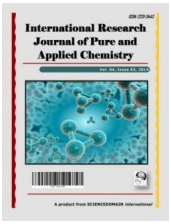

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Synthesis Antioxidant and Antibacterial Studies on 2-(2-arylamino-4-phenylthiazol-5-yl)benzofuran Derivatives

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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ABSTRACT

A series of 2-(2-arylamino-4-phenylthiazol-5-yl)benzofurans derivatives were synthesized from 1-aryl-3-(N-phenylbenzimidoyl)thiourea and 2-(2-bromoacetyl)benzofuran in the presence of triethylamine. Their structure was established on the basis of IR, ^{1}H NMR and mass spectral analyses. The entire newly synthesized compound was screened for their antioxidant and antibacterial potential. All the compounds showed low to moderate activity against the microorganisms tested.

Keywords: 2-(2-bromoacetyl)benzofuran; Triethylamine; antioxidant; antibacterial and microorganism.

1. INTRODUCTION

Natural products have the potential to provide medicine with a source of novel structures. Nature is capable of producing complex molecules with multiple chiral-centers that are designed to interact with biological systems. The marine environment is a rich source of

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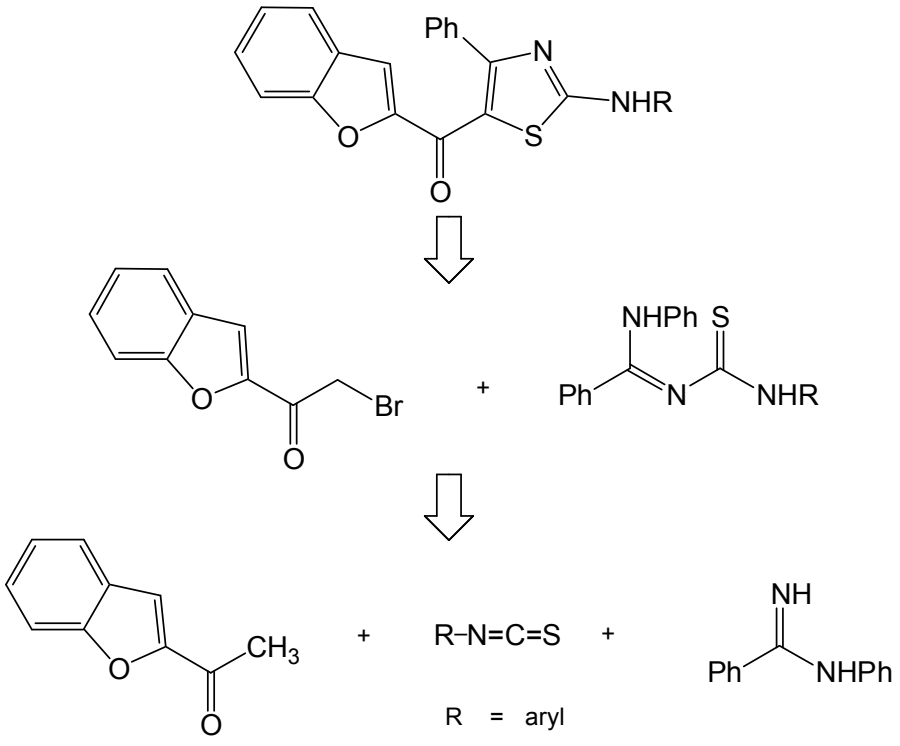
biologically active natural products, many of which have not been found in terrestrial sources [1]. Marine natural products have attracted the attention of biologists and chemists the world over for the past five decades. As a result of the potential for new drug discovery, marine natural products have attracted scientists from different disciplines such as organic chemistry, bioorganic chemistry, pharmacology, biology and ecology. This interest has led to the discovery of over 16,000 marine natural products to date and many of the compounds have shown very promising biological activity. As 2,4-diaminothiazoloylbenzofuran and 2-aminothiazoloylbenzofuran analogs of dendrodoine have good docking characteristics, anticancer, antioxidant and antimicrobial activities, we further planned to synthesize and evaluate the biological properties of 2-amino-4-phenylthiazoloylbenzofuran as further analogs of dendrodoine. This observations show that synthesis of 2-amino-4-phenylthiazoloylbenzofuran with a view to study their biological activity. They exhibit a variety of bioactivity such as antibiotic, anticancer, anti-inflammatory, antitumor, antiviral, antibacterial and antifungal activities. Benzofuran derivatives have broad spectrum of biological activities such as antimicrobial, antifungal, anticancer, anti-inflammatory and analgesic and it is understood that many natural products with benzofuran moiety exhibit interesting biological and pharmacological activities.

