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SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF 3-ARYL SUBSTITUTED 5-NITRO -7-METHOXY -1, 2, 4-TRIAZOLO-[3, 4-*b*] BENZOTHIAZOLES

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Abstract
2-nitro-4-methoxy aniline **1** on treatment with sodium thiocyanate in acetic acid afforded 2-amino-4-nitro-6-methoxy benzothiazole **2**. Compound **2** in ethylene glycol was heated at 150 ^{0}C with 80% hydrazine hydrate to get 4-nitro-6-methoxy-2-hydrazino benzothiazole **3**. This hydrazino compound **3** on heating with 2-hydroxy-3-methoxy benzaldehyde/4-hydroxy-3-methoxy benzaldehyde/2-hydroxy benzaldehyde/ napthaldehyde/ cinnamladehyde /4-dimethylamino benzaldehyde to obtain corresponding hydrazones (4a-4f).
These hydrazones (4a- 4f) in benzene independently were refluxed on water bath for three hours with Attenburrow's MnO_2 to obtain 3-(2'-hydroxy-3'-methoxy phenyl (5a)/4'-hydroxy-3'-methoxy phenyl (5b)/2'-hydroxy phenyl(6c)/1'-napthyl (5d) / cinnamyl (5e) / 4'-dimethyl amino phenyl(5f))-5-nitro-7-methoxy-1,2,4-triazolo-[3,4-*b*]-benzothiazoles respectively.

All these newly synthesized compounds were treated with seed and observe its effect on seed germination.

Introduction:
1,2,4-triazole and their derivatives are important compounds in agriculture, industrial and biological activities[2-4] , including antimicrobial[5-6] anti-convulsant[7-8] and antiinflamatory[9]. Similarly benzothiazoles are known to posses different activities such as anticancer[10], anthelmintic activity[11],antitubercular activity[12].
A survey of literature reveals such fused substituted tricyclic triazoles are prepared by different methods[13- 14] but little work is carried out on nittro derivative of such fused tricyclic triazoles. Hence it was thought worthwhile to synthesize 5-nitro-7-methoxy as a substituent on benzene moiety in the 1,2,4-triazolo-[3,4-*b*]-benzothiazole system.

As the first step, the solution of sodium thiocynate in glacial acetic acid, 2-nitro-4-methoxy aniline (1) was added .The mixture was stirred well and bromine in glacial acetic acid was added drop by drop maintaining the temp. below 5 ^{0}C. The residue filtered, dissolved in hot water and neutralized by alkali. The obtained product 2-amino-4-nitro-6-methoxy benzothiazole (2) was recrystlised by using ethanol.

On the basis of elemental analysis and spectral data the resulting product (2) has assigned the structure 2-amino-4-nitro-6-methoxy benzothiazole. The I.R. spectrum showed absorption bands at 3440 cm^{-1} and 3340 cm^{-1} due to asymmetric and symmetric stretching of -NH_2 group respectively. The PMR spectrum exhibited broad peak of δ 6.0 due to -NH_2 protons and two singlets in the region δ 7.0 - 7.5 due to two Ar-H protons. 2-amino-4-nitro-6-methoxy benzothiazole shows singlet at δ 3.4 and due to -OCH_3, while The mass spectrum reveals molecular ion peaks at 227 .
2-Amino-4-nitro-6-methoxy benzothiazole (2) in ethylene glycol as solvent was heated with 80% hydrazine hydratehydrochloride over an oil bath for three hours keeping temp. at 150°C to get the product, 4-nitro-6-methoxy-2-hydrazino benzothiazole (3). The I.R. spectrum of (3) showed absorption bands at 3320 cm^{-1} and 3203 cm^{-1} due to -NH_2 asymmetric and symmetric stretching respectively. The mass spectrum exhibits molecular ion peaks of equal intensity at 242.

