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Synthesis and biological activity of substituted 2,4,6-s-triazines

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Reaction of 7-hydroxy-4-methyl coumarin with amido/imido alcohols in ethanol containing concentrated hydrochloric acid afforded 8-aralkyl amido/imido-alkyl-7-hydroxy-4-methyl-coumarins (**1a**-**f**). Interaction of **1a**-**f** with hydrazine hydrate in pyridine resulted in 1-amino-8-aralkyl amido/imido-alkyl-7-hydroxy-4-methyl-2-oxo-quinolines (**2a**-**f**). Treatment of **2** with formaldehyde in ethanol resulted in 1,3,5-tris-(8-aralkyl amido/imido-alkyl-7-hydroxy-4-methyl-2-oxo-quinolinyl)-2,4,6-hexahydro-s-triazines (**3a**-**c**). Antiviral activity of compounds **2a**-**d** and **3a, 3b** upon *Japanese encephalitis virus* (JEV) and *Herpes simplex virus-1* (HSV-1) was evaluated on vero cells *in vitro*. **3a**-**c** were also screened for their antihypertensive activity.

Keywords: substituted 2,4,6-s-triazines, antiviral activity, antihypertensive activity

The development of selective non-nucleoside inhibitors of virus polymerases is an emerging area of research activity. Interest in discovering non-nucleoside inhibitors of virus polymerases increased after the pronounced antiviral activity of methisazone, which is truly a selective inhibitor of RNA polymerase (1). Subsequently, other synthetic compounds were developed and bioevaluated for their antiviral activity. Among various synthetic compounds, triazines have been found to be potential candidates for antiviral agents (2, 3). To find the relationship between structure and toxicity, more than 210 compounds with a symmetrical triazine nucleus in an experimental type of influenza virus infection were studied by the authors. Among various triazine derivatives, 2-amino-4-morpholinoyl-s-triazine has been administered orally and subcutaneously. The course of its absorption and elimination in white rats has also been studied. The results obtained with 2-*N*-(*p*-phenoxyphenyl)-amino-4-s-triazines were reported. This compound was found to be capable of protecting mice infected with type-8 influenza virus at a high level (4). Triazine derivative dacarbazine (dimethyl triazenoimidazole carboxamide DTIC) is employed principally for the treatment of malignant melanoma. Beneficial responces have also been reported in patients with Hodgkin's disease, particularly when the drug is used concurrently with doxorubicin, bleomycin and vinblastine (5) as well as

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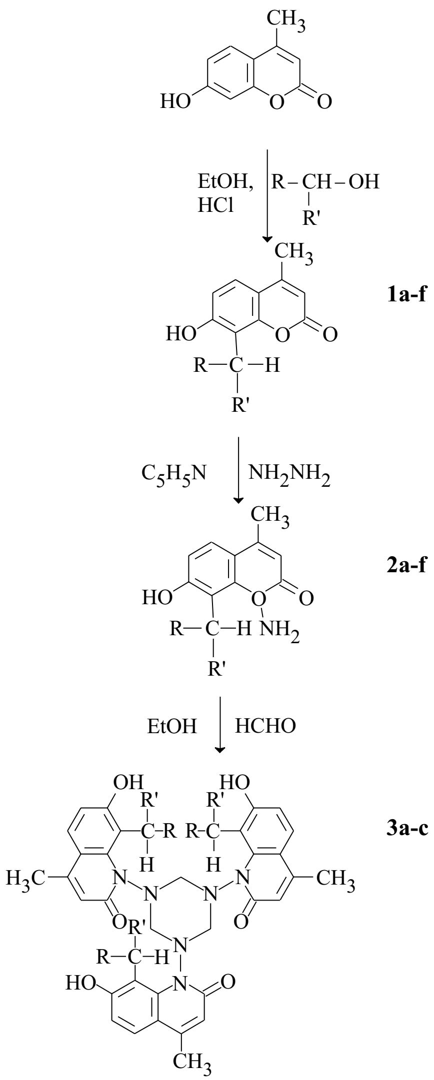
in various sarcomas when used with doxorubicin (6). Triethylenemelamine was found to suppress splenomegaly in Rouscher virus leukemia and was most active in increasing the survival time of mice with Moloney virus leukemia (7).