The retrosynthetic approach for the synthesis of targeted compound 2-(2-arylamino-4-phenylthiazol-5-yl)benzofurans is given in Scheme I.

2. EXPERIMENTAL RESULTS AND DISCUSSION

The reagents and solvents used were of AR grade. All chemicals were purchased from Merck Specialties Pvt. Ltd and Sigma - Aldrich. The spectra were recorded on Bruker Avance III, 400MHz NMR spectrometer (400MHz for ^{1}H and 400MHz for ^{13}C NMR spectra), Waters UPLC - TQD mass spectrometer (ESI – MS and APCI - MS) for ESI mass spectra and Nicolet 400D FTIR spectrometer. Melting points were uncorrected. Elemental analysis was done at the Central Drug Research Institute, Lucknow, India.



Scheme I

2.1 Preparation of N-phenylbenzamidine [2]

Benzonitrile (0.05 mol) and aniline (0.05 mol) was treated in a 250 ml flask in the presence of anhydrous aluminium chloride (0.05 mol). The reaction mixture was heated at 180-200°C for 30 min. The hot reaction mixture was poured into water containing concentrated hydrochloric acid under thorough stirring. The solution was decolorized by activated charcoal and poured in slow stream to a stirred solution of water containing sodium hydroxide. The flocculent precipitate was worked out as a white powder. The crude sample was crystallized from ethanol-water mixture (1:1), yield 7.07 g (55%), m.p. 111-112°C.

2.2 Preparation of 1-aryl-3-(N-phenylbenzimidoyl)thiourea derivatives [2] (1a-e)

N-phenylbenzamidine (5 mmol) was dissolved in N, N dimethylformamide and aryl isothiocyanate (5mmol) was added and the workup gave 1-aryl-3-(N-phenylbenzimidoyl)thiourea, Yield 1.58 g (95%), m.p. 132°C.

2.3 Preparation of 2–acetylbenzofuran [3]

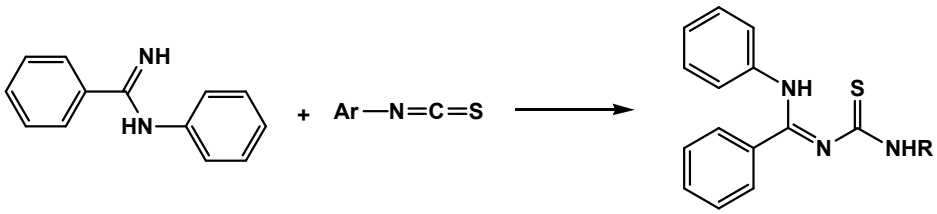
Salicylaldehyde (0.1 mol), bromoacetone (0.1 mol) and anhydrous acetone (35 mL) were taken in dried round bottomed flask and refluxed for 10 hours in a water bath. The reaction mixture was then cooled and treated with anhydrous potassium carbonate, filtered and evaporated to give pure white crystals of 2-acetylbenzofuran. Yield: 12.3 g (76.9%), m. p. 75°C.

2.4 Preparation of 2–bromoacetylbenzofuran [3]

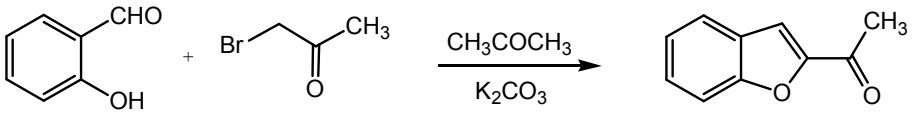
A solution of bromine (7.5 mmol) in acetic acid (10 mL) was added drop wise with stirring to a solution of 2-acetylbenzofuran (7.5 mmol) in acetic acid (10 mL) after complete addition of bromine, the mixture was stirred for 45 min and allowed to stand for 30 minutes, then the mixture was decanted in crushed ice, the solid separated was collected and crystallized from ethanol as light green crystals. Yield: 18.6g (77.8%), m. p. 94°C.

