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Synthesis of 3-(phenoxathiin-2-yl)-2-pyrazoline derivatives as new antibacterial and antifungal agents

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A new series of 3-(phenoxathiin-2-yl)-5-aryl-2-pyrazoline derivatives were synthesized from the reaction of 1-(phenoxathiin-2-yl)-3-phenyl/(4-chlorophenyl)propenones **1a** and **1b** with different nitrogen nucleophiles. The titled compounds were investigated for their antibacterial and antifungal activities and were compared with the standard drugs. Most of the synthesized compounds demonstrated potent to weak antimicrobial activity.

Keywords: phenoxathiin; pyrazoline; thiazole; antimicrobial activity

1. Introduction

Pyrazoline derivatives are biologically interesting molecules that have established utility in the pharmaceutical and the agrochemical industries. Among these derivatives, 1-(4-aryl-2-thiazolyl)-3-(2-thienyl)-5-aryl-2-pyrazolines behave as effective antimicrobial agents (*1*, *2*) and *N*-acetylpyridinylpyrazolines have analgesic activity (*3*). It was also reported that 2-pyrazolines have anticancer and anti-inflammatory activities (*4*, *5*). Moreover, most of the compounds including pyrazoline moiety, *e.g.* 1-thiocarbamoyl-2-pyrazolines, have been found to possess monoamine oxidase inhibitory (*6–10*), antidepressant and anticonvulsant properties (*11–14*).

Several methods were employed in the synthesis of pyrazolines, including the condensation of chalcones with hydrazine, hydrazine derivatives (*15–18*) and thiosemicarbazide under acidic (*15*, *16*) or basic (*19*, *20*) conditions, and the cycloaddition of nitrilimines, generated *in situ* from the corresponding hydrazonoyl halides by the action of a suitable base to carbon–carbon double bonds of a suitable dipolarophile (*21*).

On the other hand, phenoxathiin is one of the rigidly folded tricyclic compounds that were found to possess antitumor, monoamine oxidase inhibitory, antimicrobial activities (*22–24*) and have promising florescent properties (*25–27*).

In addition, thiazole derivatives have occupied a unique position in the design and the synthesis of novel biologically active agents that exert remarkable antimicrobial (*28*), anticancer (*29, 30*), analgesic and anti-inflammatory (*31*) activities.

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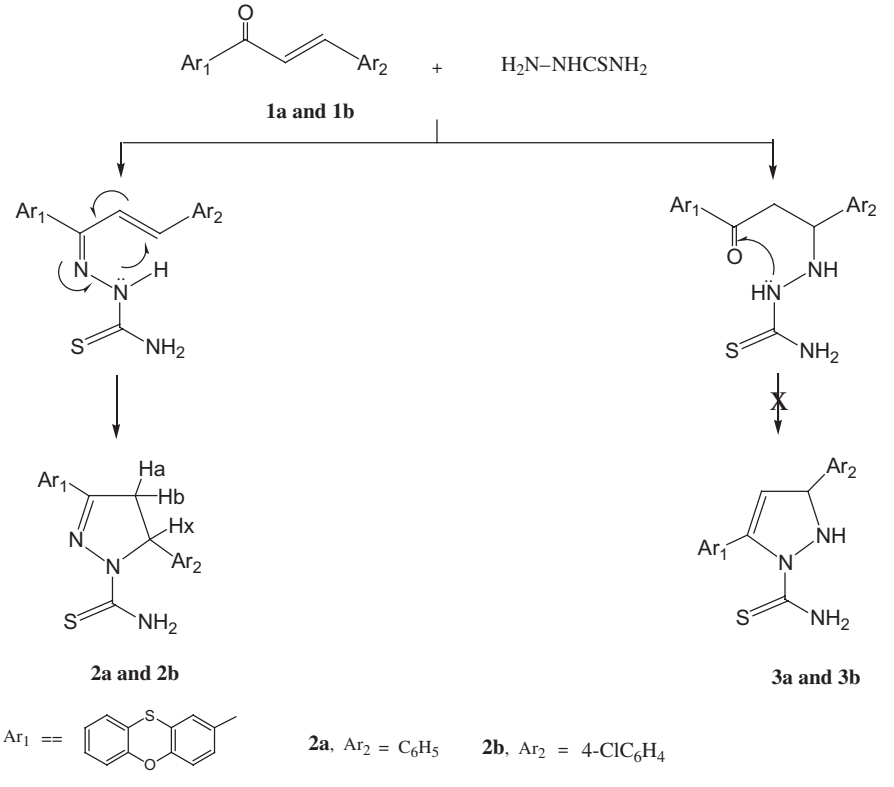
In view of the above-mentioned facts and in continuation of our research interest for the synthesis of biologically active heterocycles (*32–35*), I report herein the synthesis, antibacterial and antifungal evaluation of some novel structures incorporating both phenoxathiin and pyrazoline heterocycles. This combination was suggested in an attempt to investigate the effect of such hybridization on the anticipated biological activities of molecules including both phenoxathiin and pyrazoline moiety.

