

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

A.A.F. Wasfy, A. El-Shenawy and S.A. Nassar

Chemistry Department, Faculty of Science, Benha University,
Benha – Egypt .

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.

Nitrofurans are endowed with broad spectrum of antibacterial activities and find applications as commercial drugs¹. Attempts have been made to modify the structures of the nitrofurans by introducing carrier molecules during drug design², with a view to reducing the toxicity. Substituted 5-pyrazolones possess various biological activities³. Prompted by these observations and in continuation of our program directed towards developing new approaches for synthesis polyfunctionally substituted diazines of potential activity⁴⁻⁷, it was thought worthwhile to synthesize and study the biological activities of the title compounds having 5-alkyl- or 5-arylfuran moiety in place of 5-nitrofurans with a view to minimize the toxicity.

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

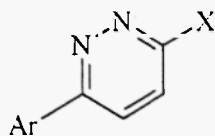
β -(dibenzothien-4-yl)acrylic acid was allowed to react with hydrazine hydrate in boiling ethanol to furnish 6-(dibenzothien-4-yl)pyridazin-3(2H)-one I (Scheme I) which upon subsequent reaction with $\text{POCl}_3 / \text{PCl}_5$

on steam bath yielded the corresponding 3-chloropyridazine derivative⁴ 2 in fairly good yield. Reaction of 2 with thiourea in boiling ethanol furnished 6-(dibenzothien-4-yl)pyridazin-3(2H)-thione⁸ 3 which underwent facile nucleophilic substitution with hydrazine hydrate to yield the key intermediate⁹ 5a. On the other hand, the reaction of 1 and 3 with ethyl chloroacetate in the presence of dry acetone and anhydrous K₂CO₃ 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 ethanol⁴. In order to study the structure-activity relationship, 5-methyl-, 5-(4-nitrophenyl)- and 5-(4-chlorophenyl)furfurals were employed 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 :

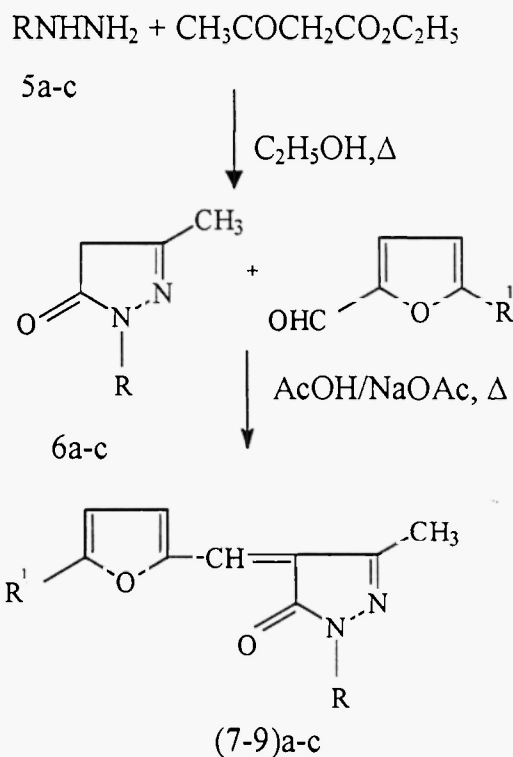
The antibacterial activity of the compounds (7-9)a-c were performed in vitro by filter paper disc method¹² against various pathogenic bacteria, such as *Bacillus cereus*, *Bacillus subtilis* and *Escherichia coli* using nitrofurazone as a reference standard. The culture medium was normal nutrient agar (NA) supplemented with 1 g yeast cm³. 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 = OCH₂ CO₂C₂H₅; 4b, X = SCH₂ CO₂C₂H₅.