2.5 Synthesis of 2-(2-arylamino-4-phenylthiazol-5-yl)benzofuran [4] (3a-e)

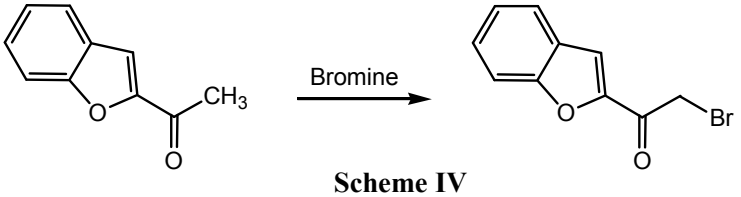
To a solution of 1-aryl-3-(N-phenylbenzimidoyl)thiourea (1 mmol) in 5 ml N, N-dimethylformamide (1 mmol) was added. The mixture was stirred well and kept at room temperature for 5h. Triethylamine (2 mmol) was then added and the mixture was heated carefully at 55°C for 1h with occasional stirring afforded yellow precipitate. It was subsequently purified by crystallization from ethanol-water [5].



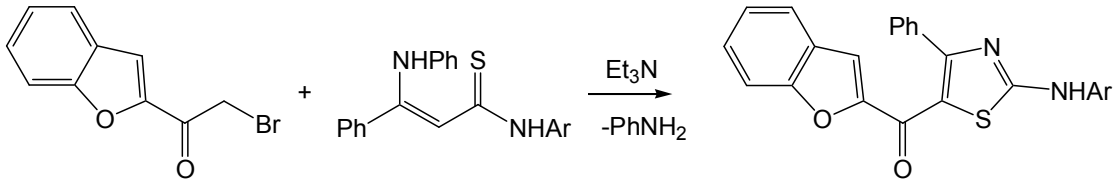
Scheme II



Scheme III



Scheme IV



Scheme V

2.5.1 2-(2-phenylamino-4-phenylthiazol-5-yl)benzofuran (3a)

Yield 71.1%, m.p. 198-201, Analysis found: C, 72.93: H, 4.11: N, 7.27%: Calc. for $C_{24}H_{16}N_2O_2S$ (396.46): C, 72.71: H, 4.07: N, 7.07.53%: **IR (KBr) cm^{-1}**: 3645, 3570, 3544, 3521, 3516, 3474, 3468, 3437, 3064, 2924, 2368, 1634, 1560, 1544, 1525, 1436, 1423, 1255, 1118, 1109, 1020, 968, 827, 748, 692. **^{1}H NMR**: (400 MHz**,** DMSO-d_6) 6.97-7.07(m, 2H, 2ArH), 7.11-7.42(m, 10H, H-5, H-6, 8ArH), 7.45-7.69(m, 3H, H-3, H-4, H-7), 10.43(s, 1H, NH).

2.5.2 2-[2-(4-chlorophenylamino)-4-phenylthiazol-5-yl]benzofuran (3b)

Yield 60.2%, m.p. 263-265, Analysis found: C, 67.07: H, 3.42: N, 6.38%: Calc. for $C_{24}H_{15}ClN_2O_2S$ (430.91): C, 66.90: H, 3.51: N, 6.50%: **IR (KBr) cm^{-1}**: 3564, 3519, 3506, 3466, 3448, 3398, 3371, 3096, 2362, 1691, 1556, 1546, 1514, 1492, 1475, 1406, 1336, 1256, 1182, 1138, 1012, 966, 865, 736, 627. **^{1}H NMR**: (400 MHz**,** DMSO-d_6) 6.91(d, 8.4 Hz, 2H, 2ArH), 7.15-7.65(m, 12H, H-3, H-4, H-5, H-6, H-7, 7ArH), 10.83(s, 1H, NH).

