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NOVEL SYNTHESIS OF SUBSTITUTED-1-(7-NITRO-10*H*-PHENOTHIAZINE-3-YL)-3-(4-NITROPHENYL) PROP-2-EN-1-ONE

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ABSTRACT
Synthesis of substituted 3-(4- amino phenyl)-1-(substituted phenyl) prop-2-en-1-one (1.1a-l) was prepared by 4-aminobenzaldehyde and 1-(substituted) phenyl and 1-(4-hydroxyphenyl)-3-(4-nitrophenyl) prop-2-en-1-one (1.2f-l) were synthesis by 4-nitro benzaldehyde and 4-hydroxy phenyl were mixed and dissolved in ethanol. 1-(substituted) phenyl 3-(4-[4-(nitro phenyl amino) Benzylidene] amino} phenyl) prop-2-en-1-one (3.1a-l) synthesis by a mixture of 1-substituted-phenyl-3-{4-[(4-hydroxybenzylidene)-amino]-phenyl}-prop-2-en-1-one (2.1) and 4-nitro aniline containing anhydrous $ZnCl_2$ in absolute ethanol is reported in this paper. The structures of synthesized products have been characterized on the basis of FT-IR, ^{1}HNMR, FAB-MS and elemental analysis. The title compounds are found to have antibacterial and antifungal activities.

KEYWORDS: 10*H*-Phenothiazine, Benzylideneacetophenone, Schiff's base etc.

INTRODUCTION

Heterocyclic compounds occur vary widely in nature and essential to life. Nitrogen containing heterocyclic molecules constitutes the largest portion of chemical entities, which are part of many natural products, fine chemicals and biologically active pharmaceuticals vital for enhancing quality of life. 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.

Various derivatives of substituted phenothiazines have been synthesized by several investigations and have been reported to exhibit a wide range of pharmalogical activities. Heterocyclic compound bearing nitrogen and sulphur atom are reported to show a broad spectrum of biological activities. It is also reported that the N-substitution heterocyclic nucleus enhances the anti-inflammatory activity.

Benzylideneacetophenone and their derivatives find application as artificial sweeteners[1-4], Scintillator[5], polymerization catalyst[6-7], fluorescent whitening agent[8],organic brightening agent[9-10], stabilizer against heat, visible light, ultraviolet light and aging.[11-15] 3,2',4 Heterocyclic compounds occur vary widely in nature and essential to life. Nitrogen containing heterocyclic molecules constitutes the largest portion of chemical entities, which are part of many natural products, fine chemicals and biologically active pharmaceuticals vital for enhancing quality of life. 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.

Various derivatives of substituted phenothiazines have been synthesized by several investigations and have been reported to exhibit a wide range of pharmalogical activities. Heterocyclic compound bearing nitrogen and sulphur atom are reported to show a broad spectrum of biological activities. It is also reported that the N-substitution heterocyclic nucleus enhances the anti-inflammatory activity.

6'-tetrahydroxy-4-propoxy-dihydrochalcone-4-β'-neohesperdoside[16] has been used as synthetic sweetener and is 2200 times sweeter than glucose. They contain a keto-ethylenic group and are therefore reactive towards several reagents e.g. (a) phenyl hydrazine, (b) 2-amino thiophenol etc. The Benzylidene acetophenone have been found useful in elucidating structure of natural products like hemlock tannin[17], cyanomaclurin[18], ploretin[19], eriodictyol and homo iodictyol[20], naringenin[21] etc. The benzylidene acetophenone are associated with different biological activities like Insecticidal[22], anticancer[23], anti-inflammatory[24], bactericidal[25], fungicidal[26], Antiviral[27], antitumor[28], antimalarial[29] and antiulcer[30]

Schiff's base has large number of synthetic used in organic chemistry. Acylation of Schiff's base[31-32] by acid unhydride, acid chlorides and acyl cyanides is initiated by attack at the nitrogen atom and leads to net addition of the acylating agents to the carbon nitrogen double bond. Reaction of these types has been put to good use in natural product synthesis.

