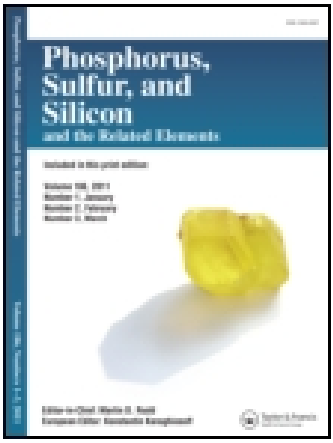

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Synthesis of S-triazolo[3, 4a] phthalazine and Related Polynuclear Heterocyclic Systems

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Synthesis of S-triazolo[3,4-a]phthalazine and Related Polynuclear Heterocyclic Systems

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The applicability and synthetic potency of the novel reagent 1-hydrazinophthalazine ***1*** *to develop an expeditious convenient synthetic route* via *the annelation reactions with appropriate reagents for polyfunctionally substituted triazoles, pyrazoles, tetrazoles, and polycyclic condensed systems are reported. Chemical and spectroscopic study for the structures of the newly synthesized compounds are investigated. The prepared compounds were tested* in vitro *for their antimicrobial activity.*

Keywords 1-Hydrazinophthalazine; annelation reactions; s-triazolo[3,4-a]phthalazine; tricyclic heterocycles

INTRODUCTION

The discovery of the pronounced antitumor, bactericidal, and other biological activities[1–5] of phthalazine derivatives has stimulated considerable research in this field. Phenoxathiin derivatives also demonstrate a great importance due to their significant potential bioresponses.[6,7] In view of the aforementioned facts, we continue our medicinal chemistry program[8,9] directed towards the development of novel heterocyclic systems. Here we report a facile and convenient access to 1-hydrazino-4-phenoxathiin-2-yl-phthalazine (**1**) required in our laboratory as a synthon for the construction of polycyclic condensed systems for biological evaluation.

RESULTS AND DISCUSSION

The key precursor 1-hydrazino-4-phenoxathiin-2-yl-phthalazine (**1**) was prepared in high yield upon refluxing equimolar amounts of

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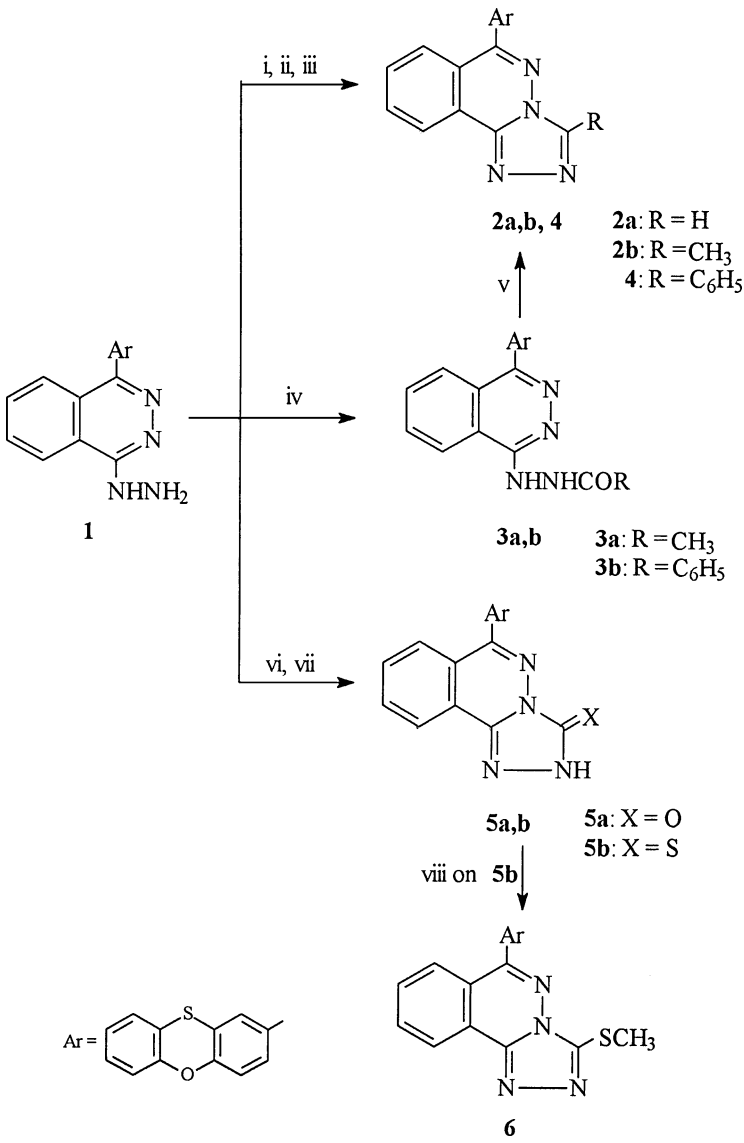
1-chloro-4-phenoxathiin-2-yl-phthalazine[10] and hydrazine hydrate in ethanol.