2. Results and discussion

The synthetic routes adopted for the synthesis of the titled compounds are depicted in Schemes 1–4. The starting chalcones,1-(phenoxathiin-2-yl)-3-phenyl/(4-chlorophenyl)-propenones **1a** and **1b** in the present study were prepared from the reaction of 2-acetylphenoxathiin (*36*) and aromatic aldehydes, namely benzaldehyde and 4-chlorobenzaldehyde (*35*, *36*) (Scheme 1).



Scheme 1. Synthetic route to pyrazolines **2a** and **2b**.

Chalcone **1** can have two stereoisomeric structures, *Z* and *E* forms (Figure 1), but on the basis of the ^{1}H NMR spectrum that showed two doublet signals for the two olefinic protons at 6.41 and 7.46 ppm with the coupling constant value $J = 14.3$ Hz, it seems to exist predominately in the *E* form.

Synthesis of 3-(phenoxathiin-2-yl)-2-pyrazoline derivatives can be achieved by the reaction of chalcones **1a** and **1b** with nitrogen nucleophiles such as thiosemicarbazide or hydrazine derivatives. Thus, the treatment of chalcone **1** with thiosemicarbazide in refluxing ethanol and

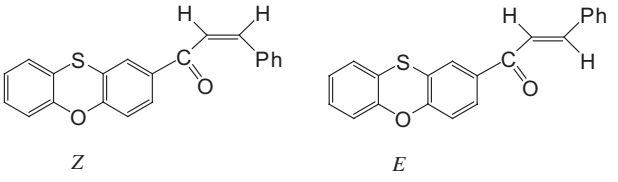
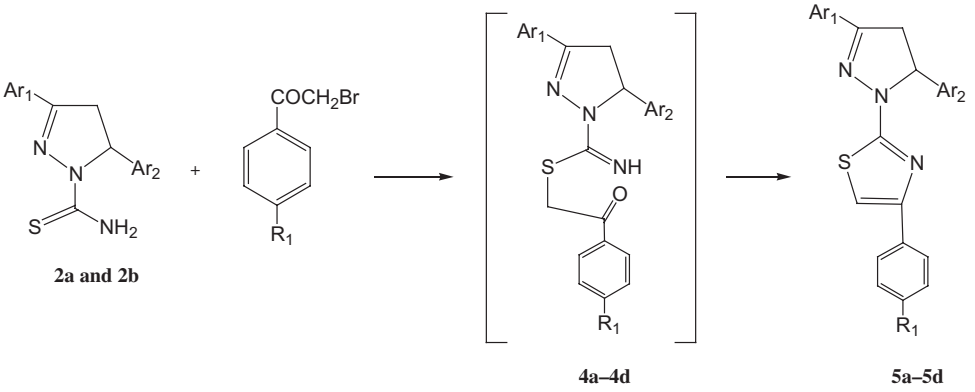


Figure 1. *Z* and *E* forms of Chalcone **1a**.

sodium hydroxide gave one isolable product whose mass spectrum is consistent with either structure **2** or **3** (Scheme 1). However, structure **2** (formed through hydrazone intermediate followed by the addition of NH to the olefinic double bond) was established for the isolated products on the basis of ^{1}H NMR and IR spectra. ^{1}H NMR spectrum of compound **2a** revealed the signals of protons Ha, Hb and Hx of pyrazoline moiety as doublet of doublet at 3.28, 3.85 and 5.20 ppm, respectively, with coupling constants Jab = 17.7 Hz, Jax = 6.8 Hz and Jbx = 11.7 Hz. Such coupling values are characteristic for the pyrazoline protons (*20*).

The reaction of pyrazolines **2a** and **2b** with phenacyl bromide derivatives in ethanol resulted in the formation of the corresponding thiazolylpyrazolines **5a**–**5d** through the non-isolable intermediates **4a**–**4d** (Scheme 2).

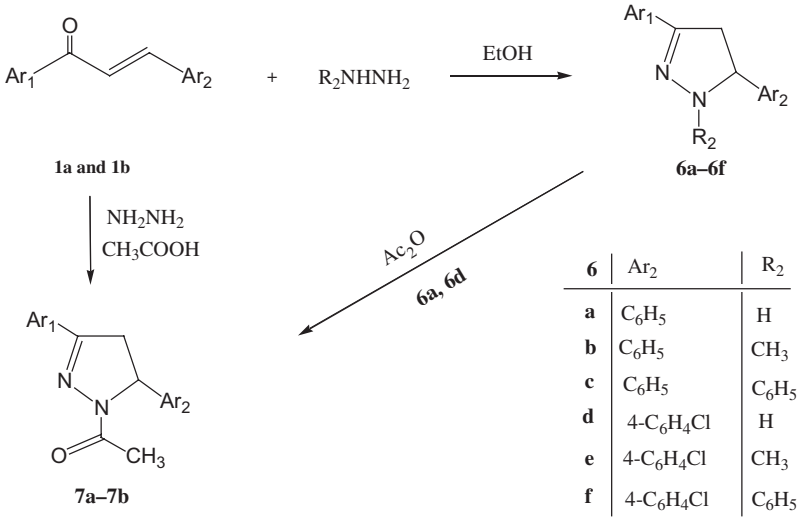


5	a	b	c	d
Ar_2	C_6H_5	C_6H_5	4-C_6H_4Cl	4-C_6H_4Cl
R_1	H	OCH_3	H	OCH_3

Scheme 2. Synthetic pathway of thiazolylpyrazolines **5a**–**5d**.

