Synthesis and Reactions of 2-(1-Oxo-4(1,2,3,4-tetrahydronaphthalen-2-yl)phthalazin-1(2H)-yl)acetohydrazide

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Abstract: The 4-(1,2,3,4-tetrahydronaphthalen-2-yl)phthalazin-1(2H)-one was prepared and reacted with ethyl chloroacetate, followed by hydrazine hydrate giving the acid hydrazide **(5).** The acid hydrazide **(5)** was subjected to different reagent giving different heterocylic molecuoles and an unexpected spirophthalazine **(4)** upon treatment with thiosemicarbazide. The structure of the prepared compounds were identified by IR,^{1}H NMR, MS and elemental analysis.

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1. Introduction

The synthesis of new compounds and testing their biological and pharmacological activities are the major goals of drug development projects. Nitrogen containing heterocyclic compounds have received much attention. Phthalazines are examples of nitrogen heterocycles that posses exciting biological properties. [1,2] They form the structural profile for several biologically active compounds and hence they are considered as important key elements. Phthalazines have been reported to possess anticonvulsant, [3] cardiotonic, [4] and vasorelaxant activities. [5] Several approaches have been reported in the literature for the synthesis of phthalazinones. [3,6] Also the 1,2,3,4-tetrahydronaphthalen-6-yl when incorporated into heterocyclic system, [7] possess a wide variety of biological activities including antibacterial, [8,9] antidepressant, [10,11] and anticancer effects. [12,13] In view of the aforementioned facts, it seemed most interesting to prepare a phthalazinone nucleus bearing a 1,2,3,4-tetrahydronaphthalen-6-yl moiety.

2. Experimental

Melting points were measured with a Gallenkamp apparatus and are uncorrected.The reactions were followed up and the purification of products was carried out on pre-coated TLC plates (Silica gel 60 F_{254},Merk), visualizing the spots in the ultraviolet light. IR spectra were recorded on a Shimadzu FT-IR 8101 PC infrared spectrophotometer. The ^{1} H NMR spectrum was determined in DMSO-d_6 at 300MHz on a Varian Mercury VX 300 NMR spectrometer and their chemical shifts (δ) are repoted with respect to TMS as internal standard. Mass spectra were measured on a GCMS-QP 1000 EX spectrometer at 70 eV.Elemental analyses were carried out at the Microanalytical Center of Cairo University.

4-(1,2,3,4-Tetrahydronaphthalen-2-yl)phthalazin-1(2H)-2-one [2]

Hydrazine hydrate (98%) 2ml was added to a solution of (2 g) (0.01 mol) of **(1)** in 20 ml absolute ethanol. The reaction mixture was refluxed for 2h, after cooling the obtained solid was filtered off and crystallized from ethanol to give **(2)** 80% yield as colorless crystals, mp 225-226 ℃; ^{1}H NMR (DMSO-d_6, 300 MHz) δ:1.2-1.7 (m, 4H, tetralin), 2.83-2.87 (m, 4H, tetralin) 7.3-7.7 (m, 7H, Ar-H), 11.3 (s, 1H, NH, exchangeable with D_2O). IR (KBr) γ: 3291 (NH), 1665 (C=O), 1602 (C=N) cm^{-1}. MS (70 eV) *m/z* (%): 276 (M$^+$, 100), 248 (43), 220 (15), 131 (25), 105 (15).Anal calcd for $C_{18}H_{16}N_2O$: C 78.23, H 5.84, N 10.14; found C 78.4, H 5.7, N 10.2.

Ethyl 2-(1-oxo-4(1,2,3,4-tetrahydronaphthalen-2-yl)phthalazin-1(2H)-yl)acetate [3]

A mixture of (2.7 g) (0.01 mol) of **(2)**, (4.5g) (0.03mol) of ethyl chloroacetate and (4.1 g) (0.03mol) potassium carbonate in 30 ml dry acetone was refluxed for 24h, cooled at room temperature and poured into water. The obtained solid was filtered off and crystallized from ethanol to give **(3)** 40% yield as colorless mp 110-112 ℃. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 1.276-1.324 (t, J= 7.2 H_Z, 3H, $CH_2\underline{CH_3}$), 1.2-1.7 (m, 4H, tetralin), 2.83-2.87 (m, 4H, tetralin), 4.22-4.29 (q, J= 7.5 H_Z, 2H, $O\underline{CH_2}CH_3$), 5.02 (s, 2H,CH_2), 7.3-7.7 (m, 7H, Ar-H). IR (KBr) γ 1750, 1650 (C=O), 1584 (C=N) cm^{-1}. MS (70 eV) *m/z* (%):362 (M$^+$, 78), 290 (100), 134 (22), 77 (39). Anal

calcd for $C_{22}H_{22}N_2O_3$: C 72.92, H 6.07, N 7.73; found C 73.2, H 5.95, N 8.10.

