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

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Abstract

A series of 5-(4-biphenylyl)-7-aryl[3,4-d] [1,2,3]-benzothiadiazoles were synthesized, characterized by IR, NMR and elemental analysis and evaluated for in vitro antibacterial activity against some Gram-positive and Gram-negative bacteria. The antibacterial data revealed that compounds **7a–j** had better activity against tested Gram-positive organisms than the reference ciprofloxacin and norfloxacin. However, the compounds were nearly inactive against Gram-negative bacteria. Compound **7c** and **7d** were the most active compounds against Gram-positive bacteria.

Keywords: Thiadiazoles; 1,2,3-Benzothiadiazoles; Synthesis; Antibacterial activity

1. Introduction

In 1955, Hurd and Mori [1] first reported the synthesis of 1,2,3-thiadiazoles from the reaction of α-methylene (or ethyl) hydrazones. 1,2,3-Thiadiazoles are an important class of biologically active compounds [2–7] as well as useful intermediates in organic synthesis [8]. For example, 4,5-bis(4′-methoxyphenyl)-1,2,3-thiadiazole was found to be an active inhibitor of collagen-induced platelet aggregation in vitro [9]. Many methods have been developed for the synthesis of 1,2,3-thiadiazoles [10,11], of which the Hurd–Mori cyclization of α-methylene ketones is the most convenient methodology [12–16]. We report here the synthesis of biphenyl substituted 1,2,3-thiadiazole and their antibacterial activity.

2. Results and discussion

The 4-acetylbiphenyl **2** [17] is obtained form acetylation of biphenyl **1** in the presence of anhydrous aluminum chloride. 4-Acetylbiphenyl on treatment with different aromatic aldehydes in the presence of base gives styryl biphenyl ketones **3** [11]. These ketones on treatment with ethyl acetoacetate in the presence of sodium ethoxide, 6-ethoxycarbonyl-3-(4-biphenyl)-5-substituted arylcyclohex-2-en-1-ones **4** are formed. The above compounds are subjected to decarboxylation; 3-(4-biphenylyl)-7-substituted arylcyclohex-2-en-1-ones **5** are obtained. The ketones are converted into their semicarbazones **6** that on further treatment with $SOCl_2$ 5-(4-biphenylyl)-7-aryl [3,4-d][1,2,3]-benzothiadiazoles **7** are formed (Fig. 1).

The IR spectra of the compound **6** displayed primary bands (cm^{-1}) at 3442, 3240 (–NHCO, $–CONH_2$), 1720 ($–CONH_2$) and 1426 (–C=N). IR spectra of **7** exhibited bands at 1582 (N=N) and 685 (C–S). The absence of bands in the region 3442, 3240 and 1426 and the presence of bands in the region 1582, 685 are regarded as positive evidence for the formation of **7**.

The antibacterial activity of **7a–j** was assessed in side-by-side comparison with ciprofloxacin and norfloxacin against some Gram-positive (*Staphylococcus aureus*, and *Bacillus subtilis*) and Gram-negative (*Escherichia coli*, *Klebsiella peneumoniae*, and *Pseudomonas aeruginosa*) bacteria using conventional agar dilution procedure and the results are summarized in Table 1. The antibacterial data indicated that compounds **7a–j** had a better activity against tested Gram-positive organisms. However, all the compounds were nearly inactive against tested Gram-negative bacteria. The antibac-