The structure of the reaction product **1** was assigned on the basis of elemental analysis and compatible spectroscopic data. Thus, its mass spectrum revealed a molecular ion peak at m/z (%) = 358 (20.1) corresponding to the molecular formula $C_{20}H_{14}N_4OS$. The IR spectrum showed absorption peaks at 3395–3150 (νNHNH$_2$) and 1621 cm^{-1} (νC=N). The ^{1}H NMR spectrum (DMSO-d$_6$) showed a broad signal (2H) at δ 6.24 ppm assigned for the NH$_2$ protons, a multiplet signal (11H) at (6.98–7.41 ppm) assigned for the aromatic protons, and a broad signal at 9.25 ppm assigned for NH, which disappeared upon addition on of D_2O to the NMR sample.

Reaction of **1** with aliphatic acids (*viz* formic acid and acetic acid) afforded 6-phenoxathiin-2-yl-[1,2,4]triazolo[3,4-a]phthalazine (**2a**) and 3-methyl-6-phenoxathiin-2-yl-[1,2,4]triazolo[3,4-a]-phthalazine (**2b**), respectively, in a comparable cyclization mechanism as recorded before[11,12] (Scheme 1), but in low yield. Since orthoesters are the reagents of choice in the preparation of fused s-triazoles, the compound **1** reacts with orthoesters (*viz* triethyl orthoformate and triethyl orthoacetate) to reproduce **2a** and **b**, albeit in a better yield.

An alternative route to obtain (**2b**) as well as the phenyl derivative **4** involved the reaction of compound **1** with an equivalent amount of acid, chloride (*viz* acetyl chloride and benzoyl chloride) in dry pyridine at 0°C. This reaction furnished the phthalazine derivatives **3a** and **3b**, which were cyclized by action of phosphorous oxychloride to afford **2b** and **4**, respectively. Compound **4** also was obtained via the direct fusion of benzoic acid with compound **1** at 200°C for 5 h. The reactants converted smoothly into the desired product; a slight decomposition was encountered but no hydrazide intermediate was isolated. This one-step procedure provided a higher yield (87%) of **4** than that obtained via the two steps procedure (51%, Scheme 1). Fusion of compound **1** with urea gave 6-phenoxathiin-2-yl-2H-[1,2,4]triazolo[3,4-a]-phthalazin-3-one (**5a**) in good yield (81%).

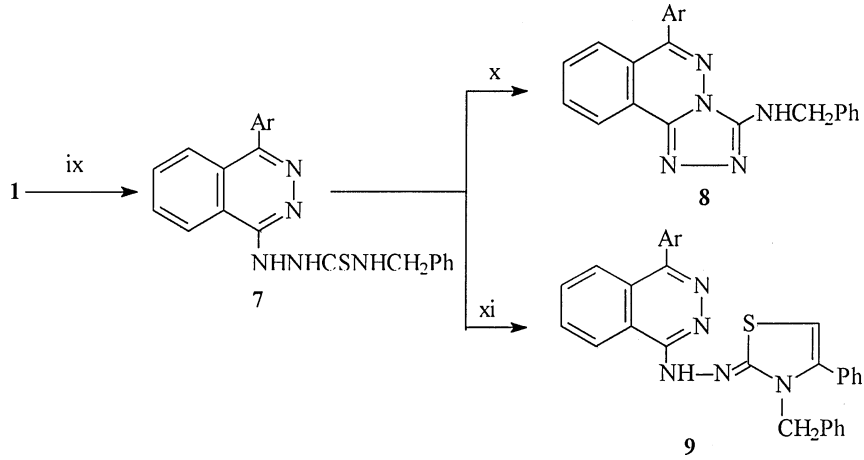
Spectral data of compound **5a** indicated that it exists predominantly in the keto-form (νCO at 1670 cm^{-1}) and revealed only minor OH stretching absorption (νOH at 3400 cm^{-1}). 6-phenoxathiin-2-yl-2H-[1,2,4]triazolo[3,4-a]phthalazin-3-thione (**5b**) was obtained via treatment of compound **1** with carbon disulfide. To reach the optimum conditions for the reaction, it was conducted under two different conditions. Thus, the refluxing of **1** with carbon disulfide in alcoholic potassium hydroxide was found to proceed much faster than performing the reflux in chloroform.[13,14] The readiness by which the former reaction proceeded



SCHEME 1 Reagents: i, RCOOH; ii, $RC(COOEt)_3$; iii, PhCOOH; iv, RCOCl; v, $POCl_3$, vi, H_2NCONH_2; vii, CS_2; and viii, CH_3I.

was attributed to feasible aggregation under these conditions. The thiol derivative **5b**, on treatment with methyl iodide in aqueous base, was converted to 3-methylsulfanyl-6-phenoxathiin-2-yl-[1,2,4]-triazolo[3,4-a]-phthalazine (**6**).

In view of the known antifungal and antiviral characteristics[15,16] inherent in substituted thiosemicarbazide derivatives, the synthesis of new compounds incorporating such a group was enhanced. Thus, the condensation of **1** with benzyl isothiocyanate in boiling ethanol afforded the corresponding thiosemicarbazide derivative **7**. The cyclodesulfurization of **7** with HgO in boiling dioxane gave benzyl-(6-phenoxathiin-2-yl-[1,2,4]-triazolo[3,4-a]phthalazin-3-yl)amine (**8**), while its cyclization with phenacyl bromide afforded thiazolylphthalazine derivative **9** (Scheme 2).