The long lasting hypotensive effect of 1-diallylamino-3,5-diamino-s-triazine in animals is due to its *N*-oxide metabolite (8). This led to the development of a very potent vasodilator antihypertensive agent, minoxidil (6-[1-piperidinyl]-2,4-pyrimidine diamine-3-oxide) (9), which is generally reserved for use in resistant hypertension. It produces



Scheme 1

reflex cardiac stimulation (10), child retention and hypertrichosis, which makes it unsuitable for chronic use. Prolonged administration in dogs resulted in a degenerative lesion of the right atrium that caused some concern about the safety of minoxidil but no similar lesion has been observed in other animal species or in man. It should be used in combination with a β-blocker, a diuretic or both (8). Minoxidil sulphate relaxes vascular smooth muscles in an isolated system where the parent drug is inactive. It is thought that it increases the permeability of the cell membrane to K^+ with resultant hyperpolarization (11). Topical use of minoxidil can cause miserable cardiovascular effects in some individuals (12). Quinoline derivatives have been established as potential antiparasitic agents, so it is suggested that the synthesis of more of such compounds should be undertaken to study their antiviral activity against different strains. These valid observations led the authors to undertake the synthesis of 1,3,5-tris(8-aralkyl amido/amido alkyl-7-hydroxy-4-methyl-2-oxo-quinolinyl-2,4,6-hexahydro-s-triazines.

EXPERIMENTAL

The melting points of synthesized compounds were determined in open capillary tubes in a Toshniwal electric apparatus (Japan) and the values recorded are therefore uncorrected. IR spectra were recorded in KBr discs using a Perkin-Elmer spectrophotometer model 337 (USA). ^{1}H NMR spectra were taken on a Varian 60D instrument (USA) using MeOH/DMSO-d_6. TMS was used as an internal standard (δ in ppm). Purity of compounds was checked by thin layer chromatography (silica gel-G plates, Merck, India, mobile phase: ethyl acetate/hexane, 1:4, *V/V*).

Amido/imido alcohols and 7-hydroxy-4-methyl coumarin were prepared according to the literature methods (13–19).

Syntheses

*8-Aralkyl amido/imido-alkyl-7-hydroxy-4-methyl-coumarins (**1a-f**).* – A mixture of an amido/imido alcohol (0.05 mol) and 7-hydroxy-4-methylcoumarin (0.05 mol) in ethanol (50 mL) containing 2 mL concentrated hydrochloric acid was heated under reflux for 4 h. Ethanol was distilled off and the residual semisolid was cooled to 0–5 °C. After about 30 minutes, solidification occurred. The solid was washed with water and dried *in vacuo*. The crude product thus obtained was recrystallized from acetone.

*1-Amino-8-aralkyl amido/imido-alkyl-7-hydroxy-4-methyl-2-oxo-quinolines (carbostyrils) (**2a-f**).* – Compound **1** (0.02 mol) was dissolved in anhydrous pyridine (30 mL) by stirring and slow heating. The solution was cooled and hydrazine hydrate (0.025 mol) was added dropwise under constant stirring. Subsequently, the resultant solution was heated under reflux for 6 h. The solution was cooled and poured carefully into diluted hydrochloric acid (4 mol L^{-1}, 100 mL). A solid separated out and was allowed to settle down. It was filtered, washed successively with water, dried and recrystallized from ethanol using animal charcoal.

