford S, Vaira MD. Polyhedron 2004;23:2967.
[7] Jalilian AR, Rowshanfarzad P, Afarideh H, Shafiee A, Sabet M, Kyoumarsi M, Raisali GR. Appl Rad Isotopes 2004; 60:659.
[8] Yamashita Y, Saito K, Mukai T, Miyashi T. Tetrahedron Lett 1989;30:7071.
[9] Jalilian AR, Sattari S, Bineshmarvasti M, Daneshtalab M, Shafiee A. Il Farmaco 2003;58:63.
[10] Balasankar T, Gopalakrishnan M, Nagarajan S. Eur J Med Chem 2005;40:728.
[11] Baron EJ, Finegold SM. Bailey and scott's diagnostic microbiology. 8th ed. St. Louis, MO: Mosby; 1990. p 184–188.