Schiff's bases appear to be an important intermediate in number of enzymatic reactions involving interaction of an enzyme with an amino or a carbonyl group of the substrate.[33] One of the most important types of catalytic mechanism is the biochemical process which involves the condensation of primary amine in an enzyme usually that of a lysine residue, with carbonyl group of substrates to form an amine, or Schiff's base. Transition metal complexes of such ligand are important enzyme model. The rapid development of these ligand resulted in an enhance research activity in the field of coordination chemistry leading to very interesting conclusions. Many biologically important Schiff's base have been reported in the literature possessing antibacterial[34-46], antifungal[47-49], antimicrobial[50-54], anticonvulsant[55], anti HIV[56], anti-inflammatory[57] and antitumor[58-64] activities also certain polymeric Schiff's bases have been found to posses antitumor activity.[65]

10H-Phenothiazine (PTZ) is a tricycle aromatic compound linked via bridges of sulfur and nitrogen. In this ring system it consists of two benzene rings ortho fused to 1, 4 – thiazine ring. It is also called as Dibenzothiazine, Thiodiphenylamine. Phenothiazine derivatives showed a wide range of biological activity which are Antihelmatic activity[10-18] Bactericidal activity[66] Antiseptic activity Antitumor activity Ant cholinergic activity Anticonvulsant activity.

RESULT AND DISCUSSION

In view of these observations, it was thought worthwhile to synthesize several compounds in which 3-(4- amino phenyl)-1-(substituted phenyl) prop-2-en-1-one, 3-(4-aminophenyl)-1-(4-chlorophenyl) prop-2-en-1-one, 4-amino Benzylidene acetophenone, 1-(4-hydroxyphenyl)-3-(4- substituted phenyl) prop-2-en-1-one, 1-(4-hydroxyphenyl)-3-(4-nitrophenyl) prop-2-en-1-one, 4-hydroxy Benzylidene acetophenone, 1-(4-hydroxyphenyl)-3-(4-nitrophenyl) prop-2-en-1-one, 3-(4-amino phenyl)-1-(substituted phenyl) prop-2-en-1-one, 3-(4-aminophenyl)-1-(4-chlorophenyl) prop-2-en-1-one, 3-{4-[4-hydroxybenzylidene) amino] phenyl}-1-phenylprop-2-en-1-one, 1-(4-chlorophenyl)-3-{4-[-(4-hydroxybenzylidene) amino] phenyl} prop-2-en-1-one, 1-(4-chlorophenyl)-3-{4-[-(4-hydroxybenzylidene) amino] phenyl}prop-2-en-1-one, 1-{4chlophenyl 3-(4-[4-(nitro phenyl amino) Benzylidene] amino phenyl)} prop-2en-1-one have been linked with new moiety.

The reaction sequence leading to the formation of desired heterocyclic compounds are outlined in Scheme-I. The starting material 3-(4- amino phenyl)-1-(substituted phenyl) prop-2-en-1-one (1.1a-1.1l) was prepared by 4-aminobenzaldehyde and 1-(substituted) phenyl ethanone were mixed and dissolved in minimum amount of ethanol. 1-(4-hydroxyphenyl)-3-(4-nitrophenyl) prop-2-en-1-one compound (1.2f-1.2l) were synthesis by 4-nitro benzaldehyde and 4-hydroxy phenyl ethanone were mixed and dissolved in minimum amount of ethanol. 1-(substituted) phenyl 3-(4-[4-(nitro phenyl amino) Benzylidene] amino} phenyl) prop-2en-1-one (3.1a-3.1l) synthesis by a mixture of 1-(substituted) phenyl 3-{4-[(4-hydroxybenzylidene) amino] phenyl} -prop-2-en-1-one compound (2.1) and 4-nitro aniline (Equimolar amount) containing anhydrous $ZnCl_2$ (1gm) in absolute ethanol.