2.5.3 2-[2-(4-methoxyphenylamino)-4-phenylthiazol-5-yl]benzofuran (3c)

Yield 77.3%, m.p. 202-205, Analysis found: C, 70.47: H, 4.35: N, 6.27%: Calc. for $C_{25}H_{18}N_2O_3S$ (434.43): C, 70.40: H, 4.25: N, 6.57%: **IR (KBr) cm^{-1}**: 3577, 3511, 3491, 3454, 3425, 3400, 3380, 3354, 3314, 3286, 3145, 3078, 3045, 3010, 2958, 2926, 2856, 1710, 1693, 1674, 1662, 1650, 1607, 1586, 1550, 1549, 1513, 1459, 1400, 1367, 1332, 1247, 1174, 1026, 826, 746, 671. **^{1}H NMR**: (400 MHz**,** DMSO-d_6) 3.74(s, 3H, OCH_3), 6.84(d, 2H, 2ArH), 7.00-7.83(m, 12H, H-3, H-4, H-5, H-6, H-7, 7ArH), 10.57(s, 1H, NH).

2.5.4 2-[2-(4-ethoxyphenylamino)-4-phenylthiazol-5-yl]benzofuran (3d)

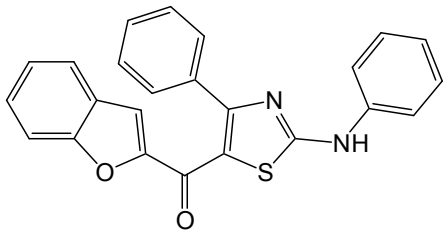
Yield 74.6%, m.p. 227-230, Analysis found: C, 70.77: H, 4.98: N, 6.66%: Calc. for $C_{26}H_{20}N_2O_3S$ (440.51): C, 70.89: H, 4.58: N, 6.36%: **IR (KBr) cm^{-1}:** 3570, 3483, 34/, 3436, 3394, 3361, 3343, 3311, 3277, 3257, 3222, 2853, 2340, 1560, 1544, 1523, 1465, 1434, 1416, 1403, 1400, 1244, 1114, 1047, 968, 923, 827, 758, 677. **^{1}H NMR**: (400 MHz**,** DMSO-d_6) 1.38(t, 5.6 Hz, 3H, CH_3), 2.87-2.94(m, 2H, CH_2), 6.60-7.71(m, 14H, H-3, H-4, H-5, H-6, H-7, 9ArH), 10.51(s, 1H, NH).

2.5.5 2-[2-(4-methylphenylamino)-4-phenylthiazol-5-yl]benzofuran (3e)

Yield 65.5%, m.p. 244 -247, Analysis found: C, 73.63: H, 4.39: N, 7.02%: Calc. for $C_{25}H_{18}N_2O_2S$ (410.49): C, 73.15: H, 4.42: N, 6.82%: **IR (KBr) cm^{-1}**: 3584, 3577, 3561, 3493, 3425, 3407, 3286, 3224, 3130, 3062, 3037, 3010, 2924, 2372, 1566, 1552, 1533, 1514, 1447, 1427, 1251, 1118, 1045, 1020, 746, 661. **^{1}H NMR**: (400 MHz**,** DMSO-d_6) 2.37(s, 3H, CH_3), 6.87 (d, 8.4 Hz, 2H, 2ArH), 7.18-7.39 (m, 7H H-5, H-6, 5ArH), 7.49-7.65(m, 4H, H-3, H-4, 2ArH), 7.87(d, 7.6Hz, H-7), 10.98(s, 1H, NH).

3. RESULTS AND DISCUSSION

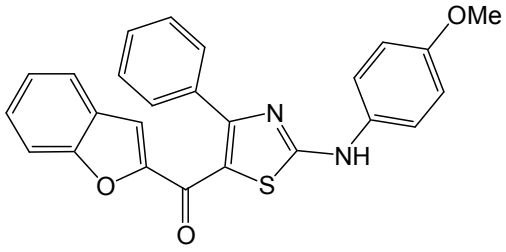
The elemental analysis of compound (3a) showed that the molecular composition was $C_{24}H_{16}N_2O_2S$. The IR (KBr) spectrum of the compound showed peaks at 3474 cm^{-1}, 3468cm^{-1} and 3437 cm^{-1}, which are assignable to ν_{N-H} bands. The peak at 3064 cm^{-1} is attributed to aromatic ν_{C-H} vibration. The highly conjugated carbonyl group gives rise to a $\nu_{C=O}$ band at 1634 cm^{-1}. The ^{1}H NMR (400MHz, $CDCl_3$) spectrum, the multiplet at δ 6.97-7.07 has been attributed two aryl hydrogens. The ten-hydrogen multiplet at δ 7.11-7.42 has been attributed to H-5 and H-6 of the benzofuran ring and eight aryl hydrogens. The H-3, H-4 and H-7 of the benzofuran ring form the multiplet at δ 7.45-7.69. The NH hydrogen of the NHAr group is observed as a one-hydrogen singlet at δ 10.43. From the above evidences, the compound was formulated as 2-(2-phenylamino-4-phenylthiazol-5-yl)benzofuran **(3a)**.