This 4-nitro-6-methoxy-2-hydrazino benzothiazole (3) in ethanol was refluxed on water bath for three hours independently with 2-hydroxy-3-methoxy-benzaldehyde/4-hydroy-3-methoxy benzaldehyde/2-hydroxybenzaldehyde/ napthaldehyde/cinna-mladehyde/4-dimethyl aminobenzaldehyde to obtain corresponding hydrazones (4a-4f). [4-bromo 2(substituted phenyl / napthyl) -4-nitro-6-methyoxy benzothiazolyl hydrazone]. The I.R. spectra of hydrazones showed stretching absorption bands in the region 3450-3100 cm^{-1} due to –N-H stretching. The presence of broad singlet in their PMR spectra in the region δ 2.5 to δ 4.5 confirmed the presence of -NH proton. The mass spectrum of the compound (4a) shows molecular peak at 344 (M^+), which corresponds to molecular weight of the compound.

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These hydrazones (4a- 4f) in benzene independently were refluxed on water bath for three hours with Attenburrow's MnO_2[1] to obtain 3-(2'-hydroxy-3'-methoxy phenyl (5a) / 4'-hydroxy-3'-methoxy phenyl (5b) / 2'-hydroxy phenyl (5c) /1'-napthyl(5d) / cinnamyl (5e) / 4'-dimethyl amino phenyl(5f)-5-nitro-7-methoxy-1,2,4-triaz-olo[3,4-*b*]-benzothiazoles respectively. The I. R. spectra of these triazolo benzothiazoles observed the absence of strong bands in the region 3450cm^{-1} - 3100 cm^{-1} due to -NH stretching , however the absence of broad singlet in PMR spectra of these triazolo benzothiazole in the region δ 2.5 - δ 4.5 confirms the formation of cyclised products.

The mass spectrum of compound (5f) exhibits molecular peak at 370 which corresponds to its molecular weight. It confirms the formation of 5-bromo-3-(4'- dimethyl amino phenyl)-4-nitro-7-methoxy 1,2,4-triazolo-[3,4-*b*]-benzothiazole products

Experimental:
Melting points were determined in open capillaries and are uncorrected. Infrared spectra were recorded in Nujol / potassium bromide pellets on Bomen MB 104FT infrared spectrophotometer. ^{1}HNMR spectra were obtained on a Gemini 200 Mz specrtometer with TMS as an internal standard and mass spectra on FT VG-7070H mass spectrometer using the GI technique at 70 ev. Elemental analysis was carried out on aHeraeus CHN-O Rapid analyser. Purity of the compound was checked by TLC and elemental analysis.

Synthesis of 2-Amino-4-nitro-6-methoxy benzothiazole (2)
2-nitro-4-methoy aniline (30.8 gm, 0.2 M) and sodium thiocynate (16 gm, 0.2 M) were dissolved in glacial acetic acid (150 ml). The solution was cooled in freezing mixture. Bromine (32 gm, 10 ml, 0.2 M) in glacial acetic acid (25 ml) was added with stirring and maintaining temperature below 25°C. The mixture was allowed to stand for one hour at room temp. The resulting hydrobromide was dissolved in hot water and neutralized with 10 % NaOH to obtain base. The amine thus obtained was filtered, washed with water and recrystallized in aq. alcohol to get the product 18 gm. M.P 158 °C., IR (KBr): 3440 cm^{-1} (Asymmetric stretching of -NH_2), 3340 cm^{-1}(N-H Symmetrical stretching of -NH_2), 3052cm^{-1} (Ar-H stretching), 1630 cm^{-1} (-C=N stretching), 1325 cm^{-1} (Ar–C-O stretching), ^{1}HNMR ($CDCl_3$) : δ 3.4 (singlet, 3H, CH_3) due to -OCH_3, δ 6.0 (broad, 2H, NH_2), δ 7.0-7.5 (two singlet, 2H, Ar-H), m/z 211 (M^+)