*1,3,5-Tris-(8-aralkyl amido/imido-alkyl-7-hydroxy-4-methyl-2-oxo-quinolinyl)-2,4,6-hexahydro-s-triazines (**3a-c**).* – Compound **2** (0.01 mol) was dissolved in ethanol (50 mL) by slow warming. To this solution, 40% aqueous formaldehyde (0.075 mol) was added slowly under stirring at room temperature. The resultant solution, after stirring vigorously for 0.5 h at room temperature, was allowed to stand for another 0.5 h. A solid separated out and was filtered and washed with cold ethanol. The resulting product was purified by rapid extraction with boiling petroleum ether (b.p. 80–100 °C, 60 mL). After removing the insoluble high polymer by hot filtration, the filtrate was cooled at room temperature and the product was filtered off.

Biological activity

Four compounds belonging to series **2** and two compounds belonging to series **3** were evaluated for their antiviral activity against two viruses, *viz. Japanese encephalitis virus* (JEV) (strain P20778), an RNA virus of high pathogenicity, and *Herpes simplex virus–1* (HSV–1) (strain 753166).

Maintenance of Japanese encephalitis virus *(JEV).* – It was maintained by intracerebral passages in 1–3 days old suckling albino Swiss mice. The brains of the infected mice with specific paralytic symptoms were triturated and a 10% homogenate *(m/V)* was made in phosphate buffered saline (PBS) of pH 7.2. The mean lethal dose (LD_{50}) of the virus in mice was calculated before each experiment.

Maintenance of Herpes simplex virus–1 (HSV-1). – Virus was maintained in 5–6 g albino Swiss mice following the same route as for JEV; a 10% virus homogenate *(m/V)* was prepared and LD_{50} was calculated as for JEV.

Maintenance of cells. – Vero cells were maintained in minimum essential medium (MEM) (Sigma, USA) with 10% foetal bovine serum (FBS) (Gibco, USA); 100 units of penicillin, 100 μg of streptomycin and 40 μg of gentamycin were added per mL of the medium.

Cytotoxicity test and antiviral assay in vitro. – Cytotoxicity and antiviral assays of the compounds were performed by the standard method (10). The experiments were performed in 96 well tissue culture plates. Equal volumes of maintenance medium and compound solution were poured into each well; concentration of 500 μg mL^{-1} of the compound tested was applied into the first well. Successive diluting by factor 2 was performed in further wells: the compound concentration in the 8^{th} well was 1.9 μg mL^{-1}. The treated cultures were incubated for a period of 24 h at 37 °C and then observed microscopically for evidence of cytotoxicity, such as distortion, swelling and sloughing of cells (21–24). For the antiviral assay, 0.1 mL of the virus (10TC ID_{50} mL^{-1}, *i.e.* the dilution previous to 1TC ID_{50}, which is the virus dilution that shows 50% cytopathic effect, where TC ID_{50} is 50% tissue culture infectious dose) was allowed to adsorb onto cell monolayers for 90 min at 37 °C (25). The unadsorbed virus was removed by washing with 0.1 mL of MEM and then 0.1 mL of MEM, with 2.5% foetal bovine serum was filled into each well. Non-toxic concentration of the compound tested, ranging from 3.6 to 125 μg mL^{-1} of the compound, was added into each well. Each dilution was tested in duplicate, keeping separate the virus control and cell control (containing only MEM with 2.5% serum). The culture plates were incubated at 37 °C for 72 h and examined microscopically for evidence of cytopathogenicity caused by the virus and its inhibition by the examined compound.

Antihypertensive activity. – Some of the substituted 2,4,6-s-triazines were evaluated for their antihypertensive activity in Sprague Dawley rats of either sex, weighing between 200–300 g. Rats were anaesthesized with sodium pentobarbitone at a dose of 40 mg kg^{-1} *i.p.* The blood pressure was recorded from the carotid artery through a pressure transducer (Stanthan P_{23}dc, Grass Instruments Co., USA) or alternatively the right common carotid artery was cannulated and the blood pressure was recorded on a smoked paper or on a kymograph. Each experiment was repeated on three animals. Control blood pressure was 125 mm Hg for 0.1 mg kg^{-1} dose and 120 mm Hg for 5.0 mg kg^{-1} dose.

