



SYNTHESIS AND BIOLOGICAL EVALUATION OF SOME NEWLY SYNTHESIZED PYRAZOLES

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ABSTRACT

Some new benzothiazoles and pyrazoles were synthesized from substituted chalcone dibromides and 6-substituted-2-hydrazinobenzothiazoles. These have been screened for their biological activity. The constitution of synthesized compounds has been characterized by elemental analysis and IR. The products have been screened for their *in vitro* biological assay like antibacterial activity.

Key words: Chalcone dibromide, Pyrazole, Antibacterial activity.

INTRODUCTION

Pyrazoles represent one of the most important classes of heterocyclic compounds. Some important drugs and dyes belong to pyrazole series. The most important pyrazole drug is phenylbutanone noted for its longer persistence in blood stream. It relieves pain in many inflammatory conditions such as arthritis and occupies a place in therapy intermediate between cortisone and the salicylates. Chalcones^{1,2} are useful intermediates in the synthesis of various heterocyclic compounds such as pyrazolines, pyrazoles, pyrimidines, flavones and flavonols.

A number of heterocycles substituted with hydroxyl phenyl moiety are used as analgesics, antitissuive and anticonvulsant agents. Literature survey reveals that pyrazole compounds have attracted attention due to their varied physiological and pharmacological properties^{3,4}. Antibacterial activity⁵ has also been reported for pyrazole and their derivatives.

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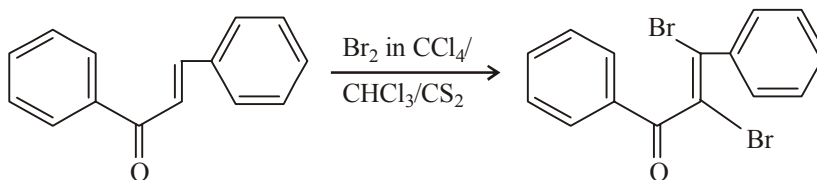
Keeping in view the biological and clinical activities of benzothiazoles and pyrazoles and encouraged with our previous works^{6,7}, we now report some new 3, 5-diphenyl-1-(6-substitutedbenzothiazolo) pyrazoles.

EXPERIMENTAL

All chemicals and solvents used were BDH products. Melting points were determined in open capillary tubes and are uncorrected. IR spectra were recorded on a Perkin-Elmer 157G grating-infrared spectrophotometer using KBr pellets. All synthesized compounds have been screened for their antibacterial activity.

Preparation of chalcone dibromide

Chalcone dibromide was prepared by the bromination of substituted chalcone in different solvents.



Preparation of 6-substituted-2-hydrazinobenzothiazole

It was prepared in the following steps:

(a) Preparation of p-substituted phenylthiourea

An appropriate p-substituted aniline (0.1 mol) was dissolved in a mixture of conc. HCl (9 mL) and water (25 mL) by warming on a water bath. The solution of amine hydrochloride thus obtained was cooled and solid ammonium thiocyanate (0.1 mol) was added. The reaction mixture was heated on a water bath for 5 h. Thereafter, the reaction mixture was cooled and the precipitated crude product was filtered, washed with water, dried and crystallized from ethanol.

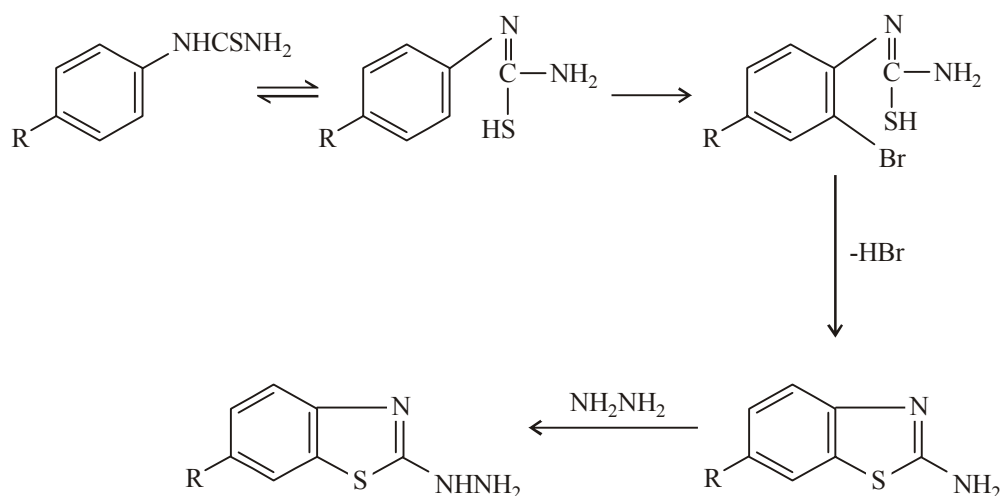
(b) Preparation of 6-substituted-2-aminobenzothiazoles