2-hydrazino -4-nitro-6-methoxy benzothiazole (3)
Hydrazine hydrate (80%, 9 ml) was taken in a flask, cooled to 5°C and concentrated HCl (6 ml) was added to it with stirring. The flask was kept at room temperature for few minutes and then 2-amino-4-nitro-6-methoxy benzothiazole (6 gm) was added in portions. Ethylene glycol (24 ml) was added into the flask. The contents of the flask were heated at 140 °C on an oil bath for three hours and then cooled. The separated product, 2-hydrazino-2-hydrazino-4- bromo-6-ethoxy benzothiazole was filtered, washed with cold water and crystallized from ethyl alcohol to give 4.2 gm, M. P. 262°C, IR (KBr) : 3320 cm^{-1} (asymmetric N-H stretching of –NH_2), 3203 cm^{-1} (symmetric N-H stretching of –NH_2) m/z: 226 (M^+)

General procedure
4-nitro- 2-substituted-6-methoxy benzothiazolyl hydrazone. (5a-5f)
The mixture of 2-hydrazino-4-nitro 6-methoxy benzothiazole (2.88 gm, 0.01M) was dissolved in ethanol (50 ml) and aromatic aldehydes (2-hydroxy-3-methoxy-benzaldehyde / 4-hydroy-3-methoxy benzaldehyde / 2-hydroxybenzal dehyde / napthaldehyde / cinnamladehyde / 4-dimethyl aminobenzaldehyde) (0.01 M) in ethanol (25 ml) was refluxed on water bath for two hours. The reaction mixture was cooled, the solid product obtained, filtered at pump, washed with ethanol and recrystallized from hot benzene.
Compound (4a-4f) IR (KBr) : 3423 cm^{-1} (O-H stretching) , 3209 cm^{-1} (N-H stretching) which conform the formation of hydrazone.

General procedure
3-Substituted-5-nitro-7-methoxy 1,2,4 triazolo [3,4-*b*]-benzothiazole. (5a-5f)
4-nitro-2-substituted -6-methoxy benzothiazolyl hydrazone (0.002 M) was taken in dry benzene (50 ml). To this was added Attenbarrow's active manganese dioxide[1] (2.0 gm, 0.016 M) and the mixture was refluxed on water bath for three hours. Contents were poured on hot condition in petridish, benzene solvent was removed by distillation. Obtained solid product was recrystallized from hot ethanol, Cream coloured compound 5f shows IR (KBr):3200 cm^{-1} (O-H stretching) Band due to N-H stretching absent. All compound (5a-5f) shows absence of N-H stretching absent.