The carotid artery and jugular vein of the rat were exposed and cannulated. The blood pressure of the rat was monitored for over 15 minutes and once a stable blood pressure was obtained, the standard responses of adrenaline hydrochloride (1 µg kg^{-1}) isoprenaline sulphate (1.2 µg kg^{-1}), histamine acid phosphate (1 µg kg^{-1}) and acetylcholine (0.1 µg kg^{-1}) were obtained. All the test substances and the above reference standards were administered through an indwelling polythene cannula in the right jugular vein (1 mg kg^{-1} *i.v.*), followed by 1 mL of normal saline. The change in blood pressure was noted for each compound. The effect of the test compound on blood pressure was monitored.

The mixture adrenaline + isoprenaline + histamine + acetylcholine was given to the control animals. The same mixture was given to the experimental animals followed by the test compound.

Animal procedures were carried out in anaesthesized rats in accordance with the standard method and were approved by UNESCO-CDR1 Workshop on the use of pharmacological techniques for the evaluations of natural products (October 18–27, 1982, CDRI, Lucknow, India).

RESULTS AND DISCUSSION

Reaction of 7-hydroxy-4-methyl coumarin with amido/imido alcohols in ethanol containing concentrated hydrochloric acid afforded 8-aralkyl amido/imido-alkyl-7-hydroxy-4-methyl-coumarins (**1a**-**f**). Interaction of **1a**-**f** with hydrazine hydrate in pyridine resulted in 1-amino-8-aralkyl amido/imido-alkyl-7-hydroxy-4-methyl-2-oxo-quinolines (**2a**-**f**). Treatment of **2** with formaldehyde in ethanol resulted in 1,3,5-tris-(8-aralkyl amido/imido-alkyl-7-hydroxy-4-methyl-2-oxo-quinolinyl)-2,4,6-hexahydro-s-triazines (**3a**-**c**). Synthetic route of the newly synthesized substituted 2,4,6-s-triazines is depicted in the Scheme 1. Analytical data for the new compounds are given in Table I.

Four compounds belonging to the series of 1-amino-8-aralkyl amidoalkyl-7-hydroxy-4-methyl-2-oxo-quinolines (**2a**-**d**) and two compounds belonging to the series of 1,3,5-tris-(8-aralkyl amido/imidoalkyl-7-hydroxy-4-methyl-2-oxo-quinolinyl)-2,4,6-hexahydro-s-triazines (**3a** and **3b**) were evaluated for their antiviral activity against two viruses, *viz. Japanese encephalitis virus* (JEV) and *Herpes simplex virus–1 (HSV-1)*. All the four compounds (**2a**-**d**) were found antivirally active against JEV (Table II). Compound **2b** was the most active compound of the series; it displayed 90% net protection against JEV *in vitro*. It is interesting to note that the presence of a 2-phenyl-3-methyl-quinazolin (3*H*)-4-one moiety at position **8** is rather significant as far as the anti-JEV activity is concerned.

Table I. Characterization data of 8-aralkyl amido/imido-alkyl-7-hydroxy-4-methyl-coumarins (1), 1-amino-8-aralkyl amido/imido-alkyl-7-hydroxy-4-methyl-2-oxo-quinolines (carbostyrils) (2), 1,3,5-tris- (8-aralkyl amido/imido-alkyl-7-hydroxy-4-methyl-2-oxo-quinolinyl)-2,4,6-hexahydro-s-triazines (3)