BIOLOGICAL ACTIVITIES

Antibacterial and Antifungal activity

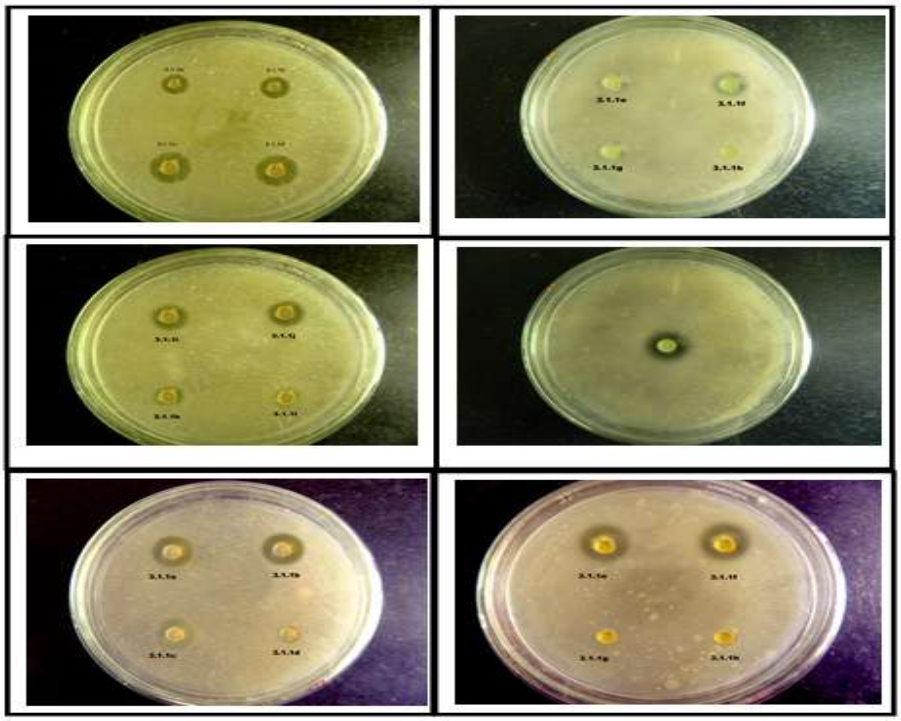
The culture of the organism was inoculated in sterilized medium. All the operations were carried out under aseptic condition. Sterile medium was melted on water bath and kept at 45^0C in constant temperature water bath. In each sterile Petridis molten medium was added so that thickness was approximately 4-5mm and subculture organism under study was inoculated. The inoculated dishes were allowed to set for 30 min at room temperature. Cups of 10mm. diameter were then made with the help of sterile stainless steel borer and 0.1 ml of stalk solution was added to each cup. Petri dish were kept in refrigerator for 30 minutes so as to allow diffusion of the solution in the medium and then incubated at 37^0c for 24 hrs for antibacterial activities and 72 hrs for antifungal activities. Simultaneously control was maintained by employing 0.1ml of DMSO which does not reveal any inhibition. Zone of inhibition produced by test compound were measured in mm in various axis and average reading was considered. The data of antibacterial and antifungal tests are depicted in following tables.

Table No.1 Antibacterial activity data of 1-4substituted phenyl-[(10*H*-phenothiazin-3-ylmethylidene) amino] phenyl} prop-2-en-1-one 3.1.1