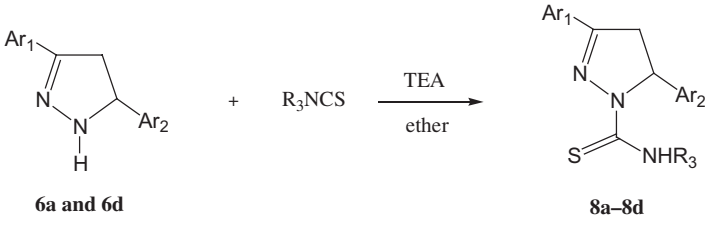
A similar reaction of chalcones **1a** and **1b** with phenyl hydrazine, methyl hydrazine and hydrazine hydrate afforded the corresponding products **6a**–**6f,** respectively. ^{1}H NMR spectra of the latter products also revealed in each case doublet of doublet signals (c.f. Section 5). On the other hand, the reaction of chalcones **1a** and **1b** with hydrazine hydrate in glacial acetic acid afforded the corresponding *N*-acetylpyrazolines **7a** and **7b**. The latter can be formed also from acetylation of pyrazolines **6a** and **6d** (Scheme 3).

Addition reaction of pyrazolines **6a** and **6d** with methyl and phenyl isothiocyanate in the presence of triethylamine in ether provided the corresponding N-substituted-thiocarbamoylpyrazolines **8a**–**8d**. The spectral (IR, ^{1}H NMR, MS) and the elemental analyses of the products are all consistent with the assigned structures **8a**–**8d** (Scheme 4).



6	Ar_2	R_2
a	C_6H_5	H
b	C_6H_5	CH_3
c	C_6H_5	C_6H_5
d	4-C_6H_4Cl	H
e	4-C_6H_4Cl	CH_3
f	4-C_6H_4Cl	C_6H_5

Scheme 3. Synthesis of pyrazolines **6a**–**6f** and N-acetylpyrazolines **7a**–**7b**.



8	a	b	c	d
Ar_2	C_6H_5	C_6H_5	4-C_6H_4Cl	4-C_6H_4Cl
R_3	CH_3	C_6H_5	CH_3	C_6H_5

Scheme 4. Synthesis of thiocarbamoylpyrazoline derivatives **8a**–**8d**.

3. Biological activity

The synthesized compounds were tested for their *in vitro* antimicrobial activity against the Gram-positive bacteria *Staphylococcus cocci* and *Bacillus subtilis* and the Gram-negative bacteria *Escherichia coli*, *Klebsiella bacilli* and *Pseudomonas aeruginosa*. They were also evaluated *in vitro* for their antifungal potential against *Candida albican* and *Aspergillus niger*. Chloramphenicol and Terbinafine were used as control drugs to evaluate the potency of the tested compounds under the same conditions. The observed data on the antimicrobial activity of the compounds and control drugs are given in Table 1.

Agar diffusion method was used for the determination of the preliminary antibacterial and antifungal activity (*37*) and the results were recorded for each tested compound as the average diameter of inhibition zones (*r*) of bacterial or fungal growth around the disks in millimeters at 100 μg concentrations in dimethyl sulfoxide.

Table 1. Antimicrobial activity of the products.

Compound	*S. cocci*	*B. subtilis*	*K. bacilli*	*P. aeruginosa*	*E. coli*	*C. albican*	*A. niger*
2a	18	22	18	16	18	22	19
2b	25	28	18	16	15	22	24
5a	28	30	23	19	23	28	31
5b	26	27	20	18	18	23	18
5c	31	33	24	26	25	18	23
6a	15	16	12	10	13	16	14
6b	12	17	14	11	13	15	18
6d	18	19	15	10	18	18	14
6e	16	14	11	11	13	16	15
7a	20	22	19	19	23	24	23
7b	24	26	20	23	24	26	28
8a	31	36	25	27	28	35	39
8b	30	33	24	27	25	38	40
8c	33	35	26	28	24	41	36
C	35	37	40	38	42	–	–
T	–	–	–	–	–	40	42

Note: Numbers in the table represent the inhibition zone diameter (r, mm) of either fungal or bacterial growth for each compound; $r > 25$ mm, highly active; $r > 14$ mm, moderately active; $r > 10$ mm, slightly active. C = Chloramphenicol as the standard antibacterial agent and T = Terbinafine as the standard antifungal agent.