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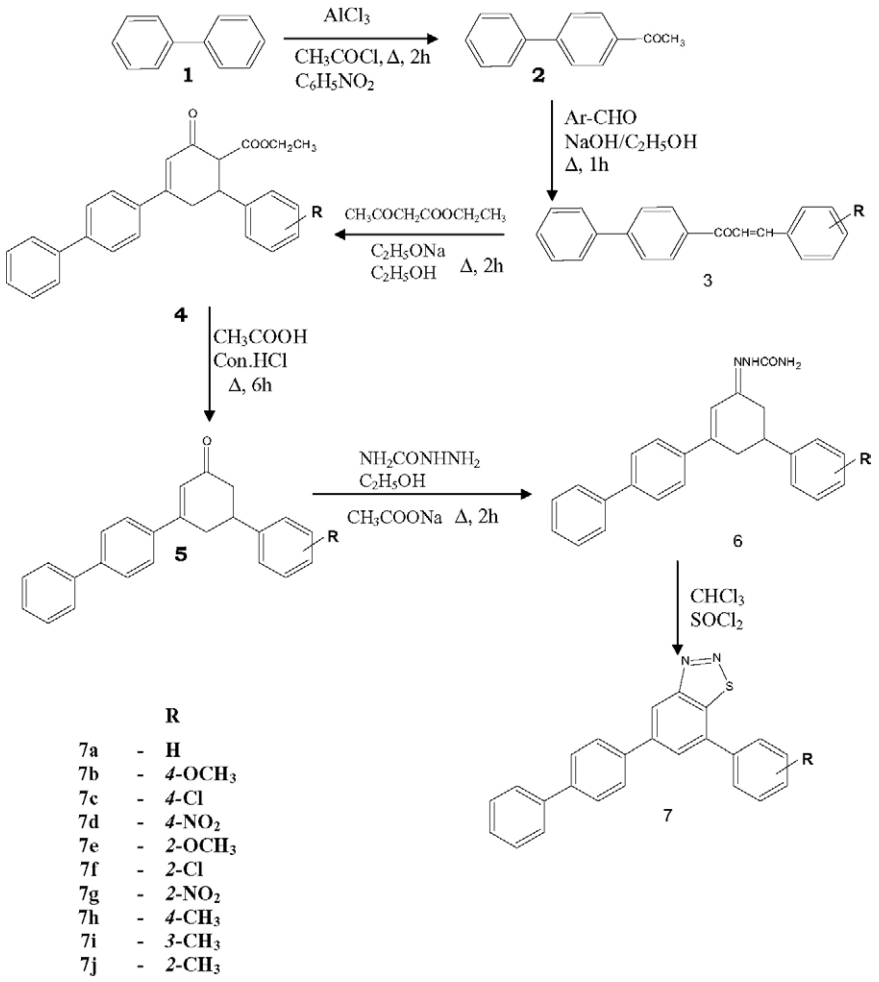

Fig. 1. Synthetic pathways to compounds **7a–j**.

terial data revealed that the 1,2,3-thiadiazole derivatives **7a–j** possesses similar antibacterial profiles. The selective antibacterial activity against Gram-positive bacteria is in contrast to the good antibacterial activity of ciprofloxacin against both Gram-positive and Gram-negative bacteria. The compounds **7c** and **d** are more active than the rest of the compounds tested. Among the methyl substituted compounds 4-methyl **7h** is more effective than 2- and 3-methyl substituted compounds. Thus the nature of the functional group and position of the substituent has strong influence on the spectrum and extent of antibacterial activity.

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

Compounds	*S. aureus*	*B. subtilis*	*E. coli*	*K. peneumoniae*	*P. aeruginosa*
7a	0.55	0.50	32	>60	>60
7b	0.40	0.40	8	24	32
7c	0.19	0.024	40	>60	>60
7d	0.20	0.024	32	>60	>60
7e	0.48	0.50	8	>60	>60
7f	0.45	0.45	37	>60	>60
7g	0.43	0.44	28	44	55
7h	0.22	0.13	26	>60	>60
7i	0.40	0.32	32	>60	>60
7j	0.41	0.35	38	>60	>60
Ciprofloxacine	0.45	0.02	0.13	0.03	1
Norfloxacin	1	0.05	0.48	0.12	3.5

The MIC values of compounds **7a–j** indicated that the **7c** and **7d** were the most active compounds. The strong antibacterial activity of this compounds against tested Gram-positive bacteria suggested further investigation on this compounds.

3. Experimental

Melting points are determined in open capillaries and are uncorrected. Infrared spectra were recorded on Perkin–Elmer (FT-IR-8300) in KBr pellets. ^{1}H NMR and ^{13}C NMR were recorded on Bruker (AMX-400) using $CDCl_3$ as solvent. TMS was used as internal reference for ^{1}H NMR.

