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Benzimidazolyl quinolinyl mercaptotriazoles as potential antimicrobial and antiviral agents

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Condensation of ethylaceto acetate (EAA) with resorcinol in concentrated H_2SO_4 afforded 7-hydroxy-4-methyl coumarin (**1**), which on reaction with thiosemicarbazide in anhydrous pyridine yielded 7-hydroxy-4-methyl-quinolinyl [1,5-c]-mercaptotriazole (**2**). Reaction of **2** with formaldehyde solution and amino acid in ethanol yielded 7-hydroxy-4-methyl-8-(*N*-methyl-aminoacid)-quinolinyl [1,5-c]-2′′-mercaptotriazole (**3a–e**). Interaction of **3** with *o*-phenylenediamine in pyridine yielded 7-hydroxy-4-methyl-8-(aminobenzimidazolyl)-quinolinyl [1,5-c]-2′′-mercaptotriazole derivatives (**4a–e**). The latter compounds were evaluated for their antiviral and antimicrobial activities.

Keywords: minimum inhibitory concentration, minimum essential medium, foetal bovine serum, cytotoxicity, mercaptotriazoles

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Benzimidazoles are remarkably effective compounds both with respect to their virus inhibitory activity and their favourable selectivity ratio. 2-[α-Hydroxy benzyl-benzimidazole] has been claimed to be a true inhibitor of picorna viruses (1, 2). Extensive biochemical and pharmacological activities have confirmed that the benzimidazole derivatives are effective against RNA viruses and inhibit the formation of virus induced RNA polymerase, thereby preventing or retarding RNA synthesis (3, 4). There are reports that other benzimidazole compounds have been considered potential antiviral agents since they were found to inhibit the multiplication of *Japanese encephalitis virus* (JEV), *Herpes simplex virus type-I* (*HSV-I*), *Encephalomyocarditis virus* (EMCV), *Influenza virus* (IV) and *Semiliki forest virus* (SFV) in addition to displaying antimicrobial activity (5–9). Further, imidazothiazole derivatives have shown great promise as agents capable of restoring impaired immune response. Thus, levamisole, an imidazothiazole, has been found to restore the delayed type of hypersensitivity in patients with an impaired immune mechanism and its utility in clinical practice has been proved by its use in cancer chemotherapy (10). Positive adjuvant effects of levamisole have also been reported (11, 12). It increases the number of survivors when combined with a cancerostatic drug such

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as cytoxan for the treatment of mouth sarcoma (13). Further, the antimicrobial and antimalarial activities of quinoline derivatives are well known. Very recently, quinolinyl isoquinolines were reported to possess antiviral activity (14). These observations urged the authors to undertake the synthesis of benzimidazolyl quinolinyl mercaptotriazoles in order to study their antiviral, antibacterial and antifungal activities.

EXPERIMENTAL

The melting points of the synthesized compounds were determined in the open capillaries in the Toshniwal Electric Apparatus (Japan) and the values reported are uncorrected. FT-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 $CDCl_3$ at 300 MHz. TMS was used as an internal standard. Purity of compounds was checked by TLC (Silica gel-G Plates, Merck, India; mobile phase: methanol/hexane, 1:4, *V*/*V*).