To a suspension of an arylthiourea (0.1 mol) in chloroform (100 mL), bromine (0.15 mol) in chloroform (100 mL) was added. The mixture was heated under reflux for 15 min.,

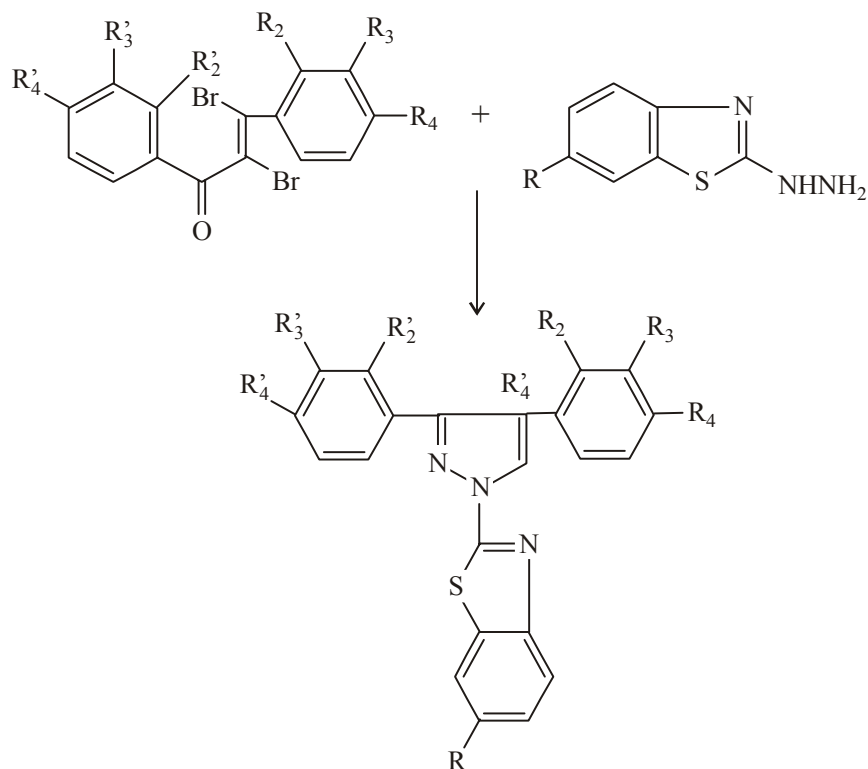
which was accompanied by the evolution of dense white fumes of hydrogen bromide. After the reaction was over, chloroform was distilled off and a semi-solid product, thus obtained was treated with sulphurous acid till the brown colour was discharged and the solid dissolved. The solution was then filtered from undissolved matter and the filtrate was treated with aq. ammonia. The solid, which separated out, was filtered; washed with water, dried and crystallized from an appropriate solvent.

(c) Preparation of 6-substituted-2- hydrazinobenzothiazoles

Conc. HCl (10 mL) was added dropwise with stirring to hydrazine hydrate (100 %, 10 mL, 0.2 mol) at 5-6⁰C (in ice bath). To this, ethylene glycol (40 mL) was added and then 6-substituted-2-aminobenzothiazoles (0.05 mol) was added in small portions. The resultant mixture was refluxed for 2 h. and cooled. A fine crystalline solid, which separated on cooling, was filtered, washed with water and dried. It was recrystallized from ethanol.



Chalcone dibromides, when refluxed with 6-substituted-2-hydrazinobenzathizoles in ethanol for 5 hours afforded the corresponding pyrazoles.



Where, R = H, CH₃, Cl; R₂ = H, OH; R₃ = R₄ = H; R₂ = H; R₃ = H, NO₂ and R₄ = H, Cl, OCH₃.

Preparation of 2'-hydroxy-4-chlorochalcone dibromide

2-Hydroxy-4-chlorochalcone (2.6 g) in carbon disulphide (100 mL) was added to bromine (0.5 mL) in the same solvent keeping the temperature 0-5°C. The solid mass obtained was filtered and washed with cold water. Recrystallization from alcohol gave yellow shining plates (2.4 g, m.p. 185-86°C).