The results revealed that the majority of the synthesized compounds showed varying degrees of inhibition against the tested microorganisms. Thiocarbamoylpyrazoline **8a** showed the highest potency against Gram-positive bacteria *B. subtilis* while pyrazoline **6e** showed the lowest activity. In general, the inhibitory activity against the Gram-positive bacteria was higher than that of the Gram-negative bacteria. The pyrazoline derivatives **6a**–**6e** displayed the least activity and the pyrazolines **5c**, **8a**–**8c** showed a high activity against Gram-positive and Gram-negative bacteria (inhibitory zone >25 mm). These compounds also possess a potent antifungal activity against *C. albican* and *A. niger* when compared with Terbinafine. All the tested compounds showed moderate (**2a**, **2b** and **6a**–**6e**) to high (**5a**, **8a** and **8b**) inhibitory effects towards tested fungi while compound **8c** exhibited the highest activity (Table 1).

4. Conclusion

The present study describes the synthesis of pyrazoline derivatives containing phenoxathiin moiety, and the chemical structures of the compounds were elucidated by IR, MS, ^{1}H NMR and ^{13}C-NMR spectroscopy. The antibacterial and the antifungal activities for some of the synthesized compounds were investigated, and it was observed that N-substituted-thiocarbamoyl pyrazolines **8a**–**8c** showed a high activity against the tested bacteria and fungi.

5. Experimental

Melting points are uncorrected and FT-IR spectra were recorded on a JASCO FT-IR 660 Plus spectrometer. NMR spectra were recorded on a Bruker Avance 400 (400 MHz) using $CDCl_3$ as the solvent. Column chromatography was run using silica gel 60 (70–230 mesh, Vetec), while TLC was conducted on precoated silica gel polyester sheets (Kieselgel 60 F254, 0.20 mm, Merck). Mass spectra were obtained using a Shimadzu GCMS-QP 1000 EX mass spectrometer in University of Salento, Lecce, Italy.

5.1. *General procedures for the synthesis of chalcones (1a and 1b)*

A mixture of 2-acetylphenoxathiin (0.01 mol), aromatic aldehyde (0.01 mol, benzaldehyde and 4-chlorobenzaldehyde) and sodium hydroxide (1 g in 10 ml water) in ethanol (30 ml) was stirred at r.t. for about 3 h. The formed solid was washed, dried and purified to give yellow crystals of chalcones **1a** and **1b**.

5.1.1. *1-(Phenoxathiin-2-yl)-3-phenylpropenone (**1a**)*

Yield, 80%; m.p. 196–198 °C. IR: 1690 (CO) and 1610 cm^{-1} (C=C); ^1H NMR ($CDCl_3$), δ ppm: 6.41 (d, 1H, α-CH olefinic, $J = 14.3$ Hz), 7.46 (d, 1H, β-CH olefinic, $J = 14.3$ Hz), 7.13–7.90 (m, 12H, Ar–H); MS: m/z: 330 (M^+); Anal. calcd. for $C_{21}H_{14}O_2S$ (330.40): C, 76.34; H, 4.27%. Found: C, 76.26; H, 4.13%.

5.1.2. *3-(4-Chlorophenyl)-1-(phenoxathiin-2-yl)propenone (**1b**)*

Yield, 78%; m.p. 193–195 °C. IR: 1685 (CO) and 1603 cm^{-1} (C=C); ^1H NMR ($CDCl_3$), δ ppm: 7.38 (d, 1H, α-CH olefinic, $J = 14.6$ Hz), 8.00 (d, 1H, β-CH olefinic, $J = 14.6$ Hz), 7.36–8.06 (m, 11H, Ar–H), Anal. calcd. for $C_{21}H_{13}ClO_2S$ (364.85): C, 69.13; H, 3.59%. Found: C, 69.02; H, 3.43%.

5.2. *Synthesis of 1-thiocarbamoyl-3-(phenoxathiin-2-yl)-5-aryl-2-pyrazoline (2a and 2b)*

Thiosemicarbazide (0.01 mol) was added to a solution of chalcones **1a** and **1b** (0.01 mol) in ethanol (30 ml) containing sodium hydroxide (0.02 mol) and all were refluxed for 6 h. After cooling, the reaction mixture was poured into cold water and the resulted precipitate was filtered and washed. The crude product was purified to give **2a** and **2b**.

5.2.1. *1-Thiocarbamoyl-3-(phenoxathiin-2-yl)-5-phenyl-2-pyrazoline (**2a**)*

Yield: 81%, m.p. 212–214 °C. IR (cm^{-1}): 3344, 3412 (NH_2), 2927, 2853 (CH_2), 1598 (C=N), 1240 (CS); ^1H NMR ($CDCl_3$), δ ppm: 3.28 (dd, 1H, Ha, Jab = 17.7 Hz, Jax = 6.8 Hz), 3.85 (dd, 1H, Hb, Jab = 17.6 Hz, Jbx = 11.7 Hz), 5.20 (dd, 1H, Hx, Jax = 11.3 Hz, Jbx = 6.8 Hz), 6.95–8.10 (m, 12H, Ar–H), 8.23 (s, 2H, NH_2, exchangeable); ^{13}C NMR $\delta = 42.23$ (CH_2), 57.76 (CH), 113.52, 116.38, 118.12, 119.32, 120.13, 120.75, 122.30, 122.68, 128.70, 128.75, 130.16, 132.09, 148.06, 155.81 (phenoxathiin and phenyl carbons), 145.11 (C-3 pyrazoline), 191.26 (CS); MS: m/z: 403 (M^+); Anal. calcd. for $C_{22}H_{17}N_3OS_2$ (403.52): C, 65.48; H, 4.25; N, 10.41%. Found: C, 65.68; H, 4.59; N, 10.70%.