Ethyl 2-(5'-mercapto-4(1,2,3,4-tetrahydronaphthalen-2-yl)-2H-spiro[phthalazine-1,3-[1,2,4]triazole]-2-yl)acetate [4]

A mixture of (5g) (0.01 mol) of **(3)**, (0.9g) (0.01 mol) thiosemicarbazide and (30ml) ethanol was refluxed for 3h and cooled at room temperature. The obtained solid was filtered off and crystallized from ethanol to give **(4)** 50% yield as colorless crystals mp 160 ℃. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 1.276-1.3 (t, J=7.2 H_Z, 3H, $CH_2\underline{CH_3}$), 1.2-1.7 (m, 4H, tetralin), 2.83-2.87 (m, 4H, tetralin), 4.22-4.29 (q, J= 7.5 H_Z, 2H, $O\underline{CH_2}CH_3$), 5.02 (s, 2H,CH_2), 7.2 (s, 1H, NH, exchangeable with D_2O), 7.3-7.7 (m, 7H, Ar-H). IR (KBr) γ 1750,1650 (C=O),1584 (C=N) cm^{-1}. MS (70 eV) *m/z* (%):433 (M^+, 1.6), 435 (M^+ +2 (0.8), 389 (13), 361 (35), 347 (25), 314 (5), 288 (100), 260(4), 248(25), 130(50). Anal calcd for $C_{23}H_{225}N_5O_2S$: C 63.72, H 5.35, N 16.15; found C 64.0, H 5.65, N 16.10.

2-(1-Oxo-4(1,2,3,4-tetrahydronaphthalen-2-yl)phthalazin-1(2H)-yl)acetohydrazide [5]

A mixture of (5g) (0.013 mol) of **(3)** and (0.4g) (0.03mol) hydrazine hydrate in 30 ml ethanol was refluxed for 3h and cooled at room temperature. The resultant solid was filtered and crystallized from ethanol to give **(5)** 80% yield as colorless crystals, mp 195-196 ℃. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 1.2-1.7 (m, 4H, tetralin), 2.83-2.87 (m, 4H, tetralin), 4.2 (s, 2H, NH_2 exchangeable with D_2O), 5.02 (s, 2H,CH_2), 7.2 (s, 1H,NH, exchangeable with D_2O), 7.3-7.7 (m, 7H, Ar-H). IR (KBr) 3298, 3207 (NH_2) 3300 (NH), 1654 (C=O), 1580 (C=N) cm^{-1}. MS (70 eV) *m/z* (%): 348 (M^+, 2), 331 (4), 290 (4), 139 (100), 105 (7). Anal calcd for $C_{20}H_{20}N_4O_2$: C 68.96, H 5.74, N 16.09; found C 69.53, H 6.12, N 15.8.

4-(1,2,3,4-Tetrahydronaphthalen-2yl)-2((5-thioxo-2,5-dihydro-1H-1,2,4-triazol-3-yl)methyl)phthalazin-1(2H)-one [6]

A mixture of (0.3g) (0.001 mol) of **(5)** and (0.076g) (0.01 mol) thiourea was fused on oil bath at 130 ℃ for 5 h. After cooling the sticky mass was dissolved in 30 ml (8%) sodium hydroxide. The filtrate was acidified with 2N HCl. The solid was separated, filtered and crystallized from ethanol to give **(6)** 60% yield as colorless crystals, mp 210-211 ℃. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 1.2-1.7 (m, 4H, tetralin), 2.83-2.87 (m, 4H, tetralin), 5.02(s, 2H,CH_2), 7.2(s,1H, NH, exchangeable with D_2O), 7.3-7.7(m, 7H, Ar-H). IR (KBr) 3368, 3198 (NH), 1647(C=O), 1580 (C=N) cm^{-1}. MS (70 eV) *m/z* (%): 389 (M^+, 76), 391 (M^+ +2, 6), 356 (78), 324 (100), 275 (42), 247 (16). Anal calcd for $C_{21}H_{19}N_5OS$: C 64.76, H 4.92, N 17.98; found C 64.53, H 5.12, N 17.8.

