Studies with Pyridazines and Condensed Pyridazines: Routes for Synthesis of 3-Amino-5-aryl-2,5-dihydro-pyridazine, 10a*H*-Pyridazino[1,6-*a*]quinazoline and Thieno[3,4-*d*]pyridazinone

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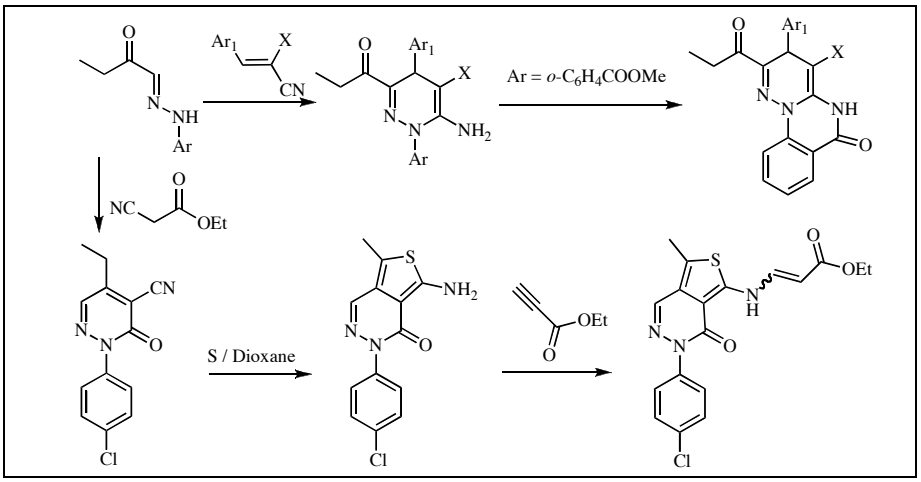

Novel routes to 3-aminopyridazines, 10a*H*-pyridazino[1,6-*a*]quinazoline and, thieno[3,4-*d*]pyridazine utilizing the reaction of 2-oxobutanal-1-arylhydrazones **3a,b** with α,β-unsaturated nitriles are described. Condensation of **3** with ethyl cyanoacetate afforded pyridazinones that reacted with sulphur yielding thienopyradazinone **10**. Reaction of **10** with maleic anhydride and acrylonitrile afforded products of addition and hydrogen sulphide elimination. On other hand reacting **10** with enaminone and ethyl propionate afforded the product of addition of the amino function to activated double bond

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INTRODUCTION

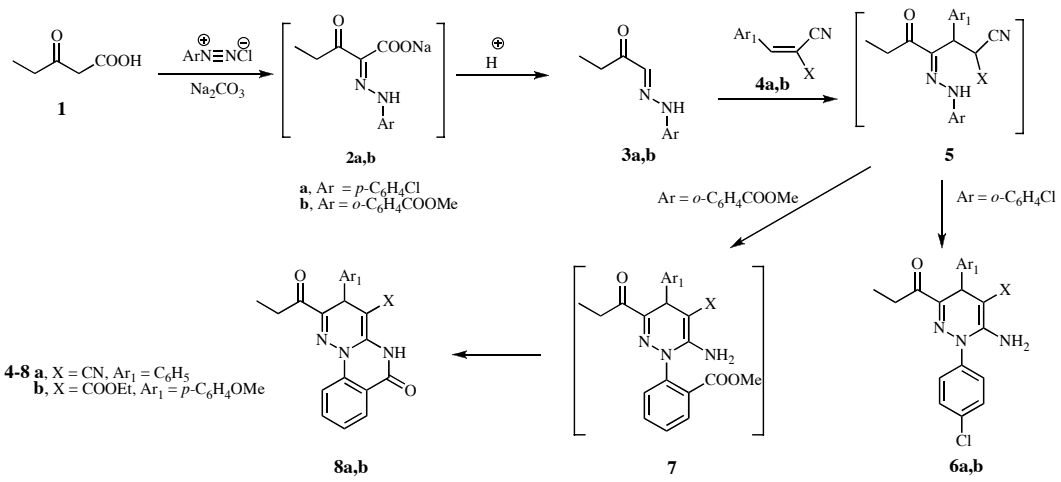
The chemistry of pyridazines and condensed pyridazines is now receiving considerable interest [1-4] As a part of our programme directed at developing efficient syntheses for biologically interesting polyfunctional heteroaromatics utilizing inexpensive and readily obtainable starting materials [5-8], we report here several efficient synthetic routes to pyridazines utilizing 2-oxobutanal-1-arylhydrazones **3a,b** as starting materials. The required prepared **3a,b** were readily obtained *via* coupling 3-oxopentanoic acid with aromatic diazonium salts following a procedure reported for synthesis of 2-oxopyruvaldhyde-1-arylhydrazones from reaction of acetoacetic acid with aromatic diazonium salts [9].

