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Green Synthesis of Novel Substituted 4, 4-Biphenothiazine Derivatives

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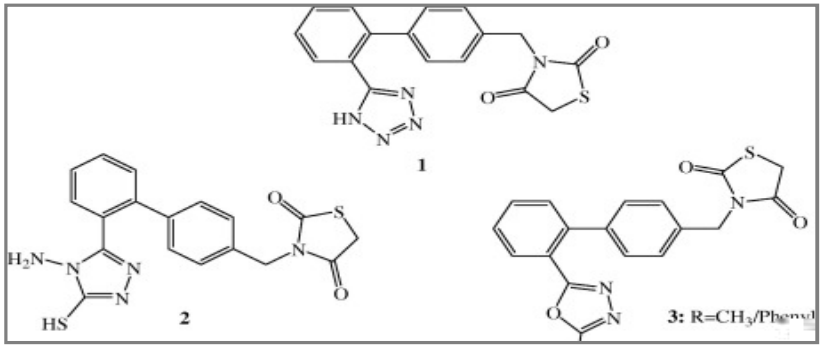
ABSTRACT

In this paper, common heterocyclic system contains nitrogen or oxygen or both plays an important role in the evolution of life. Comparison of conventional and microwave assisted synthesis of 4, 4 Biphenyl and 4, 4-Biphenothiazines is an intermediate use in the manufacture of thermoplastics such as liquid crystalline polymers, polyesters, polycarbonates and polysulfones. A new class of 4, 4-Biphenyl and 4, 4-Biphenothiazines derivatives condensed with different aldehydes under micro synthesized compounds has been characterized by IR, 1H, NMR and mass spectral data. The compounds were then evaluated for antimicrobial activities.

Graphical Abstract



Tetrazole derivatives.

Keywords: Biphenyl, Phenothiazine, Substituted aldehydes, Biological activities.

INTRODUCTION

The 4,4'-Biphenol is an organic compound which is phenolic derivative of biphenyl are estrogenic and cytotoxic .The biological activities of 4,4'- biphenol, 2,2'-biphenol and phenol are discussed in the light physicochemical parameters such as stoichiometric factor (n), BDE. Phenol is one amongst oldest antibacterial agent. The redox and acidity properties of 2, 2' and 4, 4' biphenol and the corresponding phenoxyl radicals have been determined using UV-Visible spectrophotometer pulse radiolysis and cyclic voltammeter. 4, 4' biphenol it is prepared by dealkylation of the tetra-t-butyl

derivative generated by the oxidative coupling of 2,6-di-tert-butyl phenol. Aromatic compound, are class of unsaturated chemical compounds which characterized by one or more planar rings of atoms joined by covalent bonds of two different kinds and unique stability of these compounds is referred to as aromaticity. The term aromatic originally concerned odour, but today its use in chemistry which is restricted to compounds that have particular electronic, structural, or chemical properties. There are different derivative of biphenyl name is tetrazole derivative [**1**], 1,3,4-triazole derivative [**2**] and 1,3,4-oxadiazole derivative [**3**].

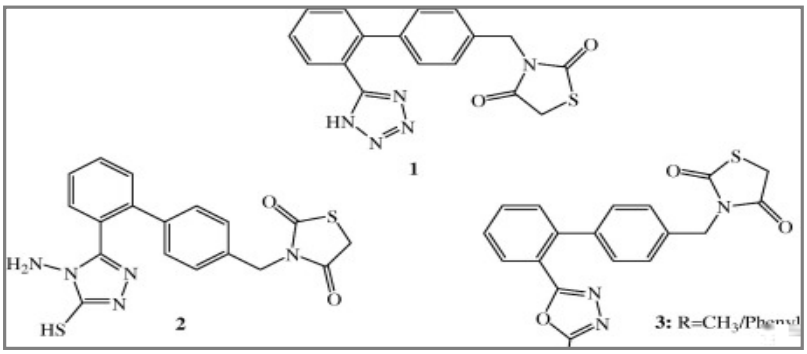


Figure 1. Tetrazole derivatives.

