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Synthesis of some novel 4-thiazolidinone compounds and their application as potential antimicrobial agent

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Abstract : 3-Chloro-l-[5′-hydroxy-2′-(phenyldiazenyl)phenyl]-4-[2″-hydroxy-5″-(1‴,3‴-benzothiazol-2‴-yl-diazenyl)phenyl]-2-azetidinone (4a-p), 3-[5′-hydroxy-2′-(phenyldiazenyl)phenyl]-2-[2″-hydroxy-5″-(1‴,3‴-benzothiazol-2‴-yl-diazenyl)phenyl]-4-thiazolidinone (5a-p) and 3-[5′-hydroxy-2′-(phenyldiazenyl)phenyl]-2-[2″-hydroxy-5″-(1‴,3‴-benzothiazol-2‴-yl-diazenyl)phenyl]-4-methylthiazolidinone have been synthesized from their Schiff bases (3a-p). They have been screened for their antimicrobial activities.

Keywords : 4-Thiazolidinone, antimicrobial agent.

Various 2-azetidinones[1] and 4-thiazolidinones[2,3] are endowed with wide range of pharmacological[4,5] activities, such as CNS, CVS, antibacterial, analgesic, antifungal etc. 2,3-Diaryl-1,3-thiazolidin-4-ones have been proved to be highly effective in inhibiting HIV-1[6] and TB[7] mycobecterias. While 2-azetidinone derivatives have been reported to possess anti-inflammatory-anticonvulsant and antifungal[8] activities.

5-(1′,3′-Benzothiazol-2-yl-diazenyl)-2-hydroxybenzaldehyde under reflux with 3-amino-4-(phenyldiazenyl)phenol, gives Schiff bases (**3a-p**). 3-Chloro-l-[5′-hydroxy-2′-(phenyldiazenyl)phenyl]-4-[2″-hydroxy-5″-(1‴,3‴-benzothiazol-2‴-yl-diazenyl)phenyl]-2-azetidinone (**4a-p**) was obtained by cycloaddition of chloro acetylchloride and triethylamine to Schiff base. The cycloaddition of thioglycolic acid and thiolactic acid to Schiff base gives the corresponding 4-thiazolidinones (**5a-p**) and (**6a-p**) according to the Scheme 1.

Results and discussion

Antimicrobial activity : The compounds were screened for antibacterial activity against *E. coli, S. aureus, Pseudomonas, Bacillus* and antifungal activity against *Candida* by disk diffusion method at a concentration of 100 μg/ml.

The stock solution of the compounds was prepared at a concentration of 5 mg/ml and from stock solution the disc was prepared at a concentration of 100 μg/ml. The testing was done on muller hinton agar plates, by swabbing the agar plates with respective cultures, and placing the disc on it and incubating at 37 °C for 24 h. In series **3a-p**, compounds **3b**, **3e**, **3f**, **3k**, **3m** and **3o** shows mild activity (zone of inhibition 4–8 mm) against *E. coli*, whereas **3g**, **3h**, **3i** and **3j** show moderate (zone of inhibition 9–12 mm) activity against *E. coli*. Compound **3f**, **3g**, **3j** show mild (zone of inhibition 4–8 mm) activity against *Pseudomonas*, while **3e**, **3h** and **3i** shows moderate activity against *Pseudomonas*. In series **3a-p**, almost all compounds are inactive against *S. aureus* and *Bacillus*, whereas these compounds show good activity against *Candida*. In the series of compounds (**4a-p**), **4e**, **4f**, **4h** and **4i** show moderate activity against *E. coli*, whereas **4a**, **4c**, **4d**, **4k** and **4m** show mild activity against the same. **4e**, **4f**, **4h** and **4i** show moderate activity against *Pseudomonas*, whereas in series **4a-p** almost all compounds are inactive against *S. aureus* and *Bacillus*. In the series of compounds (**5a-p**), **5h**, **5i** and **5j** show moderate activity against *E. coli* whereas these compounds are found to be mild active against *S. aureus* and *Bacillus*. **5c**, **5f**, **5g**, **5h**, **5j** and **5k** show good activity against *Candida*. In a series of compounds (**6a-p**), **6f**, **6i** and **6j** show moderate activity against *Candida* while they show mild activity against *E. coli* and *Pseudomonas*. Tetracycline, Ceftriazone and Greseofulvin were taken for comparison purpose.