*3.1. General procedure for the 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 60 ml ethanol), freshly distilled ethyl aceto acetate (0.01 mol) and styryl biphenyl ketone 3 (0.01 mol) was dissolved in absolute ethanol (20 ml) and refluxed for 2 h on a steambath and cooled.

Table 2
Physical and analytical data of **7**(**a**–**j**)

Compound numbers	M.p. (°C)	Yield (%)	Molecular formula	Elemental analysis		
				Carbon (found/calcd)	Hydrogen (found/calcd)	Nitrogen (found/calcd)
7a	166–167	25	$C_{24}H_{16}N_2S$	79.12/79.24	4.39/4.82	7.69/7.46
7b	125–127	30	$C_{25}H_{18}N_2S$	76.14/76.01	4.56/4.71	7.10/7.05
7c	135–138	27	$C_{24}H_{15}N_2ClS$	72.36/72.02	3.76/3.26	7.03/7.37
7d	141–142	38	$C_{24}H_{15}N_3O_2S$	70.4/70.20	3.66/3.81	10.20/10.11
7e	138–140	20	$C_{24}H_{18}N_3O_2S$	79.12/79.48	4.39/4.20	7.69/7.82
7f	159–160	29	$C_{24}H_{15}N_2ClS$	72.91/72.02	3.51/3.26	7.41/7.37
7g	167–169	37	$C_{25}H_{15}N_3O_2S$	71.34/70.20	3.91/3.80	10.18/10.11
7h	125–128	32	$C_{24}H_{18}N_2S$	79.81/79.36	4.29/4.76	7.89/7.40
7i	139–141	35	$C_{24}H_{18}N_2S$	78.12/79.36	4.91/4.76	7.68/7.40
7j	172–174	33	$C_{24}H_{18}N_2S$	80.02/79.36	4.51/4.76	7.28/7.40

The separated solid was filtered, washed with water and recrystallized from ethanol to get **4**.

*3.2. General procedure for the synthesis of 3-(4-biphenylyl)-5-arylcyclohex-2-en-1-one **5(a–j)***

A mixture of an appropriate ketone **4** (0.01 mol) in glacial acetic acid (25 ml) and concentrated hydrochloric acid (12 ml) was refluxed for 10 h over a water bath. The reaction mixture was poured into crushed ice and stirred well. The separated product **5** was recrystallized from aqueous ethanol.

*3.3. General procedure for the synthesis of 3-(4-biphenylyl)-5-arylcyclohex-2-en-1-one semicarbazone **6(a–j)***

A mixture of ketone **5** (0.01 mol), semicarbazide hydrochloride (0.01 mol) and sodium acetate (0.015 mol) in ethanol (40 ml) was refluxed for 2 h on a steam bath and cooled. The separated solid said was filtered, washed with water and recrystallized from ethanol.

*3.4. General procedure for the synthesis of 5-(4-biphenylyl)-7-aryl[3,4-d] [1,2,3] benzothiadiazole **7(a–j)***

Semicarbazone **6** (0.001 mol) was added portion wise to the thionyl chloride (1.5 ml) at 0–5 °C and then kept at room temperature for 1–2 h. Dichloromethane (10 ml) was added to the reaction mixture and decomposed with an ice-cold sodium carbonate solution. The organic layer was washed with water (four to five times each with 10 ml) and dried over anhydrous sodium sulfate. After evaporation of the solvent a gummy substance was obtained, which was solidified on treatment with cyclohexane and purified by column chromatography using silica gel (60–120 mesh, BDH) with benzene-pet-ether (60–80) (10:1) as elutents. The yield, melting point and elemental composition of **7**(**a**–**j**) are given in Table 2.

*3.4.1. **7a***

^{1}H NMR (400 MHz, $CDCl_3$), δ = 8.84 (1H, d, H-4, J = 1.2 Hz): 8.06 (1H, d, H-6, J = 1.3 Hz), 7.10–7.86 (m, aromatic protons), ^{13}C NMR (100 MHz), $CDCl_3$), δ = 160.84 (C-9), 146.34 (C-8), 143.82 (C-5), 141.99 (C-7), 138.84, 140.71, 141.07 (*ipso* carbons), 122.02 (C-4), 127.51–130.07 (C-6 and aromatic carbons).

