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Note

Synthesis, characterization and *in vitro* anti-JEV activity of N-[*p*-{3'-(2'-aryl-4'-oxo-1',3'-thiazolyl)} diphenyl]-7-hydroxy-4-methyl-2-oxoquinolines

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The synthesis of N-[*p*-{3'-(2'-aryl-4'-oxo-1',3'-thiazolyl)}diphenyl]-7-hydroxy-4-methyl-2-oxoquinolines **4** have been achieved starting from resorcinol. 7-hydroxy-4-methylcoumarin(4-methylumbelliferone) **1** is obtained by the reaction of resorcinol with ethylacetoacetate. **1** on treatment with benzidine gives N-(*p*-aminodiphenyl)-7-hydroxy-4-methyl-2-oxoquinoline **2**. **2** on treatment with different aryl aldehydes in presence of glacial acetic acid furnishes N-(*p*-arylidinoamino-diphenyl-7-hydroxy-4-methyl-2-oxoquinolines **3a-e**. The latter on treatment with thioglycollic acid in presence of anhydrous $ZnCl_2$ yields **4a-e**. The *in vitro* anti-JEV activity of these compounds has also been evaluated.

Keywords: N-(*p*-aminodiphenyl)-7-hydroxy-4-methyl-2-oxoquinoline, 7-hydroxy-4-methyl-coumarin, thioglycollic acid, benzidine, ethylacetotate, arylaldehyde

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Synthetic potential and biological activity of thiazoles have been explored to the maximum extent and several heterocyclic analogues of these compounds have been reported in recent years[1-3]. Further, thiazole nucleus is an integral part of penicillins which have wide spectrum antibacterial activity. Moreover, the compounds containing oxoquinoline nucleus possess a variety of biological activity[4-6]. In view of the above and in continuation of the research on the synthesis of pharmacologically potent heterocyclic compounds, in this paper is reported the synthesis of N-[*p*-{3'-(2'-aryl-4'-oxo-1',3'-thiazolyl)} diphenyl]-7-hydroxy-2-oxoquinolines **4a-e (Scheme I)** and their *in vitro* anti-JEV activity.