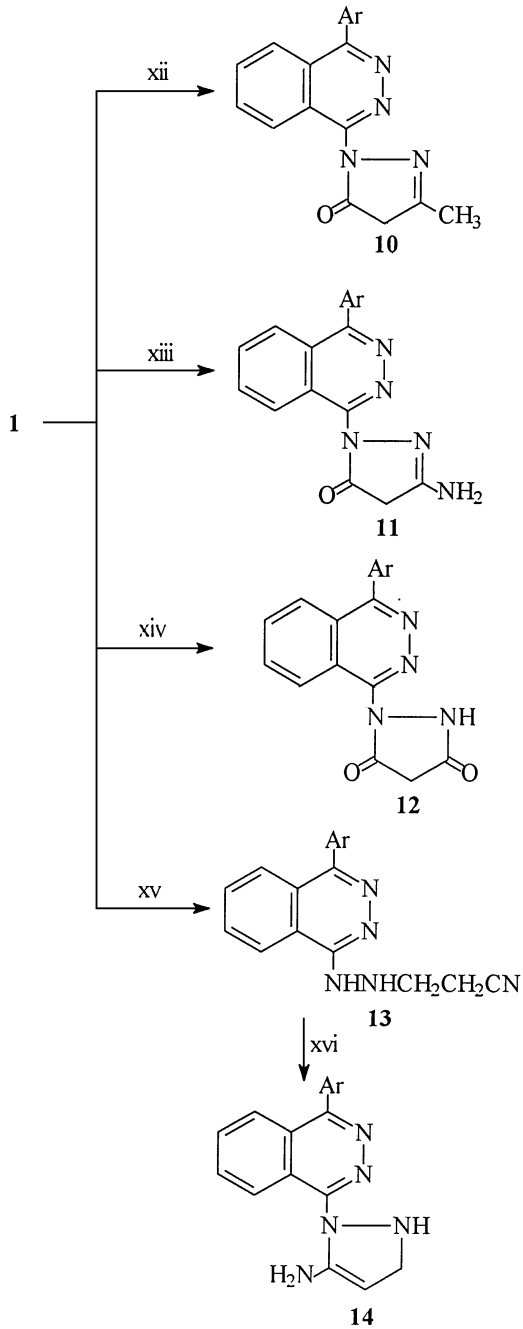


SCHEME 2 Reagents: ix, $PhCH_2NCS$; x, HgO; and xi, $PhCOCH_2Br$.

For this study, our interest also was directed towards the synthesis of pyrazolylphthalazine derivatives as possible potential antihypertensive agents.[17] Thus, compound **1** was subjected to react with active methylene compounds (*viz* ethyl acetoacetate, ethyl cyanoacetate and diethyl malonate) to afford the pyrazolyl-phthalazine derivatives **10–12**, respectively. Also, condensation of **1** with acrylonitrile in boiling pyridine gave the propionitrile derivative **13**, which underwent acid hydrolysis to give pyrazolylphthalazine derivative **14** (Scheme 3).

The scope of this investigation was further extended towards the synthesis of tetrazolophthalazine and phenanthrene derivatives. Thus, thermal cyclization[18] of **15** (150°C) obtained by diazotization of **1** afforded tetrazolophthalazine derivative **16**.

On the other hand, a tetraazaphenantherene derivative was obtained via the reaction of **1** with ethyl chloroacetate and/or chloroacetyl chloride. Although two isomeric products 9-phenoxathiin-2-yl-3H-3,4,



SCHEME 3 Reagents: xii, CH_3COCH_2COOEt; xiii, $CNCH_2COOEt$; xiv, $CH_2(COOEt)_2$; xv, $CH_2{=}CHCN$; and xvi, NaOH.

10,10a-tetraazaphenanthren-2-one (**17a**) and 9-phenoxathiin-2-yl-3H-3,4,10,10a-tetraazaphenanthren-1-one (**17b**) were expected, only one product was isolated and successfully identified by spectral data as (**17a**). Further tetraazaphenanthrene derivatives were obtained by the reaction of **1** with bromomalonitrile in the presence of potassium carbonate, and by refluxing of compound **1** with α-haloketones (*viz* chloroacetone and phenacyl bromide in dry xylene). In both reactions more than one cyclization product was anticipated. However, the former reaction afforded a tetraazaphenanthrene derivative (**18a**) rather than a mixture of (**18a and b**), while the latter furnished 1-methyl- and 1-phenyl-9-phenoxathiin-2-yl-3H-3,4,10,10a-tetraazaphenanthrene (**19a and b**) rather than a mixture of (**19a and b**) and (**20a and b**; Scheme 4). The structures of all of the synthesized compounds were confirmed by spectroscopic methods and elemental analysis data (see the experimental section).

ANTIMICROBIAL ACTIVITY

The antimicrobial activity of some synthesized compounds was determined *in vitro* using the hole plate and filter paper method.[19] All compounds were tested for activity against gram positive and gram negative bacteria and selected fungi. A qualitative screen was performed on all compounds while quantitative assays were done only on active compounds. The results are listed in Table I.