(Scheme I)



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, R¹ = CH₃; 8a-c, R¹ = C₆H₄.NO₂-p; 9a-c, R¹ = C₆H₄.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. $\text{C}_{16}\text{H}_{10}\text{N}_2\text{OS}$ 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-(dibenzothien-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 (5b; 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-(dibenzothien-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-(dibenzothien-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 %); 1H NMR: 2.4(s, 3H, $CH_3C=N$), 3.9 (s, 2H, pyrazolone protons), 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-furfurylidene)-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 ($C=N$); 1H NMR: 2.3 (s, 3H, $CH_3C=N$), 2.45 (s, 3H, furyl CH_3), 6.4 (s, 1H, olefinic), 6.7 (d, 1H, 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 %); 1H NMR: 2.2

(s, 3H, CH₃C=N), 4.2 (s, 2H OCH₂CO), 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. C₃₃H₂₁N₅O₅S₂ 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. C₃₁H₁₉ClN₄O₂S 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. C₃₃H₂₁ClN₄O₄S 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. C₃₃H₂₁ClN₄O₃S₂ requires C, 63.8; H, 3.4; N, 9.0 %); ¹H NMR: 2.4 (s, 3H CH₃C=N), 3.7 (s, 3H, SCH₂CO), 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).

Acknowledgement

The author is grateful to Dr. M. Amer, Botany Department, Faculty of Science, Benha University, for biological screening.

References

- 1-Dodd, M.C.; Stillman, W.B. *J. Pharmacol. Exp. Therap.* **1944**, 82, 11; "The Merck Index" ed. Windholz, M. 9th ed., Merck and Co. Inc., Rahway, **1976**, pp. 553, 844.
- 2- Novinson, T.; Booshan, B.; Okabe, T.; Revankar, G.R.; Robins, R.K.; Senga, K.; Wilson, H.R. *J. Med. Chem.* **1976**, 19, 512; Leshner, G.Y. US Pat. 3,516,994 / 1970 (Chem. Abstr., **1970**, 73, 56083); Berkoff, C.E.; Craig, P.N.; Gordon, B.P.; Pellerano, C. *Arzeniem Forsch.* **1970**, 23, 830 (Chem. Abstr. **1973**, 79, 78658).
- 3- Pathak, R.B.; Bahel, S.C. *J. Indian Chem. Soc.* **1980**, 57, 1108; Wrzecimono, V.; Pietkiewicz, K.; Krzysztofik, B.; Michalaska, W.; Drozdowski, M. *Pharmazie* **1978**, 33, 266 (Chem. Abstr. **1978**, 80, 129446).
- 4- Wasfy, A.A.F. *Indian J. Chem.* **1994**, 33B, 1089–1102.

- 5- Arief , M.M.H.; Essawy , S.A.; Wasfy , A.A.F.; Nassar, S.A.; Hashish, A.A. Phosphorus, Sulfur Silicon Relat. Elem . **1994**, 91, 1 .
- 6- Wasfy, A.A.F.; Amine, M.S.; Arief , M.M.H.; Aly ,A.A. Sulfur Letters **1995**, 19, 45.
- 7- Wasfy, A.A.F.; Nassar, S.A.; Eissa, A.M.F. Indian J. Chem. **1996**, 35B, 1218-1220 .
- 8- Jahine, H. ; Zaher, H.A.; Akhnookh ,Y; El-Gendy, Z. Indian J. Chem . **1978**, 16B, 1000-1003.
- 9- El-Hashash, M.; Soliman , M.F.; Amine , M.S. Morsi, M. Phosphorus Sulfur, and Silicon . **1992** , 69, 299.
- 10- Wasfy, A.A.F.; Yassin, F.A.; Eissa , A.M.F. Indian J. Chem . **1995**, 34B , 537-539.
- 11- Husain, M.I.; Kumar, V. J. Indian Chem . Soc. **1989**, 66, 831.
- 12- Baur, A.W.; Kibry, W.M.M; Sherris, J. L .; Turk ,M. Am . J. Clin . Pathol. **1966**, 45, 493.

Received on June 8, 2001