*3.4.2. **7b***

^{1}H NMR, δ = 8.80 (1H, d, H-4, J = 1.2 Hz): 8.01 (1H, d, H-6, J = 1.2 Hz), 3.91 (3H, s, CH_3), δ7.10–7.86 (m, aromatic protons), ^{13}C NMR, δ = 160.90 (C-9), 141.95 (C-8), 141.81 (C-5), 141.02 (C-7), 120.52 (C-4), 139.1, 134.91, 133.07 (*ipso* carbons), 127.77–131.54 (C-6 and aromatic carbons).

*3.4.3. **7c***

^{1}H NMR, δ = 8.85 (1H, d, H-4, J = 1.2 Hz): 8.02 (1H, d, H-6, J = 1.2 Hz), 7.04–7.785 (m, aromatic protons), ^{13}C NMR, δ = 160.87 (C-9), 142.10 (C-8), 140.94 (C-5), 140.11 (C-7), 135.79, 138.78, 139.11 (*ipso* carbons), 121.44 (C-6), 127.77–133.97 (C-6 and aromatic carbons).

*3.4.4. **7d***

^{1}H NMR, δ = 8.93 (1H, d, H-4, J = 1.2 Hz): 8.10 (1H, d, H-6, J = 1.2 Hz), 7.26–7.93 (m, aromatic protons), ^{13}C NMR, δ = 161.12 (C-9), 148.68 (C-8), 146.84 (C-5), 142.32 (C-7), 122.6 (C-4), 138.36, 140.82, 140.04 (*ipso* carbons), 122.34–132.77 (C-6 and aromatic carbons).

*3.4.5. **7e***

^{1}H NMR, δ = 8.84–8.85 (1H, d, H-4, J = 1.2 Hz), 8.10–8.02 (1H, d, H-6, J = 1.2 Hz), 3.8 (3H, s, OCH_3), 7.00–7.86 (m, aromatic protons), ^{13}C NMR, δ = 159.45 (C-9), 141.08 (C-8), 140.65 (C-5), 140.45 (C-7), 121.21 (C-4), 156.32, 138.60 (*ipso* carbons), 127.32–31.60 (*ipso* carbons), 127.16–131.73 (C-6 and aromatic carbons).

*3.4.6. **7f***

^{1}H NMR, δ = 8.91 (1H, d, H-4, J = 1.1 Hz): 8.12 (1H, d, H-6, J = 1.1 Hz), 7.12–7.98 (m, aromatic protons), ^{13}C NMR, δ = 162.71 (C-9), 143.34 (C-8), 141.22 (C-5), 141.3 (C-7), 140.4, 139.1, 134.07 (*ipso* carbons), 141.4 120.2 (C-4), 123.51–133.17 (C-6 and aromatic carbons).

*3.4.7. **7g***

^{1}H NMR, δ = 8.80 (1H, d, H-4, J = 2 Hz): 8.02 (1H, d, H-6, J = 2 Hz), 7.02–7.90 (m, aromatic protons), ^{13}C NMR,

δ = 163.81 (C-9), 144.29 (C-8), 141.2 (C-5), 141.8 (C-7), 140.7, 139.8, 136.09 (*ipso* carbons), 122.2 (C-4), 124.1–131.19 (C-6 and aromatic carbons).

3.4.8. ***7h***

^{1}H NMR, δ = 2.32(3H,s, CH_3), 8.82 (1H, d, H-4, J = 1.3 Hz): 8.10 (1H, d, H-6, J = 1.3 Hz), 7.08–7.93 (m, aromatic protons), ^{13}C NMR, δ = 21.2 (CH_3), 161.21 (C-9), 145.2 (C-8), 142.7 (C-5), 140.8 (C-7), 156.2, 140.2, 137.8,136.2 (*ipso* carbons), 121.6 (C-4), 123.4–129.9 (C-6 and aromatic carbons).