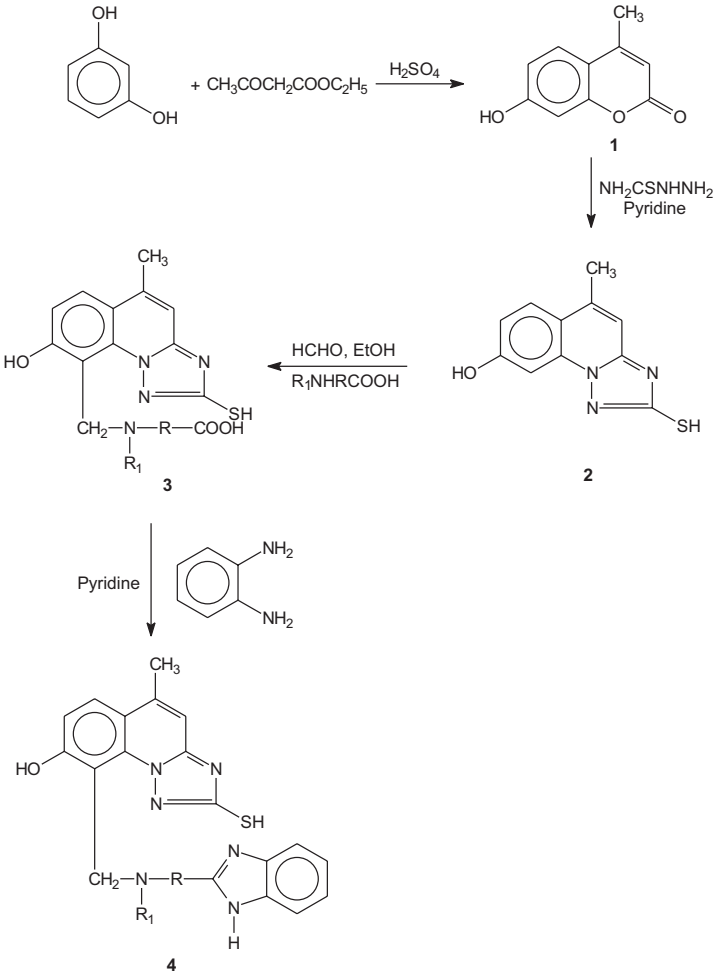
7-Hydroxy-4-methyl coumarin (4-methyl umbelliferone) (**1**) was synthesized according to the literature method (15). Synthetic route of the newly synthesized, benzimidazolyl quinolinyl mercaptotriazoles is depicted in Scheme 1.

Syntheses

7-Hydroxy-4-methyl-quinolinyl[1,5-c]-mercaptotriazole (**2**). – A mixture of 7-hydroxy-4-methyl coumarin (**1**) (0.2 mol) and thiosemicarbazide (0.2 mol) in anhydrous pyridine (50 mL) was heated under reflux for 2 hours. Subsequently, the reaction mixture was poured into crushed ice containing concentrated hydrochloric acid (10 mL). A dark brown solid separated out and was allowed to settle down for 1 h. It was filtered off, washed, dried *in vacuo* and recrystallized from methanol as a brownish yellow crystalline mass. Yield: 65%; m.p. 160–161 °C; IR (KBr, cm^{-1}): 1630 (C=N), 3600 (ArOH), 2570 (SH), 3040 (Ar) cm^{-1}; ^{1}H NMR ($CDCl_3$), δ (ppm): 5.80 (s, 1H, OH), 2.50 (s, 3H, $ArCH_3$), 3.79 (m, 2H, $\mathbf{CH_2}$NH), 3.15 (d, 2H, NH$\mathbf{CH_2}$COOH), 6.77–7.04 (m, 3H, ArH).

*7-Hydroxy-4-methyl-8-(*N*-methyl-amino acid) quinolinyl[1,5-c]-2′′-mercaptotriazole derivatives* (**3a**–**e**). – A mixture of **2**, an aminoacid (0.05 mol) and formaldehyde (1.25 mol) in ethanol (95.5%, 50 mL) containing triethylamine (1 mL) was heated under reflux for 10 h. Subsequently, the solvents were removed by distillation and the solid mass obtained was washed with water. It was dried in vacuo and recrystallized from methanol. The compounds of this category are listed in Table I.

7-Hydroxy-4-methyl-8-(aminobenzimidazolyl)-quinolinyl[1,5-c]-2′′-mercaptotriazole derivatives (**4a**–**e**). – Compounds **3a**–**e** (0.01 mol) and *o*-phenylenediamine (0.01 mol) were dissolved in dry pyridine by stirring at room temperature. The resultant solution was heated under reflux for 6 h under anhydrous reaction conditions. It was cooled and poured into ice-cold water (100 mL) containing conc. HCl (10 mL). A dark brown solid separated, which was allowed to settle down for 1 h at room temperature and was filtered off. It was air-dried and recrystallized from diluted ethanol (96%). The benzimidazolyl-quinolinyl-triazoles thus synthesized are given in Table I.



