SYNTHESIS AND BIOLOGICAL ACTIVITY OF SOME 4-(5-ALKYL- OR 5-ARYL-2-FURFURYLIDENE-1,3-DISUBSTITUTED-2-PYRAZOLIN-5-ONES.

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Abstract – A series of N-substituted-3-methyl-4-(5-alkyl- or 5-aryl-2-furfurylidene)-2-pyrazolin-5-ones(7-9)a-c have been synthesised by the reaction of N-substituted-3-methyl-2-pyrazolin-5-ones 6a-c with 5-alkyl- or 5-aryl-2-furfuraldehyde. The compounds were evaluated for their antibacterial activity against both Gram-positive and Gram-negative bacteria.

Nitrofuran derivatives are endowed with broad spectrum of antibacterial activities and find applications as commercial drugs[1]. Attempts have been made to modify the structures of the nitrofuran drugs by introducing carrier molecules during drug design[2], with a view to reducing the toxicity. Substituted 5-pyrazolones possess various biological activities [3] . Prompted by these observation and in continuation of our program directed towards developing new approaches for synthesis polyfunctionally substituted diazines of potential activity[4-7], it was thought worthwhile to synthesis and study the biological activities of the title compounds having 5-alkyl- or 5-arylfuran moiety in place of 5-nitrofuran with a view to minimise the toxicity.

For the synthesis of the target compound 5a-c sequence of reactions is summarized in the following :

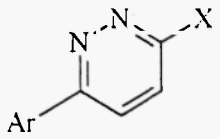
β-(dibenzothien-4-oyl)acrylic acid was allowed to react with hydrazine hydrate in boiling ethanol to furnish 6-(dibenzothien-4-yl)pyridazin-3(2H)-one1 (Scheme I) which upon subsequent reaction with $POCl_3$ /PCl_5

on steam bath yielded the corresponding 3-chloropyridazine derivative[4] 2 in fairly good yield . Reaction of 2 with thiourea in boiling ethanol furnished 6-(dibenzothein-4-yl)pyridazin-3(2H)-thione[8] 3 which underwent facile nucleophilic substitution with hydrazine hydrate to yield the key intermediate[9] 5a . On the other hand, the reaction of 1 and 3 with ethyl chloroacetate in the presence of dry acetone and anhydrous K_2CO_3 yielded 4a,b which subsequently converted to their corresponding hydrazides 5b,c by treatment with hydrazine hydrate in refluxing ethanol [10,11] .

The required 3-methyl-5-pyrazolones 6a-c suitably substituted at position 1 by 6-(dibenzothien-4-yl)pyridazin-3-yl, 6-(dibenzothien-4-yl)pyridazin-3-yloxyacetyl and 6-(dibenzothien-4-yl)pyridazin-3-ylthioacetyl were conveniently prepared by refluxing the respective hydrazides with ethyl acetoacetate in boiling ethanol[4] . In order to study the structure-activity relationship, 5-methyl-, 5-(4-nitrophenyl)- and 5-(4-chlorophenyl)furfurals were empolyed for the condensation . The pyrazolones 6a-c were then refluxed with the alkyl- and/ or arylfurfurals in acetic acid medium employing sodium acetate as the catalyst to furnish the corresponding N-substituted-3-methyl-4-(5-alkyl- or 5-aryl-2-furfurylidene)-2-pyrazolin-5-ones (7-9)a-c (Scheme II) . The structures of the above compounds were confirmed from their physical and spectral data .