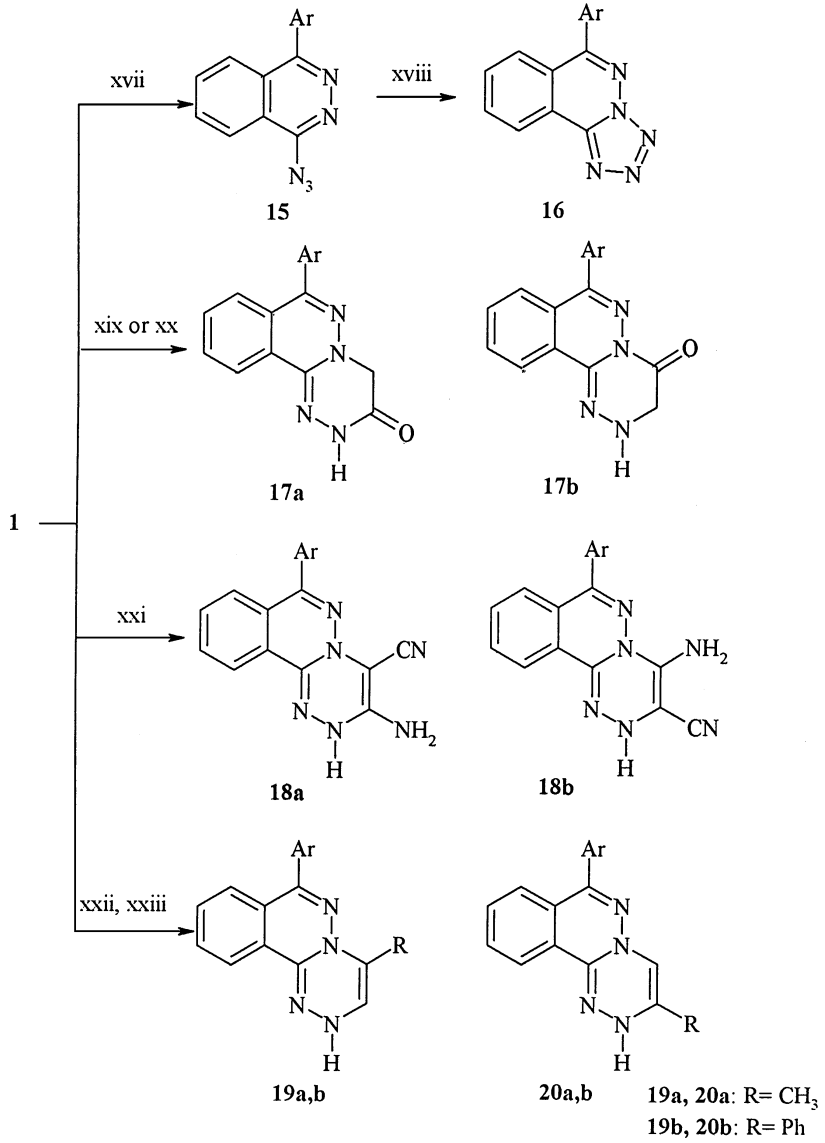
In conclusion, the readily available 1-hydrazinophthalazine provides an easy and convenient route to various inaccessible phthalazine derivatives of biological interest.

EXPERIMENTAL

Melting points were taken in open capillary tubes and were uncorrected. IR spectra in KBr are recorded on a Shimadzu 470 spectrophotometer. ^{1}H NMR spectra in DMSO-d_6 were recorded on Varian Gemini and 200 MHz (chemical shifts are expressed as δ, ppm) and the mass spectra were obtained on a Shimadzu GCMS QP 1000 Ex-mass spectrometer (70 eV EI mode).

1-Hydrazino-4-phenoxathiin-2-yl-phthalazine (1)

A mixture of 1-chloro-4-phenoxathiin-2-ylphthalazine[10] (20 mmol) and hydrazine hydrate (20 mmol) in (30 mL) ethanol was refluxed for 6 h. The reaction mixture was cooled, filtered, and recrystallized from ethanol to give **1**. Yield, 72%; mp 252–4°C. IR: ν = 3395–3150 ($NHNH_2$),



SCHEME 4 Reagents: xvii, $NaNO_2/H_2O$; xviii, DMF; xix, $ClCH_2COOEt$; xx, $ClCH_2COCl$; xxi, $BrCH(CN)_2$; xxii, $ClCH_2COCH_3$; and xxiii, $PhCOCH_2Br$.

1621 cm^{-1} (C=N); ^1H NMR: $\delta = 6.24$ (br s, 2H, NH_2), 6.98–7.41 (m, 11H, ArH), 9.25 (br s, 1H, NH, exchangeable with D_2O); MS: m/z: 358 (M^+); Anal. Calcd. for $C_{20}H_{14}N_4OS$: C, 67.02; H, 3.94; N, 15.63%; Found: C, 67.15; H, 3.81; N, 15.75%.