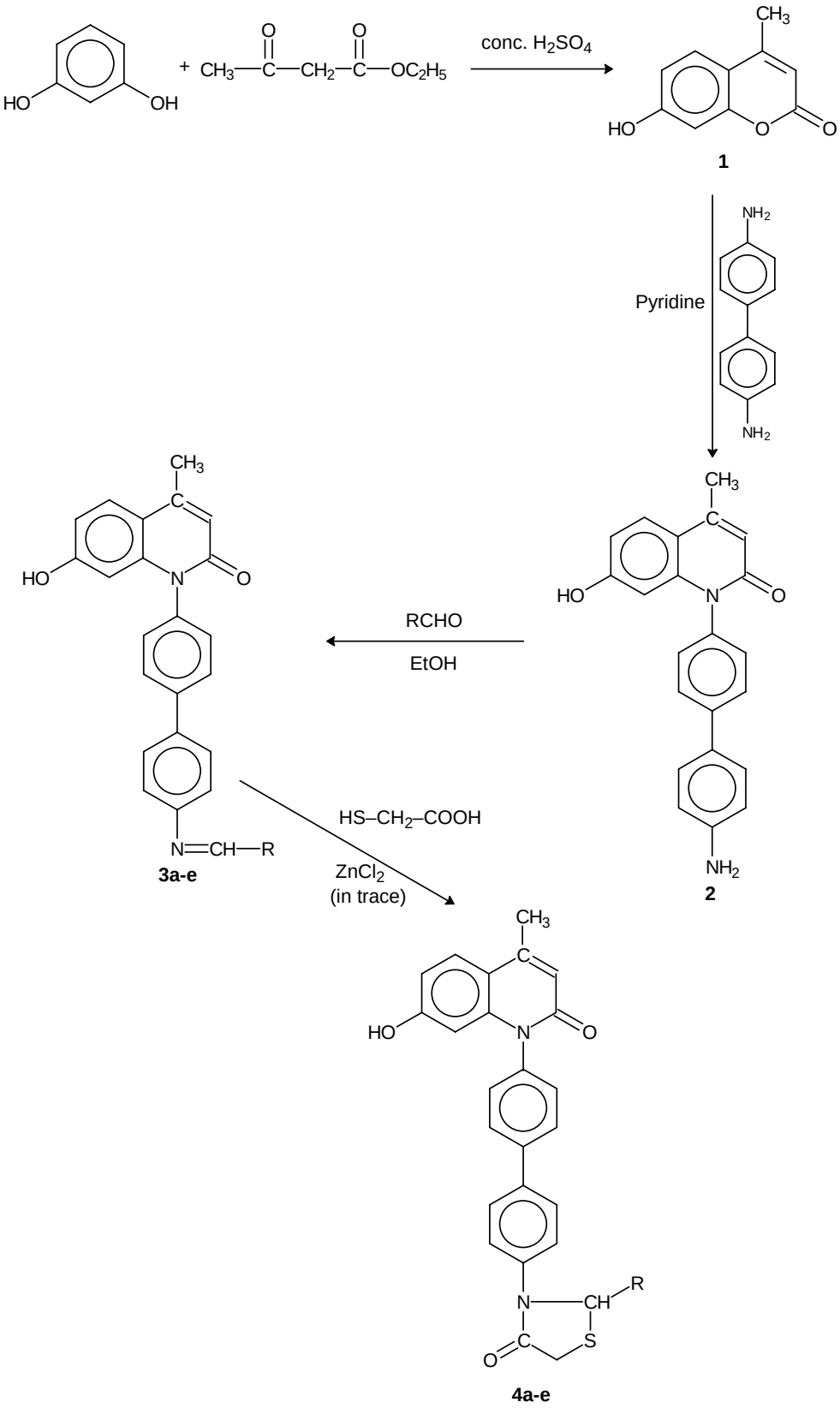
Pharmacological Activity

Compounds **4a-e** were bioevaluated for their antiviral activity against an animal virus *viz.* Japanese encephalitis virus (JEV) (P20778), an RNA virus of greater pathogenicity *in vitro*. The mean lethal dose (LD_{50}) of the virus in mice was calculated before each experiment following the procedure of Read and Muench[7]. The standard method of Sidwell and Huffman[8] was followed for performing cytotoxicity test and antiviral assay *in vitro* with slight modification[9]. The physical and spectral characterization data of evaluated compounds are presented in **Table I**.

The antiviral activity data recorded in **Table II** for these compounds indicate extremely positive results. All the five compounds were found to exhibit antiviral activity ranging from 50% to 100%. It is very interesting to observe that two compounds **4a** and **4d** of this category displayed 100 percent inhibition of the multiplication of virus *in vitro* and two such compounds **4b** and **4e** exhibited equal degree of antiviral activity (75% inhibition of virus). One compound **4e** was found to show moderate activity against JEV *in vitro*. It was seen that when the positions of the two groups were interchanged in the molecules **4d** and **4e**, the antiviral activity was found to be reduced considerably. This decrease in anti-JEV activity may be attributed to the lower preference for compound **4e** at the receptor site as compared to compound **4d**. A better fit at the receptor site may lead the molecule to penetrate more readily in the glycoprotein of the virus thus retarding or completely blocking the bio-synthesis of RNA induced polymerase. Since all the compounds of this category show a measurable degree of anti-JEV activity *in vitro*, it appears quite reasonable to assume that the various substituents play a minor role in the constitution of the molecular architecture whereas the presence of two heterocyclic nuclei *viz.* quinoline and thiazole is crucial.

Experimental Section

All melting points were determined in open capillary tube and are uncorrected. Homogeneity of the compounds were checked by TLC. IR spectra were recorded on Perkin-Elmer 1430 spectrophotometer, using KBr pellets and ^1H NMR spectra were recorded on a Bruker F 200 MHz NMR spectrometer in $CDCl_3$ using TMS as an internal standard. Mass spectra were recorded on a V_G 70-70H spectrometer at 70 eV.


conc. H_2SO_4
1
Pyridine
2
RCHO
EtOH
3a-e
$HS–CH_2–COOH$
$ZnCl_2$
(in trace)
4a-e

Scheme I

Table I—Physical and spectral characterization data of compound **3a-e** and **4a-e**