(I) Synthesis of 3-(2'-hydroxyphenyl)-5-(4-chlorophenyl)-1-(6-chlorobenzothiazolo)pyrazole

2-Hydroxy-4-chlorochalcone dibromide (0.21 g) in ethanol (30 mL) was added to 6-chloro-2-hydrazinobenzothiazole (0.30 g). The contents were refluxed for about 4 h and allowed to cool to room temperature. It was diluted with water, filtered, washed with water and dried. It was then recrystallized from a mixture of chloroform and alcohol (1 : 1) when dark yellow crystals were obtained.

IR: ν_{\max} (KBr): 3340, 3020, 1670, 1590, 1570, 1490, 1450, 1380, 1330, 1270, 1200, 1170, 1150, 1100, 1070, 1060, 1030, 1000, 980, 930, 920, 870, 810, 780, 680 and 660 cm^{-1} .

Preparation of 2'-hydroxy-4- methoxychalcone dibromide

2-Hydroxy-4- methoxychalcone (5 g) was dissolved in dry carbon tetrachloride (25 mL) and to this, bromine (1 mL) dissolved in carbon tetrachloride (8.0 mL) was added drop wise. The temperature was kept below 5^oC with occasional shaking. The reaction mixture was kept for one night. It was filtered under suction, a yellow solid separated, which was crystallized from chloroform as yellow crystals (4.9 g, m.p. 163 ^oC).

(II) Synthesis of 3-(2'-hydroxyphenyl)-5-(4-methoxyphenyl)-1-benzothiazolopyrazole

2-Hydroxy-4- methoxychalcone dibromide (0.41 g) in ethanol (40 mL) was added to 2-hydrazinobenzothiazole (0.16 g). The mixture was refluxed for 4 hours and then cooled to room temperature. The solid thus separated was filtered, washed with water and dried. It was then crystallized from a mixture of chloroform and alcohol (1 : 1), when light orange crystals were obtained.

IR: ν_{\max} (KBr): 3420, 3060, 2940, 1610, 1570, 1550, 1440, 1360, 1330, 1270, 1030, 1020, 930, 870, 750, 700, 610, 600 and 580 cm^{-1} .

(III) Synthesis of 3-(2'-hydroxyphenyl)-5-(4-methoxyphenyl)-1-(6-chlorobenzothiazolo) pyrazole

2-Hydroxy-4- methoxychalcone dibromide (0.41 g) in ethanol (40 mL) was added to chloro-2-hydrazinobenzothiazole (0.20 g). The mixture was refluxed for 4 hours and then cooled to room temperature. The solid thus separated was filtered, washed with water and dried. It was then crystallized from a mixture of chloroform and alcohol (1 : 1), when dark yellow crystals were obtained.

IR: ν_{\max} (KBr): 3420, 3020, 2900, 1680, 1610, 1600, 1530, 1450, 1350, 1330, 1300, 1270, 1220, 1140, 1110, 1080, 1020, 970, 930, 810, 760, 730, 690, 660 and 590 cm^{-1} .

Preparation of 3-nitrochalcone dibromide

3-Nitrochalcone (10 g) was dissolved in dry carbon tetrachloride (100 mL) and to this, bromine (4 mL in 25 mL carbon tetrachloride) was added drop wise. The reaction mixture was kept as such for 12 h with occasional shaking after the addition of bromine. It was then filtered under suction. Yellow solid separated was recrystallized from ethanol as light yellow crystalline substance (8.6 g, m.p. 187 ^oC).

(IV) Synthesis of 3-phenyl-5-(3-nitrophenyl)-1-benzothiazolo pyrazole

3-Nitrochalcone dibromide (0.86 g) in ethanol (30 mL) was added to 2-hydrazinobenzothiazole (0.33 g). The mixture was refluxed for 7 hours and then cooled to room temperature. The solid thus separated was filtered, washed with water and dried. Recrystallization was done with a mixture of chloroform and alcohol (1 : 1), when orange crystals were obtained.

IR: ν_{\max} (KBr): 1680, 1610, 1570, 1550, 1520, 1450, 1400, 1260, 1180, 1130, 1100, 1030, 910, 850, 760, 660 and 620 cm^{-1} .

(V) Synthesis of 3-phenyl-5-(3-nitrophenyl)-1-(6-methylbenzothiazolo) pyrazole

3-Nitrochalcone dibromide (0.86 g) in ethanol (30 mL) was added to 6-methylhydrazinobenzothiazole (0.35 g). The mixture was refluxed for 9 hours and then cooled to room temperature. The solid thus separated was filtered, washed with water and dried. It was recrystallized from a mixture of chloroform and alcohol (1 : 1) to afford dark orange crystals.