5.2.2. *1-Thiocarbamoyl-5-(4-chlorophenyl)-3-(phenoxathiin-2-yl)-2-pyrazoline (**2b**)*

Yield: 83%, m.p. 223–225 °C. IR (cm^{-1}): 3335, 3387 (NH_2), 2915, 2825 (CH_2), 1615 (C=N), 1295 (CS); ^1H NMR ($CDCl_3$), δ ppm: 3.36 (dd, 1H, Ha, Jab = 17.3 Hz, Jax = 7.5 Hz), 3.98 (dd, 1H, Hb, Jab = 17.1 Hz, Jbx = 12.5 Hz), 5.06 (dd, 1H, Hx, Jax = 11.8 Hz, Jbx = 7.7 Hz), 7.12–7.98 (m, 11H, Ar–H), 8.11 (s, 2H, NH_2, exchangeable); ^{13}C NMR $\delta = 43.86$ (CH_2), 59.16 (CH), 115.40, 116.23, 117.26, 117.56, 121.33, 121.87, 122.40, 126.64, 128.58, 129.25, 131.38, 139.13, 150.15, 157.65 (phenoxathiin and phenyl carbons), 142.80 (C-3 pyrazoline), 193.32 (CS); Anal. calcd. For $C_{22}H_{16}ClN_3OS_2$ (437.97): C, 60.33; H, 3.68; N, 9.59%. Found: C, 60.49; H, 3.85; N, 9.77%.

5.3. *General procedures for synthesis of 1-(4-aryl-2-thiazolyl)-3-(phenoxathiin-2-yl)-5-aryl-2-pyrazoline (5a–5d)*

A mixture of pyrazoline **2a** and **2b** (0.01 mol) and an equivalent amount of phenacyl bromide derivatives namely phenacyl bromide and *p*-methoxyphenacyl bromide in ethanol (30 ml) was heated under reflux for 2h and then left to cool. The solid product was filtered and purified.

5.3.1. *1-(4-Phenyl-2-thiazolyl)-3-(phenoxathiin-2-yl)-5-phenyl-2-pyrazoline (**5a**)*

Yield: 75%, m.p. 205–207 °C. IR (cm^{-1}): 1620 (C=N); ^{1}H NMR ($CDCl_3$), δ ppm: 3.17 (dd, 1H, Ha, Jab = 16.9 Hz, Jax = 7.5 Hz), 4.02 (dd, 1H, Hb, Jab = 17.5 Hz, Jbx = 8.1 Hz), 5.15 (dd, 1H, Hx, Jax = 7.1 Hz, Jbx = 12.6 Hz), 6.92 (s, 1H, thiazole–H), 6.96–8.02 (m, 17H, Ar–H); ^{13}CNMR δ = 41.11 (CH_2), 52.06 (CH), 103.42 (C-5 thiazole), 115.64, 117.14, 117.67, 118.20, 120.17, 121.43, 122.32, 122.56, 123.16, 128.36, 128.85,129.22, 130.45, 131.28, 136.85, 139.74, 151.62, 156.36 (phenoxathiin and phenyl carbons), 149.48 (C-3 pyrazoline), 150.38 (C-4 thiazole) 168.15 (C-2 thiazole); MS: m/z: 503 (M^+); Anal. calcd. for $C_{30}H_{21}N_3OS_2$ (503.64): C, 71.54; H, 4.20; N, 8.34%. Found: C, 71.42; H, 4.28; N, 8.43%.

5.3.2. *1-[4-(p-Methoxyphenyl)-2-thiazolyl]-3-(phenoxathiin-2-yl)-5-phenyl-2-pyrazoline (**5b**)*

Yield: 69%, m.p. 186–188 °C. IR (cm^{-1}): 1615 (C=N); ^{1}H NMR ($CDCl_3$), δ ppm: 2.94 (s, 3H, OCH_3), 3.42 (dd, 1H, Ha, Jab = 16.9 Hz, Jax = 6.9 Hz), 4.23 (dd, 1H, Hb, Jab = 17.2 Hz, Jbx = 7.8 Hz), 4.83 (dd, 1H, Hx, Jax = 6.8 Hz, Jbx = 12.7 Hz), 6.77–7.95 (m, 16H, Ar–H), 6.85 (s, 1H, thiazole–H); MS: m/z: 533 (M^+); Anal. calcd. for $C_{31}H_{23}N_3O_2S_2$ (533.67): C, 69.77; H, 4.34; N, 7.87%. Found: C, 69.55; H, 4.41; N, 8.01%.