Compd No.	R	R'	M.p. (°C)	Yield (%)	Molecular formula (M_r)	Calcd./found (%)			IR (KBr) (ν_{max}, cm^{-1})	^{1}H NMR (MeOH/DMSO-d$_6$) (δ, ppm)
						C	H	N		
1a	H	Phthalimido methyl	315–317	65	$C_{20}H_{15}NO_5$ (349.34)	68.76 68.72	4.29 4.32	4.01 4.00	1152 (C-O-C), 1500 (C...C), 1652 (C=C), 1685 (lactam C=O), 1736 (lactone C=O), 3295 (Ar-OH)	6.68–8.33 (m, 6H, ArH) 6.30 (s, 1H, CH) 5.09 (s, 1H, ArOH) 3.86 (t, 2H, NCH_2) 2.80 (t, 2H, CCH_2) 1.78 (s, 3H, CH_3)
1b	H	2-Phenyl- -3-methyl- quinazolin (3*H*)-4-one	165–167	62	$C_{26}H_{20}N_2O_4$ (424.45)	73.58 73.55	4.71 4.75	6.60 6.53	1152 (C-O-C), 1502 (C...C), 1580 (C=N), 1652 (C=C), 1735 (lactone C=O), 1685 (quinazolone C=O), 3294 (Ar-OH)	6.68–7.90 (m, 11H, ArH) 6.28 (s, 1H, CH) 5.50 (s, 1H, ArOH) 3.50 (t, 2H, NCH_2) 2.86 (t, 2H, CCH_2) 1.75 (s, 3H, CH_3)
1c	H	*N*-hydroxy- methyl- 4-methyl- 7-hydroxy- carbostyril	170–172	58	$C_{22}H_{19}NO_5$ (377.39)	70.02 69.08	5.03 5.06	3.71 3.64	1152 (C-O-C), 1506 (C...C), 1654 (C=C), 1687 (carbostyril C=O), 1730 (lactone C=O), 3575–3300 (Ar-OH)	6.69–7.30 (m, 5H, ArH) 6. 33 (s, 1H, CH carbo-styril moiety) 6.19 (s, 1H, CH of cou-marinyl moiety) 5.09 (s, 2H, ArOH) 3.36 (t, 2H, NCH_2) 2.90 (t, 2H, CCH_2) 1.87 (s, 6H, CH_3)
1d	*o*-OH-C_6H_4	Salicyl- amido	94–96	65	$C_{24}H_{19}NO_6$ (417.41)	69.06 69.02	4.55 4.59	3.35 3.31	1154 (C-O-C), 1515–1495 (C...C), 1652 (C=C), 1672 (amide C=O), 1730 (lactone C=O), 3695–3285 (Ar-OH)	8.31 (s, 1H, NH) 6.31–7.85 (m, 10H, ArH) 6.09 (s, 1H, CH) 5.45–5.92 (s, 3H, ArOH) 1.82 (s, 3H, CH_3)
1e	H	Phthalimido	206–208	64	$C_{19}H_{13}NO_5$ (335.31)	68.05 68.02	3.88 3.92	4.17 4.14	1152 (C-O-C), 1490–1504 (C...C), 1652 (C=C), 1685 (lactam C=O), 1736 (lactone C=O), 3415–3330 (Ar-OH)	6.65–8.20 (m, 6H, ArH) 6.29 (s, 1H, CH) 5.69 (s, 1H, ArOH) 4.92 (s, 2H, CH_2) 1.79 (s, 3H, CH_3)