Scheme 1

Biological activity

Compounds **4a**–**e** were screened for their antifungal, antibacterial and antiviral activities.

Antifungal activity. – The compounds were assayed for their antifungal activity against five fungi, *viz.*, *Candida albicans* (MTCC 183), *Cryptococcus himalayensis* (MTCC 1436), *Sporotrichum schenkii* (MTCC 1152), *Trichophyton rubrum* (MTCC 296) and *Aspergillus fumigatus* (MTCC 343/870) *in vitro*. The two-fold serial dilution technique was adopted for *in vitro* testing of compounds. The test samples were dissolved in 5% (DMSO) (not toxic at this concentration) to obtain a 1.0 mg mL^{-1} stock solution. Appropriate seeded broths, *i.e.*, Sabouraud broths were prepared. A solution of test material (0.2 mL) was added 1/6

*Table I. Characterization data of 7-hydroxy-4-methyl-8-(N-methyl-aminoacid) [1,5c]-2″-mercaptotriazole derivatives (**3a–e**) and 7 hydroxy-4-methyl-8-(aminobenzimidazolyl)-quinolinyl [1,5c]-2″-mercaptotriazole derivatives (**4a–e**)*

Compd. No.	R	R_1	M.p. (°C)	Yield (%)	Molecular formula (M_r)	Nitrogen (%)		Spectral data	
						Found	Calcd.	IR (KBr) (cm^{-1})	^1H NMR ($CDCl_3$) (δ, ppm)
3a	CH_2	H	160–163	50	$C_{14}H_{14}N_4O_3S$ (318.17)	17.13	17.60	1635 (C=N), 3540 (OH), 3400 (NH), 2550 (SH), 3040 (Ar), 1750 (C=O), 2920 (C-H)	4.75 (s, 1H, ArOH), 2.50 (s, 3H, $ArCH_3$), 3.79 (m, 2H, CH_2NH), 3.15 (d, 2H, $NHCH_2$, COOH), 6.77–7.04 (m, 3H, ArH)
3b	$CHCH_3$	H	169–173	45	$C_{15}H_{16}N_4O_3S$ (332.18)	16.28	16.85	1637 (C=N), 3580 (OH), 3393 (NH), 2560 (SH), 3080 (Ar), 1745 (C=O), 2928 (C-H)	6.39 (s, 1H, ArOH), 2.48 (s, 3H, $ArCH_3$), 3.80 (d, 2H, CH_2NH), 2.60 (m, 1H, $CHCH_3$), 2.42 (d, 3H, $CHCH_3$), 6.70–7.22 (m, 3H, ArH)
3c	$CHCH_2CH_2COOH$	H	155–158	30	$C_{17}H_{18}N_4O_5S$ (390.18)	14.00	14.35	1635 (C=N), 3545 (OH), 3410 (NH), 2555 (SH), 3075 (Ar), 1748 (C=O), 2925 (C–H)	5.65 (s, 1H, ArOH), 2.45 (s, 3H, $ArCH_3$), 2.10 (m, 2H, $CHCH_2CH_2$), 3.59 (m, 2H, $CHCH_2CH_2$), 6.74–7.40 (m, 3H, ArH)
3d	CHC_6H_5	H	174–178	45	$C_{20}H_{18}N_4O_3S$ (394.23)	13.80	14.20	1638 (C=N), 3598 (OH), 3385 (NH), 2559 (SH), 3082 (Ar), 1749 (C=O), 2928 (C-H)	6.00 (s, 1H, ArOH), 2.49 (s, 3H, $ArCH_3$), 3.75 (d, 2H, CH_2NH), 5.20 (m, 1H, $NHCHCOOH$), 6.90–7.60 (m, 8H, ArH)
3e	CH_2	CH_3	162–164	45	$C_{15}H_{16}N_4O_3S$ (332.18)	16.40	16.85	1640 (C=N), 3540 (OH), 3412 (NH), 2548 (SH), 3060 (Ar), 1730 (C=O), 2918 (C-H)	5.82 (s, 1H, ArOH), 2.42 (s, 3H, $ArCH_3$), 3.70 (s, 2H, CH_2NCH_2COOH), 2.58 (s, 3H, NCH_3), 3.30 (s, 2H, CH_2COOH)

