Synthesis of some new quinolinyylimidazoles for their antiviral and antifungal activities

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Condensation of resorcinol with ethyl acetoacetate in conc. H$_2$SO$_4$ yields 7-hydroxy-4-methyl coumarin 1 which on reaction with thiosemicarbazide affords 1-thiouryl-7-hydroxy-4-methyl carbostyril 2. Compound 2 on heating with a dil. NaOH undergoes cyclization to give 7-hydroxy-4-methylquinolinyl[1,5-c]-2-mercaptoimidazole 3. Interaction of 3 with 5-oxo-2-phenyl-1,3-oxazolo-1,3-oxazolidino-7-hydroxy-4-methylquinolinyl [1,5-c] imidazole 4. Reaction of 4 with aromatic aldehyde yield 2-[5'-oxo-2'-phenyl sulphoarylideno-1,3-oxazolo]-7-hydroxy-4-styryl-quinolinyl [1,5-c]imidazoles 5. The new compounds 5 have been screened for their antiviral and antifungal activities.

Imidazoline derivatives have shown great promise as agents capable of restoring an impaired immune response. Levamisole, an imidazole derivative, has been found to restore the delayed type of hypersensitivity in patients with damaged immune mechanism and its utility in chemical practise has been proved by its use in cancer chemotherapy. Positive adjuvant effects of levamisole have also been observed in the case of many other diseases including aphthous stomatitis, herpes and certain skin infections. Its use in rheumatic diseases is also well documented. Several derivatives of this compound were evaluated for their immunostimulant activity in various test systems. Recently, anti-AIDS, anticancer and immunomodulatory properties of levamisole have been reported. Levamisole, an anthelmintic drug with immune modulating property, has antitumor activity when administered with 5-fluorouracil in patients with Duke's C colorectal carcinoma. These valid observations led the authors to undertake the synthesis of some new compounds 3-5 containing imidazole moiety (Scheme I).

Results and Discussion

All the synthesized compounds have been characterised on the basis of their UV, IR and $^1$H NMR spectral studies. In the IR spectra of 2, both NH and carbonyl stretching bands appeared [NH 3250, C=O 1680 cm$^{-1}$]. Furthermore, in the $^1$H NMR spectrum of 2 and 3, the signals at $\delta$ 8.35 and $\delta$ 4.5, 4.38 were assigned to NH proton of H-N-C=S and Ar-OH, respectively, on the basis of the D$_2$O exchange studies. Absence of peak at 1680 cm$^{-1}$ in IR spectra of 3 but rather a peak at 1630 cm$^{-1}$ (C=N) along with a peak at 2575 cm$^{-1}$ (SH), confirms the formation of 3. The UV, IR and $^1$H NMR spectra of compounds 4 and 5 confirmed the assigned structures.

Pharmacological activity

Compounds 5a-d were screened for their antiviral and antifungal activities against Tobacco Mosaic Virus (TMV) from Nicotiana glutinosa plants both in vivo and in vitro and Fusarium solani, a causative agent of Guava wilt disease, respectively. For antiviral activity the solutions of the test compounds were prepared by dissolving 5 mg of the compound in 1 mL methanol and the volume was made to 100 mL with distilled water. All the experiments were performed in an insect free glass house at about 22±4°C. Local lesions were counted after 5-6 days of virus inoculation and percent inhibition was calculated from 100 (C-T)/C where C is the number of local lesions on controlled and T on treated leaves.

20 mL sterilized potato-destrose agar medium was poured in sterilized petridish (10 cm) to which 1 mL spore suspension of fungus (F. solani) was added. Discs of (0.5 cm) filter paper (Whatmann No. 1) were...
were found to exhibit anti-TMV and antifungal activities (moderate to high). It was observed that anti-TMV activity in vitro was more pronounced than anti-TMV in vivo as well as antifungal activity against F. solani.

**Experimental Section**

Melting points are uncorrected. IR spectra (ν in cm⁻¹) were recorded in KBr on a FTR 8201 VC spectrometer; ¹H NMR spectra on a DRX (200 MHz) and DRX (300 MHz) NMR spectrometer using TMS as an internal standard (chemical shifts in δ ppm).