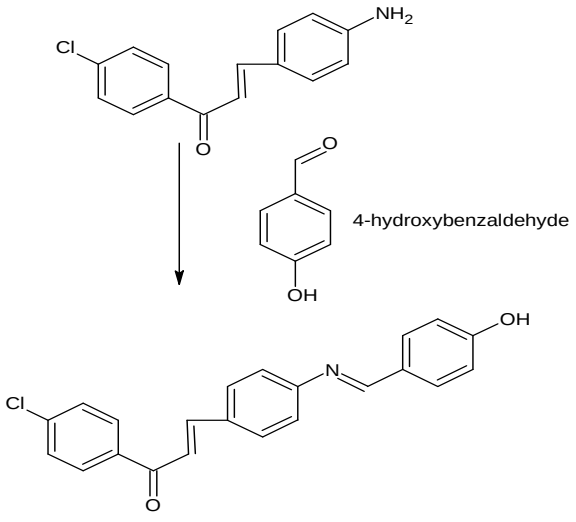
Compound	Bacteria along with zone of inhibition					
	S.aureus	B.substilis	B.cereus	E.Coli	P.aeruginosa	*P. vulgaris*
3.1.1a	09	06	09	09	10	05
3.1.1b	11	16	15	12	10	12
3.1.1c	12	14	14	13	10	15
3.1.1d	12	08	09	19	09	09
3.1.1e	13	15	10	15	15	10
3.1.1f	17	19	15	19	11	11

3.1.1g	10	07	05	-	-	-
3.1.1h	15	09	15	10	17	14
3.1.1i	12	11	09	15	16	12
3.1.1j	11	15	08	11	10	10
3.1.1k	09	11	18	12	09	09
3.1.1l	-	-	-	10	15	11
Streptomycine	23	20	24	26	20	22

As noted in tables maximum zone of inhibition were found to inhibit the growth of all tested strains of bacteria and fungi. It may be due to more penetrating power of compounds to the cell wall of bacteria, which prevents the biosynthesis of peptidoglycan or may find better fit the receptor site as compared to other compounds. Through the compounds exhibited antibacterial and antifungal activity against all the tested strains.



Photographs showing zone of inhibition by 1-4 substituted phenyl-[(7-nitro 10*H*-phenothiazin-3-ylmethylidene) amino] phenyl} prop-2-en-1-one compound 3.1.1 against bacteria E. Coli Photograph showing zone of inhibition by slandered against bacteria E. Coli.



SCHEME 1

EXPERIMENTAL

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 vapors. The characterization data of the compounds is given in **Table.**

1. Synthesis of 3-(4- amino phenyl)-1-(substituted phenyl) prop-2-en-1-one (1.1)

Equimolar quantities (0.05mol) of 4-aminobenzaldehyde and 1-(substituted) phenyl ethanone were mixed and dissolved in minimum amount of ethanol. To this, solution aqueous sodium hydroxide solution (50%, 7.5 ml) was added slowly drop wise with constant stirring at

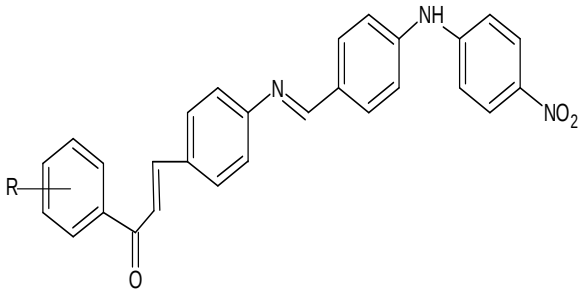
room temperature till a dark yellow mass was obtained. The reaction mixture was kept 10-12 hr. and acidified with dilute hydrochloric acid, and the solid that separated was isolated by filtration, washed with cold water and dried and it was crystallized by ethanol.

2. Synthesis of 3-(4-aminophenyl)-1-(4-chlorophenyl) prop-2-en-1-one (1.1c) by Claisen-Schmidt condensation

Equimolar quantities (0.05mol) of 4-aminobenzaldehyde and 1-(4-chloro) phenyl ethanone were mixed and dissolved in minimum amount of ethanol. To this, solution aqueous sodium hydroxide solution (50%, 7.5 ml) was added slowly drop wise with constant stirring at room temperature till a dark yellow mass was obtained. The reaction mixture was kept 10-12 hr. and acidified with dilute hydrochloric acid, and the solid that separated was isolated by filtration, washed with cold water and dried and it was crystallized by ethanol. Yield 10g, 68%, m. p.180^{0}C

3. Microwave Irradiation Method: Equimolar quantities of 4-aminobenzaldehyde and 1-(4-chloro) phenyl ethanone were mixed and dissolved in minimum amount of ethanol (15ml).To this K2CO3 was added and the reaction mixture was placed in microwave oven and refluxed at power level-1(210watt) for 10 min. In between the completion of the reaction was monitored by TLC. After completion of the reaction, ethanol was removed by distillation and the residue was poured into crushed ice. Then it was made alkaline by using 10% NaOH to get the solid product (Compound 1.1c). The product was filtered, dried and recrystallized from ethanol. Yield 80%.