RESULTS AND DISCUSSION

Compounds **3a,b** reacted with benzylidenemalononitrile (**4a**) and with ethyl arylidenecyanoacetate **4b** to yield 1:1 adducts. These were assumed to result from Michael addition to activated double bond in **4a,b**. Reactivity of aldehydic hydrazones toward electrophilic reagents as a result of hydrazone lone pair delocalization has recently been intensively investigated [10-13], but to our knowledge with exception of our recent report on reactivity of 2-oxopropanal-1-arylhydrazones [14], no other report on reactivity of such hydrazones in Michael reaction has been made. The formed adducts were assigned the pyridazine structure **6a,b** and are believed to be formed *via* intermediacy of acyclic **5a,b**. On the other hand reacting **3b** with **4a,b** resulted in formation of tricyclic **8a,b** formed most likely *via* intermediates **7a,b** that could not be isolated (Scheme 1). Formation of such tricyclic products supports our suggested formation of **5a,b** rather than possible isomeric 6H-pyridazine derivatives. This finding thus parallel reported [14] formation of 4H-pyridazines from reaction of 2-oxopropanal-1-arylhydrazones with **4**.

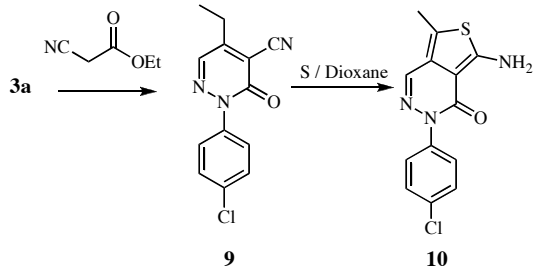
In conjunction to our recent previous work [15] compound **3a** was condensed on heating with ethyl cyanoacetate in presence of ammonium acetate for 15 min to yield the pyridazinone **9**. Compound **9** reacted with

Scheme 1



sulfur in dioxane in presence of piperidine to yield the thieno[3,4-*d*]pyridazine **10** (Scheme 2).

Scheme 2



Compound **10** reacted with maleic anhydride and acrylonitrile to yield products of addition and hydrogen sulphide elimination. These were assigned structure **12** and **14** and are assumed to be formed *via* cycloaddition. In contrast to this compound **10** reacted with the enaminone **15** and with ethyl propiolate to yield only product of addition of amino function at double bond affording **16**, **17** and stereo-isomeric **18**. While **16** existed solely in *cis* form, compound **17** proved to be a 1:1 mixture of *cis* and *trans* forms. Stereochemistry of the reaction products could be readily concluded from *J* values of olefinic protons (Scheme 3). Thus olefinic protons in **16** have *J* = 8.1 Hz while product of reaction with ethyl propiolate revealed four olefinic doublets at δ 5.03, 5.65, 8.08, 5.03 ppm. The doublets at 5.03 and 8.08 have *J* = 7.3 Hz while others have *J* = 12.2 Hz with half integral per each signal.