TABLE I Activity (A) and Minimum Inhibitory Concentration (MIC) Calculated as μg/mL for Compounds 3–19

	Bacillus Subtilis		Bacillus Cereus		Escherichia Coli		Penicillium Chrysogenium	
Compound	A	MIC	A	MIC	A	MIC	A	MIC
3b	++	500	+	250	+	250	–	—
5b	++	250	++	500	+	250	+	500
8	++	500	+	250	++	250	+	250
11	++	250	+	500	+	250	–	—
14	++	500	++	250	+	250	+	250
17	–	–	++	250	++	250	–	—
18	++	500	+	250	+	500	+	250
19b	+	500	+	250	+	125	–	—

Antimicrobial activity (A): + + +, highly active; ++, moderately active; +, slightly active, and inactive.

Preparation of Triazolophthalazine Derivatives 2a,b

Method A

A mixture of 1-hydrazinophthalazine **1** (10 mmol) and aliphatic acids (21 mmol), namely formic acid, and/or acetic acid, was heated under reflux for 7 h. The excess acid was removed under reduced pressure on a steam bath and the residual viscous oil was basified with a 30% NaOH solution. The alkaline solution was extracted with $CHCl_3$ (3 50-mL portions) and the combined extracts were dried (Na_2SO_4). After removal of chloroform, the solid product was crystallized from a suitable solvent to afford **2a**,**b**. Yield for **2a**, 59%; **2b**, 62%.

Method B

A mixture of 1-hydrazinophthalazine **1** (15 mmol) and orthoesters (31 mmol), namely triethyl orthoformate and/or triethyl orthoacetate, was refluxed for 4 h. The excess ortho ester and alcohol were removed on a steam bath under reduced pressure. The crude product was crystallized to give a product, which was identified by its mp and mmp determination as **2a**,**b**. Yield for **2a**, 79%; **2b**, 80%.

Independent Synthesis of 2b

Phosphorous oxychloride (15 mL) was added slowly to **3a** (15 mmol), and the mixture was refluxed for 6 h. After removal of the excess of phosphorous oxychloride under reduced pressure, the residue was cautiously made alkaline with a cold sodium hydroxide solution. This solution

was extracted with chloroform (3 40-mL portions), and the combined extracts were dried (Na_2SO_4). After removal of chloroform, the residue crystallized to give a solid product, which was identified as **2b** by mp and mmp determination. Yield, 51%.

6-Phenoxathiin-2-yl-[1,2,4]triazolo[3,4-a]phthalazine (2a)

Mp, 273–5°C (benzene), IR: $\nu = 3050$ (Ar—H), 1610 cm^{-1} (C=N); MS m/z: 368 (M^+), Anal. Calcd. for $C_{21}H_{12}N_4OS$: C, 68.46; H, 3.28; N, 15.21%; Found: C, 68.59; H, 3.16; N, 15.37%.

3-Methyl-6-phenoxathiin-2-yl-[1,2,4]triazolo[3,4-a]phthalazine (2b)

Mp, 296–8°C (benzene), IR: $\nu = 3060$ (Ar—H), 1618 cm^{-1} (C=N); ^1H NMR: $\delta = 3.19$ (s, 3H, CH_3), 7.11–8.25 (m, 11H, ArH); Anal. Calcd. for $C_{22}H_{14}N_4OS$: C, 69.09; H, 3.69; N, 14.65%; Found: C, 69.20; H, 3.55; N, 14.79%.

2-Acetyl- and 2-benzoyl-1-[4-(phenoxathiin-2-yl)phthalazin-1-yl]-hydrazine (3a,b)

Hydrazinophthalazine **1** (20 mmol) in dry pyridine (25 mL), the acid chlorides (20 mmol), namely, and acetyl chloride and/or benzoyl chloride were added dropwise. The reaction mixture was stirred at room temperature for 45 min and then heated for 2 h on a steam bath. The reaction mixture was poured on crushed ice (40 g). The solid products were crystallized from an appropriate solvent to give **3a,b**.

3a, Yield, 80%; mp 276–8°C (ethanol); IR: $\nu = 3360$–3190 (NH), 1675 (CO), 1615 cm^{-1} (C=N); ^1H NMR: $\delta = 2.31$ (s, 3H, CH_3), 7.13–8.11 (m, 11H, ArH); 9.51–10.43 (br s, 2H, 2NH, exchangeable); Anal. Calcd. for $C_{22}H_{16}N_4O_2S$: C, 65.98; H, 4.03; N, 13.99%; Found: C, 65.83; H, 4.19; N, 13.82%.

3b, Yield, 86%; mp 266–8°C (ethanol); IR: $\nu = 3340$–3180 (NH), 1670 (CO), 1618 cm^{-1} (C=N); Anal. Calcd. for $C_{27}H_{18}N_4O_2S$: C, 70.11; H, 3.92; N, 12.11%; Found: C, 70.25; H, 3.80; N, 12.27%.