Compd No.	R	R'	M.p. (°C)	Yield (%)	Molecular formula (M_r)	Calcd./found (%)			IR (KBr) (ν_{max}, cm^{-1})	^{1}H NMR (MeOH/DMSO-d$_6$) (δ, ppm)
						C	H	N		
1f	H	Salicyl-amido	85–86	60	$C_{18}H_{15}NO_5$ (325.32)	66.46 66.41	4.61 4.63	4.30 4.26	1154 (C-O-C), 1499–1520 (C…C), 1654 (C=C), 1673 (amide C=O), 1732 (lactone C=O), 3512–3315 (Ar-OH)	8.20 (s, 1H, NH) 6.62–7.85 (m, 6H, Ar-H) 6.26 (s, 1H, CH) 5.49–6.10 (s, 2H, Ar-OH) 4.50 (s, 2H, CH_2) 1.79 (s, 3H, CH_3)
2a	H	Phthalimido methyl	218	60	$C_{20}H_{17}N_3O_4$ (363.37)	66.11 66.07	4.68 4.73	11.57 11.51	1185 (N-N), 1500 (C…C), 1652 (C=C), 1684 (lactam C=O), 1710 (cyclic imide C=O), 3295 (Ar-OH)	6.61–8.35 (m, 6H, Ar-H) 6.25 (s, 1H, CH) 5.50 (s, 1H, Ar-OH) 3.85 (t, 2H, N-CH_2) 3.30 (s, 2H, NH_2) 2.80 (t, 2H, C-CH_2) 1.78 (s, 3H, CH_3)
2b	H	2-phenyl--3-methyl-quinazolin-(3*H*)-4-one	158	58	$C_{26}H_{22}N_4O_3$ (438.48)	71.23 71.19	5.02 5.06	12.78 12.75	1183 (N-N), 1502 (C…C), 1580 (C=N), 1652 (C=C), 1685 (quinazolone C=O), 1731 (cyclic imide C=O), 3295 (Ar-OH)	6.42–7.92 (m, 11H, Ar-H) 6.21 (s, 1H, CH) 5.80 (s, 1H, Ar-OH) 3.48 (t, 2H, N-CH_2) 3.32 (s, 2H, NH_2) 2.86 (t, 2H, C-CH_2) 1.75 (s, 3H, CH_3)
2c	H	*N*-hydroxy-methyl-4-methyl-7-hydroxy-carbostyril	156	55	$C_{22}H_{21}N_3O_4$ (391.42)	67.51 67.46	5.37 5.40	10.74 10.70	1186 (N-N), 1506 (C…C), 1654 (C=C), 1687 (carbostyril C=O), 1710 (cyclic imide C=O), 3574–3302 (Ar-OH)	6.34–7.59 (m, 5H, Ar-H) 6.29 (s, 2H, CH) 5.10–5.23 (s, 2H, Ar-OH) 3.38 (t, 2H, N-CH_2) 3.31 (s, 2H, NH_2) 2.92 (s, 2H, C-CH_2) 1.87 (s, 6H, CH_3)
2d	*o*-OH-C_6H_4	Salicyl-amido	110	60	$C_{24}H_{21}N_3O_5$ (431.44)	66.82 66.79	4.87 4.91	9.74 9.70	1187 (N-N),1506 (C…C), 1654 (C=C), 1697 (cyclic imide C=O), 1670 (amide C=O), 3573–3301 (Ar-OH)	8.01 (s, 1H, NH) 6.42–7.89 (m, 10H, Ar-H) 6.24 (s, 1H, CH) 6.10 (s, 1H, NH-CH) 5.7–5.90 (s, 3H, Ar-OH) 3.30 (s, 2H, NH_2) 1.84 (s, 3H, CH_3)