Biological activity :

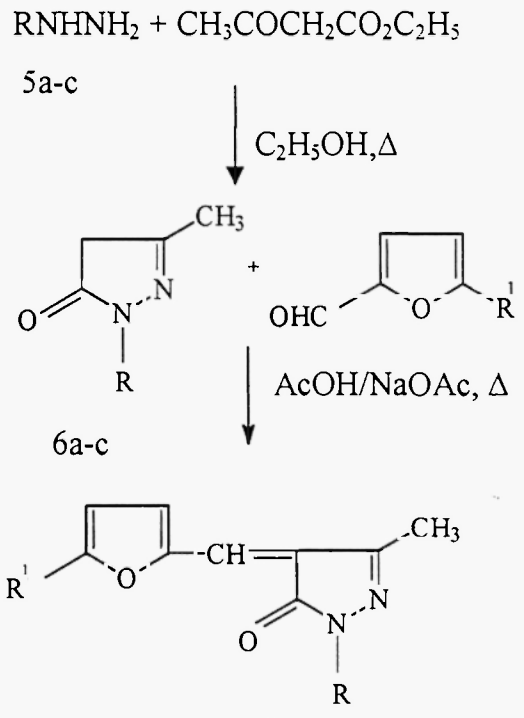
The antibacterial activity of the compounds (7-9)a-c were performed in vitro by filter paper disc method[12] against various pathogenic bacteria, such as Bacillus cereus, Bacillus subtilis and Escherichia coli using nitrofurazone as a reference standard . The culture medium was normal nutrient agar (NA) supplemented with 1 g yeast cm^3. According to the solubility of the tested compounds different polar and



Ar = (Dibenzothien-4-yl); 1,X = OH ; 2 , X = Cl; 3,X = SH;

4a,X = $OCH_2\ CO_2C_2\ H_5$; 4b, X= $SCH_2\ CO_2C_2\ H_5$.

(Scheme I)



(7-9)a-c

R= a, 6-(dibenzothien-4-yl)pyridazin-3-yl ;

b, 6-(dibenzothien-4-yl)pyridazin-3-yloxyacetyl;

c,6-(dibenzothien-4-yl)pyridazin-3-ylthioacetyl .

7a-c, $R^1 = CH_3$; 8 a-c, $R^i = C_6\ H_4.\ NO_2$-p; 9a-c, $R^1 = C_6\ H_4$.Cl-p.

(Scheme II)

nonpolar solvent were used, a good solubility was shown in 15% acetone (v/v) for all test compounds. Preliminary tests were carried out to estimate the minimum inhibitory concentration (MIC) of the test compounds . Based on the previous preliminary test, closely spaced test concentrations were selected, they are 500, 250 125 μgm^{-1} . Nintrofurazone was dissolved in filter sterilized 10 ml of 15% acetone (v/v) and employed in similar concentration as control .

The results obtained from antibacterial activity showed that compounds 7a ,8a and 9a were inactive against Bacillus cereus and Escherichia coli . Others compounds showed a moderate or weak activity against different strains of bacteria except 7c, 8c and 9c (zone of inhibition = 11-17mm; MIC=125 μgm^{-1}) were showed promising activity when compared with the standard (13-20mm;125 μgm^{-1}) . These data indicate that the presence of the thioacetyl group flanked by pyridazine and pyrazole moieties enhance activity compared with oxyacetyl group. Also, it was found that the removal of both groups from the compounds decrease or eliminate the activity .Other biological studies are still in progress .

Experimental

Melting points were taken in open capillary tubes and are uncorrected . IR spectra in KBr were recorded on a shimadzu 470 spectrophotometer and ^1H NMR spectra in DMSO on a JOEL Fx 90 Q9 MHz (Fourier transform NMR spectrometer) using TMS as internal reference (chemical shifts are expressed as δ , ppm) .

The following compounds were prepared as described in the literature.[4,8-11]

6-(Dibenzothien-4-yl)pyridazin-3(2H)-one (1;78%), m.p. 195-97° (from ethonol) (Found: C, 69.2; H,3.8; N,10.3. $C_{16}H_{10}N_2OS$ requires C, 69.1; H,3.6;