6-Phenoxathiin-2-yl-3-phenyl-[1,2,4]triazolo[3,4-a] phthalazine (4)

Method A

A mixture of **3b** (10 mmol) and phosphorous oxychloride (15 mL) in toluene (30 mL) was heated under reflux for 6 h. The excess solvent was

removed under reduced pressure and the residue was basified carefully with ice and a 30% NaOH solution. The solid product was crystallized from ethanol to give **4**. Yield, 51%, mp 303–5°C, IR: $\nu = 3100$ (Ar—H), 1610 cm^{-1} (C=N); ^1H NMR: $\delta = 7.14$–8.26 (m, 16H, ArH); Anal. Calcd. for $C_{27}H_{16}N_4OS$: C, 72.95; H, 3.63; N, 12.60%; Found: C, 72.81; H, 3.75; N, 12.79%.

Method B

A mixture of **1** (10 mmol) and benzoic acid (10 mmol) was heated at 200°C for 5 h. After cooling to room temperature, the reaction mixture was dissolved in aqueous ethanol and the solution was made alkaline with a dilute sodium hydroxide solution. The solid product was crystallized and was identified as **4** by its mp and mmp determination. Yield, 87%.

6-Phenoxathiin-2-yl-2H-[1,2,4]triazolo[3,4-a]phthalazin-3-one (5a)

A mixture of **1** (10 mmol) and urea (13 mmol) was heated at 180–190°C for 6 h. The reaction mixture was cooled and added to a solution of sodium hydroxide (5%, 20 mL), filtered, and the filterate was acidified with dil. HCl. The solid product was crystallized from ethanol to give **5a**. Yield, 81%; mp 290–2°C, IR: $\nu = 3400$ (OH), 3260 (NH), 1670 (CO), 1619 cm^{-1} (C=N); MS m/z: 384 (M^+); Anal. Calcd. for $C_{21}H_{12}N_4O_2S$: C, 65.61; H, 3.15; N, 14.57%; Found: C, 65.50; H, 3.27; N, 14.69%.

6-Phenoxathiin-2-yl-2H-[1,2,4]triazolo[3,4-a]phthalazin-3-thione (5b)

Method A

To a suspension solution of **1** (15 mmol) in ethanol (30 mL), carbon disulfide (30 mmol) and potassium hydroxide (50 mmol) were added and the reaction mixture was refluxed for 4 h, then filtered while hot. The filterate was acidified with hydrochloric acid and the precipitate was crystallized from ethanol to give **5b**. Yield, 81%; mp 312–4°C; IR: $\nu = 3205$ (NH), 1615 (C=N), 1240 cm^{-1} (CS); MS m/z: 400 (M^+); Anal. Calcd. for $C_{21}H_{12}N_4OS_2$: C, 62.98; H, 3.02; N, 13.99%; Found: C, 62.83; H, 3.17; N, 13.81%.

Method B

A mixture of **1** (10 mmol), chloroform (50 mL) and carbon disulfide (4 mL) were heated under reflux until the evolution of hydrogen sulfide

ceased (30 h). Upon cooling, the product, which separated from the reaction mixture, was crystallized and identified as **5b** by mp and mmp determination. Yield, 95%.

3-Methylsulfanyl-6-phenoxathiin-2-yl-[1,2,4]triazolo[3,4-a]-phthalazine (6)

A solution of thiol **5b** (10 mmol) in sodium hydroxide (20 mL, 1.5 N solution) and methyl iodide (30 mmol) was stirred at room temperature for 1 h. The reaction mixture was extracted with chloroform, dried over Na_2SO_4, and evapourated to give a solid product which crystallized from dioxane to give **6**. Yield, 78%; mp 230–2°C; IR: $\nu = 3090$ (Ar—H), 2950 (alkyl-H), 1618 cm^{-1} (C=N); ^1H NMR: $\delta = 2.85$ (s, 3H, SCH_3), 7.09–8.11 (m, 11H, ArH); Anal. Calcd. for $C_{22}H_{14}N_4OS_2$: C, 63.75; H, 3.40; N, 13.52%; Found: C, 63.86; H, 3.29; N, 13.39%.

4-Benzyl-1-[(4-phenoxathiin-2-yl)phthalazin-1-yl]thiosemicarbazide (7)

To a solution of **1** (20 mmol) in ethanol (30 mL), benzyl isothiocyanate (20 mmol) was added. The reaction mixture was left to stand at room temperature for 1 h, whereupon a yellow crystalline product precipitated. The reaction mixture was left overnight, filtered, and crystallized from ethanol to give **7**. Yield, 78%; mp 211–3°C; IR: $\nu = 3320$–3215 (NH), 1620 (C=N), 1250 cm^{-1} (CS); ^1H NMR: $\delta = 4.10$ (s, 2H, CH_2), 7.03–8.11 (m, 16H, ArH), 9.12, 10.22, 10.75 (3s, 3H, 3NH, exchangeable); Anal. Calcd. for $C_{28}H_{21}N_5OS_2$: C, 66.25; H, 4.17; N, 13.80%; Found: C, 66.10; H, 4.29; N, 13.68%.