3a

The elemental analysis of compound (3c) showed that the molecular composition was $C_{25}H_{18}N_2O_3S$. The IR (KBr) spectrum of the compound showed peaks at 3491 cm^{-1}, 3454 cm^{-1} and 3425 cm^{-1}, which are assignable to ν_{N-H} bands. The peak at 3078 cm^{-1} is attributed to aromatic ν_{C-H} vibration. The highly conjugated carbonyl group gives rise to a $\nu_{C=O}$ band at 1693 cm^{-1}.

The ^1H NMR (400 MHz, $CDCl_3$) spectrum consists of a three-hydrogen singlet at δ 3.74 due to the presence of the methoxy group. The two-hydrogen doublet at δ 6.84 is the characteristic signals for two aryl hydrogen The twelve-hydrogen multiplet at δ 7.00-7.83 is due to H-3, H-4, H-5, H-6 and H-7 of the benzofuran ring and seven aryl hydrogens. The NH hydrogen of the NHAr group is observed as a one-hydrogen singlet at δ 10.57. The ESI-Mass Spectrum showed MH^+ peak at 435, which confirms the molecular mass of the compound to be 434 in accordance with the elemental analysis data. The ^{13}C NMR gives twenty five peaks corresponding to the twenty five carbons. Hence the compound is formulated as 2-[2-(4-methoxyphenylamino)-4-phenylthiazol-5-yl]benzofuran [6,7,8] **(3c)**.



3c

We have performed the similar reaction using other 1-aryl-3-(N-phenylbenzimidoyl)thiourea to obtain 2-[2-(4-chlorophenylamino)-4-phenylthiazol-5-yl]benzofuran **(3b),** 2-[2-(4-ethoxyphenylamino)-4-phenylthiazol-5-yl]benzofuran **(3d)** and 2-[2-(4-methylphenylamino)-4-phenylthiazol-5-yl]benzofuran **(3e)**. The structure assignment is based on the physical data, elemental analysis data, IR, ^1H NMR & ^{13}C NMR spectral data. The reaction can be depicted as (Scheme II).

3.1 Antioxidant Studies

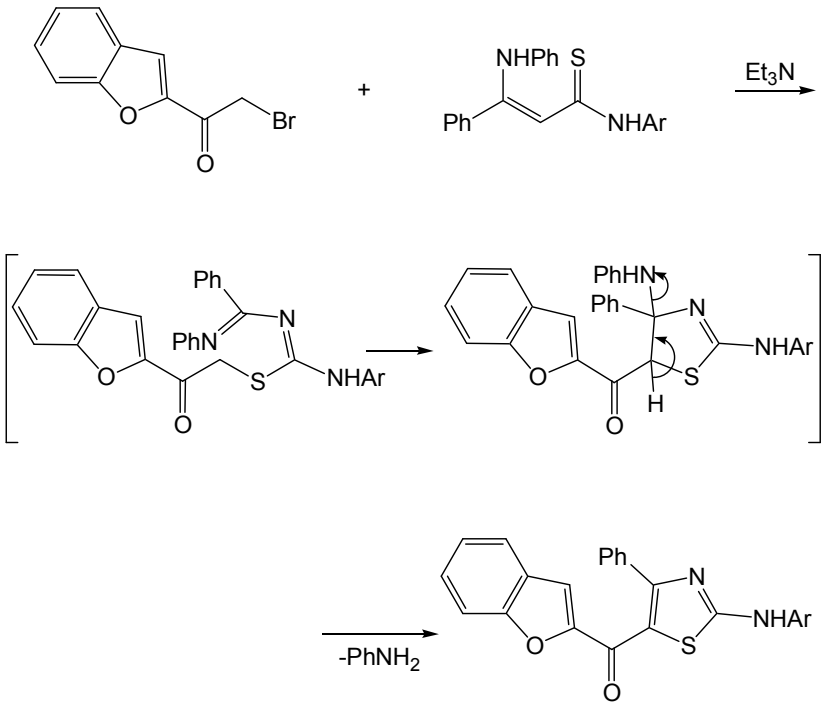
The newly synthesized compound was screened for their antioxidant potentials, DPPH (1 mg) in methanol was prepared in 250 mL standard flask (10^{-5} mol) (control: 2.8 mL of this solution + 0.05 mL methanol) with different concentrations (0.1, 0.25, 0.5, 0.75 & 1 mM) were prepared. BHA (standard) solutions of different concentrations (0.1, 0.25, 0.5, 0.75 & 1 mM) were prepared. The absorbance of the control and the test solutions were recorded at 517 nm. By following similar procedure the absorbance will be measured for BHA solutions [9,10,11]. From the absorbance values, percentage of inhibition was calculated. Then the percentage of inhibition was plotted against different concentrations of different samples as well as BHA. The percentage of reduction and IC_{50} were calculated. The IC_{50} value indicates that compound with less IC_{50} has more antioxidant capacity. The standard BHA shows the IC_{50} value of 624 µM.

