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Synthesis, characterization and antimicrobial activity of benzene-(1′, 4′-diimine)-substituted-4,4-10*H*-diphenothiazine derivatives

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ABSTRACT

A novel series of the benzene-(1′, 4 ′-di-imine)-4, 4-di-hydroxy-di-phenyl ***(2a-i)*** *, benzene-(1′. 4′-di-imine)-substituted-4, 4- diphenylamine* ***(3a-i)*** *and benzene-(1′, 4′-di-imine)-substituted-10H-di- phenothiazine* ***(4a-i)*** *were prepared by the reaction of 1, 4-di-imine with different aromatic aldehydes in excellent yield. Elemental analysis, 1R, H^1NMR, C^{13}NMR and mass spectral data established identification of the compounds* ***(4a-i)*** *was evaluated for their antimicrobial & antifungal activity.*

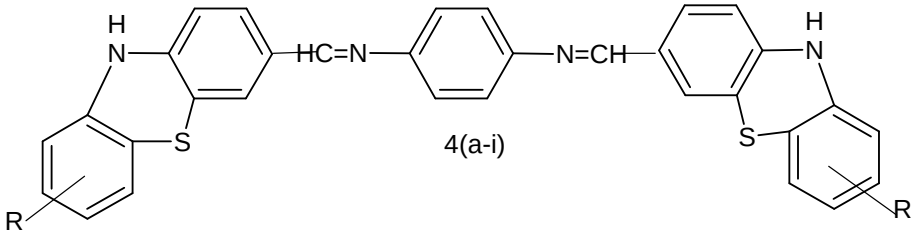
INTRODUCTION

Schiff bases are typically formed by the condensation of a primary amine & an aldehyde the resultant functional group RHC=N-R is called imine & is particularly for binding metal ions via N- atom lone pair. Phenothazines are pharmaceutical active compounds & have diverse biological application their anti inflammatory and Tranquillizer properties are widely reported. Various phenothiazines have been reported as important antifungal[1], anti-tumor[2], bactericidal and anti-histamine properties[3-5]. Slight modification in phenothiazine nucleus causes marked difference in activity6 and therefore phenothiazine with varied substituents arc being synthesized and as a better medical agents Phenothiazine derivatives possess diverse biological activities like antiparkinsonian[7-8], anticonvulsant [9], antihistaminic[10], antihelmatic[11], antiviral[12], antiparasitic[13] and CNS depressant[14].

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. H NMR 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 vapours. The characterization data of the compounds is given in **Table –II.**

Table – II Characterization data of compounds 4a –i



Comp.	R★	Mol. Formula	M. Pt (°C)	RF Value Eluent*	% Yield	Analysis Found (Calcd)%		
						C	H	N
4a	H	$C_{32}H_{22}N_4S_2$	152°	0.90	70	79.1 (79.3)	5.5 (5.4)	7.1 (7.0)
4b	2-OH	$C_{30}H_{24}N_4O_2S_2$	182°	0.71	65	67.5 (67.4)	4.7 (4.6)	6.0 (6.1)
4c	3-OH	$C_{30}H_{24}N_4O_2S_2$	137°	0.75	67	67.5 (67.4)	4.7 (4.6)	6.0 (6.1)
4d	4-OH	$C_{30}H_{24}N_4O_2S_2$	153°	0.82	62	67.5 (67.4)	4.7 (4.6)	6.0 (6.1)
4e	2-NO_2	$C_{30}H_{24}N_6O_2S_2$	142°	0.77	57	64.4 (64.1)	4.1 (4.0)	11.5 (11.4)
4f	3-NO_2	$C_{30}H_{24}N_6O_2S_2$	136°	0.54	62	64.4 (64.1)	4.1 (4.0)	11.5 (11.4)
4g	4-NO_2	$C_{30}H_{24}N_6O_2S_2$	129°	0.86	52	64.4 (64.1)	4.1 (4.0)	11.5 (11.4)
4h	2-Cl	$C_{30}H_{24}N_4S_2Cl$	143°	0.75	64	67.4 (67.3)	4.3 (4.2)	6.9 (6.2)
4i	4-Cl	$C_{30}H_{24}N_4S_2Cl$	157°	0.78	59	67.4 (67.3)	4.3 (4.2)	6.9 (6.2)

* *Eluents for TLC: Benzene – acetone (6 : 4) for 4a-i*

★ *Solvent for crystallization; aq. ethanol for 4a-i.*

General procedure for preparation of compounds

I. Synthesis of benzene-(1′, 4′-di-imine)-4, 4-di-hydroxy-di-phenyl.

A mixture of 1, 4 di-imine (1 mole) and 4-hydroxy benzaldehyde (2 mole) in ethanol (25 ml) was refluxed for 6 hrs. A resulting solid material reported which was crystallized from DMF similarly other compounds were also prepared.