### 7-Hydroxy-4-methylcoumarin 1

A mixture of resorcinol (11 g, 0.15 mole) and ethyl acetoacetate (6.55 mL) in conc. H₂SO₄ (50 mL) was refluxed on a water-bath at 100°C for 0.5 hr. The resultant dark green solution was cooled and stirred in crushed ice, the product thus separated out was allowed to settle. Crude product was filtered off and repeatedly washed with water and recrystallised from methanol as pale yellow plates, m.p. 185-86°C (lit. 185°C), yield 70%.

### 5-Oxo-2-phenyl-3-styryl-1,3-oxazole

A mixture of benzaldehyde (13.3 g, 0.125 mole), hippuric acid (22.4 g), acetic anhydride (35 mL) and anhydrous sodium acetate (10.3 g) was stirred mechanically, and then refluxed on a water-bath for 2 hr. Subsequently, 100 mL alcohol was added to it and allowed to stand overnight. Yellow solid which separated out was filtered off and washed successively with hot and cold water. It was recrystallised from benzene, m.p. 158°C (lit. 158°C) (δ H NMR (DMSO-d₆): 8 2.35 (s, 3H, Ar-CH₃), 7.32 (m, 9H, Ar-H), 4.7 (s, 1H, Ar-OH, exchangeable with D₂O), 2.31 (s, 3H, Ar-CH₃), 4.5 (s, 1H, Ar-OH, exchangeable with D₂O).

### 7-Hydroxy-4-methylquinolinyl [1,5-c]-2-mercaptoimidazole 3

A mixture of 2 (7.47 g, 0.03 mole) and NaOH solution (25 mL, 4.4%) containing ethanol (20 mL) was heated under reflux for 2 hr on a water-bath. It was cooled to 0°C and treated with 5 N, HCl (15 mL). A dark brown solid separated out which was allowed to settle down for 1 hr. It was filtered off, washed successively with water, dried in vacuo and recrystallised from MeOH as brownish yellow crystalline mass. m.p. 160°-61°C, yield 60%; UV (MeOH): 226, 238, 262; IR: 1630 (C=N), 3615 (OH), 3050 (Ar), 2575 cm⁻¹ (SH); ¹H NMR: δ 6.68-7.1 (m, 4H, Ar-H), 4.38 (s, 1H, Ar-OH, exchangeable with D₂O), 2.27 (s, 3H, Ar-CH₃).

### 2-[5'-Oxo-2'-phenylsulphobenzylideno-1,3-oxazolo]-7-hydroxy-4-methylquinolinyl [1,5-c]-imidazole 4a

A mixture of 5-oxo-2-phenyl-3-styryl-1,3-oxazole (4.98 g, 0.02 mole) and 7-hydroxy-4-methylquinolinyl [1,5-c]-2-mercaptoimidazole (4.62 g, 0.02 mole) in dioxan (25 mL) was heated under reflux for 3 hr on a steam-bath. Dioxan was distilled off and the residual solid mass obtained was dried in vacuum desiccator. It was recrystallised from benzene, m.p. 148°C, yield 50%, UV (DMSO): 245, 270, 315; IR (KBr): 1680 (C=O), 1635 (C=N), 3650 (OH), 3030 cm⁻¹ (C₆H₄); ¹H NMR (DMSO-d₆): δ 2.35 (s, 3H, Ar-CH₃), 6.8 (m, 4H, C₆H₄), δ 7.2 (m, 10H, ArH), 2.5 (s, 1H, H-C-C=O), 4.7 (s, 1H, Ar-OH, exchangeable with D₂O). (Found : N, 11.8; S, 6.60. C₂₇H₂₅N₄O₅S requires N 11.9; S, 6.60%).

### 2-[5'-Oxo-2'-phenylsulphobenzylideno-1,3-oxazolo]-7-hydroxy-4-methylquinolinyl [1,5-c]-imidazole 4b

Compound 4b was obtained from 5-oxo-2-phenyl-3-(o-methoxy styryl)-1,3-oxazole (5.9 g, 0.02 mole) and 3 (4.62 g, 0.02 mole) as described above, m.p. 134°C; ¹H NMR (DMSO-d₆): δ 2.28 (s, 3H, Ar-CH₃), 7.32 (m, 9H, Ar-H), 4.7 (s, 1H, Ar-OH, exchangeable with D₂O), 2.35 (s, 1H, H-C-C=O), 3.43 (s, 3H, O-CH₃), 6.71 (m, 4H, C₆H₄) (Found: N, 11; S, 6.27). C₂₇H₂₅O₅N₄S requires N 11.9; S, 6.27%.

