SYNTHESIS AND BIOEFFICACY TEST OF SOME NOVEL HALOGENATED -4-[(SUBSTITUTED-BENZOTHIAZOL-2-YL)-HYDRAZONO] -2- (SUBSTITUTED PHENYL)-5-METHYL -2, 4-DIHYDRO-PYRAZOL-3-ONE

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Abstract :

Some new 4-[(substituted-benzothiazol-2-yl)-hydrazono]-2-(substituted phenyl) -5-methyl- 2, 4-dihydro-pyrazol-3-one (3) have been prepared by reacting substituted benzothiazol-2-yl amine with acetoacetic ester, 2-[substituted benzothiazol -2-yl)-hydrazono]-3-oxo-butyric acid ethyl ester (2) react with different hydrazines to give the title compounds. These compounds are evaluated for their antimicrobial activity. The structures of all these compounds have been confirmed by I.R., ^{1}HNMR,Mass spectra and elemental analysis data.

Introduction

Pyrazoles are very useful as antibacterial[1], antifungal[2] and antiviral[3] agents.In continuation of our work on heterocyclic[4,5]compounds, we have synthesized some new halogenated hydrazono pyrazol-3-one. The compounds containing thiazole[6,7] nucleus along with pyrazole enhance their biological activity. Fungicidal activity was evaluated against *Alternaria burnsii* and *Macrophomina phaseolina.*

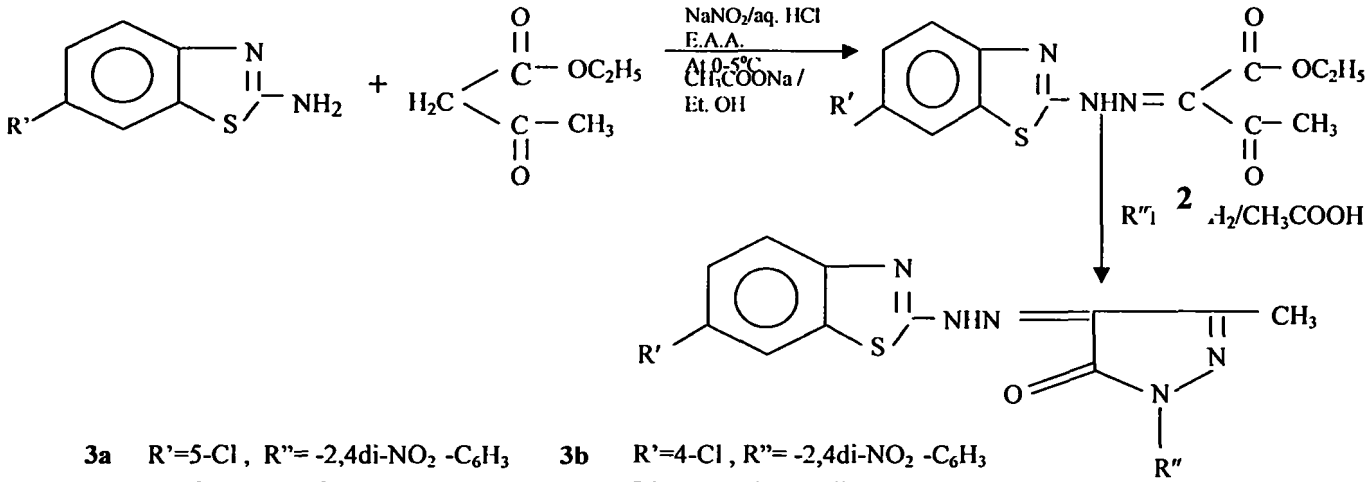
The reaction of diazonium salt[8] (formed by the diazotization of substituted benzothiazol-2-yl amino by $NaNO_2$ in aq. HCl) with acetoacetic ester in the presence of sodium acetate and ethanol gave 2-[(substituted benzothiazol-2-yl)-hydrazono]-3-oxo-butyric acid ethyl ester (2), which on further reaction with hydrazines gave title compound (3). (SCHEME-1)

Result and discussion

2-[(Substituted benzothiazol-2-yl)-hydrazono]-3-oxo-butyric acid ethyl ester (2) have been prepared by diazotization of substituted benzothiazol-2-yl amino with aceto acetic ester at 0-5°C with continuous stirring for 2 ½ h. The diazotized form has been reacted with hydrazine in presence of acetic acid on water bath for 4-5 h to yield hydrazono pyrazol-3-one (3).