4-(5,6,7,8-Tetrahydronaphthalen-2yl)-2((5-thio-1,3,4-oxadiazol-2-yl)methyl)phthalazin-1(2H)-one [7]

(0.34g) (0.001mol) of **(5)** in absolute ethanol was added to (0.8g) of potassium hydroxide solution followed by 3 mL carbon disulphide portion-wise. The reaction mixture was refluxed till complete evolution of hydrogen disulphide. The reaction mixture was poured onto ice water and neutralized with HCl. A solid was separated, filtered and crystallized from ethanol to give **(7)** 30% yield as colorless crystals, mp 160-161 ℃. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 1.2-1.7(m, 4H, tetralin), 2.83-2.87 (m, 4H, tetralin), 5.02 (s, 2H,CH_2), 7.2(s, 1H,NH, exchangeable with D_2O), 7.3-7.7 (m, 7H, Ar-H). IR (KBr) 3137 (NH), 1645 (C=O), 1578 (C=N), 1318(C-O), 1150 (C=S) cm^{-1}. Anal calcd for $C_{21}H_{18}N_4O_2S$: C 64.60, H 4.65, N 14.35; found C 64.80, H 5.02, N 14.8.

2-(2-(1-Oxo-4(1,2,3,4-tetrahydronaphthalen-2yl)phthalazin-2(1H)-yl) acetyl) hydrazinecarbothioamide (8)

A mixture of (0.34g) (0.001mol) of **(5)** and (0.097) (0.001mol) potassium thiocyanate, 0.8 mL conc HCl and 20 mL water was refluxed for 12 h. After cooling a solid was formed, filtered and crystallized from ethanol to give **(8),** 40% yield as colorless crystals, mp 200-202 ℃. IR (KBr) 3288, 3192 (NH_2), 3443 (NH), 1622 (C=O), 1578 (C=N), 1158 (C=S) cm^{-1}. Anal calcd for $C_{21}H_{21}N_5O_2S$: C 61.90, H 5.19, N 17.19; found C 61.80, H 5.12, N 17.8.

Another method for the preparation of (6)

A mixture of 15 mL (8%) NaOH and (0.04g) (0.001 mol) of **(8)** in 20 mL ethanol was refluxed for 10 h. The solution was cooled and neutralized with 2N HCl. After cooling a ppt. was formed, filtered and crystallized from ethanol to give **(6),** 40% yield as colorless crystals, mp 210 ℃.

2-(2-(1-Oxo-5(5,6,7,8-tetrahydronaphthalen-2yl)phthalazin-2(1H)-yl)phenylhydrazinecarbothioamide (9)

A mixture of (0.3g) (0.001mol) of **(5),** (0.34g) (0.001mol) phenylisothiocyanate and 20 mL dry N,N dimethylformamide was refluxed for 24 h. After cooling the reaction mixture was poured on ice water and HCl. The obtained solid was collected, dried and crystallized from ethanol as colorless crystals, yield 80%, mp 175 ℃. IR (KBr) γ 3408, 3364, (NH), 1685,

1622 (C=O), 1579 (C=N), 1158 (C=S) cm^{-1}.. Anal calcd for $C_{27}H_{25}N_5O_2S$: C 67.06, H 5.21, N 14.49; found C 67.63, H 6.1, N 14.8.

2-(5-(Phenylamino)-1,3,4-thiadiazol-2-yl)-4-(5,6,7,8-Tetrahydronaphthalen-2yl)-phthalazin-1(2H)-one [10]

(0.48 g) (0.001 mol) Thiocarbamate **(9)** was mixed with 5 mL conc sulphuric acid and left overnight. The reaction mixture was poured onto ice water. The obtained solid was collected, dried and crystallized from ethanol, as colorless crystals, yield 70%, and mp 135 ℃. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 1.2-1.7 (m, 4H, tetralin), 2.83-2.87 (m, 4H, tetralin), 5.25 (s, 2H,CH_2), 7.2 (s, 1H,NH, exchangeable with D_2O), 6.8-8.17(m, 12H, Ar-H). IR (KBr) γ 3408, (NH), 1615 (C=O), 1579 (C=N), cm^{-1}. MS (70 eV) *m/z* (%): 465 (M^+, 1.6) 437 (M^++2, 0.9), 289 (4), 276 (43), 262 (100), 247 (23). Anal calcd for $C_{27}H_{23}N_5OS$: C 69.65, H 4.94, N 15.04; found C 70.3 3, H 5.1, N 14.8.