Benzyl-(6-phenoxathiin-2-yl-[1,2,4]triazolo[3,4-a]phthalazin-3-yl)-amine (8)

To a solution of **7** (10 mmol) in dry dioxane (25 mL), freshly prepared yellow HgO (10 mmol) was added and the reaction mixture was heated under reflux for 8 h, and then filtered while hot. The filtrate was evaporated under reduced pressure and the obtained product was crystallized from benzene-petroleum ether (60–80°C) to give **8**. Yield, 73%; mp 197–9°C; IR: $\nu = 3240$ (NH), 1620 cm^{-1} (C=N); ^1H NMR: $\delta = 4.25$ (s, 2H, CH_2), 7.06–8.13 (m, 16H, ArH), 10.11 (s, 1H, NH, exchangeable); Anal. Calcd. for $C_{28}H_{19}N_5OS$: C, 71.02; H, 4.04; N, 14.79%; Found: C, 71.16; H, 4.17; N, 14.63%.

N-(3-benzyl-4-phenyl-3H-thiazol-2-ylidene)-N′-(4-phenoxathiin-2-ylphthalazin-1-yl)hydrazine (9)

A suspension solution of **7** (10 mmol) and phenacyl bromide (13 mmol) in absolute ethanol (25 mL) was heated under reflux for 3 h, then (13 mmol) of anhydrous sodium acetate was added. The reaction mixture was heated for an additional 1 h, then cooled and poured into ice-cold water. The solid product was crystallized from ethanol to afford **9**. Yield, 81%; mp 186–8°C; IR: $\nu = 3260$ (NH), 1621–1610 cm^{-1} (C=N); MS, m/z: 607 (M^+); Anal. Calcd. for $C_{36}H_{25}N_5OS_2$: C, 71.15; H, 4.15; N, 11.52%; Found: C, 71.28; H, 4.33; N, 11.40%.

Preparation of Pyrazolylphthalazine Derivatives 10–12

A solution of **1** (10 mmol) and active methylene compounds, namely ethyl acetoacetate, ethyl cyanoacetate, and/or diethylmalonate (12 mmol), in ethanol (25 mL) containing catalytic amount of piperidine (1 mL) was refluxed for 4 h. The solid compound obtained after cooling was crystallized from a suitable solvent to give the compounds **10–12**.

5-Methyl-2-(4-phenoxathiin-2-ylphthalazin-1-yl)-2,4-dihydro-pyrazol-3-one (10)

Yield, 71%; mp 270–2°C (benzene); IR: $\nu = 1675$ (CO), 1612 cm^{-1} (C=N); ^{1}H NMR: $\delta = 2.61$ (s, 3H, CH_3), 3.83 (s, 2H, CH_2), 6.98–7.89 (m, 11H, ArH); Anal. Calcd. for $C_{24}H_{16}N_4O_2S$: C, 67.91; H, 3.80; N, 13.20%; Found: C, 67.80; H, 3.94; N, 13.33%.

5-Amino-2-(4-phenoxathiin-2-yl-phthalazin-1-yl)-2,4-dihydro-pyrazol-3-one (11)

Yield, 68%; mp 223–5°C (ethanol); IR: $\nu = 3300$–3220 (NH), 1670 (CO), 1615 cm^{-1} (C=N); MS m/z: 425 (M^+); Anal. Calcd. for $C_{23}H_{15}N_5O_2S$: C, 64.93; H, 3.55; N, 16.46%; Found: C, 64.80; H, 3.68; N, 16.32%.

1-(4-Phenoxathiin-2-yl-phthalazin-1-yl)pyrazolidine-3,5-dione (12)

Yield, 71%; mp 236–8°C (ethanol); IR: $\nu = 3320$ (NH), 1675–1665 (2CO), 1618 cm^{-1} (CN); ^{1}H NMR: $\delta = 3.79$ (s, 2H, CH_2), 6.97–7.89 (m, 11H, ArH), 9.87 (s, 1H, NH, exchangeable); Anal. Calcd. for $C_{23}H_{14}N_4O_3S$: C, 64.78; H, 3.31; N, 13.14%; Found: C, 64.62; H, 3.46; N, 13.25%.

3-[N′-(4-Phenoxathiin-2-yl-phthalazin-1-yl)-hydrazino]propionitrile (13)

A solution of **1** (10 mmol) and acrylonitrile (10 mmol) was refluxed in pyridine (25 mL) for 4 h. After cooling, the reaction mixture was poured onto ice and HCl and the solid formed was crystallized from benzene to give **13**. Yield, 65%; mp 281–3°C; IR: $\nu = 3300$–3200 (NH), 2230 (C≡N), 1616 cm^{-1} (C=N); MS m/z: 411 (M^+); Anal. Calcd. for $C_{23}H_{17}N_5OS$: C, 67.13; H, 4.16; N, 17.02%; Found: C, 67.25; H, 4.28; N, 17.15%.

1-(4-Phenoxathiin-2-yl-phthalazin-1-yl)-2,3-dihydro-1H-pyrazol-5-ylamine (14)

A solution of **13** (10 mmol) in ethanol (25 mL) and sodium hydroxide (15 mL, 20%) was refluxed for 8 h. The reaction mixture was cooled to room temperature and acidified with hydrochloric acid to give a solid product which was crystallized to give **14**. Yield, 51%; mp 207–9°C (benzene); IR: $\nu = 3380$–3150 (NH and NH_2), 3080 (Ar–H), 1612 cm^{-1} (C=N); ^1H NMR: $\delta = 4.10$ (s, 2H, CH_2), 4.55 (s, 1H, methine proton), 6.23 (br s, 2H, NH_2), 7.01–8.03 (m, 11H, ArH), 9.92 (s, 1H, NH, exchangeable); Anal. Calcd. for $C_{23}H_{17}N_5OS$: C, 67.13; H, 4.16; N, 17.02%; Found: C, 67.27; H, 4.05; N, 17.18%.