It is of value to report that reaction of thienoazines with dipolarophile has been reported by Elnagdi *et al* [16-20] as well as Döpp *et al* [21] to afford either products of 4+2 cycloaddition, products of C-1 alkylation or product of initial addition of aminofunction to the dipolarophile. However reaction of methyl 5-amino-7-methyl-4-oxo-3-phenyl-3,4-dihydro-thieno[3,4-*d*]pyridazine-1-carboxylate with acrylonitrile has been shown earlier to afford 6-amino-8a-methyl-2,5-dioxo-4-phenyl-4,5,8,8a-tetrahydro-2*H*-1-thia-3,4-diazaacenaphthylene-7-carbonitrile [22]. Although it was believed earlier [23] that the reaction of condensed aminothiophenes with acetylenic esters affords thiepines Elnagdi *et al* [24] has shown that the formed products are actually C-1 alkylation products.

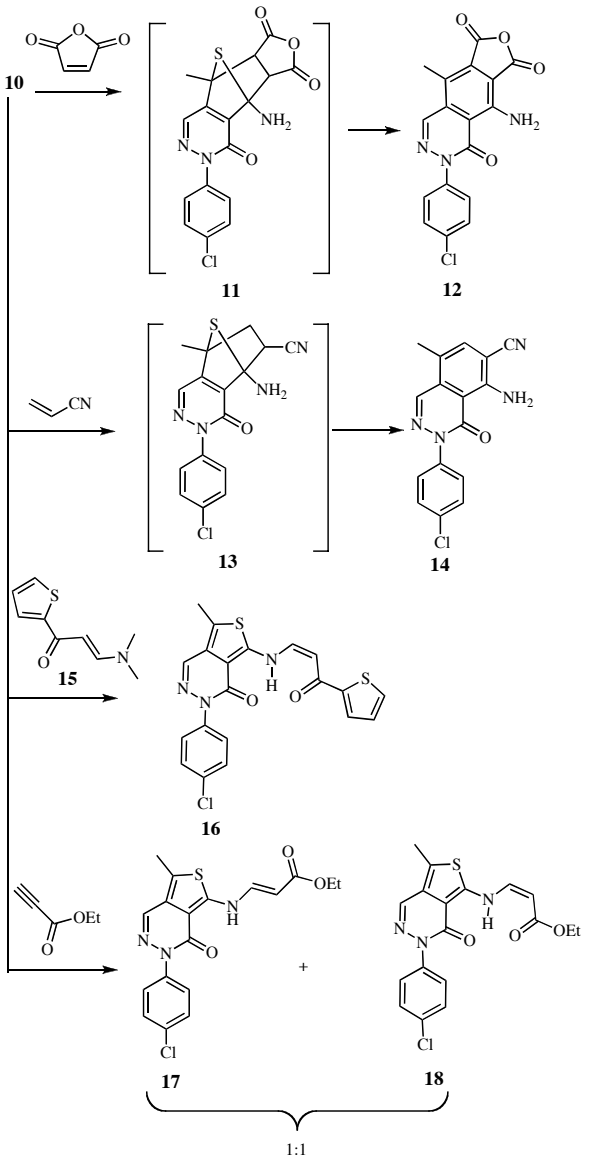
In conclusion, we could show that the readily obtainable 1-(aryl-hydrazono)-butan-2-ones are versatile starting for synthesis of pyridazines and condensed pyridazines of biological interest.

EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded in KBr disks using a Pye Unicam SP-3000 IR spectrophotometer and Testscan Shimadzu FT-IR 8000 series. ^{1}H and ^{13}C NMR spectra were measured in DMSO-d_6 at 400/100 and 300/75 MHz on a Varian Gemini relative to DMSO (2.50 ppm for ^{1}H and 39.5 ppm for ^{13}C); chemical shifts are reported in δ units (ppm). Mass spectra were measured on a GCMS-QP 1000-EX Shimadzu. Microanalyses were performed on a LECO CHNS-932 Elemental Analyzer.