Polybrominated biphenyls are chemicals that were added to plastics which is used in a variety of consumer products, such as computer monitors, televisions, textiles, and plastic foams, to make them difficult to burn. Because PBBs were mixed into plastics rather than bound to them, they leave the plastic and find their way into the environment.

The intense research work in the field of medicinal chemistry has enhanced. The significance of Biphenyl moiety is as pharmacologically important compound. Some of the compounds which bearing biphenyl moiety and it possess important medicinal properties like antihypertensive and calcium channel blocker, anti-inflammatory, diuretic [**4**], anti-diabetic activity [**5**], antipsychotic [**6**] and anxiolytic activity [**7-11**]. Some of the Biphenyl hydrazide-hydrazone is also known which exhibit very good antimicrobial activity [**12-20**] Fluorinated biphenyl derivatives are essential building blocks in fluorinated liquid crystals. The fluoro-substitution of benzene rings in mesomorphic molecules may produce some changes in the melting point, viscosity, birefringence, dielectric anisotropy and other physical properties. Phenothiazine derivatives showed a wide range of different types of biological activity such as Antiemetic activity [**21**], Bactericidal activity [**22**], Antiseptic activity[**23**], Antitumor activity[**24**], Ant cholinergic activity [**25-27**], Anticonvulsant activity, Antihistamine activity, Narcobiotic activity, Analgesic activity, Antiemetic activity, Anti-inflammatory activity.

MATERIALS AND METHODS

Melting points were taken in open capillary tubes and are uncorrected. IR spectra were run in KBr pellets on a Perkin-Elmer 157 spectrometer. ^{1}HNMR spectra were recorded in $CDCl_3$ on a Bruker-Variah 300MHz FT NMR spectrometer using TMS as internal standard. Purity of the compounds was checked by TLC on silica gel G plates and the spots were located by exposure to iodine vapors. The characterization data of the compounds is given in table 1.

Synthetic method of 4, 4-dihydroxy biphenyl: 50 g of Benzedrine are dissolved in a liter of water and 60 mL of concentrated hydrochloric acid. The solution is diluted to 5 L, 200 g of concentrated sulphuric acid added, and the whole diazotized in the usual way with a solution of 37 g of sodium nitrite in 200 mL of water. The clear solution is then heated to boiling by blowing in steam,

and maintained at this temperature about twenty minutes. The solution is filtered hot, and the biphenylcrystallizes out on cooling. It forms colorless needles melting at 272°C, yield 80%.

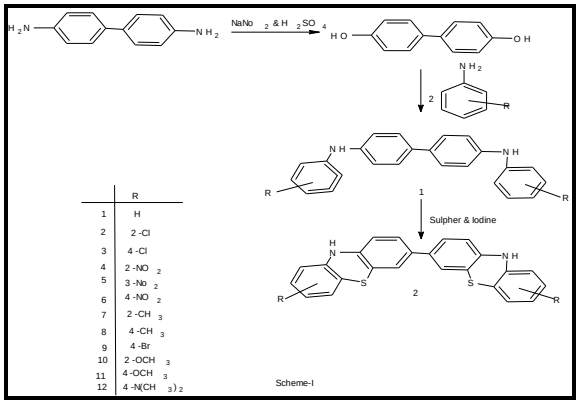
Synthesis of 4, 4-Biphenothiazines: A mixture of biphenyl-4-Benzylidene and sulphur were condensed in the presence of iodine as a catalyst about 5hrs. The product is cooled and poured ice, filtered, dried and crystallized from ethanol. Yield 64%, M.P.168°C.

Table 1. Physical characterization data and Elemental analysis of newly synthesized 4, 4-Biphenothiazines 2(a-l).