4a	CH_2	H	123–125	45	$C_{20}H_{18}N_6OS$ (390.25)	21.48	21.52	3592 (OH), 3300 (NH), 3093 (Ar), 2928 (CH), 2573 (S-H), 1630 (C=N)	5.50 (s, 1H, ArO**H**), 2.28 (s, 3H, ArC**H**$_3$), 4.50 (s, 2H, ArC**H**$_2$NH), 4.35 (s, 2H, NHC**H**$_2$C), 4.70 (s, 1H, ArN**H**), 7.20–7.90 (m, 7H, Ar**H**)
4b	$CHCH_3$	H	153–158	40	$C_{21}H_{20}N_6OS$ (404.26)	20.62	20.77	3580 (OH), 3340 (NH), 3090 (Ar), 2920 (CH), 2570 (SH), 1635 (C=N)	5.53 (s, 1H, ArO**H**), 4.75 (s, 1H, ArN**H**), 2.25 (s, 3H, ArC**H**$_3$), 4.54 (s, 2H, ArC**H**$_2$NH), 4.47 (m, 1H, NHC**H**C), 3.35 (d, 3H, NHCHC**H**$_3$), 7.35–7.95 (m, 7H, Ar**H**)
4c	$CHCH_2CH_2COOH$	H	158–162	30	$C_{23}H_{22}N_6O_3S$ (462.26)	18.00	18.17	3620 (OH), 3310 (NH), 3085 (Ar), 2920 (CH), 2572 (SH), 1628 (C=N)	5.59 (s, 1H, ArO**H**), 2.29 (s, 3H, ArC**H**$_3$), 4.60 (s, 2H, ArC**H**$_2$NH), 4.50 (m, 1H, NHC**H**CH$_2$), 1.40 (m, 2H, C**H**$_2$-CH$_2$COOH), 2.20 (m, 2H, CH$_2$C**H**$_2$COOH), 6.90–7.88 (m, 7H, ArH)
4d	CHC_6H_5	H	150–155	35	$C_{26}H_{22}N_6OS$ (466.31)	17.88	18.01	3590 (OH), 3410 (NH), 3080 (Ar), 2923 (CH), 2570 (SH), 1632 (C=N)	5.55 (s, 1H, ArO**H**), 4.73 (s, 1H, ArN**H**), 2.30 (s, 3H, ArC**H**$_3$), 4.57 (s, 2H, ArC**H**$_2$NH), 4.45 (s, 1H, NHC**H**C), 7.15–7.54 (m, 12H, ArH)
4e	CH_2	CH_3	132–137	35	$C_{21}H_{20}N_6OS$ (404.26)	20.47	20.77	3585 (OH), 3390 (NH), 3092 (Ar), 2928 (CH), 2580 (SH), 1632 (C=N)	5.52 (s, 1H, ArO**H**), 2.27 (s, 3H, ArC**H**$_3$), 5.49 (s, 2H, ArC**H**$_2$NCH$_3$), 3.00 (s, 3H, CH$_2$NC**H**$_3$CH$_2$), 4.38 (s, 2H, NCH$_3$C**H**$_2$C), 4.72 (s, 1H, ArN**H**), 7.10–7.80 (m, 7H, ArH)

mg/mL to 1.0 mL of seeded broth and this formed the first dilution. Subsequently, 1 mL of this dilution was further diluted with 1 mL of seeded broth to give the second dilution and so on untill 10–12 such dilutions were obtained. A set of tubes containing only seeded broth and suitable solvent controls were also maintained under identical conditions. The tubes were incubated at 28 °C and the minimum inhibitory concentration (*MIC*) (based upon visual appearance of growth) was noted after 72/96 h post incubation. The last tube with no apparent growth of the microorganism was taken to represent the *MIC* of the test compound and was expressed in μg mL^{-1} (16). Antifungal activity data are presented in Table II.