II. Synthesis of benzene-(1′. 4′-di-imine)-substituted-4, 4- diphenylamine.

A mixture of Benzene-(1′, 4′ -di-imine)-4, 4-di-hydroxy-di-phenyl **1** (1 mole) & different anilines (2 mole) methanol was refluxed for 3 hrs and resulting solid was washed and crystallized from DMF similarly other compound were also prepared.

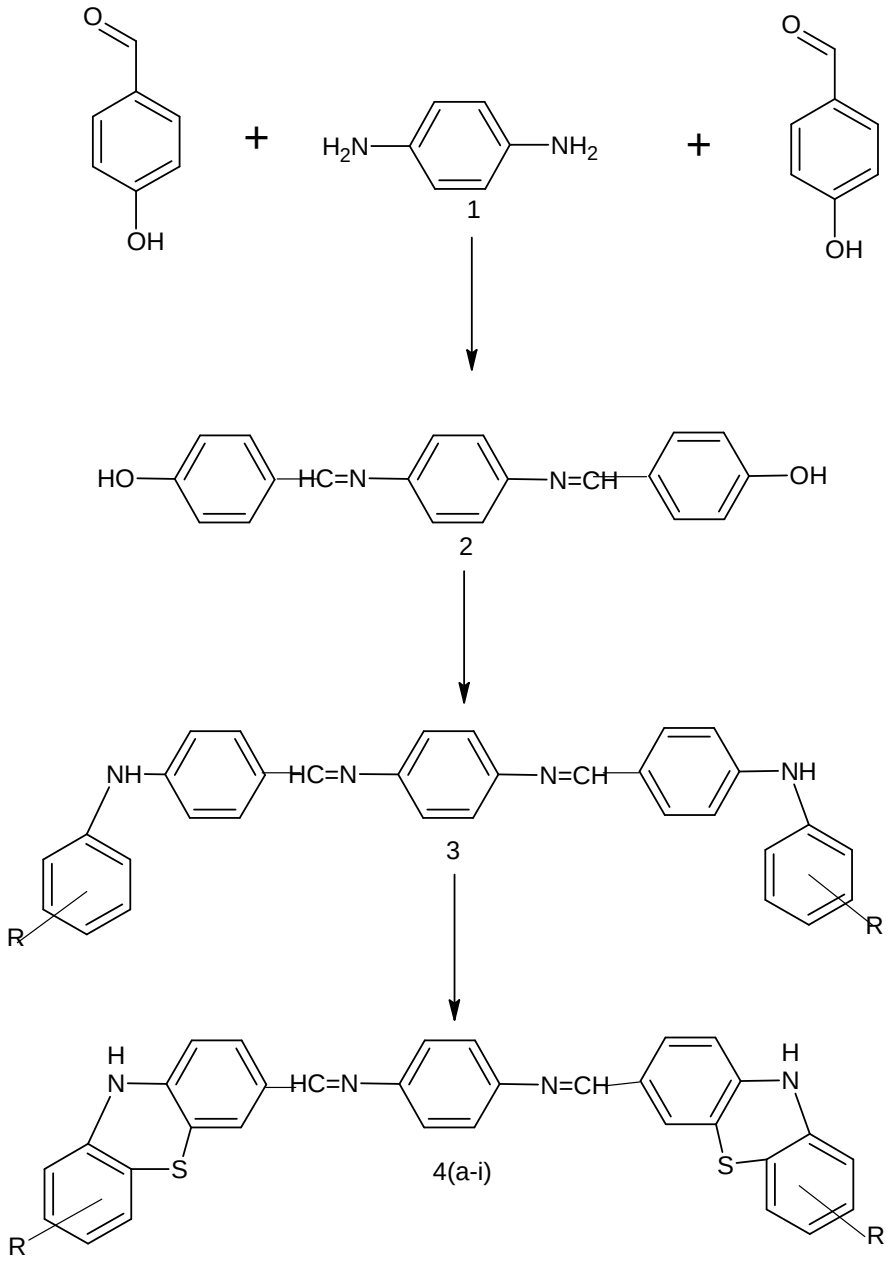
Ill. Synthesis of benzene-(1′, 4′–di–imine)-substituted-10*H*-4, 4-10*H*-di-phenothiazine.

A mixture of Benzene-(1′. 4′-di-imine)-substituted-4, 4- diphenylamine (0.01 mole), sulphur (0.1 mole) and Iodine (0.5 g) was heated at 1200C in an oil bath for 2 hr. reaction mixture of Benzene-(1′, 4′–di–imine)-substituted-10*H*-4, 4-di-phenothiazine was obtain, then crushed into fine powder & washed with ethanol and recrystallized from DMF.