The results are given below :

	Zone of inhibition of standard drug in mm				
E. coli	*Pseudomonas*	*S. aureus*	*Bacillus*		*Candida*
Tetracycline	16	14	15	17	-
Ceftriazone	30	28	30	28	-
Greseofulvin	-	-	-	-	15-20

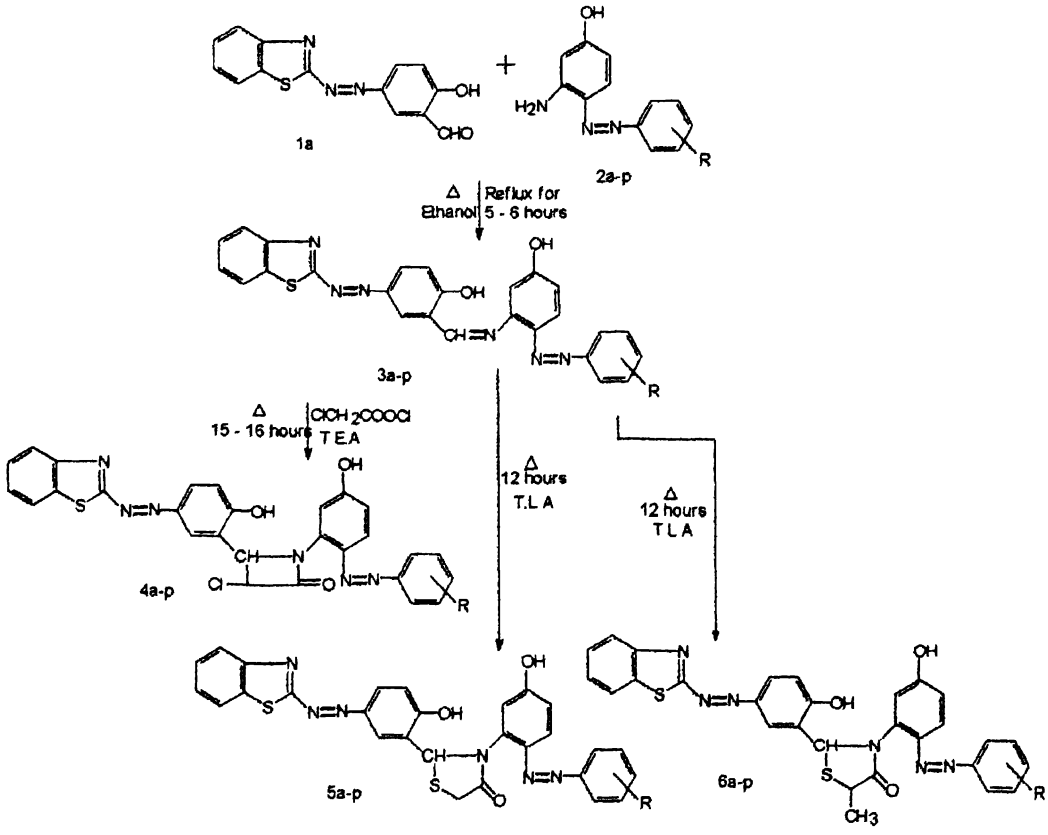
Experimental

All m.ps. were taken in open capillaries using Toshniwal apparatus and are uncorrected. IR spectra (KBr) were recorded on Shimadzu FT-IR 8300 spectrophotometer, ^{1}H NMR spectra on a Varian Geminy 200 MHz spectrometer using TMS as the internal standard. Purity of the compounds in addition to elemental analysis was checked by TLC.