Antibacterial activity. – Compounds **4a–c** were evaluated for their antibacterial activity against five bacteria, *viz.*, *Streptococcus faecalis* (MTCC 459), *Klebsiella pneumoniae* (MTCC 618/530), *Escherichia coli* (MTCC 443/739), *Pseudomonas aeruginosa* (MTCC 424/741) and *Staphylococcus aureus* (MTCC 96/740). Species cultured in the medium containing 2500 units of penicillin were used. Bacteria were maintained on nutrient agar slants. Testing was done in a peptone broth. After inoculation with a loop full of culture from the slant, seeded broths were incubated at 37 ± 1 °C for 24 h. The two-fold serial dilution technique was used. The test compound was dissolved in 5% DMSO to obtain 1.0 mg mL^{-1} solution. This solution (0.2 mL) was added to 1.0 mL of seeded broth and formed the first dilution. One milliliter of this dilution was further diluted until six such dilutions were obtained. A set of tubes containing only inoculated broth was kept as a control. After incubation for 24 h, the last tube with no growth of microorganisms was taken to represent *MIC* expressed in μg mL^{-1} (17). The antibacterial activity data are given in Table II.

Antiviral activity. – Antiviral activity of compounds **4a–e** was tested against two viruses, *viz.*, *Japanese encephalitis virus* (*JEV*) (P20778), a RNA virus of higher pathogenicity, and *Herpes simplex virus* type-I (*HSV-I*) (753166), the most common virus present in the environment. *Japanese encephalitis virus* (*JEV*) was maintained by intracerebral passage of 1–3 days old suckling Swiss albino mice. The brains of infected mice with specific paralytic symptoms were triturated and a 10% homogenate (*m/V*) was made in phosphate buffered saline (PBS) pH 7.2. This was clarified by low speed centrifugation (1000 rpm) for 30 min at 4 °C and 0.5 mL aliquots were made and stored at –20 °C as stock virus. The $TCID_{50}$ (tissue culture 50% infective dose) and LD_{50} (lethal dose of a drug required to kill 50% of the test material) of the virus stock were estimated before performing *in vi-*

*Table II. Antifungal activity of compounds **4a–e***

Compd. No.	*MIC* against fungi (μg mL^{-1})					*MIC* against bacteria (μg mL^{-1})				
	Ca	Ch	Ss	Tr	Af	Sf	Kp	Ec	Pa	Sa
4a	3.5	3.5	20	20	25	–	–	–	–	–
4b	20	25	50	50	25	–	50	25	–	–
4c	–	–	50	–	–	–	–	–	–	50
4d	–	–	50	50	–	–	–	–	25	–
4e	–	–	–	30	–	–	50	–	–	–

Ca – *Candida albicans*, Ch – *Cryptococcus himalayensis*, Ss – *Sporotrichum schenkii*, Tr – *Trichophyton rubrum*, Af – *Aspergillus fumigatus*, Sf – *Streptococcus faecalis*, Kp – *Klebsiella pneumoniae*, Ec – *Escherichia coli*, Pa – *Pseudomonas aeruginosa*, Sa – *Staphylococcus aureus*

tro and *in vivo* experiments, was maintained in 5–6 g Swiss albino mice following the same route as JEV; 10% virus homogenate (*m/V*) was prepared and LD_{50} was calculated as for JEV. Vero cells were maintained in the minimum essential medium (MEM) (Sigma, USA) with 10% foetal bovine serum (FBS) (Gibco, USA), and 100 units of penicillin, 100 μg of streptomycin and 40 μg mL^{-1} of gentamycin were added in 1 mL of the mixture (18). The antiviral activity data are given in Table III.