N,10.1%); 3-chloro-6-(dibenzothien-4-yl)pyridazine (2;69%),m.p.178-80° (from ethanol) (Found : C,64 .6; H,2.9; N, 9.2. $C_{16}H_9ClN_2S$ requires C, 64.8; H, 3.0 ; N,9.4%); 6-(dibenzothien-4-yl)pyridazin-3(2H)-thione (3;65%), m.p .225-27° (from xylene) (Found : C, 65.1 ; H, 3.6; N, 9.2. $C_{16}H_{10}N_2S_2$ requires C, 65.3; H, 3.4; N, 9.5%) ; ethyl [6-(dibenzothien-4-yl)pyridazin-3-yloxy]acetate (4a ; 68%), m.p. 108-10° (from ethanol) (Found: C,65.6; H,4.7; N,7.9. $C_{20}H_{16}N_2O_3S$ requires C,65.9; H,4.4; N,7.7%); ethyl [6-(dibenzothien-4-yl)pyridazin-3-ylthio]acetate (4b; 65%), m.p. 128-30° (from toluene) (Found : C,63.5; H , 4.5; N, 16.4. $C_{20}H_{16}N_2O_2S_2$ requires C, 63.2; H, 4.2; N, 16.8%); 6-(dibenzothein-4-yl)-3-hydrazinopyridazine (5a; 72%) , m.p. 166-68° (from ethanol) (Found : C , 65.6; H, 4.3; N, 19.5. $C_{16}H_{12}N_4S$ requires C, 65.8; H,4.1 ; N, 19.2%) ; ethyl [6-(dibenzothien-4-yl)-pyridazin-3-yloxy]acetic acid hydrazide (5 b ; 69%) , m.p. 184-86° (from ethanol (Found : C, 61.4; H , 4.4; N , 16.3. $C_{18}H_{14}N_4O_2S$ requires C, 61. 7; H, 4.0; N, 16.0%); [6-(dibenzothein-4-yl)pyridazin-3-ylthio]acetic acid hydrazide (5c; 66%), m.p. 194-96° (from ethanol) (Found : C, 58.9; H,4.1; N, 15.6. $C_{18}H_{14}N_4OS_2$ requires C, 59.0 ; H, 3,8; N, 15.3%). N_1-[6-(dibenzothien-4-yl)pyridazin-3-yl]-,N_1-[6-(dibenzothien-4-yl)pyridazin-3-yloxyacetyl]- and / or N_1-[6-(dibenzothein-4-yl) pyridazin-3-ylthioacetyl]-3-methyl-5-pyrazolones 6a-c.

A mixture of 5a-c (0.01 mole) and ethyl acetoacetate (0.015 mole) in ethanol (30ml) was refluxed for 6 hr .The solid that separated , after concentration and cooling , was crystallised from ethanol to give 6a-c :

6a; yield 67%; m.p. 220 -22° (Found : C, 67.2 ; H, 4.0; N, 15.7. $C_{20}H_{14}N_4OS$ requires C, 67.0; H,3.9; N, 15.6%) ; IR : 1670-1650 (amidic CO),1615-1605 cm^{-1} (C= N) ; ^1H NMR : 2.5 (s, 3H , $CH_3C=N$), 4.1 (s, 2H, pyrazolone protons), 6.9-7.8(m,9H , Ar-H).

6b; yield 69% , m.p . 236-37 ° (Found : C, 63.7; H, 4.0; N, 13.9.

$C_{22}H_{16}N_4O_3S$ requires C, 63 . 5; H, 3.8; N, 13.5 %); ^{1}H'NMR: 2.4(s,3H, CH_3C=N), 3.9 (s ,2H pyrazolone protones), 4.4(s, 2H, OCH_2CO), 6.8-8.1 (m, 9H , Ar-H).

6c; yield 68%, m.p. 250-52° (Found : C , 61.4; H,3.8; N,12.9. $C_{22}H_{16}N_4O_2S_2$ requires C, 61.1; H , 3.7; N , 13.0 %) .

N_1-[6-(dibenzothien-4-yl)pyridazin-3-yl]-, N_1-[6-(dibenzothien-4-yl)pyridazin-3-yloxyacetyl]- and /or N_1-[6-(dibenzothien-4-yl)pyridazin-3-yl-thioacetyl]-3-methyl-4-(5-alkyl- or 5-aryl-2-furfurylidine)-2-pyrazolin-5-ones (7-9)a-c.

