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N. Ingarsal[a]; P. Amutha[a]; S. Nagarajan[a]
[a] Department of Chemistry, Annamalai University, Tamil Nadu, India

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RESEARCH ARTICLE

Synthesis and antibacterial activities of some 2-amino-4-(1,1′-biphenyl-4-yl)-6-aryl-6H-1,3-thiazines

N. INGARSAL, P. AMUTHA and S. NAGARAJAN*

Department of Chemistry, Annamalai University, Annamalainagar-608 002, Tamil Nadu, India

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A series of new 2-amino-4-(1,1′-biphenyl-4-yl)-6-aryl-6H-1,3-thiazines has been synthesized, characterized by IR, ^{1}H NMR, ^{13}C NMR, mass and elemental analyses and evaluated for *in vitro* antibacterial activity against some Gram-positive and Gram-negative bacteria. The antibacterial data revealed that the compounds had better activity against tested organisms than the reference norfloxacin.

Keywords: 1,3-Thiazines; Antibacterial activity; 2-Amino-1,3-thiazines

1. Introduction

The 1,3-thiazines and their derivatives constitute an important class of compounds possessing diverse type of biological properties such as antibacterial [1], antitumor activities [2], etc. The antibiotic activities of cephalosporins are due to the presence of 1,3-thiazine part [3]. The 5,6-dihydro-1,3-thiazine derivatives of particular interest for their use as anti-radiation agents and as radiation-sickness drugs [4]. They have also displayed some insecticidal and fungicidal activities [5–7]. The importance of substituted 6H-1,3-thiazines as synthetic intermediate is related to their polydentate reactivity [8]. Synthesis of enantiomerically pure 5,6-dihydro-4*H*-[1,3]thiazines [9], synthesis of dihydro- and tetrahydro-1,3-thiazine derivatives from β-aryl-β-amino acids [10], microwave activated solvent-free synthesis of 1,3-thiazines [11] and synthesis of 1,3-thiazines and their transformation into 1-substituted-6-alkyluracils [12] have been reported.

We have recently described the synthesis and antibacterial activity of a series of biphenyl substituted 1,2,3-thiadiazoles and 2-aminopyrimidines [13,14]. Based on the above reports and in continuation of our research on the synthesis of biologically active small heterocyclic molecules, we report here the synthesis of some biphenyl substituted 1,3-thiazines and their antibacterial activity.

*Corresponding author. Email: nagarajan.au@gmail.com

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2. Results and discussion

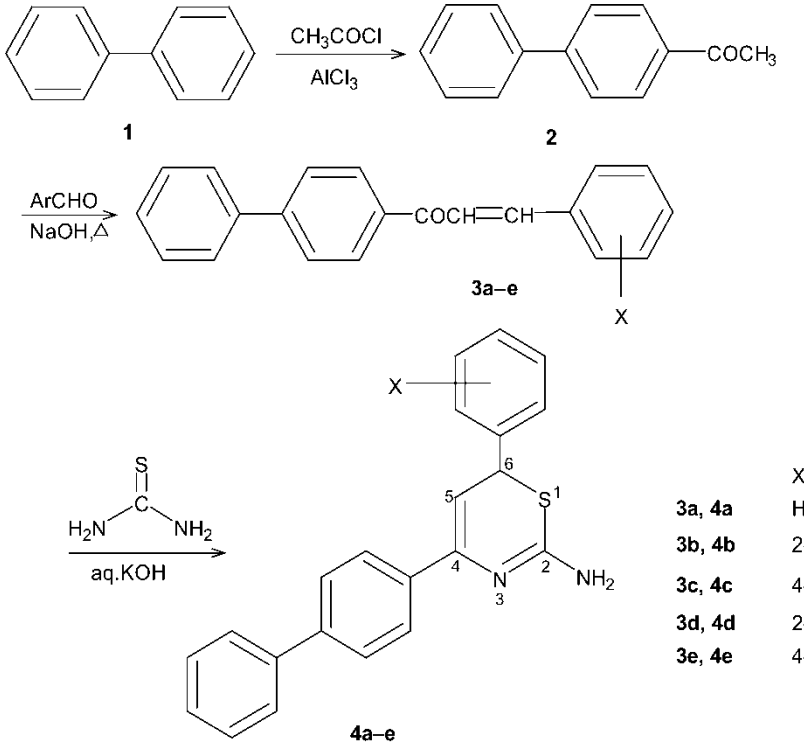
The 1-(1,1′-biphenyl-4-yl)ethanone **2** is obtained by acetylation of biphenyl **1** in presence of anhydrous aluminium chloride. The 1-(1,1′-biphenyl-4-yl)ethanone on treatment with different aromatic aldehydes in presence of base gives substituted 1-(1,1′-biphenyl-4-yl)-3-aryl-prop-2en-1-ones **3a–e**. The ethanolic solution of **3a–e** refluxed with thiourea in aq. KOH gives 2-amino-4-(1,1′-biphenyl-4-yl)-6-aryl-6H-1,3-thiazines **4a–e**. The formation of 1,3-thiazines is given in scheme 1.

