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Synthesis and Biological Activities of New 2-substituted-5,6-dichlorobenzothiazoles

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New 2-(4-formyl-3-phenylpyrazolo-1-yl)-amidomethyl-5,6-dichloro-benzothiazole (III) was synthesized by reacting acetophenone-5,6-dichlorobenzothiazol-2-yl-amidomethylhydrazone (II) with Vilsmeier-Haack reagent ($DMF/POCl_3$). Benzaldehyde/4-nitrobenzaldehyde/4-methoxy benzaldehyde-5,6-dichlorobenzothiazol-2-yl amidomethylhydrazones (IV-VI) were obtained by the reaction of 2-hydrazinoamidomethyl-5,6-dichlorobenzothiazole (I) with various aromatic aldehydes. All these compounds were characterised by analytical and spectral data. Compound (III) exhibited good antiinflammatory and antibacterial properties while the rest of the compounds were moderately active, on evaluation.

Substituted benzothiazoles and pyrazoles are well known for their antiinflammatory[1-6] and other biological properties[7-11]. On the other hand, chloroacetyl group[12] on some heterocyclic systems was known to enhance the antiinflammatory activity. Keeping in view of all these observations, we report in this communication, synthesis and biological activities of some new acetamido-5,6-dichlorobenzothiazoles.

2-Hydrazinoamidomethyl-5,6-dichloro benzothiazole (I), which was obtained by reacting 2-amino-5,6-dichloro benzothiazole with chloroacetyl chloride and further with hydrazine hydrate, on condensation with acetophenone in presence of ethanol using a catalytic amount of glacial acetic acid gave acetophenone-5,6-dichlorobenzothiazol-2-yl amidomethylhydrazone (II). The hydrazone (II) on treatment with Vilsmeier-Haack reagent ($DMF/POCl_3$)[13] yielded 2-(4-formyl-3-phenylpyrazol-1-yl)-amido methyl-5,6-dichlorobenzothiazole (III). Compound I was treated with different aromatic aldehydes in ethanol to give compounds IV-VI in good yields (Scheme 1).

EXPERIMENTAL

Melting points were taken in open capillaries and were uncorrected. The synthesized compounds were checked for their purity by TLC using Silica gel-G. IR Spectra were recorded in KBr on Perkin-Elmer infrared spectrophotometer, while PMR spectra on Perkin-Elmer EM-390-90 MHz spectrophotometer using TMS as an internal standard.

*For Correspondence

Synthesis of acetophenone-5,6 dichlorobenzothiazol-2-yl amidomethyl hydrazone (II)

A mixture of compound I (0.01 mol, 2.93 g) and acetophenone (0.01 mol, 0.4 ml) in ethanol (30 ml) containing a drop of glacial acetic acid was refluxed for 7 h. Excess solvent was distilled off and residue was poured onto crushed ice. The seperated solid was filtered out and recrystallized from ethanol. With the use of glacial acetic acid there was significant improvement in the yield of this compound qualitatively and quantitatively and further, it was also helpful in bringing down the reaction time below 10 h which was not observed in its absence.

IR spectrum (KBr) exhibited characteristic absorption bands at (in cm^{-1}): 3380 (NH), 1684 (amido-C=O) and 1649 (C=N).

Synthesis of 2-(4-formyl-3-phenylpyrazol-1-yl)-amidomethyl-5,6-dichlorobenzothiazole (III)

To the Vilsmeier-Haack reagent prepared from DMF (10 ml) and $POCl_3$ (0.012 mol, 1.1 ml), hydrazone (II) (0.004 mol, 1.46 g) was added, and the reaction mixture

Table I - Physical, analytical and pharmacological data of 2-substituted 5,6-dichlorobenzothiazoles

Compd	R	Yield %	M.P. °c	Mol. formula	Antibacterial activity* (M.I.C. in µg/ml)		Antifungal activity*		Antiinflammatory activity % protection	
					B.s	E.c	T.m	Ca27	2 h	4 h
III	-	71	140	$C_{19}H_{12}N_4O_2SCl_2$	25	NA	NA	50	64	81
IV	phenyl	67	203	$C_{16}H_{12}N_4OSCl_2$	50	NA	NA	50	53	64
V	p-nitrophenyl	72	195	$C_{16}H_{11}N_5O_3SCl_2$	50	NA	NA	50	59	78
VI	p-methoxy-phenyl	60	161	$C_{17}H_{14}N_4O_2SCl_2$	50	NA	NA	50	65	75
Ibuprofen					-	-	-	-	82	92
Streptomycin					12.5	50	-	-	-	-
Amphotericin-B					-	-	12.5	12.5	-	-

*All compounds were recrystallized from ethanol. All compounds were pale yellow in colour. *Minimum inhibitory concentrations of the compounds in µg/ml. Microorganisem used were.*
B.s. - B. subtilis; E.c. - E. coli; Ca27 - C. albicans and T.m. - T. mentagrophytes. N.a. - No activity

was stirred at 60-65° for 2h and then poured onto ice cold water. The solid that separated out on neutralisation with sodium bicarbonate was filtered, washed with water and recrystallized from ethanol.