Table III. Anti-JEV and anti-HSV activity of compounds ***4a–e***

Compd. No.	*In vitro*			*In vivo*			
	CT_{50} (μg mL^{-1})	EC_{50} (μg mL^{-1})	*TI*	CPE inhibition (%)	Dose (μg per mouse per day)	MST (days)	Protection (%)
				Anti-JEV			
4a	125	4	31	30	200	–	–
4b	125	8	16	90	200	4	16
4c	–	–	–	–	–	–	–
4d	125	4	31	30	200	–	–
4e	250	62.5	4	50	200	2	10
				Anti-HSV			
4a	125	62.5	2	33	–	–	–
4b	125	62.5	2	46	–	–	–
4c	–	–	–	–	–	–	–
4d	125	31.25	4	53	200	–	–
4e	250	7.8	32	64	200	–	–

CT_{50} – 50% cytotoxic concentration, EC_{50} – 50% effective concentration, *TI* –therapeutic index ($TI = \frac{CT_{50}}{EC_{50}}$), *CPE* – cytopathic effect, *MST* – mean survival time

RESULTS AND DISCUSSION

Condensation of ethylaceto acetate (EAA) with resorcinol in concentrated H_2SO_4 afforded 7-hydroxy-4-methyl coumarin (**1**), which on reaction with thiosemicarbazide in anhydrous pyridine yielded 7-hydroxy-4-methyl-quinolinyl[1,5-c]-mercapto triazole (**2**). Reaction of **2** with formaldehyde solution and amino acid in ethanol yielded 7-hydroxy--4-methyl-8-(*N*-methyl-aminoacid)-quinolinyl[1,5-c]-2′′-mercaptotriazoles (**3a–e**). Interaction of **3** with *o*-phenylenediamine in pyridine yielded 7-hydroxy-4-methyl-8-(aminobenzimidazolyl)-quinolinyl[1,5-c]-2′′-mercaptotriazole derivatives (**4a–e**). The synthetic pathway is given in Scheme 1.

The newly synthesized compounds **3** and **4** were characterized by IR and ^1H NMR spectroscopy. IR spectrum of the central nucleus of **3** showed bands corresponding to the OH group at ~ 3400, SH group at ~ 2550, C=C (aromatic) at ~ 3040 and C=O group at ~ 1750 cm^{-1}. Its ^1H NMR spectrum showed the presence of the aromatic OH group by a singlet at δ ~ 4.70 for one hydrogen, aromatic hydrogen by a multiplet between δ 6 and 7 for three hydrogens, $ArCH_3$ by a singlet for three hydrogens at δ ~ 2.50, CH_2NH by a

multiplet at δ ~ 3.8 ppm for two hydrogens. IR spectrum of the central nucleus of **4** showed bands corresponding to the OH group at ~ 3500, NH group at ~ 3300, C=C (aromatic) at ~ 3000, SH group at ~ 2550 and C=N at 1630 cm^{-1}. Its ^1H NMR spectrum showed the presence of the aromatic OH group by a singlet at δ ~ 5.50 for one hydrogen, aromatic hydrogen by a multiplet between δ 7 and 8 for seven hydrogens, $ArCH_3$ by a singlet at δ ~ 2.28 for three hydrogens, $ArCH_2NH$ by a singlet at δ ~ 4.5 for two hydrogens. Spectra for different derivatives **3a–e** and **4a–e** are given in Table I.