Table: 1. Physical characterization data and Elemental analysis of newly synthesized compound 3.1a-3.1l



Compound	R	Molecular Formula	Relative Molecular Mass (RMM)	Melting Point (o C)	Yield (%)	C	H	N
						Calculated Found (%)		
3.1a	H	$C_{28}H_{21}N_3O_3$	447	198	65	75.15 74.78	4.73 4.65	9.39 9.23
3.1b	2-Cl	$C_{28}H_{20}ClN_3O_3$	481	195	69	69.78 69.66	4.18 4.00	8.72 8.55
3.1c	4-Cl	$C_{28}H_{20}ClN_3O$	481	221	66	69.78 69.66	4.18 4.01	8.72 8.54
3.1d	2-NO_2	$C_{28}H_{20}N_4O_5$	492	156	59	68.29 68.21	4.09 4.00	11.38 11.21
3.1e	3-NO_2	$C_{28}H_{20}N_4O_5$	492	161	52	68.29 67.89	4.09 4.00	11.38 11.19
3.1f	4-NO_2	$C_{28}H_{20}N_4O_5$	492	152	60	68.29 67.89	4.09 4.00	11.38 11.19
3.1g	2-CH_3	$C_{29}H_{23}N_3O_3$	461	201	70	75.47 75.09	5.02 4.91	9.10 9.76
3.1h	4- CH_3	$C_{29}H_{23}N_3O_3$	461	220	65	75.47 75.23	5.02 4.99	9.10 9.00
3.1i	4-Br	$C_{28}H_{21}N_3O_4$	463	201	70	72.56 71.77	4.57 4.42	9.07 9.01
3.1j	2-OCH_3	$C_{29}H_{23}N_3O_4$	477	187	68	72.94 72.75	4.85 4.86	8.80 8.48
3.1k	4-OCH_3	$C_{29}H_{23}N_3O_4$	477	165	65	72.94 72.74	4.85 4.78	8.80 8.45
3.1l	4-$N(CH_3)_2$	$C_{29}H_{23}N_4O_3$	475	198	63	73.25 73.10	4.88 4.21	11.78 11.80

Table 2:- Comparisation of conventional and microwave assisted synthesis of compound 3.1a to 3.1l

COMP.	YIELD (%)		REACTION TIME		ENERGY	
	Conventional	Microwave	Conventional (hr)	Microwave (min)	Conventional (Temp. ^{o}C)	Microwave (Power. Watt)
3.1a	62	87	5	5-7	50-60	400
3.1b	48	88	5	5-7	50-60	400
3.1c	60	77	5	5-7	50-60	400
3.1d	52	72	5	5-7	50-60	400
3.1e	48	80	5	5-7	50-60	400
3.1f	50	82	5	5-7	50-60	400
3.1g	59	85	5	5-7	50-60	400
3.1h	50	85	5	5-7	50-60	400
3.1i	44	80	5	5-7	50-60	400
3.1j	49	79	5	5-7	50-60	400
3.1k	43	77	5	5-7	50-60	400
3.1l	60	80	5	5-7	50-60	400

Characterization of the compound 3.1c

FT- IR. The, β-unsaturated carbonyl group (C=O) usually appear as a prominent band at 1669 cm-1, 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.).

^{1}H-NMR in DMSO (d, ppm): 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: [M+]: [$C_{28}H_{20}ClN_3O_3$], 482.

Elemental analysis: $C_{28}H_{20}ClN_3O_3$: C, 69.78, H, 4.18, N, 8.72. Found C, 69.66, H, 4.01, N, 8.54.