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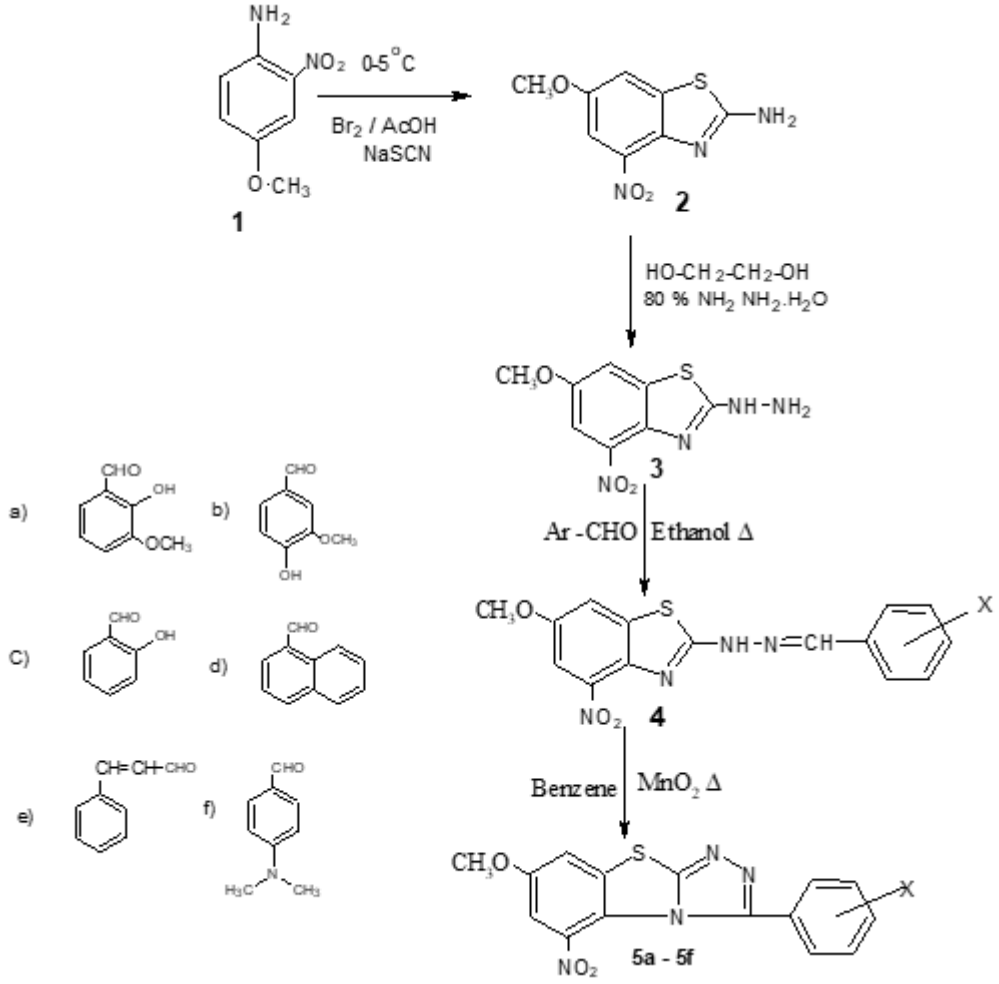
Scheme



Result and Discusion

The structures of these tricyclic triazolo benzothiazoles (5a- 5f) were assigned on the basis of their elemental analysis and spectral data The I. R. spectra of these triazolo benzothiazoles, observed the absence of strong bands in the region 3450cm^{-1} - 3100 cm^{-1} due to -NH stretching , however the absence of broad singlet in PMR spectra of these triazolo benzothiazole in the region δ 2.5 - δ 4.5 confirms the formation of cyclised products.

The mass spectrum of compound (5f) exhibits molecular peak at 470 which corresponds to its molecular weight. It confirms the formation of 5-nitro-3-(4'-dimethylamino phenyl)-7-methoxy 1,2,4-triazolo-[3,4-*b*]-benzothiazole products.

Antibacterial Activity

The compound 5a to 5f were tested for their antimicrobial activity by cup plate agar diffusion method against *E.coli* (Gram –ve) *B.subtilis* (Gram +ve), *E. carotovara* and *Xanthomonas citri* using ampicillin, streptomycin. and penicillin as a standard for comparison. The antibacterial screening data of the compounds is presented in table No.1. Dimethyl sulphoxide was used as a control (solvent).

Table: 1

Sr. No.	Comp.	Antimicrobial activity (zone of inhibition in mm)			
		E.coli	***Erwinia***	***Bacillus***	***Xanthom-Onas citri***
1	5a	14	12	10	12
2	5b	16	14	12	13
3	5c	12	04	06	08
4	5d	00	04	03	04
5	5e	14	13	10	12
6	5f	10	10	08	07
Ampicillin		16	18	17	15
Streptomycin		20	18	22	18
Penicillin		15	20	18	17
Control		00	00	00	00

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Result and discusion

The compounds 5a to 5f were tested for their antimicrobial activity by the cup plate agar diffusion method against *E. Coli, Erwinla carotovara, Bacillus substilis, and Xanthomonas citri.* The antibacterial screening data of the compound shows compound 5b is more active against *E. Coli, Erwinla carotovara and Xanthomonas citri* while compound 5e is more active against *E. Coli, Erwinla carotovara*

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