2-((4-(Phenyl-5-thio-4,5-dihydro-1H-1,2,4-triazol-3-yl)methyl)-4-(5,6,7,8-tetrahydronaphthalen-2yl)-phthalazin-1(2H)-one [11]

(0.48 g) (0.001 mol) Thiocarbamate **(9)** was dissolved in (2N, 20 mL) sodium hydroxide. The solution was heated on water bath for 2 h, cooled and neutralized with dil HCl. The obtained solid was collected, dried and crystallized from ethanol, as colorless crystals, yield 40%, mp 210 ℃. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 1.2-1.7 (m, 4H, tetralin), 2.83-2.87 (m, 4H, tetralin), 5.25 (s, 2H, CH2), 6.8-8.17 (m, 12H, Ar-H). IR (KBr) γ 3302, (NH), 1656 (C=O), 1579 (C=N), 1087 (C=S) cm^{-1}. Anal calcd for $C_{27}H_{23}N_5OS$: C 69.65, H 4.98, N 15.04; found C 70.33, H 5.1, N 14.8.

N'-naphthylidene-2-(4-(1,2,3,4-tetrahydronaphthalen-2-yl)-1-oxophthalazin-2(1H)-yl)acetohydrazide(12)

A mixture of (0.3g) (0.001 mol) of **(5)** and (0.15g) (0.001mol) of naphthaldehyde in 20 ml ethanol was refluxed for 3h. The obtained solid was filtered and crystallized from ethanol to give **(12),** 30% yield as colorless crystals, mp 135-137 ℃. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 1.7 -1.9 (m, 4H, tetralin), 2.4-2.51 (m, 4H, tetralin), 5.25 (s, 2H, CH2), 7.25-8.72 (m, 14H, Ar-H), 11.8 (s, 1H, NH, exchangeable with D_2O). IR (KBr) 3463 (NH), 1664, 1647 (C=O), 1579 (C=N) cm^{-1}. MS (70 eV) *m/z* (%): 486 (M^+, 1.5), 333 (18), 317 (33), 289 (100), 262 (30), 131 (52). Anal calcd for $C_{31}H_{26}N_2O_4$: C 76.70, H 5.39, N 11.52; found C 75.83, H 6.0, N 12.32,

2-(Naphthalene-1-yl methyl)-3-(2-(1-oxo-4-(5,6,7,8)-tetrahydronaphthalen-2-yl)phthalazin-2(1H)-yl acetyl) thiadiazolidin-4-one (13)

A mixture of (0.4g) (0.001mol) of **(12)**, (0.098g) (0.001mol) thioglycolic acid and few drops of piperidine was refluxed for 3 h on a water bath. After cooling the obtained solid was washed with petroleum ether, dried and crystallized from ethanol to give (**13**) as beige crystals, yield 50%, mp 200-201 ℃. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 1.2-1.7 (m, 4H, tetralin), 2.4-2.5 (m, 4H, tetralin), 5.25 (s, 2H,CH_2), 6.8-8.17 (m, 14H, Ar-H). IR (KBr) 1690, 1655 (C=O), 1579 (C=N) cm^{-1}. MS (70 eV) *m/z* (%): 576 (M^+, 2.7), 578 (M^+ +2, 0.35), 560 (4) 420 (25), 388 (24), 360 (25), 346 (12). Anal calcd for $C_{33}H_{28}N_4O_4S$: C 70.69, H 5.03, N 9.9; found C 70.31, H 4.62, N 9.8.

2-(Naphthalen-yl(2-(2-(1-oxo-4-(5,6,7,8)-tetrahydronaphthalen-2-yl)phthalazin-2(1H)-yl acetyl) hydrazinyl)methylthio)acetic acid (14)

A mixture of (0.4g) (0.001mol) of **(12)**,(0.098g) (0.001mol) thioglycolic acid and 20 mL benzene was refluxed for 3 h. After cooling the obtained solid was collected, dried and crystallized from methanol to give (**14**) as beige crystals, yield 70%, mp 170-171 ℃. IR (KBr) 3433 (broad), 3192 (NH), 1706, 1637, (C=O), 1500 (C=N) cm^{-1}. Anal calcd for $C_{33}H_{30}N_4O_4S$: C 68.49, H 5.23, N 9.68; found C 69.1, H 5.12, N 9.8.