The mechanism [15] involves the formation of a Michael adduct and its subsequent heterocyclisation with a tautomeric change (scheme 2).

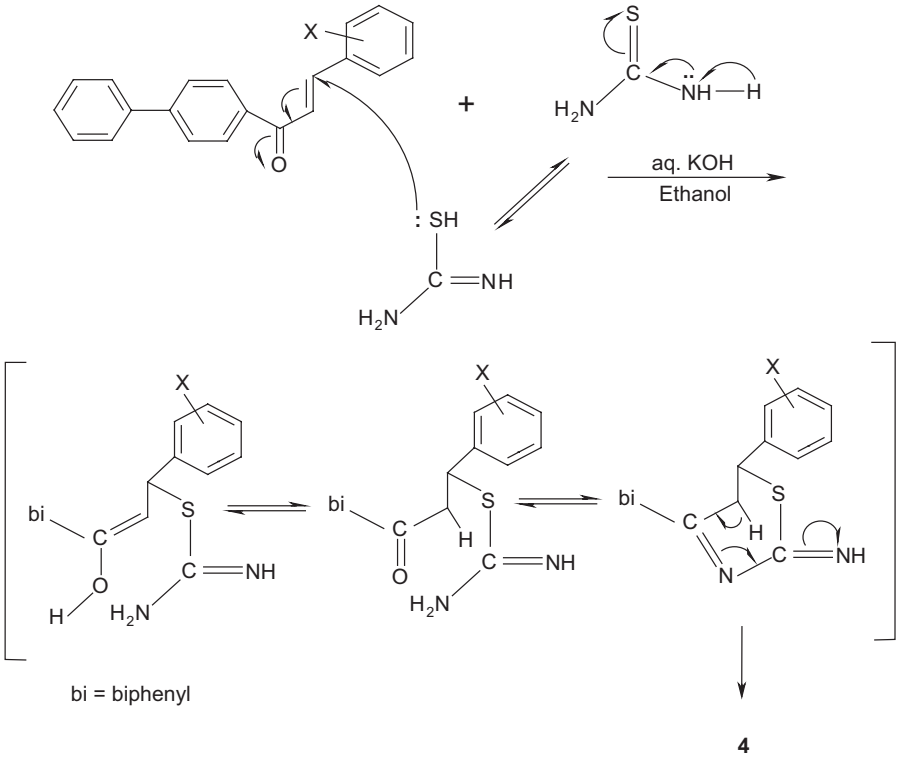
The IR spectra of the 1,3-thiazines **4a–e** displays characteristic absorption bands in the region of 3190–3200 cm^{-1} (NH str.), 1660–1670 cm^{-1} (C=N stretching), around 1560 cm^{-1} (C=C str.), around 1241 cm^{-1} (C−N str.). The ^1H NMR shows characteristic peaks around δ: 5.26 ppm (H-6 proton), 5.29 ppm (H-5 proton), 7.25–7.72 ppm (aromatic protons), the amino protons signals are merged in the aromatic region. ^{13}C NMR displays characteristic peaks around δ: 51.6–57.3 ppm (C-6), 99.2–100.8 ppm (C-5), 142.5 ppm (C-4), 175.6 ppm (carbon bearing amino group), 125.6–134.6 ppm (aromatic carbons).

The anti-bacterial activities of **4a–e** were assessed in comparison to norfloxacin against Gram-positive (*S. aureus* and *B. subtilis*) and Gram negative (*K. pneumoniae* and *P. aeruginosa*) bacteria using conventional agar dilution procedure and the results are summarized in table 1.

The anti-bacterial data indicated that compounds **4a–e** had a better activity against tested Gram-negative organisms. However, all the compounds were nearly inactive against tested



SCHEME 1



SCHEME 2

Table 1. *In vitro* anti-bacterial activity of **4a–e** and standard (MIC $\mu g\,ml^{-1}$).