4a: (M. P. 152° yield 70 %.). IR(KBr): 3322 (N-H-phenothiazine), 2945 (C-H-Aromatic stretch), 1792.9, 1714 , 1650, 1524, 783 (C-S); H^1NMR (300MHz DMSO) δ 2.34, 4.22, 3.52; ^{13}C NMR(300MHz, DMSO-d_6) 14.1, 13.2, 13.6, 22.0, 37.9, 38.2, 34.5, 39.4, 40.0, , 58.5, 76.8, 77.2, 77.6, 111.8, 159.1, 126.2, 137.3, 160.2, 162.1.

4b: (M. P. 182° yield 65%). IR(KBr): 3333 (N-H-phenothiazine), 2944 (C-H-Aromatic stretch), 1742.9, 1714, 1640, 1552, 1332, 745 (C-S); H^1NMR (300MHz DMSO) δ 2.46, 4.28, 3.54; ^{13}C NMR(300MHz, DMSO-d_6), 11.3, 13.4, 13.4, 27.0, 38.9, 39.2, 39.5, 39.7, 40.0, 40.3, 58.5, 76.8, 77.2, 77.6, 111.8, 119.1, 126.2, 134.3, 162.2, 165.5.

4c :(M. P.137° yield 67 %.). IR(KBr): 3444 (N-H-phenothiazine), 2957 (C-H-Aromatic stretch), 1752.9, 1754, 1650, 1555, 1336, 785 (C-S); H^1NMR (300MHz DMSO) δ 2.56, 4.58, 3.55;^{13}C NMR(300MHz, DMSO-d_6) 11.5, 13.5, 13.9, 27.0, 38.9, 34.2, 39.5, 39.7, 40.0, 40.3, 58.5, 76.8, 77.2, 77.6, 111.8, 119.1, 126.2, 137.3, 162.2, 164.6.



R=H, 2-OH, 4-OH, 2-NO_2, 4-NO_2, 3-NO_2, 2-Cl, 4-Cl, -OCH_3, -$N(CH_3)_2$.

Scheme-I

4d: (M. P. 153° yield 62 %.). IR(KBr): 3327 (N-H-phenothiazine), 2967 (C-H-Aromatic stretch), 1762.9, 1714 , 1650, 1362, 765 (C-S), 706 ; H^1NMR (300MHz DMSO) δ 2.66, 4.28, 3.54;^{13}C NMR(300MHz, DMSO-d_6), 11.3, 13.4, 13.9, 27.0, 38.9, 34.2, 39.5, 39.7, 40.0, 46.3, 58.5, 76.8, 77.2, 77.6, 111.8, 119.1, 126.2, 137.3, 166.2, 165.3.

4e: (M. P. 142° yield 57 %.). IR(KBr): 3360 (N-H-phenothiazine), 2966 (C-H-Aromatic stretch), 1792.9, 1714, 1650, 1362, 785 (C-S) 766; H^1NMR (300MHz DMSO) δ 2.56, 4.28, 3.54; ^{13}C NMR(300MHz, DMSO-d_6), 11.3, 13.6, 13.9, 26.0, 38.9, 39.2, 39.5, 39.7, 40.0, 40.3, 58.5, 76.8, 77.2, 77.6, 111.8, 119.1, 126.2, 137.6, 162.2, 166.1.

4f: (M. P. 136° yield 62 %.). IR(KBr): 3326 (N-H-phenothiazine), 2967 (C-H-Aromatic stretch), 1792.9, 1714, 1650, 1332, 785,726; H^1NMR (300MHz DMSO) δ 2.56, 4.28, 3.54; ^{13}C NMR(300MHz, DMSO-d_6), 11.3, 13.4, 12.9, 25.0, 38.9, 39.2, 39.5, 39.7, 40.0, 40.3, 58.5, 76.8, 77.2, 77.6, 111.8, 119.1, 123.2, 137.3, 164.2, 165.3.

4g: (M. P. 129° yield 52 %.). IR(KBr):3552 (N-H-phenothiazine), 2959 (C-H-Aromatic stretch), 1792.9, 1714, 1650, 1332, 755 (C-S); H^1NMR (300MHz DMSO) δ 2.56, 4.25, 3.54; ^{13}C NMR(300MHz, DMSO-d_6), 11.3, 13.4, 13.9, 27.0, 38.9, 35.2, 39.5, 39.7, 40.5, 40.3, 58.5, 75.8, 77.2, 77.6, 111.8, 115.1, 126.2, 137.3, 162.2, 165.0.