IR: ν_{\max} (KBr): 3000, 2920, 1680, 1600, 1580, 1550, 1520, 1440, 1400, 1250, 1170, 1140, 1030, 1010, 920, 850, 810, 760, 660 and 630 cm^{-1} .

Preparation of 2'-hydroxychalcone dibromide

2-Hydroxychalcone (8.96 g) was dissolved in chloroform (28 mL). To this, bromine (2 mL) dissolved in chloroform (16 mL) was added with occasional shaking keeping the temperature 0-5⁰C for one hour. The solid thus separated was filtered, washed with cold ether. Crystallization from carbon tetrachloride gave yellow crystals (8.0 g, m.p. 191 ⁰C).

(VI) Synthesis of 3-(2'-hydroxyphenyl)-5-phenyl-1-(6-chlorobenzothiazolo) pyrazole

To 2-hydroxychalcone (0.38 g) in ethanol (30 mL), 6-chloro-2-hydrazinobenzothiazole (0.20 g) was added. The mixture was refluxed for 4 hours and then cooled to room temperature. The solid thus separated was filtered, washed with water and dried. It was then recrystallized from a mixture of chloroform and alcohol (1 : 1) to afford pale yellow crystals.

IR: ν_{\max} (KBr): 3400, 3000, 1620, 1610, 1570, 1480, 1450, 1400, 1330, 1260, 1210, 1170, 1150, 1140, 1070, 1050, 1030, 980, 940, 910, 850, 830, 800, 770, 660, 590 and 510 cm^{-1} .

RESULTS AND DISCUSSION

Structure of pyrazole compounds were characterized by elemental analysis and IR spectra. The physical data of the synthesized compounds are recorded in Table 1.

Table 1: Physical data of synthesized pyrazole compounds

Product code	Molecular formula	m.p. (°C)	Yield (g)	Colour	Elemental analysis (%)		
					Found (Calc.)		
					C	H	N
I	C ₂₂ H ₁₃ N ₃ SO ₂ Cl	216-17	0.20	Dark yellow	63.15 (63.01)	2.94 (3.10)	9.38 (10.02)
II	C ₂₃ H ₁₇ N ₃ SO	309-10	0.32	Light orange	72.01 (72.06)	4.21 (4.44)	10.48 (10.96)
III	C ₂₃ H ₁₆ N ₃ SO ₂ Cl	216-17	0.39	Dark yellow	63.19 (63.59)	3.60 (3.69)	9.60 (9.68)
IV	C ₂₂ H ₁₄ N ₄ SO ₂	153-54	0.87	Orange	66.18 (66.33)	3.54 (3.52)	14.10 (14.07)
V	C ₂₃ S ₁₆ N ₄ SO ₂	156-57	0.79	Dark orange	68.90 (69.34)	3.84 (4.02)	10.49 (10.55)
VI	C ₂₂ H ₁₄ N ₃ SOCl	188-89	0.42	Pale yellow	65.38 (65.35)	3.40 (3.46)	10.34 (10.40)

The IR spectra of the pyrazoles show 3-4 absorption bands in the 1620-1500 cm⁻¹ region and it is difficult to ascribe any of these to either C=C or C=N stretching vibrations with certainty⁸. Absorption peaks due to -OH group appear in the region 3430-3300 cm⁻¹.

Antibacterial activity

All the compounds synthesized were subjected to *in vitro* antibacterial screening against Gram positive (*Staphylococcus aureus* and *B. subtilis*) and Gram negative (*S. paratyphi-A* and *Escherichia coli*) by agar cup plate method⁹ at concentration of 40 µg/mL in solvent DMF using nutrient agar medium. The zone of inhibition was measured in mm. Under similar conditions, control experiment was carried out using chloramphenicol and streptomycin as standard. The results are recorded in Table 2.

Table 2: Comparable antimicrobial activity with known chosen standard drugs

Standard drugs	Compd.	Gram positive		Gram negative	
		<i>S. aureus</i>	<i>B. subtilis</i>	<i>E. coli</i>	<i>S. paratyphi-A</i>
	I	9	8	-	-
	II	8	11	-	-
	III	10	10	-	-
	IV	13	14	11	-
	V	12	12	10	-
	VI	8	9	-	-
Chloramphenicol		26	24	20	26
Streptomycin		22	23	24	18

It was observed that compounds **IV** and **V** showed moderate activity against *S. aureus* and *B. subtilis*. The remaining compounds were found to be less active against the same bacteria. In case of gram negative bacteria *E. coli*, compound **IV** and **V** showed good activity and the remaining compounds showed no activity. None of the compounds showed any activity against *S. paratyphi-A*.

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