Compd No.	R	R'	M.p. (°C)	Yield (%)	Molecular formula (M_r)	Calcd./found (%)			IR (KBr) (ν_{max}, cm^{-1})	^1H NMR (MeOH/DMSO-d_6) (δ, ppm)
						C	H	N		
2e	H	Phthalimido	178	60	$C_{19}H_{15}N_3O_4$ (349.34)	65.32 65.29	4.29 4.34	12.03 12.01	1186 (N-N), 1490–1504 (C...C), 1652 (C=C), 1685 (lactam C=O), 1712 (cyclic imide C=O), 3416–3330 (Ar-OH)	6.43–8.21 (m, 6H, Ar-H) 6.29 (s, 1H, CH) 5.6 (s, 1H, Ar-OH) 4.92 (s, 2H, N-CH_2) 3.34 (s, 2H, NH_2) 1.75 (s, 3H, CH_3)
2f	H	Salicyl-amido	99	58	$C_{18}H_{17}N_3O_4$ (339.35)	63.71 68.68	5.01 5.05	12.38 12.31	1187 (N-N), 1506 (C...C), 1654 (C=C), 1697 (cyclic imide C=O), 1672 (amide C=O), 3317 (Ar-OH)	8.19 (s, 1H, NH) 6.46–7.85 (m, 6H, Ar-H) 6.21 (s, 1H, CH) 5.52–6.09 (s, 2H, Ar-OH) 4.61 (s, 2H, CH_2) 3.30 (s, 2H, NH_2) 1.77 (s, 3H, CH_3)
3a	*o*-OH-C_6H_4	Salicyl-amido	> 300	60	$C_{75}H_{63}N_9O_{15}$ (1330.37)	67.72 67.69	4.74 4.79	9.48 9.41	1193 (N-N), 1668 (amide C=O), 1697 (cyclic imide C=O), 3572–3292 (Ar-OH)	8.02 (s, 3H, NH) 6.44–7.99 (m, 10H, Ar-H) 6.24 (s, 3H, CH) 6.11 (s, 3H, NH-CH) 5.7–5.92 (s, 9H, Ar-OH) 4.15 (s, 6H, CH_2) 1.84 (s, 9H, CH_3)
3b	H	Phthal-amido	> 300	58	$C_{60}H_{45}N_9O_{12}$ (1084.07)	66.48 66.43	4.15 4.21	11.63 11.61	1188 (N-N), 1685 (lactam C=O), 1714 (cyclic imide C=O), 3410–3321 (Ar-OH)	6.44–8.44 (m, 18H, Ar-H) 6.31 (s, 3H, CH) 5.62 (s, 3H, Ar-OH) 4.90 (s, 12H, CH_2), 1.75 (s, 9H, CH_3)
3c	H	Salicyl-amido	225 (d)	55	$C_{57}H_{51}N_9O_{12}$ (1054.08)	64.95 66.90	4.84 4.87	11.96 11.92	1192 (N-N), 1673 (amide C=O), 1699 (cyclic imide C=O), 3319 (Ar-OH)	8.24 (s, 3H, NH) 6.46–7.94 (m, 18H, Ar-H) 6.24 (s, 3H, CH) 5.52–6.16 (s, 6H, Ar-OH) 4.82 (s, 12H, CH_2) 1.79 (s, 9H, CH_3)

*Table II. Antiviral activity of 1-amino-8-aralkyl amido/imido-alkyl-7-hydroxy-4-methyl-2-oxo-quinolines (carbostyrils) (**2**) and 1,3,5-tris-(8-aralkyl amido/imido-alkyl-7-hydroxy-4-methyl-2-oxo-quinolinyl)-2,4,6-hexahydro-s-triazines (**3**)*

Compd. No.	Anti-JEV *in vitro*		TI	Inhibition (%)	Anti-HSV-1 *in vitro*		TI	Inhibition (%)
	CT_{50} (μg mL^{-1})	EC_{50} (μg mL^{-1})			CT_{50} (μg mL^{-1})	EC_{50} (μg mL^{-1})		
2a	500	7.8	64	50	–	–	–	–
2b	250	15.6	16	90	–	–	–	–
2c	500	7.8	64	50	–	–	–	–
2d	62.5	7.8	8	50	–	–	–	–
3b	Non-toxic	15.62		60	Non-toxic	62.5		70

CT_{50} – 50% cytotoxic concentration, EC_{50} – 50% effective concentration
TI – therapeutic index (CT_{50}/EC_{50})
– not active

*Table III. Antihypertensive activity of 1,3,5-tris-(8-aralkyl amido/imido-alkyl-7-hydroxy-4-methyl-2-oxo-quinolinyl)-2,4,6-hexahydro-s-triazines (**3**) in rats*