Compound	R	Molecular Formula	Relative Molecular Mass (RMM)	Melting Point (°C)	Yield (%)	C	H	N
						Calculated	Found (%)	
2a	H	$C_{24}H_{16}N_2S_2$	396	122	50	70.42 70.22	4.01 3.99	8.80 8.54
2b	2-Cl	$C_{24}H_{15}N_2S_2Cl$	430	128	56	65.69 65.53	3.54 3.44	8.21 8.10
2c	4-Cl	$C_{24}H_{15}N_2S_2Cl$	430	138	45	65.69 65.53	3.54 3.45	8.21 8.09
2d	2-NO_2	$C_{24}H_{15}N_3S_2O_2$	441	149	65	64.36 64.23	3.47 3.29	10.72 10.56
2e	3-NO_2	$C_{24}H_{15}N_3S_2O_2$	441	121	45	64.36 64.22	3.47 3.29	10.72 10.55
2f	4-NO_2	$C_{24}H_{15}N_3S_2O_2$	441	101	54	64.36 64.23	3.47 3.24	10.72 10.51
2g	2-CH_3	$C_{25}H_{18}N_2S_2$	410	169	53	70.86 69.00	4.31 4.25	8.55 8.30
2h	4-CH_3	$C_{25}H_{18}N_2S_2$	410	162	43	70.86 70.09	4.31 4.25	8.55 8.30
2i	4-Br	$C_{24}H_{15}N_2S_2Br$	465	172	44	60.44 60.01	3.26 3.25	7.55 7.31
2j	2-OCH_3	$C_{25}H_{18}N_2S_2O$	426	121	47	68.62 68.32	4.17 4.01	8.28 8.02
2k	4-OCH_3	$C_{25}H_{18}N_2S_2O$	426	126	47	68.62 68.31	4.17 4.01	8.28 8.02
2l	4-$N(CH_3)_2$	$C_{26}H_{21}N_3S_2$	409	124	48	69.21 69.10	4.65 4.10	10.76 10.69

Microwave method

Synthesis of 4, 4-Biphenothiazines: A mixture of biphenyl-4-Benzylidene and sulphur were condensed in the presence of Iodine as a catalyst in minimum quantity of anhydrous ethanol were taken in RB flask, which was placed in microwave oven and a reflux condenser was attached. The contents were subjected to microwave irradiation. The reaction was completed in 4-5 min (monitored with T.L.C at 300W. The solid obtained washed with distill water, dried and recrystallized from dioxane. Yield 80%, M.P.160°C (Table 2).



Scheme 1. Heterocyclic compounds.

Biological Activities: A slight change in the substitution pattern of Phenothiazine nucleus brings a marked difference in their biological activities. So it has been considered worthwhile to synthesize Phenothiazine incorporated heterocyclic compounds as antimicrobial agents. Antibacterial activity data of 4, 4-Biphenothiazines are presented in the table 3.

Table 2. Comparision of conventional and microwave assisted synthesis of 4, 4-Biphenothiazines 2(a-l)

Compound	Yield (%)		Reaction Time		Energy	
	Conventional	Microwave	Conventional (h)	Microwave (min)	Conventional (Temp.°C)	Microwave (Power. Watt)
2a	55	78	5	4-5	50-60	300
2b	58	83	5	4-5	50-60	300
2c	64	80	5	4-5	50-60	300
2d	50	78	5	4-5	50-60	300
2e	55	82	5	4-5	50-60	300
2f	49	85	5	4-5	50-60	300
2g	60	80	5	4-5	50-60	300
2h	53	79	5	4-5	50-60	300
2i	47	83	5	4-5	50-60	300
2j	50	67	5	4-5	50-60	300
2k	55	87	5	4-5	50-60	300
2l	62	81	5	4-5	50-60	300

Table 3. Antibacterial activity data of 4, 4-Biphenothiazines 2(a-l)