3.4.9. ***7i***

^{1}H NMR, δ = 2.41 (3H,s, CH_3), 8.83 (1H, d, H-4, J = 1.3 Hz): 8.16 (1H, d, H-6, J = 1.3 Hz), 7.10–7.89 (m, aromatic protons), ^{13}C NMR, δ = 21.7 (CH_3), 160.82 (C-9), 146.2 (C-8), 141.9 (C-5), 140.5 (C-7), 155.2, 139.8, 139.2,135.2 (*ipso* carbons), 122.1 (C-4), 124.2–130.4 (C-6 and aromatic carbons).

3.4.10. ***7j***

^{1}H NMR, δ = 2.37(3H,s, CH_3), 8.91 (1H, d, H-4, J = 1.3 Hz): 8.21 (1H, d, H-6, J = 1.3 Hz), 7.18–7.91 (m, aromatic protons), ^{13}C NMR, δ = 21.4 (CH_3), 161.41 (C-9), 144.02 (C-8), 142.1 (C-5), 140.1 (C-7), 156.2, 140.4, 138.1,137.2 (*ipso* carbons), 121.9 (C-4), 122.6–130.1 (C-6 and aromatic carbons).

3.5. Antibacterial activity

The in vitro antibacterial activity of the synthesized compounds against Gram-positive organisms (*S. aureus*, and *B. subtilis)* and Gram-negative (*E. coli*, *K. peneumoniae* and *P. aeruginosa*) organisms by the conventional agar dilution procedures [18] and compared with that of ciprofloxacin and norfloxacin. Twofold serial dilutions of the compounds and reference drugs 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. The minimum inhibitory concentration (MIC) was the lowest concentration of the test compound, which resulted in no visible growth on the plate. To ensure that the solvent had no effect on bacterial growth, a control test was performed with test medium supplemented with DMSO at the same dilutions as used in the experiment.

References

[1] C.D. Hurd, R.I. Mori, J. Am. Chem. Soc. 77 (1955) 5359–5364.
[2] P. Stanetty, M. Kremslehner, Heterocycles 48 (1998) 259–266.
[3] T.C. Britton, T.J. Lobl, C.G. Chidester, J. Org. Chem. 49 (1984) 4773–4780.
[4] P. Stanetty, M. Kremslehner, M. Müllner, J. Heterocycl. Chem. 33 (1996) 1759–1763.
[5] D. BhaskarReddy, A. Somasekhar, T. Chandra, V. Padmavathi, J. Ecotoxicol. Environ. Monit. 9 (3 and 4) (1999) 225–229.
[6] G.S. Lewis, P.H. Nelson, J. Med. Chem. 22 (1979) 1214.
[7] T.C. Britton, T.J. Chidester, J. Org. Chem. 49 (1984) 4773.
[8] C. Rovira, J. Veciana, N. Santalo, J. Tarres, J. Cirujeda, E. Molins, et al., J. Org. Chem. 59 (1994) 3307.
[9] E.W. Thomas, E.E. Nishizawa, D.C. Zimmermann, J. Williams, J. Med. Chem. 28 (1985) 442.
[10] E.W. Thomas, in: K.T. Potts, A.R. Katritzky, C.W. Rees (Eds.), Comprehensive Heterocyclic Chemistry, Pergamon Press, London, 1984, pp. 447 6, Part 4B.
[11] M. Fujita, T. Kobari, T. Hiyama, K. Konda, Heterocycles 36 (1993) 33.
[12] P. Stanetty, M. Kremhslehner, M. Mullner, J. Heterocycl. Chem. 33 (1996) 1759.
[13] D.J. Byron, G.W. Gray, R.C.J. Wilson, J Chem. Soc. (C) 13 (1966) 840.
[14] S. Tumkevicius, L. Labanauskas, V. Bucinskaite, A. Brukstus, G. Urbelis, Tetrahedron Lett. 44 (35) (2003) 6635–6638.
[15] H. Ghandi, C. Anfoka, Crop Protection 19 (6) (2000) 401–405.
[16] S. Smeets, W. Dehaen, Tetrahedron Lett. 39 (52) (1998) 9841–9844.
[17] T. Balasankar, S. Nagarajan, Heterocycl. Commun. 10 (5) (2004) 451–456.
[18] E.J. Baron, S.M. Finegold, in: Bailey and Scott's Diagnostic Microbiology, eighth ed., Mosby, St. Louis, MO, 1990, pp. 184–188.