Compound (2) showed the presence of >NH group in IR spectrum at 3375 cm^{-1} and in ^{1}HNMR spectrum showed a singlet at δ 8.6 ppm.

The IR spectrum of compound **3a** showed peak at 3360 (>NH),1510(>NHN=C), 1645(>C=O),3040(aromatic)cm^{-1}IR spectrum. ^{1}HNMR showed peaks at δ 9.2 ppm (>NH),δ 2.5ppm ($-CH_3$) and δ 7.2-7.8 ppm for aromatic protons. Finally mass spectrum of **3a** shows M^+ at m/z 459 .



3a R'=5-Cl , R"= -2,4di-NO_2 -C_6H_3 **3b** R'=4-Cl , R"= -2,4di-NO_2 -C_6H_3

3c R'=6-F , R"= -C_6H_5 **3d** R'= 4-F, R"= -2,4di-NO_2 -C_6H_3

3e R'=5-Cl , R"= -C_6H_5 **3f** R'=4-Cl , R"= -C_6H_5

3g R'=4-F , R"= -C_6H_5 **3h** R'= 6-F, R"= -2,4di-NO_2 -C_6H_3

3 a-h

SCHEME-1

Fungicidal activity

The synthesized compounds were evaluated for their antifungal activities against two plant pathogenic fungi viz. *Alterneria burnsii* causing blight in cumin and *Macrophomina phaseolina* (Tassi) Goid, causing stem rot in cluster beans. Pure culture of fungi raised on potato dextrose agar medium and activity of compounds were tested adopting food poison technique and measurement of radial growth. Each fungus was tested at two dosages (100 ppm and 500 ppm) with each dose replicated thrice. The radial growth of fungal colony was measured for seven days. The % inhibition of fungal growth of compounds was calculated using following formula.

$$\% \text{ inhibition} = \frac{DC - DT}{DC} \times 100$$

DC = Diameter of radial growth in untreated petriplate.

DT= Diameter of radial growth in treated (compound mixed in fungal medium) petriplate.

All the compounds showed low to high level of antifungal activity. The compounds were found more effective (higher % inhibition) against *Alternaria burnsii* as compared to *Macrophomina phaseolina*.Among the eight tested compounds maximum antifungal activity (84.5-92.3 % inhibition at 500 ppm dose) was found in compound **3d** and **3h** followed by compound **3c** and **3g** (60.4-72.2 % inhibition at 500 ppm dose). The remaining four compounds showed relatively low level of antifungal activity (20.7-40.1% inhibition at 500 ppm dose).

Thus the fluorine containing compounds were found to have more antifungal activity as compared to chlorine containing compounds. The presence of $-NO_2$ group appeared to have enhancing effect on the antifungal property of fluorine containing compounds.

Experimental

Purity of all the compounds was checked on silica gel G plates using iodine as the detecting agent. Melting points were determined in open capillary and were uncorrected. IR spectra were recorded on a SHIMADZU 8400S FT-IR spectrometer in KBr pellets. ^{1}HNMR (chemical shifts in δ ppm) were recorded using JEOL DRX-300 spectrometer

(300MH_Z) apparatus with TMS as the internal standard. Mass spectra were recorded on a Jeol SX 102/Da-600 mass spectrometer.

2-[(5-chloro-benzothiazol-2-yl)-hydrazono]-3-oxo butyric acid ethyl ester (2)

5-choloro benzothiazol-2-ylamine (0.01 mole) was dissolved in a mixture of concentrated HCl (8ml) and water (6ml) and cooled to 0°C on ice bath. A cold aqueous solution of sodium nitrite (0.02 mole) was added. The cold diazonium salt solution was filtered into a cooled solution of ethyl acetoacetate (0.01 mole) and sodium acetate (0.05 mole) in ethanol (25 ml) and stirred it for 2 hrs and resulting solid was filtered, dried and crystallized from ethanol m.p.190°C,yield(68%);IR(KBr)V_{max}:3375(>NH),1490(>NHN=C),1635(>C=O),3035(Aromatic)^{1}HNMR(DMSO-d_6)δ:1.5(t,3H,CH3),2.6(s,3H,COCH3),4.2(q,2H,OCH2),7.4-7.8(m,ArH),
8.6(s,H,>NHN=C),(foundC,47.85,H,3.64,N,12.01,S,9.75,$C_{13}H_{12}ClN_3O_3S$ requires C, 47.93, H,3.71,N,12.9,S, 9.84 %)