Compounds	*S. aureus*	*B. subtilis*	*K. pneumoniae*	*P.aeruginosa*
4a	>60	42	0.51	0.59
4b	40	>60	0.38	0.41
4c	39	41	0.38	0.42
4d	>60	36	0.22	0.18
4e	>60	>60	0.31	0.21
Norfloxacin	1	0.05	0.41	1.8

Gram-positive bacteria. The anti-bacterial data revealed that the compounds **4a–e** possesses similar anti-bacterial profiles. The selective anti-bacterial activity against Gram-negative bacteria is in contrast to the good anti-bacterial activity of norfloxacin against both Gram-positive and Gram-negative bacteria. Compounds **4d** and **4e** are the most active among the compounds tested. Between the two chloro compounds, 2-chloro isomer **4d** is more effective than the 4-chloro (**4e**) substituted compound. Thus the nature and position of the group has strong influence on the spectrum and extent of anti-bacterial activity.

3. Experimental

Melting points are determined in open capillaries and are uncorrected. The ^1H NMR and ^{13}C NMR were recorded on a Brucker AMX-400 spectrometer operating at 400 MHz and

100.6 MHz respectively. Mass spectra were recorded on CLASS-5000 mass spectrometer with an ion source temperature 200 °C was used. The FT-IR spectra were recorded on NICOLET AVATAR 360-FT-IR instrument by using KBr pellets. Elemental analyses were done on Vario EL. CHNOS elemental analyzer.

3.1 *General procedure for preparation of 1-(1,1′-biphenyl-4-yl)ethanone (2)*

The compound was prepared from acetylation of biphenyl using acetyl chloride in the presence of anhydrous aluminium chloride [16].

3.2 *Preparation of 1-(1,1′-biphenyl-4-yl)-3-arylprop-2-en-1-ones (3a–e)*

A solution of aromatic aldehyde (0.01 mol) and 1-(1,1′-biphenyl-4-yl) ethanone (0.01 mol) in 65% aqueous ethanol (50 mL) containing NaOH (0.5 g) was heated over a water bath for 30 mins and the solution was cooled, the 1-(1,1′-biphenyl-4-yl)-3-arylprop-2-en-1-ones were formed as yellow crystals.

3.3 *Preparation of 2-amino-4-(1,1′-biphenyl-4-yl)-6-aryl-6H-1,3-thiazines (4a–e)*

A mixture of appropriate 1-(1,1′-biphenyl-4-yl)-3-arylprop-2-en-1-one (5 mmol), thiourea (5 mmol) and KOH (10 mmol) in ethanol was refluxed for 4 hours. The solvent was removed under reduced pressure and the residue was treated with crushed ice. The solid thus separated was subjected to column chromatography using benzene as eluent.

3.3.1 Compound 4a. ^{1}H NMR, δ (ppm) 5.26 (1H, d, H-6), 5.29 (1H, d, H-5), 7.25–7.72 (aromatic protons), amino protons signal is merged with the aromatic region. ^{13}C NMR, δ (ppm) 57.36 (C-6), 100.66 (C-5), 142.54 (C-4), 175.60 (carbon bearing amino group), 133.71, 139.99, 142.36 (*ipso* carbon), 125.61–132.09 (aromatic carbons). Mass spectrum m/z: 342 (molecular ion peak), 265.0, 189.1, 113.0, 77.1 and 44. $C_{22}H_{18}N_2S$, C: 77.40/77.15, H: 5.38/5.29, N: 8.98/8.78. Yield: 55%, mp: 125–126 °C.

3.3.2 Compound 4b. ^{1}H NMR, δ (ppm) 5.34 (1H, d, H-6), 5.67 (1H, d, H-5), 3.90 (3H, s, OCH_3), 6.92–7.66 (aromatic protons), the amino protons signal is merged with the aromatic region. ^{13}C NMR, δ (ppm) 51.65 (C-6), 99.45 (C-5), 140.64 (C-4), 176.25 (carbon bearing amino group), 56.14 (methoxy carbon), 135.42, 132.97 (*ipso* carbon), 121.76–130.33 (aromatic carbons). Mass spectrum m/z: 360 (molecular ion peak), 265.0, 219.0, 113.0, 107.05, 77.1 and 44. $C_{23}H_{20}N_2SO$, C: 74.20/74.16, H: 5.62/5.41, N: 7.43/7.52. Yield: 50%, mp: 118–120 °C.

3.3.3 Compound 4c. ^{1}H NMR, δ (ppm) 5.25 (2H, d, H-5, H-6), 3.81 (3H, s, OCH_3), 6.72–7.68 (aromatic protons), amino protons signal may be merged with aromatic region. ^{13}C NMR δ (ppm) 53.38 (C-6), 100.80 (C-5), 175.21 (carbon bearing amino group), 142.5 (C-4), 159.91 (carbon bearing methoxy group), 56.79 (OCH_3), 134.49, 133.44, 132.05 (*ipso* carbon), 125.48–128.9 (aromatic carbons). Mass spectrum m/z: 360 (molecular ion peak), 265.0, 219.01, 113.0, 77.1 and 44. $C_{23}H_{20}N_2SO$, C: 74.39/74.16, H: 5.70/5.41, N: 7.82/7.52. Yield: 60%, mp: 127–129 °C.