Compounds **4a–e** were evaluated for their antiviral and antimicrobial activities. Two compounds were found to exhibit antifungal activity against all the fungi. Thus, compound **4a** displayed promising antifungal activity against *Candida albicans* and *Cryptococcus himalayensis*, since the *MIC* value in each case was found to be 3.5 μg mL^{-1} and lower. Compound **4b** showed low to moderate antifungal activity against all the five fungi. It is interesting to note that a minor alteration in the molecular configuration of investigated compounds may have a profound effect on activity. Thus, compound **4a** bearing CH_2 as R showed high to moderate antifungal activity against all the five fungi while compound **4b** containing $CHCH_3$ as R exhibited less pronounced antifungal activity. The antibacterial activity data given in Table III clearly demonstrate that such compounds are not active as antibacterial agents. All but one of the five compounds were found active against JEV. Compound **4b** displayed 90% *CPE* (cytopathic effect) *in vitro* with an effective concentration of 8 μg mL^{-1} while its *in vivo* activity was less significant (16% protection with a *MST* of 4 days). It seems quite reasonable to suggest that these compounds are better anti-JEV agents than anti-HSV agents, since two such compounds *viz*., **4b** and **4e**, also displayed a measurable degree of anti-JEV activity *in vivo*. It is interesting to note that when R is CH_2 and R_1 is H, the anti JEV activity *in vitro* is 30% (compound **4a**) while when R is $CHCH_3$ and R is H (compound **4b**) the anti JEV activity increased considerably (90%). Compound **4c** was found antivirally inactive against both viruses. The anti HSV-I activity was found to be in the order of 33, 46, 53 and 64% for compounds **4a, 4b, 4d** and **4e**, respectively. Since among compounds **4a** to **4e** only compound **4e** contains a methyl group instead of H as R_1, it follows that R_1 does not seem to be responsible for the biological activity.

CONCLUSIONS

Substituted benzimidazolyl quinolinyl mercaptotriazoles have been shown to be potential antiviral agents against animal viruses as well as possible antifungal agents. The foregoing results point to the conclusion that even a minor alteration to the molecular architecture has a profound effect on their activity. Thus, benzimidazolyl quinolinyl mercaptotriazole containing an ethyl group attached to the 2-position of the benzimidazole is a better antiviral agent than the other substituted compounds having different substituents. On the other hand, benzimidazolyl quinolinyl mercaptotriazole containing a methyl group attached to the 2-position of the benzimidazole nucleus is a comparatively better antifungal agent than the other compounds.

Since *Japanese encephalitis virus* (JEV) is a RNA virus of higher pathogenicity, benzimidazolyl quinolinyl mercaptotriazoles substituted with more appropriate pharmaco-

phoric groups might result in improved therapeutic results. However, more extensive studies are required to prove the potentials of benzimidazolyl quinolinyl mercaptotriazoles in designing and developing more effective compounds against RNA and DNA viruses.

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S A Ž E T A K

Benzimidazolil-kinolinil-merkaptotriazoli kao potencijalni antimikrobni i antivirusni agensi

VINOD KUMAR PANDEY, MRIDULA UPADHYAY, MRINALINI UPADHYAY, VISHNU DEV GUPTA i MEENAL TANDON

Kondenzacijom etil-acetoacetata (EAA) s rezorcinolom u koncentriranoj H_2SO_4 dobiven je 7-hidroksi-4-metil kumarin (**1**), koji u reakciji s tiosemikarbazidom u bezvodnom piridinu daje 7-hidroksi-4-metil-kinolinil[1,5-c]-merkaptotriazol (**2**). Reakcijom spoja **2** s otopinom formaldehida i aminokiselinom u etanolu nastao je 7-hidroksi-4-metil-8-(*N*-metil-aminokiselina)-kinolinil[1,5-c]-2′′-merkaptotriazol (**3**), koji je s *o*-fenilendiaminom u piridinu dao 7-hidroksi-4-metil-8-(aminobenzimidazolil)-kinolinil[1,5-c]-2′′-merkaptotriazol derivate (**4a–e**). Ispitano je antivirusno i antimikrobno djelovanje spojeva **4**.

Ključne riječi: minimalna inhibitorna koncentracija, minimalni esencijalni medij, fetalni goveđi serum, citototoksičnost, merkapto triazoli

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