4h: (M. P. 143° yield 64 %.). IR(KBr): 3390 (N-H-phenothiazine), 2967 (C-H-Aromatic stretch), 1792.9, 1714, 1670, 1379, 775 (C-S). H^1NMR (300MHz DMSO) δ 2.56, 4.28, 3.54, ^{13}CNMR(300MHz,DMSOd_6), 11.3,13.4,13.9,27.0,38.9,39.2,39.5,39.7,40.0,40.3,57.5,6.8,77.2,77.6,111.8,119.1,126.2,137.3,167.2.

4i: (M. P. 157^0 yields 59 %.). IR(KBr): 3335(N-H-phenothiazine), 2961 (C-H-Aromatic stretch), 1742.9, 1744, 1650, 1332, 785 (C-S), 518; H^1NMR(300MHz DMSO) δ 2.54, 4.28, 3.54; ^{13}CNMR(300MHz,DMSOd_6), 11.4,13.4,13.9,7.0,38.9,9.2,39.5,39.7,40.0,40.3,58.5,76.8,77.2,77.6,111.4,119.1, 124.2,147.

RESULTS AND DISCUSSION

In view of these observations, it was thought worthwhile to synthesize several compounds in which benzene-(1′, 4′-di-imine)-4, 4-di-hydroxy-di-phenyl, benzene-(1′. 4′-di-imine)-substituted-4, 4- diphenylamine, benzene-(1′, 4′–di–imine)-substituted-10*H*-4, 4-10*H*-di-phenothiazine have been linked with new moiety

Table I-Antibacterial and antifungal activities of compounds 4a-i

	Antibacterial activity			Antifungal activity	
Compd	*S .aureus*	*B. substillis*	*E. coli*	*C. albicans*	*A. niger*
4 a	++	++	+	++	++
4b	+	+++	+++	+++	+++
4c	-	++	+++	+++	++
4d	+++	++	++	++	++
4e	+	++	+	+++	+++
4f	++	+++	++	+++	++
4 g	+++	++	-	++	++
4 h	++	-	+	-	+++
4i	+++	++	+++	+++	-
SM	+++	+++	++++		
GF				++++	+++

SM (Streptomycin) and GF (Griesofulvin). The inhibition diameter in Mm: (-) <6, (+) 7-9, (++) 10-15,(+++) 16-22, (++++) 23-28.

The reaction sequence leading to the formation of desired heterocyclic compounds are outlined in **Scheme-I**. The starting material benzene-(1′, 4′-di-imine)-4, 4-di-hydroxy-di-phenyl **(2a-i)** was prepared by the reaction of substituted aldehydes with 1, 4-di-imine in presence of ethanol. Synthesis of benzene-(1′. 4′-di-imine)-substituted-4, 4- diphenylamine **(3a-i)** by reaction of benzene-(1′, 4′-di-imine)-4, 4-di-hydroxy-di-phenyl **(2a-i)** with different aromatic aniline in presence of ethanol. The substituted benzene-(1′, 4′–di–imine)-substituted-10*H*-4, 4-10*H*-di-phenothiazine (4a-i) was prepared by reaction of benzene-(1′. 4′-di-imine)-substituted-4, 4- diphenylamine **(3a-i)**

with sulphur and Iodine in the presence of DMF. The IR, H^1NMR, C^{13} NMR, Mass spectra of the benzene-(1′, 4′–di–imine)-substituted-10*H*-4, 4-10*H*-di-phenothiazine **(4a-i*)*** were recorded.

Biological studies

Comparative study of 1, 4 di-imine with different aromatic aldehydes & Benzene-(1′, 4′-di-imine)-substituted-4,4-10*H*-di-phenothiazine **(4a-i)** have been observed by using Norfloxacine and Griseofulvine as standards. The enhancement in biological activity of compound (1) as compared with the newly synthesized **(4a-i)** has been observed. The synthesized compounds were tested at 100g/ml concentration against Escherichia *coli*, Staphylococcus *aureus*, Ps. *acruginosa*, P.*vulgaris*, A. *niger* and C. *albicans* for its antibacterial and antifungal screening as shown in **Table-I.**

CONCLUSION

It is concluded for scheme that and efficient method for the synthesis of Benzene-(1, 4–di–imine)-substituted-10*H*-4′, 4′-di-phenothiazine **4a-i** with excellent yield have been developed. The result of this study indicate that the present synthetic method is a simple efficient, inexpensive and easy synthesis of biologically active compounds Benzene-(1, 4–di–imine)-substituted-10*H*-4′, 4′-di-phenothiazine **4a-i**. These compounds showing good result tested at 100 mg/ml 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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