Compd. No.	Dose (mg kg^{-1}, *i.v.*)			
	1.0		5.0	
	Fall in blood pressure (%)[a]	Duration (min)	Fall in blood pressure (%)[a]	Duration (min)
3a	60	tr	33	tr
3b	32	tr	56	tr
3c	–	–	33	tr

– not active; tr – transitory
[a] mean of 3 results

Other three compounds, **2a, 2c** and **2d**, showed activity to the magnitude of 50% each. Of the two s-triazines (**3a** and **3b**) evaluated for their antiviral activity (Table II), only compound **3b** bearing a phthalimido substituent was found 60% active against JEV and 70% against HSV-1. Since compound **3b** showed activity against both human viruses, one RNA and the other DNA, it can be regarded as a general and not selective antiviral compound.

None of the triazines **3a-c** showed reduction in blood pressure for an observable period of time (Table III) at the two *i.v.* dose levels *viz.* 1.0 mg kg^{-1} and 5.0 mg kg^{-1}. Compound **3a** containing hydroxy phenyl and salicylamido substituents showed a transitory decrease of 75 mm Hg at 1.0 mg kg^{-1} while the activity decreased at 5.0 mg kg^{-1} (40 mm Hg transitory). In the same way, compound **3b** having phthalimido substitutent showed a fall in blood pressure at both dose levels but the effect was transitory. Compound **3c** having salicylamido residue was found inactive at 1.0 mg kg^{-1} while at 5.0 mg kg^{-1} it caused a transitory fall in blood pressure to the level of 40 mm Hg. It is interesting to note that even a slight variation in molecular configuration may cause a profound effect on antihypertensive activity. Thus, compound **3a** having *o*-hydroxy phenyl and salicylamido substituent caused a reduction of blood pressure to the extent of 75 mm Hg at 1.0 mg kg^{-1} while compound **3c** bearing only salicylamido substituent showed no noticeable fall in blood pressure at 1.0 mg kg^{-1}. However, both compounds showed a fall of 40 mm Hg at 5.0 mg kg^{-1}.

CONCLUSIONS

Japanese encephalitis virus (JEV) is a RNA virus of higher pathogenicity and mortality rate. Its infection is very high. Quinoline derivatives if properly substituted with more appropriate pharmacophoric groups, might be proved potential agents in the fight against diseases caused by JEV. However, more chemical, biochemical and pharmacological studies are required to prove the potentials of quinoline derivatives in designing and developing new compounds against RNA viruses.

There is a need to synthesize more of quinoline derivatives with other substituents, since several symmetrical triazines have been claimed to be potential agents against several viruses, particularly against *Cytomegalovirus*, *Requine virus*, *Moloney virus*, *etc.*

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S A Ž E T A K

Sinteza i biološko djelovanje supstituiranih 2,4,6-s-triazina

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Reakcijom 7-hidroksi-4-metilkumarina s amido/imido alkoholima u etanolu s koncentriranom kiselinom pripravljeni su 8-aralkil amido/imido-alkil-7-hidroksi-4-metilkumarini (**1a**-**f**). Ti spojevi su s hidrazin hidratom u piridinu dali 1-amino-8-aralkil amido/imido-alkil-7-hidroksi-4-metil-2-okso-kinoline (**2a**-**f**). Iz spojeva **2** i formaldehida u alkoholnoj otopini sintetizirani su 1,3,5-tris-(8-aralkil amido/imido-alkil-7-hidroksi-4-metil-2-okso-kinolinil)-2,4,6-heksahidro-s-triazini (**3a**-**c**). Antiviralno djelovanje spojeva **2a**-**d**, **3a** i **3b** testirano je na *Japanese encephalitis virus* (JEV) i *Herpes simplex virus-1* (HSV-1) na vero stanicama *in vitro*. Osim toga ispitano je i antihipertenzivno djelovanje produkata **3a**-**c**.

Ključne riječi: supstituirani 2,4,6-s-triazini, antiviralno djelovanje, antihipertenzivno djelovanje

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