N'-((2-aminophenylthio)(naphthalen-1-yl) methyl)-2-(1-oxo-4-(5,6,7,8)-tetrahydronaphthalen-2-yl)phthalazin-2(1H)-yl)acetohydrazide (15)

A mixture of (0.4g) (0.001mol) of **(12)**,(0.012g) (0.001mol) o-aminothiophenol and 20 mL ethanol was refluxed for 2 h. After cooling the obtained solid was collected, dried and crystallized from ethanol to give (**15**) as colorless crystals, yield 30%, mp 90-91 ℃. IR (KBr) 3457, 3333, (NH_2), 3211 (NH), 1644, 1602 (C=O), 1579 (C=N). MS (70 eV) *m/z* (%): 611(M^+, 12), 131 (14), 76 (100) Anal calcd for $C_{37}H_{33}N_5O_2S$: C 72.66, H 5.40, N 11.45; found C 72.43, H 5.12, N 11.8.

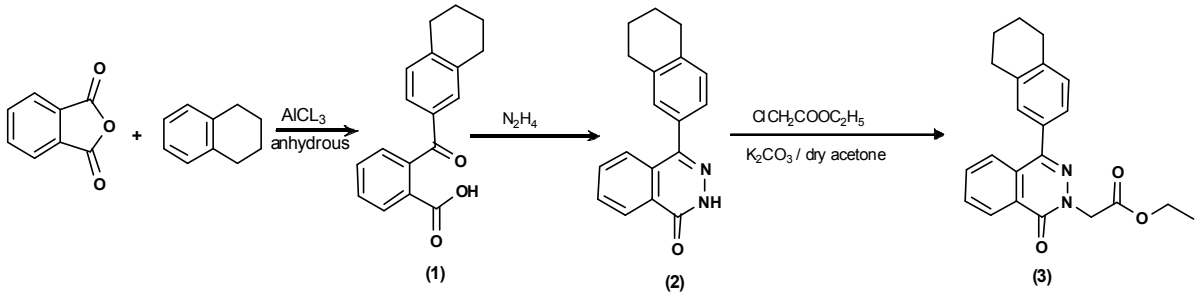
3. Results and Discussion

Aroylation of an aromatic system by reaction with phthalic anhydride under Freidel Craft's conditions yields the o-aroyl benzoic acid. [14] Thus the reaction of tetralin with phthalic anhydride in the presence of anhydrous aluminium chloride was carried out to produce 2-(1,2,3,4-tetrahydronaphthalen-6-yl benzoyl) benzoic acid. Merchant et al prepared phthalazin-1-ones via the condensation of the aroyl benzoic acid with