### 2-[5'-Oxo-2'-phenylsulphobenzylideno-1,3-oxazolo]-7-hydroxy-4-styrylquinolinyl [1,5-c]-imidazole 5a

A mixture of 4a (2.88 g, 0.006 mole) and benzaldehyde (1.9 g, 0.01 mole) in gl. AcOH (40 mL) was heated under reflux for 2 hr on a sand-bath. Subsequently, the reaction mixture was poured into ice-cold MeOH where upon an yellow solid separated out which was allowed to settle. It was filtered off and...
dried in vacuo. Crude quinolinyl imidazoles thus obtained were recrystallised from benzene, m.p. 162°C; UV (DMSO-d$_6$): 268, 310, 359.6; IR (KBr): 1685 (C=O), 1645 (C=N), 3650 (OH), 3030 cm$^{-1}$ (C$_6$H$_5$); $^1$H NMR (DMSO-d$_6$): δ 3.0 (d, 1H, =CH-Ar), 7.42 (m, 15 H, Ar-H), 2.6 (d, 1H, -CH=CH-R), 4.55 (s, 1H, Ar-OH, exchangeable with D$_2$O), 2.35 (s, 1H, H-C=C=O), 6.83 (m, 4H, Ar-H) (Found: N, 9.62; S, 5.65. C$_{34}$H$_{24}$O$_3$N$_4$S requires N, 9.74; S, 5.65%).

2-[5'-Oxo-2'-phenylsulphobenzylideno-1,3-oxazolo]-7-hydroxy-4-(o-methoxystyrly)-quinolinyl[1,5-c]imidazole 5b Compound 5b was obtained from 4a (2.88 g, 0.006 mole) and anisaldehyde (1.36 g, 0.01 mole) as described above, m.p. 153°C; $^1$H NMR (DMSO-d$_6$): δ 3.14 (d, 1H, =CH-Ar), 6.4 (m, 4H, Ar-H), 7.35 (m, 10H, Ar-H), 6.72 (m, 4H, Ar-H), 2.38 (s, 1H, H-C=C=O), 4.82 (s, 1H, Ar-OH, exchangeable with D$_2$O). (Found: N, 9.20; S, 5.29. C$_{35}$H$_{25}$O$_4$N$_4$S requires N, 9.38; S, 5.34%).

2-[5'-Oxo-2'-phenylsulpho(o-methoxy)benzylideno-1,3-oxazolo]-7-hydroxy-4-styrly-quinolinyl [1,5-c]imidazole 5c Compound 5c was obtained from 4b (3.06 g, 0.006 mole) and benzaldehyde (1.9 g, 0.01 mole) as described above, m.p. 158°C; $^1$H NMR (DMSO-d$_6$): δ 3.14 (d, 1H, =CH-Ar), 6.4 (m, 4H, Ar-H), 7.35 (m, 10H, Ar-H), 6.72 (m, 4H, Ar-H), 2.38 (s, 1H, H-C=C=O), 4.82 (s, 1H, Ar-OH, exchangeable with D$_2$O). (Found: N, 9.30; S, 5.34. C$_{35}$H$_{25}$O$_4$N$_4$S requires N, 9.38; S, 5.34%).

2-[5'-Oxo-2'-phenylsulpho(o-methoxy)benzylideno-1,3-oxazolo]-7-hydroxy-4-(o-methoxystyrly)-quinolinyl[1,5-c]imidazole 5d Compound 5d was obtained from 4b (3.06 g, 0.006 mole) and anisaldehyde (1.36 g, 0.01 mole) as described above, m.p. 142°C; IR (KBr): 1700 (C=O), 1650 (C=N), 3655 (OH), 3030 cm$^{-1}$ (C$_6$H$_5$); $^1$H NMR (DMSO-d$_6$): δ 7.55 (m, 8H, Ar-H), 6.78 (m, 5H, Ar-H), 3.2 (d, 1H, =CH-Ar), 3.47 (s, 3H, O-CH$_3$), 4.80 (s, 1H, Ar-OH exchangeable with D$_2$O), 6.90 (m, 4H, Ar-H), 2.45 (d, 1H, CH=CH-R) (Found: N, 8.83 ; S, 5.14. C$_{36}$H$_{25}$O$_4$N$_4$S requires N, 8.93; S, 5.14%).

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