Compd	R	m.p. (°C)	Yield (%)	N% Found (Calcd.)	^{1}H NMR ($CDCl_3$) (δ ppm)	MS (m/z)
3a	*p*-Chlorophenyl	217	81	5.9 (6.03)		
3b	*o*-Hydroxyphenyl	180	75	6.23 (6.27)	7.38-6.25(m,16,Ar*H*), 6.30(br,1H,N=C*H*-R), 4.7-4.5(s,2H,Ar-OH, exchangeable with D_2O), 2.31(s,3H,Ar- CH_3)	
3c	*p*-Hydroxyphenyl	112	68	6.23 (6.27)		$C_{29}H_{22}N_2O_3^+$ 446, $C_{22}H_{16}O_2N^+$340, $C_{19}H_{14}NO^+$272, $C_{10}H_8NO_2^+$174, $C_9H_8NO^+$146, $C_7H_6NO^+$120, $C_7H_6O^+$106
3d	4-OH, 3-OCH_3 phenyl	96	70	5.85 (5.88)		
3e	3-OH, 4-OCH_3 phenyl	202	60	5.85 (5.88)		
4a	*p*-Chlorophenyl	95	85	5.29 (5.33)	7.83-6.95(m,15H,Ar-*H*), 4.82(s,A-O*H*), 4.15 (s,1H,N-C*H*-R) 3.69 (s, 2H,S-CH_2-C), 2.21(s,Ar-CH_3)	
4b	*o*-Hydroxyphenyl	102	82	5.51 (5.55)	7.77-6.85(m,15H,Ar-*H*), 4.95(s,1H,Ar-O*H*), 4.75(s,1H, N-C*H*-R), 3.75(s,2H, S-CH_2-C), 2.15(s,Ar-CH_3),	
4c	*p*-Hydroxyphenyl	170	60	5.51 (5.55)		$C_{31}H_{24}N_2O_4S^+$520, $C_{31}H_{26}N_2O_3S^+$504, $C_{25}H_{21}N_2O_2S^+$413, $C_{21}H_{16}NO_2S^+$360, $C_{22}H_{16}O_2N^+$340, $C_{21}H_{18}NOS^+$332, $C_9H_{10}NOS^+$180, $C_{10}H_8NO_2^+$174, $C_9H_8NO^+$146, $C_7H_5^+$89, $C_7H_7^+$91
4d	4-OH, 3-OCH_3 Phenyl	162	75	5.05 (5.09)	7.92-6.77(m,14H,Ar-*H*), 4.65-4.50(s,2H, Ar-O*H*), 4.45(s,1H,N-C*H*-R), 3.85(m,3H,OCH_3), 3.67(s,2H,S-CH_2-C), 2.34(s,Ar-CH_3),	$C_{32}H_{23}N_2O_5S^+$547, $C_{31}H_{24}N_2O_3S^+$504, $C_{25}H_{16}N_2O_3S^+$424, $C_{22}H_{18}NO_3S^+$376, $C_{22}H_{16}NO_2^+$326, $C_{10}H_{10}NO_3S^+$224, $C_{10}H_8NO_2^+$174, $C_9H_8NO^+$146, $C_7H_7O_2^+$123,
4e	3-OH, 4-OCH_3 Phenyl	117	80	5.05 (5.09)		

Table II—Anti-Japanese encephalitis virus (JEV) *in vitro*, activity data of compound **4a-e**

Compd	Dose μg/mL	% cytopathic effect (CPE inhibition)
4a	250	100
4b	250	75
4c	25	74
4d	125	100
4e	250	50

7-Hydroxy-4-methylcoumarin-(4-methylumbelliferone), 1

A mixture of resorcinol (0.1 mole) and ethylacetoacetate (0.1 mole) with 70% sulphuric acid (50 mL) was heated carefully for 0.5 hr. The resulting dark green solution was cooled and poured over crushed ice (250 g). The crude product was filtered off and washed repeatedly with water and dried at 100°C. The anhydrous coumarin thus obtained was insoluble in methanol but was purified

by recrystallization with difficulty from benzene to obtain pale yellow needles m.p. 185°C [185-86°C][10,11]. Yield 75%.

N-(*p*-Aminodiphenyl)-7-hydroxy-4-methyl-2-oxoquinoline, 2

A mixture of 7-hydroxy-4-methoxycoumarin (0.01 mole) and benzidine (0.01 mole) in anhydrous pyridine (50 mL) was heated under reflux for 4 hr under anhydrous conditions. Subsequently, the reaction mixture was poured into ice cold water (100 mL) containing HCl (10 mL). A solid separated out which was filtered off and washed successively with water and purified by recrystallization from dilute aqueous ethanol. m.p. 164°C [168°C][12]. Yield 70%.

N-(*p*-Arylidenoaminodiphenyl-7-hydroxy-4-methyl-2-oxoquinolines, 3a-e

A mixture of N-(*p*-aminodiphenyl)-7-hydroxy-4-methy-2-oxoquinoline (0.01 mole) and 0.01 mole of an appropriate arylaldehyde in absolute EtOH (30 mL) in presence of glacial acetic acid (1 mL) was refluxed for 8-10 hr. Excess of solvent was removed under reduced pressure. The solid obtained was washed with cold water several times and purified by recrystallization from methanol. Similarly, the other compounds of this category were synthesized and their physical and spectral characterization data are shown in **Table I**.

N-[*p*-{3'-(2'-Aryl-4-oxo-1', 3'-thiazolyl)} diphenyl]-7-hydroxy-4-methyl-2-oxoquinoline, 4a-e

A mixture of N-(*p*-arylidenoaminodiphenyl-7-hydroxy-4-methy-2-oxoquinoline (0.01 mole) and thioglycollic acid (0.01 mole) containing $ZnCl_2$ (0.1 g) in DMF was heated under reflux for 4 hr. It was poured into crushed ice and stirred vigorously. Solidification occurred after 15 min. The solid was filtered off and washed with cold water. Purification by recrystallization from ethanol gave analytically poor sample. Similarly, the other compounds of this category were synthesized and their physical and spectral characterization data are shown in **Table I**.

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