1-(Aryl-hydrazono)-butan-2-one (3a,b). In a beaker equipped with a mechanical stirrer a solution of 3.5 g. (53 mmol) of 85 % potassium hydroxide in 112 ml of water with 6.5 g (0.05 mol) of methyl 3-oxo-pentanoate. The mixture is allowed to stand at room temperature for 24 hrs. The solution was cooled to 0 °C, and 4.5 ml of conc. HCl in 15 ml. of ice water was added slowly with stirring. The diazonium salt solution was added (50 mmol); prepared by adding a solution of sodium nitrite (3.6 g into 10 ml H_2O) to cold solution of aniline hydrochloride derivatives (50 mmol of aniline derivatives in 20 ml concentrated HCl); over a period of 20 min, and the mixture is made basic by the addition of 8.2 g. of sodium acetate dissolved in 30 ml. of water. The temperature of the reaction mixture is raised slowly to 50°C and maintained at this value for

Scheme 3



1 hr; the solid product, so formed, was collected by filtration and crystallized from ethanol [9].

1-[(4'-Chloro-phenyl)-hydrazono]-butan-2-one (3a). Red crystal, (yield 76%, 7.9 g) mp 130-131 °C; ir (KBr): ν_{max} 3236 (NH), 1650 cm^{-1} (CO); ms (70 eV) m/z: 210 (M^+, 35%), (111, 100%); ^1H nmr (300 MHz, DMSO-d_6): 1.01 (t, 3H, *J* = 7.4 Hz, CH_3), 2.80 (q, 2H, *J* = 7.4 Hz, CH_2), 6.98-7.10 (m, 4H, Ar-H), 7.30 (s, 1H, CH), 11.21 (brs, 1H, NH) ^{13}C nmr (75 MHz; DMSO-d_6): 200.1, 142.0, 134.3, 131.4, 130.8x2, 114.4x2, 30.0, 9.5. *Anal.* calcd. for $C_{10}H_{11}ClN_2O$ C, 57.01; H, 5.26; N, 13.30. Found C, 56.78; H, 5.10; N, 13.72 %

Methyl 2-[*N*'-(2-oxo-butylidene)-hydrazino]-benzoate (3b). Orange crystal, (yield 74%, 8.6 g) mp 65 °C; ir (KBr): ν_{max} 3258 (NH), 1684 cm^{-1} (CO); ms (70 eV) m/z 234 (M^+, 22%), (175, 35%); ^1H nmr (300 MHz, DMSO-d_6): 1.01 (t, 3H, *J* = 7.2 Hz, CH_3), 2.83 (s, 3H, CH_3), 2.90 (q, 2H, *J* = 7.2 Hz, CH_2), 7.00-7.59 (m, 1H, Ar-H), 7.60-7.99 (m, 4H, CH and Ar-H), 11.34 (brs, 1H, NH). *Anal.* calcd. for $C_{12}H_{14}N_2O_3$ C, 61.53; H, 6.02; N, 11.96. Found C, 61.17; H, 6.33, N, 11.73 %

3-Amino-2-(4'-chloro-phenyl)-5-aryl-6-propionyl-2,5-dihydro-pyridazine-4-derivates (6a,b). A mixture of **3a** (0.01 mol), benzylidenemalononitrile **4a**, or ethyl 2-cyano-3-(4-methoxy-phenyl)-acrylate **4b** (0.01 mol) and piperidine (0.5 ml) in ethanol (20 ml) was refluxed for 5 hrs. The solvent was then evaporated under reduced pressure and the residue poured onto water and neutralized by HCl. The product was collected by filtration and crystallized from ethanol.