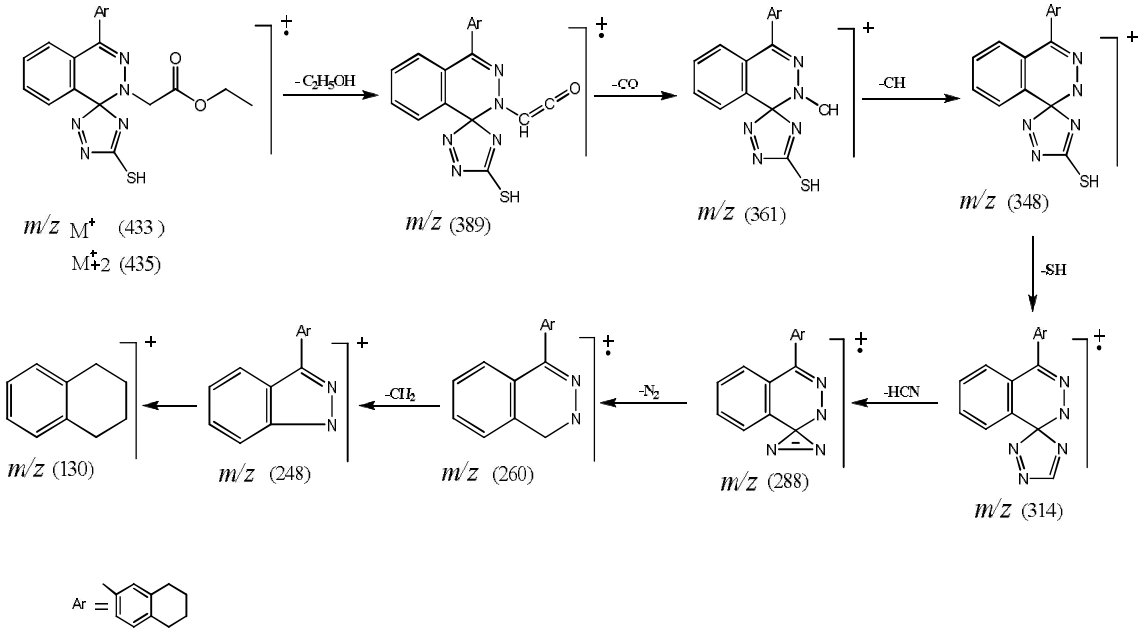
hydrazine hydrate in boiling ethanol. [15] Accordingly, our phthalazinone **(2)** namely 4-(1,2,3,4-tetrahydronaphthalen-2-yl)phthalazin-1(2H)-one was obtained. The IR spectrum showed a characteristic absorption bands at γ 1665 cm^{-1} corresponding to (C=O). The mass spectrum shows the correct ion peak at *m/z* 276 (Scheme 1).

Compound **(2)** was treated with ethyl chloroacetate to afford the corresponding phthalazine aetic acid ethyl ester **(3)** (Scheme2). The structure of **(3)** was confirmed on the basis of elementary analysis as well as spectal data. The IR spectrum showed a characteristic absorption band at γ 1750 cm^{-1} corresponding to C=O of ester with a disappearance of NH band. The ^{1}H NMR spectrum showed a triplet signal at δ 1.34 assigned for CH_3CH_2, a quartet signal for CH_2CH_3 at δ 4.22 and the mass spectrum shows a correct ion peaks at *m/z* 362.

The phthalazine acetic acid ethyl ester **(3)** was allowed to react with thiosemicarbazide gave the spirophthalazine **(4),** which was confirmed by IR showing bands at γ 1752 cm^{-1} corresponding to C=O of ester. The ^{1}HNMR confirmed **(5)** as well as the mass spectrum which shows a correct ion peak at *m/z* 433 and 435 (M^{+} and M^{+}+2) with a good pathway.



Scheme1.