Mass spectral data of compound 3.1.1c m/z 511, 257, 256, 244, 269, 228, 138, 112.

Characterization of the compound 3.1.1c

FT- IR. 1706 (C=O), 1664 (N=CH-), and 3203 (Ar-H), 1550 (C=C), 869 (C-Cl) , 1336 NO2 sharp IR bands at and broad IR bands at 3439-3476 cm-1(NH Streching), C–S–C str.1336 , C–N str. 1243

^{1}H-NMR in DMSO (d, ppm) 2.55 (s, 1H, C-CH-Cl), 8.0-8.4 (m, 2H, Ar-H), 8.9 (s, 1H,N=CH),7.6-7.66 (m,4H,Ar-H), 3.44 (s,1H,NH), 7.09 (1H, s, -CO-CH), 7.05-7.33(m, Ar-CH), 7.88 (1H, d, =CH-Ar).

MS: [M+]: [$C_{28}H_{18}ClN_3O_3S$], 511.

Elemental analysis: $C_{28}H_{18}ClN_3O_3S$: C, 65.69, H,3.54, N, 8.21. Found C, 65.53, H, 3.45, N, 8.09.

Mass spectral data of compound 3.2f m/z 389, 253, 105, 176, 137.

Characterization of the compound 3.2f

FT- IR. The α, β-unsaturated carbonyl group (C=O) usually appear as a prominent band at 1680 cm-1, 1545 (C=C str), and 3178 (Ar-H), 2814 (C-H str), 1386 NO_2 sharp IR bands and broad IR bands at 3500-3570 cm-1 for (N-H str.).

^{1}H-NMR in DMSO (d, ppm): 8.00-8.3 (m,4H,Ar-H), 3.4 (s,1H,NH), 6.7 (1H, s, -CO-CH), 7.05-7.33(m, Aromatic-CH), 7.65 (1H, d, =CH-Ar).

MS: [M+]: [$C_{21}H_{15}N_3O_5$], 389 (100%)

Elemental analysis: [$C_{21}H_{15}N_3O_5$]: C, 64.78, H, 3.88, N, 10.79.FoundC, 64.72, H, 3.77, N, 10.71.

Mass spectral data of compound 3.2.1f m/ z 419, 271, 244, 214, 176, 169.

Characterization of the compound 3.2.1f

IR: The IR spectra of the compounds were recorded on SHIMADZU FTIR using KBr discs and the values are expressed in cm-1. 1546 (C=C str), 3128 (Ar-CH). 1545 (CH=CH), 855 (C-Cl), 1678 (C=O), 3485 N-H str.

^{1}H-NMR: The NMR spectrum of the product exhibited signals at δH 6.6-6.8 (2H,in ethylenic –CO-CH=CH-,dd), 7.6-7.8 (m,4H,Ar-H), 3.4 (s,1H,NH), 7.5 (1H, s, -CO-CH), 7.05-7.33(m, Aromatic-CH), 7.65 (1H, d, =CH-Ar).
MS [M+]: [$C_{21}H_{13}N_3O_5S$], 419.
Elemental analysis: $C_{21}H_{13}N_3O_5S$: C, 60.69, H,3.20, N, 6.85. Found C, 60.40, H,3.01, N, 6.66.

CONCLUSION

A series of 2, 5-Disubstituted phenyl-6-substituted phenyl sulfonamide - pyrimidines **(2a-m)**, 2, 5-Disubstituted phenyl-6-substituted Azomethine - pyrimidines **(3a-m)**, substituted 2, 5-Disubstituted phenyl-6-azo-pyrimidines **(4a-m)**, substituted 2, 5-Disubstituted phenyl-6-N-phenylthiourea-pyrimidines **(5a-m)** from 2, 5-Disubstituted phenyl-6-amine-pyrimidines **(1a-m)**. These compounds were screened for their antibacterial activity against *S. aureus* and *E. coli* as well as for their antifungal activity against *C. albicans* and *A. niger* Showing good result.

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