3.3.4 Compound 4d. ^{1}H NMR, δ (ppm) 5.38 (1H, d, H-6), 5.76 (1H, d, H-5), 6.93–7.80 (aromatic protons), the amino protons signal may be merged with aromatic region. ^{13}C NMR, δ (ppm) 54.27 (C-6), 99.29 (C-5), 143.23 (C-4), 176.63 (C-2), 135.27, 139.73, 140.57 (*ipso* carbon), 126.28–132.57 (aromatic carbons). Mass spectrum m/z: 376 (molecular ion peak), 223.0, 113.0, and 111.01. $C_{22}H_{17}N_2SCl$, C: 70.56/70.10, H: 4.99/4.54, N: 7.99/7.72. Yield: 65%, mp: 107–110 °C.

3.3.5 Compound 4e. ^{1}H NMR, δ (ppm) 5.22 (1H, d, H-6), 5.28 (1H, d, H-5), 7.25–7.77 (aromatic protons), the amino protons signal may be merged with aromatic region. ^{13}C NMR, δ (ppm) 56.62 (C-6), 100.14 (C-5), 142.68 (C-4), 175.5 (carbon bearing amino group), 140.90, 139.93 ppm (*ipso* carbon), 125.64–134.63 (aromatic carbons). Mass spectrum m/z: 376 (molecular ion peak), 223.0, 153.1, 113.0, and 111.1. $C_{22}H_{17}N_2SCl$, C:70.66/70.10, H: 5.02/5.94, N: 8.01/8.83. Yield: 55%, mp: 130–132°C.

3.4 *Preparation of medium and antibacterial activity studies*

The *in vitro* anti-bacterial activity of the synthesized compounds were tested against Gram-positive organisms (*Staphylococcus aureus* and *Bacillus subtilis)* and Gram-negative (*Klebsiella pneumoniae* and *Pseudomonas aeruginosa*) organisms by the conventional agar dilution procedures [17] and compared with that of norfloxacin. A two-fold serial dilution of the compounds and reference drug was prepared in Muller–Hinton agar. The drug was dissolved in dimethylsulfoxide (DMSO; 1 ml) and the solution was diluted with water (9 ml). Further progressive double dilution with melted Muller–Hinton agar were 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] H.S. Patel, N.P. Patel. *Orient. J. Chem.*, **13**, 69 (1997).
[2] H.I. El-Subbagh, A.H. Abadi, I.E. Al-Khawad, K.A. Al-Rashood. *Arch. Pharm.*, **332**, 1924 (1999).
[3] G.C. Barret, V.V. Kane, G. Lowe. *J. Chem. Soc.*, 783 (1964).
[4] E. Campaigne, P.K. Nargund. *J. Org. Chem.*, **29**, 224 (1964).
[5] M. Koketsu, K. Tanaka, Y. Takenaka, C.D. Kwong, H. Ishihara. *Eur. J. Pharma. Sci.*, **15**, 307(*2002).*
[6] B. Tozkoparan, G. Aktay, E. Yeilada. *Il Farmaco*, **57**, 145 (2002).
[7] D. Bózsing, P. Sohár, G. Gigler, G. Kovács. *Eur. J. Med. Chem*., **31**, 663 (1996).
[8] L.D.S. Yadav, S. Yadav, V.K. Rai. *Tetrahedron*, **61**, 10013 (2005).
[9] A. Harrison-Marchand, S. Collet, A. Guingant, J. Pradère, L. Toupet. *Tetrahedron*, **60**, 1827 (2004).
[10] N. Leflemme, P. Dallemagne, S. Rault. *Tetrahedron Lett.*, **45**, 1503 (2004).
[11] L.D.S. Yadav, A. Singh. *Tetrahedron Lett*., **44**, 5637 (2003).
[12] V.N. Yuskovets, B.A. Ivin. *Tetrahedron Lett.*, **44**, 5279 (2003).
[13] T. Balasankar, M. Gopalakrishnan, S. Nagarajan. *Eur. J. Med. Chem*., **40**, 728 (2005).
[14] S. Chandrasekaran, S. Nagarajan. *IL Farmaco*, **60**, 279 (2005).
[15] A.C. Jain, A.K. Prasad. *Indian J. Chem.*, **34(B)**, 496 (1995).
[16] A.I. Vogel. *Elementary Practical Organic Chemistry, Part 1: Small scale preparations*, ELBS Publishers, New York (1966).
[17] E.J. Baron, S.M. Finegold. *Bailey and Scott's Diagnostic Microbiology*, 8th edn., Mosby, St. Louis, MO (1990).