$$\% \text{ inhibition} = \frac{\text{Control absorbance - Sample absorbance}}{\text{Control absorbance}} \times 100$$

Table 1. Antioxidant activities of 2-(2-arylamino-4-phenylthiazol-5-yl)benzofurans

Compd.	IC_{50} Value (µM)
3a	323
3b	305
3c	373
3d	194
3e	52
BHA(std)	624

The above table shows that the compound 2-[2-(4-methylphenylamino)-4-phenylthiazol-5-yl]benzofuran **(3e)**, has IC_{50} value 52µM and possesses excellent antioxidant activity. The thiazole containing 4-methylphenyl group **3e** in the second position has the highest activity among the arylamino substituent ie, **(3e>3d>3b>3a>3c)**.



Scheme VI

Compd.	Ar
3a	phenyl
3b	4-chlorophenyl
3c	4-methoxyphenyl
3d	4-ethoxyphenyl
3e	4-methylphenyl

3.2 Anti-bacterial Activities

3.2.1 Method used

The stock cultures of bacteria were revived by inoculating in broth media and grown at 37ºC for 18 hrs. The agar plates (20g in 1 L distilled water) of the above media were prepared and wells were made in the plate. Each plate was inoculated with 18 h old cultures (100 µL, 10^4 CFU) and spread evenly on the plate. After 20 min, the wells were filled with compound and antibiotic at different concentrations. All the plates were incubated at 37ºC for 24 h and the diameter of inhibition zone were noted [12,13].

The synthesized compounds have been screened for antibacterial activity against Gram-positive *Staphylococcus aureus, Bacillus subtilis* and Gram-negative *Escherichia coli, Pseudomonas aeruginosa*. As a reference, *Gentamycin* is used and a comparison of the data obtained from the study shows that almost all the new compounds now screened appeared to have remarkable antibacterial activity. These are classified into highly active (inhibition zone > 15mm), fairly active (inhibition zone > 10 mm), moderately active (inhibition zone > 8 mm) and somewhat active (inhibition zone = 6 mm).

The measured antibacterial activities of 2-(2-arylamino-4-phenylthiazol-5-yl)benzofurans are presented in the **Table 2** The compound 2-(2-phenylamino-4-phenylthiazol-5-yl)benzofuran (**3a**) is somewhat active against *Staphylococcus aureus, Escherichia coli and Bacillus subtilis*. The compound 2-[2-(4-methoxyphenylamino)-4-phenylthiazol-5-yl]benzofuran (**3c)** is somewhat active against *Escherichia coli* and no activity against *Staphylococcus aureus, Bacillus subtilis* and *Pseudomonas aeruginosa.* The compound 2-[2-(4-ethoxyphenylamino)-4-phenylthiazol-5-yl]benzofuran (**3d)** is somewhat active against *Staphylococcus aureus* and *Escherichia coli*,