5.3.3. *1-(4-Phenyl-2-thiazolyl)-3-(phenoxathiin-2-yl)-5-(4-chlorophenyl)-2-pyrazoline (**5c**)*

Yield: 74%, m.p. 201–203 °C. IR (cm^{-1}): 1618 (C=N); ^{1}H NMR ($CDCl_3$), δ ppm: 2.72 (dd, 1H, Ha, Jab = 17.1 Hz, Jax = 7.3 Hz), 3.85 (dd, 1H, Hb, Jab = 17.1 Hz, Jbx = 7.9 Hz), 5.30 (dd, 1H, Hx, Jax = 6.9 Hz, Jbx = 12.3 Hz), 6.65 (s, 1H, thiazole–H), 6.78–8.13 (m, 16H, Ar–H); Anal. calcd. for $C_{30}H_{20}ClN_3OS_2$ (538.08): C, 66.96; H, 3.75; N, 7.81%. Found: C, 67.12; H, 3.86; N, 7.90%.

5.3.4. *1-[4-(p-Methoxyphenyl)-2-thiazolyl]-3-(phenoxathiin-2-yl)-5-(4-chlorophenyl)-2-pyrazoline (**5d**)*

Yield: 72%, m.p. 210–212 °C. IR (cm^{-1}): 1624 (C=N); ^{1}H NMR ($CDCl_3$), δ ppm: 2.89 (s, 3H, OCH_3), 3.12 (dd, 1H, Ha, Jab = 17.1 Hz, Jax = 7.2 Hz), 3.89 (dd, 1H, Hb, Jab = 17.5 Hz, Jbx = 7.6 Hz), 5.20 (dd, 1H, Hx, Jax = 6.9 Hz, Jbx = 11.8 Hz), 6.97 (s, 1H, thiazole–H), 7.11–8.02 (m, 15H, Ar–H); ^{13}C NMR δ = 40.65 (CH_2), 53.12 (CH), 54.32 (CH_3), 101.06 (C-5 thiazole), 117.45, 118.36, 120.23, 121.12, 121.46, 121.78, 122.89, 123.41, 126.51, 128.38,129.13, 131.30, 131.74, 135.31, 141.13, 153.43, 157.42, 158.60 (phenoxathiin and phenyl carbons), 150.48 (C-3 pyrazoline), 151.22 (C-4 thiazole) 166.51 (C-2 thiazole); MS: m/z: 568 (M^+); Anal. calcd. for $C_{31}H_{22}ClN_3O_2S_2$ (568.11): C, 65.54; H, 3.90; N, 7.40%. Found: C, 65.67; H, 3.96; N, 7.49%.

5.4. *Synthesis of pyrazolines (6a–6f)*

To a solution of chalcone **1a** or **1b** (0.01 mol) in ethanol (30 ml), phenyl hydrazine, hydrazine hydrate or methyl hydrazine (0.01 mol) was added. The reaction mixture was heated under reflux for 4 h. After cooling, the precipitated solid was collected by filtration and purified to give the corresponding pyrazoline.

5.4.1. *3-(Phenoxathiin-2-yl)-5-phenyl-2-pyrazoline (**6a**)*

Yield: 78%, m.p. 241–243 °C. IR (cm^{-1}): 3360 (NH), 2935, 2850 (CH_2), 1596 (C=N); ^{1}H NMR ($CDCl_3$), δ ppm: 3.44 (dd, 1H, Ha, Jab = 17.5 Hz, Jax = 6.8 Hz), 3.75 (dd, 1H, Hb, Jab = 17.2 Hz, Jbx = 11.9 Hz), 4.69 (dd, 1H, Hx, Jax = 11.1 Hz, Jbx = 12.2 Hz), 7.21–7.95 (m, 12H, Ar–H), 9.3 (s, 1H, NH, exchangeable); MS: m/z: 344 (M^+)T; Anal. calcd. for $C_{21}H_{16}N_2OS$ (344.43): C, 73.23; H, 4.68; N, 8.13%. Found: C, 73.32; H, 4.63; N, 8.19%.

5.4.2. *1-Methyl-3-(phenoxathiin-2-yl)-5-phenyl-2-pyrazoline (**6b**)*

Yield: 71%, m.p. 210–212 °C. IR (cm^{-1}): 2925, 2820 (CH_2), 1610 (C=N); ^{1}H NMR ($CDCl_3$), δ ppm: 2.85 (s, 3H, CH_3), 2.98 (dd, 1H, Ha, Jab = 17.2 Hz, Jax = 7.7 Hz), 3.45 (dd, 1H, Hb, Jab = 17.2 Hz, Jbx = 11.7 Hz), 4.10 (dd, 1H, Hx, Jax = 11.5 Hz, Jbx = 8.2 Hz), 7.22–7.85 (m, 12H, Ar–H); ^{13}C NMR 36.22 (NCH_3), 39.90 (CH_2), 63.79 (CH), 114.32, 116.87, 118.44, 120.12, 120.33, 120.69, 121.20, 122.77, 123.06, 126.52, 129.31, 133.72, 134.22, 155.03 (phenoxathiin and phenyl carbons), 147.96 (C=N); MS: m/z: 358 (M^+); Anal. calcd. for $C_{22}H_{18}N_2OS$ (358.46): C, 73.71; H, 5.06; N, 7.82%. Found: C, 73.82; H, 5.09; N, 7.89%.