Compound	Bacteria along with zone of inhibition					
	S.aureus	*B.substilis*	*B.cereus*	*E.Coli*	*P.aeruginosa*	*P. vulgaris*
2a	10	09	08	09	10	05
2b	11	16	15	12	10	12
2c	12	14	14	13	10	15
2d	12	08	09	19	09	09
2e	13	15	10	15	15	10
2f	17	19	15	19	11	11
2g	10	07	05	-	-	-
2h	15	09	15	10	17	14
2i	12	11	09	15	16	12
2j	11	15	08	11	10	10
2k	09	11	18	12	09	09
2l	-	-	-	10	15	11
Streptomycin	23	20	24	26	20	22

Table 4. FT-IR and ^{1}H-NMR spectral Data of newly synthesized 4, 4-Biphenothiazines 2(a-l)

FT-IR	^{1}H-NMR
1642 N=CH-, 1545(C=C str), and 3178 (Ar-H),2810 (C-H str), 729 (C-Cl), 1382 NO2 sharp IR bands and broad IR bands at 3425-3442 cm-1 for (N-H str.).	2.5 (d, 1H, C-CH-Cl), 6.9-8.3(m, 2H, Ar-H), 8.88 (s, 1H,N=CH) ,8.00-8.3 (m,4H,Ar-H), 3.4(s,1H,NH). 6.57(1H, s, -CO-CH), 7.05-7.33(m, Aromatic-CH), 7.65 (1H, d, =CH-Ar). **MS**[14-16]: [M+]:[$C_{28}H_{20}ClN_3O_3$], 482.

RESULTS AND DISCUSSION

In view of these observations, it was thought worthwhile to synthesize several compounds in which 4,4-Biphenyl derivatives have been linked with moiety. The reaction sequence leading to the formation of desired heterocyclic compounds are outlined in scheme 1. The starting material of Benzedrine is dissolved in water and concentrated hydrochloric acid. The solution is concentrated sulphuric acid added, and the whole diazotized in the usual way with a solution of sodium nitrite.

Antimicrobial activity of Biphenyl: In recent years, derivatives of biphenyl are an extensively investigated class of compounds, which exhibits various important biological activities, such as anti-tuberculosis, antibacterial, antifungal and anticancer. These observations place new emphasis on the synthesis of azo derivatives a view to incorporation of a biphenyl fragment, for the evaluation of associated important antibacterial activity.

Antimicrobial activity of biphenyl hydrazine–hydrazine: Development of new chemotherapeutic agents is challenging task for the medicinal chemists and different new research programs are directed towards the design and synthesis of new drugs for their chemotherapeutic usage. Hydrazones are the compounds which consist of an important class for new drug development in order to discover an effective compound against multidrug resistant microbial infection.

Antiviral activity of biphenyl: A new co-drug, a-DDB-FNCG was synthesized via coupling of a-biphenyl dimethyl dicarboxylate and also the nucleoside analogue FNCG, through an ester bond. The anti-HBV activity and also their hepatoprotective effects of this compound were investigated both in vitro and in vivo.

Anticancer activity of biphenyl: The biphenyl compound shows the anti-tumor activity both in vitro and in vivo, which can produce apoptosis and which prevent proliferation of a cell line for colorectal cancer, lung cancer, liver cancer, breast cancer or pancreatic cancer in vitro, and inhibit tumor for the liver cancer and the colorectal cancer in vivo, so that the it can be applied in the preparation of anti-tumor drugs.

APPLICATION

These compounds has the various advantages of easy obtainment of different sources of raw materials and mild reaction conditions, simple operation of the reaction process, cheap and easy obtainment of used reagents.

CONCLUSION

It is the efficient method for the synthesis of 4, 4-Biphenothiazines **2(a-l)**. These compounds showing good result tested at 100 mg mL^{-1} concentration against *E. coli, S. aureus, Ps. acruginosa, P. vulgaris, A. niger and C. albicans* as compare to simple di-amine.

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