4-(1′,3′-Benzothiazol-2′-yl-diazenyl)-2-{[5″-hydroxy-2″-(phenyldiazenyl)phenyl]imino}methylphenol (**3a-p**) : 5-(1′,3′-Benzothiazol-2′-yldiazenyl)-2-hydroxybenzaldehyde (0.01 mol, 2.83 g) is mixed with 3-amino-4-(phenyldiazenyl)phenol (0.01 mol, 2.13 g) and then refluxed in ethanol at 90 °C for 5–6 h. After the reaction is over the solvent was removed by vacuum distillation. The solid product was filtered, dried and recrystallised from absolute alcohol. Other substituted Schiff bases were prepared in the same way : m.p. 85 °C; IR (KBr) 3460–3455 (–OH), 1605–1600 (C=N), 850–800 cm^{-1} (tri-substituted benzene); δ ($CDCl_3$) **3e** : 5.635 (1H, s, N=CH-Ar), 6.90–7.96 (14H, m, Ar-H), 9.20 (2H, s, Ar-OH).

3-Chloro-1-[5′-hydroxy-2′-(phenyldiazenyl)phenyl]-4-[2″-hydroxy-5″-(1‴,3‴-benzothiazol-2‴-yl-diazenyl)phenyl]-2-azetidinone (**4a**) :

A solution of **3a** (0.01 mol, 4.78 g) in benzene was added to a well stirred mixture of chloroacetyl chloride (0.012 mol) and triethylamine (0.012 mol) in benzene. The reaction mixture was refluxed for 15–16 h. The product was isolated and recrystallized from ethanol : m.p. 140 °C; IR (KBr) 3630 (–OH), 1754–1738 (C=O), 1650 (C=N, thiazole), 776 (C–S, thiazole), 894–873 (tri-substituted benzene), 800–600 cm^{-1} (C–Cl); δ ($CDCl_3$) **4d** :



where R = **a**; H, **b**; 2-OCH_3, **c**; 3-OCH_3, **d**, 4-OCH_3, **e**; 2-Br, **f**; 3-Br, **g**; 4-Br, **h**; 2-Cl, **i**; 3-Cl, **j**; 4-Cl, **k**, 2-NO_2, **l**, 3-NO_2, **m**; 4-NO_2, **n**; 2-CH_3, **o**; 3-CH_3, **p**; 4-CH_3

Scheme 1. Synthesis of 4-thiazolidinone compounds (**3a-p**), (**4a-p**), (**5a-p**) and (**6a-p**).

6.97–7.77 (14H, m, Ar-H), 8.2 (1H, s, Ar-OH), 3.85 (3H, d, OCH_3), 7.38 (1H, s, -N-CH).

3-[5′-Hydroxy-2′-(phenyldiazenyl)phenyl]-2-[2″-hydroxy-5″-(1‴,3‴-benzothiazol-2‴-yl-diazenyl)phenyl]-4-thiazolidinone (**5a**) :

The Schiff bases (0.01 mol, 5.0 g) in benzene were mixed with thioglycolic acid (0.01 mol, 0.7 ml) in benzene and were refluxed for 15–16 h. The reaction mixture was cooled and treated with 10% $NaHCO_3$ solution. The product was isolated and crystallized from ethanol : m.p. 289 °C; IR (KBr) 3540 (-OH), 1735 (C=O, thiazolidinone), 752 (C-S-C), 890–882 (tri-substituted benzene); δ ($CDCl_3$) **5b** : 6.9–7.94 (14H, m, Ar-H), 7.99 (2H, s, Ar-OH), 3.902 (3H, d, OCH_3), 8.2 (1H, s, -N-CH).

3-[5′-Hydroxy-2′-(phenyldiazenyl)phenyl]-2-[2″-hydroxy-5″-(1‴,3‴-benzothiazol-2‴-yl-diazenyl)phenyl]-4-methylthiazolidinone (**6a**) :

A mixture of Schiff base (0.01 mol, 5.0 g) and thiolactic acid (0.01 mol) was heated at 120–125 °C for 12 h. The reaction mixture was cooled and treated with 10% $NaHCO_3$ solution. The product was isolated and crystallized from ethanol : m.p. 73 °C; IR (KBr) 3500 (-OH), 1755–1750 (C=O, thiazolidinone), 894–873 (tri-substituted benzene), 700–650 cm^{-1} (C-S-C); δ ($CDCl_3$) **6a** : 2.6 (3H, s, CH-CH_3), 8.3 (1H, q, CH-CH_3), 7.95–8.5 (1H, s, N-CH), 6.9–7.5 (14H, m, Ar-H), 6.38 (2H, s, Ar-OH).

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