IR spectrum (KBr) exhibited characteristic absorption bands at (in cm^{-1}): 3355 (NH), 1665 (amido-C=O), 1650(C=O) and 1642 (C=N).

PMR Spectrum (in $CDCl_3$) showed characteristic absorption peaks at (in δ ppm): 11.25 (bs, 1H, NH), 9.37 (s, 1H, CHO), 7.25-7.96 (m, 8H, CH of pyrazole ring and Ar-H) and 6.55 (bs, 2H, CO-CH_2, enolic).

Synthesis of (benzaldehyde/4-nitrobenzaldehyde/4-methoxy benzaldehyde-5,6-dichlorobenzothiazol-2-yl)amidomethyl hydrazones (IV-VI).

A mixture of compound I (0.01 mol) and various aromatic aldehydes (0.01 mol) in absolute alcohol (30 ml) was refluxed for 8 h on water bath. The contents were cooled and the product isolated was recrystallized from ethanol to give compounds IV-VI.

IR spectrum (KBr) exhibited characteristic absorption bands at (in cm^{-1}): 3355(NH), 1670(amido C=O), and 1640 (C=N).

PMR Spectrum (in $CDCl_3$) showed characteristic absorption peaks at (in δ ppm) : 10.25 (bs, 2H, NH, 2 x NH), 9.05 (s, IH, CH=C) 7.45-8.10 (m, 7H, Ar-H) and 6.90 (s, 2H, CO-CH_2, enolic).

Antiinflammatory activity

Antiinflammatory activity of title compounds (III-VI) was determined by carrageenin-induced rat-paw edema method[14] at a dose of 100 mg/kg body weight in albino rats and ibuprofen as a reference standard, however, after performing the toxicity and gross behavioural studies[15-16] and the results are given in Table-1.

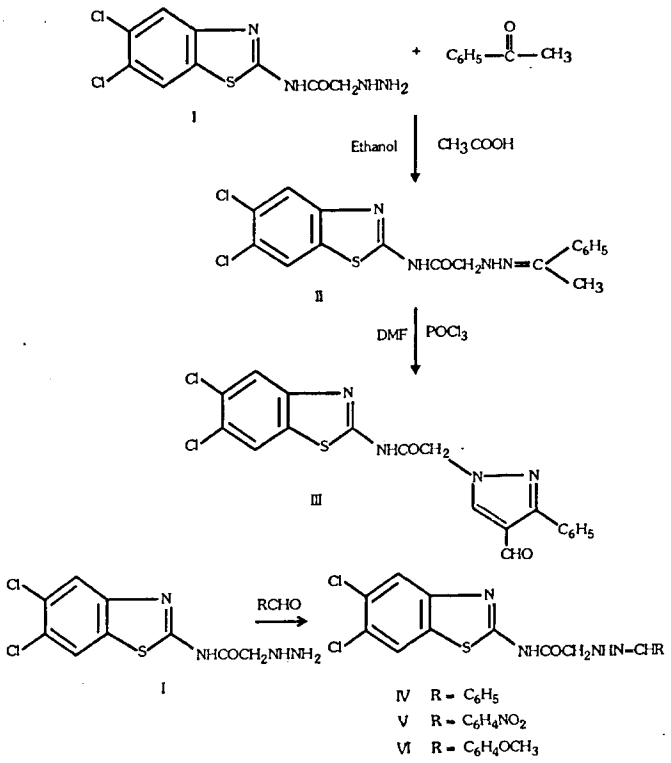
Antimicrobial activity

Antibacterial activity of title compounds (in DMSO) was determined by two-fold dilution method[17] at a concentration of 12.5 µg/ml to 100 µg/ml against gram positive bacteria, *Bacillus subtilis* and gram negative bacteria, *Escherichia coli*, employing streptomycin as the standard, while antifungal activity was determined in a similar way against *Candida albicans* (Ca27) and *Trichophyton mentagrophytes* using amphotericin-B as the standard. Solvent control was also maintained in both the studies under similar conditions. The results are presented in Table-1.

RESULTS AND DISCUSSION

Gross behavioural and acute toxicity studies reveal that all the compounds were non-toxic even at the dose

SCHEME



of 1000 mg/kg. Therefore, 1/10th of the toxic dose, which is 100 mg/kg was used for antiinflammatory activity study employing ibuprofen as standard under similar conditions. Almost all the compounds showed antiinflammatory activity when compared to the solvent control at the second and fourth hour. Compound III exhibits significant antiinflammatory activity compared with the rest of the compounds under investigation and this could be attributed to the presence of pyrazole nucleus.

Results on antibacterial activity shows that compounds III-VI were found to be active against *B. subtilis* at a concentration of 50 µg/ml but not active against *E. coli.* Among the four test compounds for antifungal activity, compound III possesses activity against *Candida albicans* at a concentration of 25 µg/ml and the remaining compounds IV-VI showed activity at a concentration of 50 µg/ml, but all the four compounds fail to show activity against *Tricophyton mentagrophytes.*

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