5.4.3. *3-(Phenoxathiin-2-yl)-1,5-diphenyl-2-pyrazoline (**6c**)*

Yield: 74%, m.p. 216–218 °C. IR (cm^{-1}): 2953, 2834 (CH_2), 1585 (C=N); ^{1}H NMR ($CDCl_3$), δ ppm: 3.14 (dd, 1H, Ha, Jab = 17.1 Hz, Jax = 7.2 Hz), 3.82 (dd, 1H, Hb, Jab = 17.0 Hz, Jbx = 12.4 Hz), 5.27 (dd, 1H, Hx, Jax = 7.2 Hz, Jbx = 12.3 Hz), 6.81–7.78 (m, 17H, Ar–H); ^{13}C NMR 44.32 (CH_2), 56.85 (CH), 113.22, 114.28, 115.16, 115.19, 115.25, 118.17, 118.76, 122.75, 122.81, 128.52, 129.06, 132.31, 132.78, 133.15, 137.21, 157.30, 159.95 (phenoxathiin and phenyl carbons), 150.19 (C=N); MS: m/z: 420 (M^+)T; Anal. calcd. for $C_{27}H_{20}N_2OS$ (420.53): C, 77.11; H, 4.79; N, 6.66%. Found: C, 77.20; H, 4.87; N, 6.61%.

5.4.4. *5-(4-Chlorophenyl)-3-(phenoxathiin-2-yl)-2-pyrazoline (**6d**)*

Yield: 69%, m.p. 235–237 °C. IR (cm^{-1}): 3372 (NH), 2923, 2840 (CH_2), 1610 (C=N); MS: m/z: 378 (M^+), 379 ($M^+ + 1$); Anal. calcd. for $C_{21}H_{15}ClN_2OS$ (378.88): C, 66.57; H, 3.99; N, 7.39%. Found: C, 66.46; H, 3.86; N, 7.32%.

5.4.5. *5-(4-Chlorophenyl)-1-methyl-3-(phenoxathiin-2-yl)-2-pyrazoline (**6e**)*

Yield: 70%, m.p. 224–226 °C. IR (cm^{-1}): 2935, 2825 (CH_2), 1605 (C=N); ^{1}H NMR ($CDCl_3$), δ ppm: 3.12 (s, 3H, CH_3), 3.36 (dd, 1H, Ha, Jab = 16.8 Hz, Jax = 8.3 Hz), 3.80 (dd, 1H, Hb, Jab = 17.2 Hz, Jbx = 11.1 Hz), 5.22 (dd, 1H, Hx, Jax = 11.8 Hz, Jbx = 7.8 Hz), 6.96–8.04 (m, 11H, Ar–H) Anal. calcd. for $C_{22}H_{17}ClN_2OS$ (392.90): C, 67.25; H, 4.36; N, 7.13%. Found: C, 67.12; H, 4.43; N, 7.17%.

5.4.6. *5-(4-Chlorophenyl)-3-(phenoxathiin-2-yl)-1-phenyl-2-pyrazoline (**6f**)*

Yield: 68%, m.p. 206–208 °C. IR (cm^{-1}): 2922, 2835 (CH_2), 1615 (C=N); ^{1}H NMR ($CDCl_3$), δ ppm: 3.25 (m, 1H, Ha), 4.35 (dd, 1H, Hb, Jab = 17.1 Hz, Jbx = 7.6 Hz), 5.20 (dd, 1H, Hx, Jax = 8.2 Hz, Jbx = 12.3 Hz), 6.87–8.22 (m, 16H, Ar–H); Anal. calcd. for $C_{27}H_{19}ClN_2OS$ (454.97): C, 71.28; H, 4.21; N, 6.16%. Found: C, 71.39; H, 4.28; N, 6.21%.

5.5. *Synthesis of 1-acetyl-3-(phenoxathiin-2-yl)- 5-aryl-2-pyrazolines (7a and 7b)*

A mixture of chalcone **1** (0.01 mol) and hydrazine hydrate (0.02 mol) in glacial acetic acid (20 ml) was heated under reflux for 4 h. The reaction mixture was poured into ice and the product obtained was filtered, washed with water, dried and purified.

5.5.1. *1-Acetyl-3-(phenoxathiin-2-yl)-5-phenyl-2-pyrazoline (**7a**)*

Yield: 65%, m.p. 203–205 °C. IR (cm^{-1}): 1710 (CO), 1640 (C=N); ^{1}H NMR ($CDCl_3$), δ ppm: 3.18 (dd, 1H, Ha, Jab = 17.2 Hz, Jax = 7.1 Hz), 3.45 (s, 3H, $COCH_3$), 3.75 (dd, 1H, Hb, Jab = 16.9 Hz, Jbx = 11.5 Hz), 4.97 (dd, 1H, Hx, Jax = 12.2 Hz, Jbx = 6.7 Hz), 6.87–7.96 (m, 12H, Ar–H); Anal. calcd. for $C_{23}H_{18}N_2O_2S$ (386.47): C, 71.48; H, 4.69; N, 7.25%. Found: C, 71.57; H, 4.55; N, 7.15%.