1-Azido-4-phenoxathiin-2-yl-phthalazine (15)

To a well-stirred mixture of **1** (5 mmol) and sodium nitrite (15 mmol) in H_2O (15 mL), conc HCl (1 mL) was added (1 mL) at 0–3°C. The reaction mixture was stirred for additional 1 h at the same temperature. The precipitate thus obtained was filtered and crystallized from benzene to give **15**. Yield, 60%; mp 170–3°C (with decomposition); IR: $\nu = 2235$ (N_3), 1615 cm^{-1} (C=N).

6-Phenoxathiin-2-yl-tetrazolo[5,1-a]phthalazine (16)

A mixture of **15** (10 mmol) and DMF (10 mL) was heated at 150°C for 15 min. The reaction mixture was evaporated to dryness in vacuo and the residue was recrystallized from ethanol to yield **16**. Yield, 49%; mp 156–8°C; IR: $\nu = 1620$ (C=N), 1090–1040 cm^{-1} (tetrazole ring[20]); ^1H NMR: $\delta = 7.01$–8.15 (m, 11H, ArH); Anal. Calcd. for $C_{20}H_{11}N_5OS$: C, 65.03; H, 3.00; N, 18.96%; Found: C, 65.18; H, 3.17; N, 18.82%.

9-Phenoxathiin-2-yl-3H-3,4,10,10a-tetraazaphenanthren-2-one (17a)

Method A

A mixture of **1** (10 mmol) and ethyl chloroacetate (10 mmol) in absolute ethanol (35 mL) was refluxed for 8 h. The solid separated on cooling and was filtered off and recrystallized from benzene to give **17a**. Yield, 56%; mp 321–3°C; IR: $\nu = 3320$ (NH), 1670 (CO), 1620 cm^{-1} (C=N); ^1H NMR: $\delta = 4.11$ (s, 2H, CH_2), 7.12–8.15 (m, 11H, ArH), 9.13 (s, 1H, NH, exchangeable); Anal. Calcd. for $C_{22}H_{14}N_4O_2S$: C, 66.32; H, 3.54; N, 14.06%; Found: C, 66.45; H, 3.41; N, 14.19%.

Method B

A mixture of **1** (10 mmol) and chloroacetyl chloride (10 mmol) in dry dioxane (30 mL) stood at room temperature overnight. The precipitated solid was filtered off and crystallized to give **17a**, which identified by mp and mmp. Yield, 60%.

2-Amino-9-phenoxathiin-2-yl-3H-3,4,10,10a-tetraazaphenanthrene-1-carbonitrile (18a)

To a solution of anhydrous potassium carbonate (10 mmol) in ethanol (30 mL) were added equimolar amounts of compound **1** (10 mmol) and bromomalononitrile (10 mmol). The reaction mixture was heated under reflux for 5 h. The reaction mixture was allowed to cool to room temperature, then the formed solid was filtered off and recrystallized from dioxane to produce **18a**. Yield, 65%; mp 322–4°C; IR: $\nu = 3360$–3160 (NH and NH_2), 2240 (C=N), 1615 cm^{-1} (C=N); ^1H NMR: $\delta = 6.01$ (br s, 2H, NH_2), 7.09–8.11 (m, 11H, ArH), 9.85 (s, 1H, NH, exchangeable); Anal. Calcd. for $C_{23}H_{14}N_6OS$: C, 65.39; H, 3.34; N, 19.89%; Found: C, 65.23; H, 3.48; N, 19.72%.

1-Methyl- or 1-phenyl-9-phenoxathiin-2-yl-3H-3,4,10,10a-tetraazaphenanthrenes (19a,b)

A mixture of **1** (10 mmol) and α-haloketones namely chloroacetone and/or phenacyl bromide in dry xylene (30 mL) was heated under reflux for 6 h. The solid precipitate, which separated upon cooling was filtered off and crystallized from a proper solvent to give **19a, b**.

19a, Yield, 57%; mp 290–2°C (dioxane); IR: $\nu = 3290$ (NH), 1617 cm^{-1} (C=N); MS m/z: 396 (M^+); Anal. Calcd. for $C_{23}H_{16}N_4OS$: C, 69.68; H, 4.07; N, 14.13%. Found: C, 69.54; H, 4.19; N, 14.28%.

19b, Yield, 55%; mp 272–4°C (dioxane); IR: $\nu = 3275$ (NH), 1620 cm^{-1} (C=N); ^1H NMR: $\delta = 7.12$–8.11 (m, 17H, ArH and triazine H-2), 9.81 (s, 1H, NH, exchangeable); Anal. Calcd. for $C_{28}H_{18}N_4OS$: C, 73.34; H, 3.96; N, 12.22%; Found: C, 73.49; H, 3.83; N, 12.36%.

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