Table 2. Anti-bacterial activities of 2-(2-arylamino-4-phenylthiazol-5-yl)benzofurans

Compd.	Zone of inhibition (mm)			
	Staphylococcus aureus	***Bacillus subtilis***	***Escherichia coli***	***Pseudomonas aeruginosa***
1a	6	2	5	NA
1b	13	12	8	9
1c	0	0	3	NA
1d	3	0	7	10
1e	2	2	6	3
Gentamycin	34	25	31	29

fairly active aganist *Pseudomonas aeruginosa* but no activity against *Bacillus subtilis*. The compound 2-[2-(4-chlorophenylamino)-4-phenylthiazol-5-yl]benzofuran (**3b)** is fairly active against *Staphylococcus aureus* and *Bacillus subtilis* and moderately active against *Escherichia coli* and *Pseudomonas aeruginosa*. The compound 2-[2-(4-methylphenylamino)-4-phenylthiazol-5-yl]benzofuran (**3e)** shows somewhat activity against *Staphylococcus aureus, Bacillus subtilis, Escherichia coli* and *Pseudomonas aeruginosa.*

4. CONCLUSION

The newly synthesized compounds were established on the basis of elemental analysis, IR, ^{1}H NMR, and mass spectral data and tested for in vitro antimicrobial activity. It may be concluded that the newly synthesized compound 2-[2-(4-methylphenylamino)-4-phenylthiazol-5-yl]benzofuran **(3e)** has excellent antioxidant activity, also compound 2-[2-(4-chlorophenylamino)-4-phenylthiazol-5-yl]benzofuran (**3b)** is fairly active against *Staphylococcus aureus* and *Bacillus subtilis* in antibacterial studies.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Brad .C. Bioscience. 1996;46:271.
2. Thomas KK, Reshmy R, Ushadevi KS. Synthesis of a novel bioactive 2-substituted amino-5-indol-3-oyl-4-phenylthiazoles. J. Indian Chem. Soc. 2007;84:1016-1019.
3. Kamble VS, Habade BM, Patil GK, Agasimundin Y. Synthesis and evaluation of 4-(1-benzofuran-2-yl)-1,3-oxazole-2-amine and its derivatives, Int. J. Res. Pharm. Chem. 2012;2:32-36.
4. Reji TFAF, Rajasekharan KN. Synthesis of 3-(2,4-diaminothiazol-5-oyl)indoles. J. Saudi Chem. Soc. 2008;12:269-274.
5. Silverstein RM, Bassler GC, Morrill TC. Spectrometric identification of organic compounds. Fourth edn. John Wiley & Sons, Inc., New York, USA; 1981.
6. Binu R, Thomas KK, Jenardanan GC, Rajasekharan KN. Synthesis and cyclization of 1-(N-nitroamidino)thioureas to 2,4-diaminothiazoles. Org. Prep. Procedures Int. 1998;30:93-96.
7. Devi SKC, Ph.D. Dissertation. University of Kerala; 1999.
8. Nair KP, Phil M. Dissertation. University of Kerala; 1979.
9. Li LJ. Antioxidants and oxidative stress in exercise. Exp Bio Med. 1999;222:283.
10. Sanja SD, Sheth NR, Patel NR, Dhaval P, Biraju P. Characterisation and evaluation of antioxidant activity of portulaca Oleracea. Int J Pharm Pharm Sci. 2009;1:74.
11. Kuntal H, Nargund LVG, Rashmi P, Narendra SC. Synthesis and antioxidant activity of some novel fluorobenzothiazolopyrazoline. Der. Chemica Sinica. 2011;2:149.

12. Threlfall EJ, Fisher IST, Ward L, Tschape H, Gerner-Smidt P. Harmonization of antibiotic susceptibility testing for *Salmonella:* Results of a study by 18 national reference laboratories within the European Union-funded Enter-Net group. Microb. Drug Resist. 1999;5:195–199.

13. Walker RD. Antimicrobial susceptibility testing and interpretation of results. *In:* Antimicrobial Therapy in Veterinary Medicine, Prescott J.F., Baggot J.D., Walker R.D., eds. Ames, IA, Iowa State University Press. 2000;12–26.

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