4-[5-chloro-benzothiazol-2-yl)-hydrazono]-2-(2,4-dinitro-phenyl)-5-methyl-2,4-dihydro -pyrazol-3-one

2-[(5-chloro benzothiazol-2-yl)-hydrazono]-3-oxo-butyric acid ethyl ester (0.01 mole) dissolved in glacial acetic acid (5ml) and a solution of 2,4-dintro phenyl hydrazine (0.01 mole) in glacial acetic acid (5 ml) was added and the mixture was refluxed for 4-5 h on a water bath. Resulting solid was dried and crystallized from ethanol **3a** m.p. 202°C yield (64 %);IR (KBr) V_{max}: 3360 (> NH), 1510(>NHN=C), 1645(> C =O), 3040(Aromatic), 1315 (–NO_2), ^{1}HNMR (DMSO-d_6) δ: 9.2 (s,H >NHN=C),2.5 (s,3H,–CH_3),7.2-7.8 (m, Ar–H), MS (m/z) : 459 (M^+). (Found C,44.31, H,2.10, N,21.26, S,6.91, $C_{17}H_{10}N_7O_5SCl$ requires C, 44.40, H, 2.19, N, 21.32, S, 6.97 %).

Compounds 3a-h were prepared similarly. Their physical and analytical data are recorded in table **1**.

Table 1 : Physical and Analytical Data of the Compound 3a-h

Compounds	`Yield (%)	M.P. (°C)	Mol. Formula (mol. wt.)	Analysis % found/(calcd)			
				C	H	N	S
3a	75 %	202	$C_{17}H_{10}N_7O_5SCl$ (459.82)	44.31 (44.40)	2.10 (2.19)	21.26 (21.32)	6.91 (6.97)
3b	69 %	220	$C_{17}H_{10}N_7O_5SCl$ (459.82)	44.32 (44.40)	2.11 (2.19)	21.25 (21.32)	6.90 (6.97)
3c	72 %	155	$C_{17}H_{12}N_5OSF$ (353.37)	57.70 (57.78)	3.36 (3.42)	19.75 (19.82)	9.00 (9.07)
3d	70 %	178	$C_{17}H_{10}N_7O_5SF$ (443.37)	46.01 (46.05)	2.21 (2.27)	22.05 (22.11)	7.18 (7.23)
3e	75 %	120	$C_{17}H_{12}N_5OSCl$ (369.83)	55.16 (55.21)	3.21 (3.27)	18.88 (18.94)	8.60 (8.67)
3f	65 %	135	$C_{17}H_{12}N_5OSCl$ (369.83)	55.15 (55.21)	3.21 (3.27)	18.86 (18.94)	8.60 (8.67)
3g	70 %	110	$C_{17}H_{12}N_5OSF$ (353.37)	57.71 (57.78)	3.36 (3.42)	19.77 (19.82)	9.00 (9.07)
3h	65 %	170	$C_{17}H_{10}N_7O_5SF$ (443.37)	46.00 (46.05)	2.24 (2.27)	22.07 (22.11)	7.19 (7.23)

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References

1. A.Mohammed, S. M. Hassan and A.Wadood, *Orient. J. Chem.*,**18**,351 (2002).
2. S.K. Sahu, M.Banerjee, A.Samantray,C.Behara and M.A. Azam,*Trop J. Pharm. Res.*,7 ,961(2008).

3. G.Ouyang, Z.Chen, X. J.Cai, B.A.Song, P.S.Bhadury, S.Yang, L.H.Jin, W.Xue, DY. Hu and S.Zeng, *Bioorg Med Chem.,* **16** , 9699 (2008).
4. U.Gupta,V.Sareen,V.Khatri and S.Chug,*Indian J. Heterocyclic Chem.,* **15,** 305(2006).
5. V.Sareen,V.Khatri,U.Garg,P.Jain and K.Sharma, *Phosphorous, Sulphur and Silicon,* **182** ,2943 (2007).
6. J.Rudolph, H.Thesis, R.Hanke, R.Endermann, L. Johannsed and F.U. Geschke, *J. Med Chem.,* **44**,619 (2001).
7. M.J. Gorezynski, R.M. Leal, S.L. Moberry, J.H. Bushweller and M.L. Brown , *Bioorg Med Chem.,***12**,1029 (2008).
8. K.Sharma, V. Sareen and V. Khatri *Indian J. Heterocyclic Chem.,***14**, 161(2004).

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