To N_1-substituted-3-methylpyrazolin-5-one (0.01 mole) dissolved in glacial acetic acid (25ml) , were added anhydrous sodium acetate (0.025mole) and 5-alkyl- or 5-aryl-2-furfural (0.01 mole) and the reaction mixture was refluxed for 5 hr . It was then cooled and poured in cold water . The solid separated was crystallized from suitable solvents :

7a; yield 68 % , m.p . 185-87 ° (from aq. ethanol) (Found : C, 69.0; H, 3.8; N, 12.1 . $C_{26}H_{18}N_4O_2S$ requires C, 69.3 ; H , 4.0; N, 12.4%) ; IR : 2925- 2870 (aliphatic CH), 1675-1660 (amidic CO), 1630-1610 (C=N) ; ^{1}H NMR : 2.3 (s, 3H, CH_3C =N), 2.45(s, 3 H, furyl CH_3), 6.4 (s, 1H, olefinic), 6.7 (d, 1 H , furyl 3-H), 7.0 (d, 1H, furyl 4-H), 7.2-7.9 (m, 9H , Ar-H).

7b; yield 66 % , m.p. 202-04° (from benzene) (Found : C, 66.4; H , 3.6; N, 11.4.$C_{28}H_{20}N_4O_4S$ requires C, 66.1; H,3.9; N , 11.0%) .

7c, yield 69%, m.p. 194-96° (from ethanol) (Found : C, 64.4; H , 4.1; N , 10.9. $C_{28}H_{20}N_4O_3S_2$ requires C, 64.1 ; H, 3.8; N, 10 .7 %) .

8a; yield 64%, m.p. 245-47° (from toluene) (Found : C,66.4; H , 3.6; N. 12.8. $C_{31}H_{19}N_5O_4S$ requires C, 66.8; H, 3.4 ; N , 12.6 %) .

8b; yield 67% , m.p. 215-17° (from ethanol) (Found : C, 64. 7; H, 3.7; N, 11.6. $C_{33}H_{21}N_5O_6S$ requires C, 64.4; H, 3.4; N, 11.4 %); ^{1}H NMR : 2.2

(s, 3H,CH_3C=N),4.2 (s,2H OCH_2CO), 6.2 (s,1H , olefinic), 6.6 (d, 1H , furyl 3-H), 6.9 (d, 1H, furyl 4-H), 7.0 -7.9(m,13H, Ar-H).

8c; yield 66%, m.p .206 – 08 °(from benzene) (Found: C, 62.5; H ,3.6; N, 11.4 .$C_{33}H_{21}N_5O_5S_2$ requires C, 62 .8; H, 3.3 ; N, 11.1 %) .

9a; yield 69%, m.p. . 265-67 ° (from ethanol) (Found : C,68.4; H , 3.7; N, 10.4. $C_{31}H_{19}ClN_4O_2S$ requires C, 68.1; H , 3.5; N, 10.2%) .

9b; yield 63%, m.p. 222-24° (from toluene) (Found : C, 65.8 ; H, 3.7; N,9.4.$C_{33}H_{21}ClN_4O_4S$ requires C, 65.5 ; H, 3.5; N, 9.3%) .

9c; yield 68% , m.p. 285-87° (from ethanol) (Found : C, 63.9; H , 3.7; N , 9.4. $C_{33}H_{21}ClN_4O_3S_2$ requires C, 63.8; H, 3.4 ; N, 9.0 %); ^{1}H NMR : 2.4 (s,3H CH_3C=N),3.7 (s,3H , SCH_2CO), 6.3(s,1H , olefinic), 6.6 (d, 1H, furyl 3-H) , 6.8 (d, 1H, furyl 4-H) , 7.1-7.9(m,13H , Ar-H) .

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