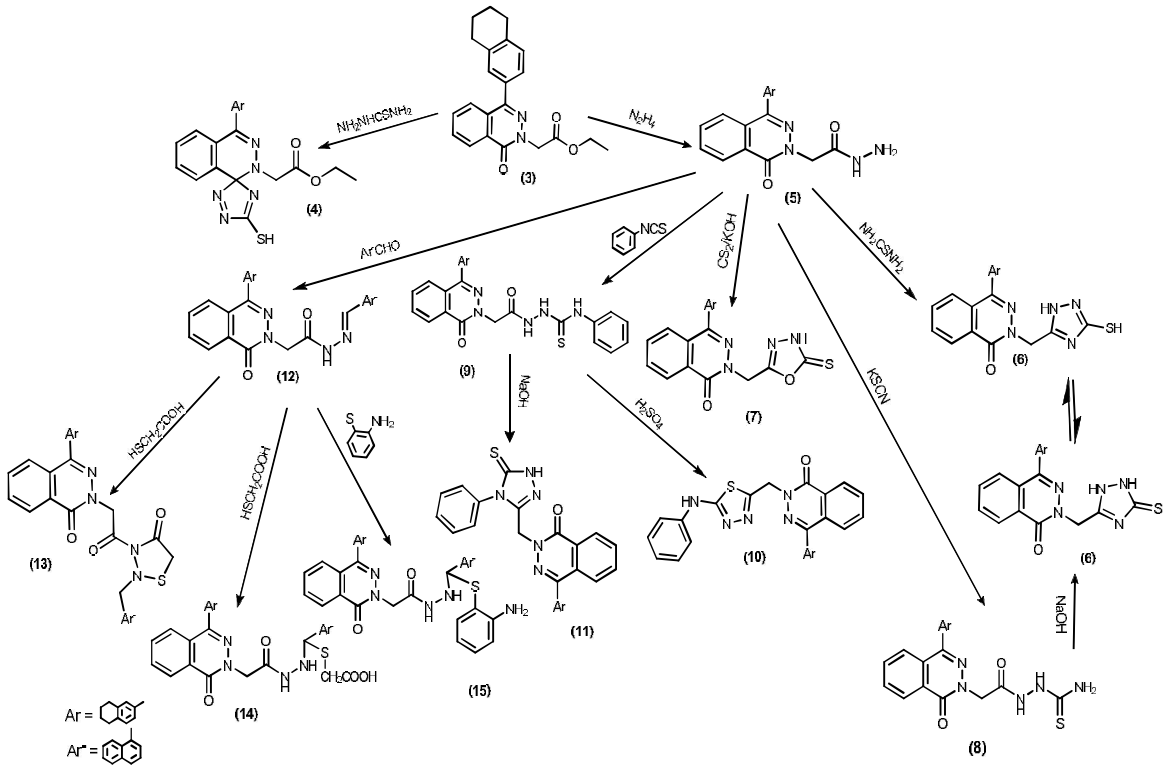


The formation of the spirophthalazine **(4)** could be explained on the basis of double nucleophilic attack of the nitrogen on the carbon center with the elimination of one molecuole of water. The phthalazine acetic acid ethyl ester **(3)** was converted to the hydrazide **(5)** by the reaction with hydrazine hydrate (Scheme 2). The hydrazide revealed absorption bands at γ 3298, 3207, 3300, 1654, cm^{-1} corresponding to NH_2, NH, and C=O. The mass spectrum shows a correct ion peak at *m/z* 348. When the hydrazide **(5)** was fused with thiourea gave the corresponding triazole **(6)** in good yield.It's structure

was confirmed by IR, ^{1}H NMR (see experimental). The mass spectrum shows a correct ion peak at *m/z* 389, 391 (M^+, M^++ 2). Also the triazole **(6)** was obtained upon reacting **(5)** with potassium thiocyanate giving the carbothioamide **(8)** which was cyclized upon treatment with sodium hydroxide to give **(6)** once more. Extending the work of cyclization of **(5)**, and synthesizing new heterocyclic molecuoles, **(5)** was allowed to react with carbon disulphide in alcoholic potassium hydroxide gave the corresponding oxadiazolo-2-thione derivative **(7)**. The IR revealed the presence of NH, C=O as well as C-O and C=S at γ 3137, 1645, 1315 and 1150 cm^{-1} respectively. Also ^{1}H NMR agreed with **(7).**

The hydrazide **(5)** reacted with phenyl isocyanate to produce the corresponding thiocarbamate derivative **(9)**. The IR spectra of **(9)** showed a characteristic band at γ 1194 cm^{-1} characteristic of C=S in addition to γ 3443, 3644, 1685, 1622 cm^{-1} characteristic of NH and C=O respectively. The thiocarbamate derivative **(9)** was cyclized to the corresponding thiadiazolo phthalazine derivative **(10)** by using conc. sulfuric acid while it was cyclized to the corresponding triazolo derivative **(11)** by treatment with sodium hydroxide. The structures were verified by spectral datae.

The hydrazide **(5)** reacted with naphthaldehyde, in ethanol to give **(12)** which reacted with o-amino thiophenol afforded an addition reaction on the double bond giving the thia Michael adduct type **(15).** The IR spectrum of **(15)** revealed strong bands at γ 1644, 1684, 2855, 2924, 3211, 3333 and 3457 cm^{-1} attributed to C=O, CH, and NH. On the other hand upon reacting **(12)** with thioglycollic acid in boiling benzene and few drops of piperidine gave **(13)** which was formed via thia Michael type addition of thioglycolic acid to C=N followed by ring closure, while upon using benzene only on water bath gave **(14).** The IR spectrum of **(13),** showed bands at γ 1690 and 1655 cm^{-1} corresponding to C=O. The structure was also confirmed by the mass spectrum which showed a correct ion peak at *m/z* 576. Moreover the IR spectrum of **(14)** showed bands at γ 3433 cm^{-1} (broad), due to (OH), and γ 1709 cm^{-1} to C=O revealing the presence of an acid (Scheme 2).



Scheme 2. Synthetic pathway for compounds 4 and16.

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