5.5.2. *1-Acetyl-3-(phenoxathiin-2-yl)-5-(4-chlorophenyl)-2-pyrazoline (**7b**)*

Yield: 67%, m.p. 211–213 °C. IR (cm^{-1}): 1717 (CO), 1645 (C=N); ^{1}H NMR ($CDCl_3$), δ ppm: 3.21 (dd, 1H, Ha, Jab = 17.8 Hz, Jax = 8.2Hz), 3.39 (s, 3H, $COCH_3$), 3.88 (dd, 1H, Hb, Jab = 17.3 Hz, Jbx = 12.1 Hz), 4.82 (dd, 1H, Hx, Jax = 11.5 Hz, Jbx = 7.8 Hz), 6.98–8.11 (m, 11H, Ar–H); MS: m/z: 420 (M^+), 421 ($M^+ + 1$); Anal. calcd. for $C_{23}H_{17}ClN_2O_2S$ (420.91): C, 65.63; H, 4.07; N, 6.66%. Found: C, 65.74; H, 4.15; N, 6.71%.

5.6. *General procedures for synthesis of 1-N-Substituted thiocarbamoyl-3-(phenoxathiin-2-yl)-5-aryl-2-pyrazolines (8a–8d)*

Methyl or phenyl isothiocyanate (0.01 mol) and few drops of triethylamine were added to the solution of pyrazoline **6a** or **6d** (0.01 mol) in ether (20 ml) and all were stirred at room temperature for 3 h. The mixture was evaporated to dryness and the residue was purified.

5.6.1. *1-N-Methylthiocarbamoyl-3-(phenoxathiin-2-yl)-5-phenyl-2-pyrazoline (**8a**)*

Yield: 62%, m.p. 175–177 °C. IR (cm^{-1}): 3365 NH, 1605 (C=N), 1315 (C=S); ^{1}H NMR 3.11 (dd, 1H, Ha, Jab = 17.3 Hz, Jax = 8.4 Hz), 3.84 (dd, 1H, Hb, Jab = 16.9 Hz, Jbx = 12.3 Hz), 4.91 (dd, 1H, Hx, Jax = 11.7 Hz, Jbx = 8.3 Hz), 6.97–8.12 (m, 12H, Ar–H), 7.85 (b, H, NH); MS: m/z: 417 (M^+); Anal. calcd. for $C_{23}H_{19}N_3OS_2$ (417.55): C, 66.16; H, 4.59; N, 10.06%. Found: C, 66.37; H, 4.68; N, 10.18%.

5.6.2. *1-N-Phenylthiocarbamoyl-3-(phenoxathiin-2-yl)-5-phenyl-2-pyrazoline (**8b**)*

Yield: 58%, m.p. 162–164 °C. IR (cm^{-1}): 3338 NH, 1618 (C=N), 1321 (C=S); ^{1}H NMR 2.85 (dd, 1H, Ha, Jab = 17.1 Hz, Jax = 8.3 Hz), 3.32 (dd, 1H, Hb, Jab = 17.1 Hz, Jbx = 12.2 Hz),

4.60 (dd, 1H, Hx, Jax = 11.6 Hz, Jbx = 8.1 Hz), 7.07–7.98 (m, 17H, Ar–H), 8.22 (bs, 1H, NH); MS: *m/z*: 479 (M^+); Anal. calcd. for $C_{28}H_{21}N_3OS_2$ (479.62): C, 70.12; H, 4.41; N, 8.76%. Found: C, 70.02; H, 4.56; N, 8.64%.

5.6.3. *1-N-Methylthiocarbamoyl-3-(phenoxathiin-2-yl)-5-(4-chlorophenyl)-2-pyrazoline (**8c**)*

Yield: 55%, m.p. 191–193 °C. IR (cm^{-1}): 3350 NH, 1596 (C=N), 1340 (C=S); MS: *m/z*: 451 (M^+),452 ($M^+ + 1$); Anal. calcd. for $C_{23}H_{18}ClN_3OS_2$ (451.99): C, 61.12; H, 4.01; N, 9.30%. Found: C, 61.38; H, 4.25; N, 9.38%.

5.6.4. *1-N-Phenylthiocarbamoyl-3-(phenoxathiin-2-yl)-5-(4-chlorophenyl)-2-pyrazoline (**8d**)*

Yield: 60%, m.p. 197–199 °C. IR (cm^{-1}): 3345 NH, 1610 (C=N), 1332 (C=S); ^{1}H NMR 3.12 (dd, 1H, Ha, Jab = 16.8 Hz, Jax = 8.7 Hz), 3.47 (dd, 1H, Hb, Jab = 17.3 Hz, Jbx = 11.8 Hz), 4.66 (dd, 1H, Hx, Jax = 12.1 Hz, Jbx = 8.5 Hz), 6.89–7.93 (m, 16H, Ar–H), 8.75 (b, 1H, NH); Anal. calcd. for $C_{28}H_{20}ClN_3OS_2$ (514.06): C, 65.42; H, 3.92; N, 8.17%. Found: C, 65.57; H, 4.02; N, 8.05%.

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