3-Amino-2-(4'-chloro-phenyl)-5-phenyl-6-propionyl-2,5-dihydro-pyridazine-4-carbonitrile (6a). Brown crystal, (yield 82%, 2.9g) mp 177-178 °C; ir (KBr): ν_{max} 3473, 3309 (NH_2), 2190 (CN) 1687 cm^{-1} (CO); ms (70 eV) m/z 364 (M^+, 11%), (307, 100%); ^1H nmr (400 MHz, DMSO-d_6): 0.93 (t, 3H, *J* = 7.3 Hz, CH_3), 2.75 (q, 2H, *J* = 7.3 Hz, CH_2), 4.73 (s, 1H, CH), 6.19 (brs, 2H, NH_2), 7.16-7.36 (m, 5H, Ar-H), 7.56 (d, 2H, *J* = 8.6 Hz, CH), 7.58 (d, 2H, *J* = 8.6 Hz, CH),) ^{13}C nmr (100 MHz; DMSO-d_6): 199.4, 151.3, 144.6, 142.9, 140.0, 133.0, 130.4, 130.0x2, 128.4x2, 128.3x2, 127.8x2, 121.5, 57.8, 37.2, 30.6, 8.9. *Anal.* calcd. for $C_{20}H_{17}ClN_4O$ C, 65.84; H, 4.70; N, 15.36. Found C, 65.41; H, 4.93; N, 15.58. %

Ethyl 3-amino-2-(4'-chloro-phenyl)-5-(4-methoxy-phenyl)-6-propionyl-2,5-dihydro-pyridazine-4-carboxylate (6b). Yellow crystal, (yield 81%, 3.5 g), mp 150 °C; ir (KBr): ν_{max} 3365, 3270 (NH_2), 1688, 1652 cm^{-1} (CO); ms (70 eV) m/z : 441 (M^+, 7%), (369, 100%); ^1H nmr (300 MHz, DMSO-d_6): 0.95 (t, 3H, *J* = 8.7 Hz, CH_3), 1.16 (t, 3H, *J* = 8.4 Hz, CH_3), 2.80 (q, 2H, *J* = 8.7 Hz, CH_2), 3.68 (s, 3H, CH_3), 4.05 (q, 2H, *J* = 8.4 Hz, CH_2), 5.13 (s, 1H, CH), 6.81-7.11 (m, 8H, Ar-H), 7.57 (brs, 2H, NH_2), ^{13}C nmr (75 MHz; DMSO-d_6): 198.6, 168.1, 158.0, 151.0, 147.0, 139.0, 135.0, 132.0, 129.5x2, 128.1x2, 127.3x2, 113.9x2, 76.3, 58.8, 54.9, 33.2, 29.6, 14.4, 8.1. *Anal.* calcd. for $C_{23}H_{24}ClN_3O_4$ C, 62.51; H, 5.47; N, 9.51. Found C, 62.92; H, 5.33; N, 9.12 %

10*a*H-Pyridazino[1,6-*a*]quinazoline derivatives (8a,b). A mixture of **3b** (0.01 mol), benzylidenemalononitrile **4a**, or ethyl 2-cyano-3-(4-methoxy-phenyl)-acrylate **4b** (0.01 mol) and piperidine (0.5 ml) in ethanol (20 ml) was refluxed for 7 hrs. The solvent was then evaporated under reduced pressure and the residue poured onto water and neutralized by HCl. The product was collected by filtration and crystallized from ethanol.

6-Oxo-3-phenyl-2-propionyl-5,6-dihydro-3*H*-pyridazino[1,6-*a*]quinazoline-4-carbonitrile (8a). Dark green solid (yield 80%, 78 g), mp 220-221 °C; ir (KBr): ν_{max} 3444 (NH), 2200 (CN), 1684, 1652 cm^{-1} (CO); ms (70 eV) m/z 356 (M^+, 12.5%), (299, 43%), (279, 21%); ^1H nmr (300 MHz, DMSO-d_6): 0.93 (t, 3H, *J* = 7.3 Hz, CH_3), 2.75 (q, 2H, *J* = 7.3 Hz, CH_2), 4.73 (s, 1H, CH), 6.19 (brs, 1H, NH), 7.24-7.37 (m, 5H, Ar-H) 7.80-7.98 (m, 4H, Ar-H); ^{13}C nmr (75 MHz, DMSO-d_6): 198.0, 158.3, 145.0, 141.2, 140.7, 135.5, 129.0, 128.6x2, 127.8, 127.6x2, 127.2, 124.7, 117.3, 115.7, 114.9, 63.3, 36.9, 30.2, 7.7. *Anal.* calcd. for $C_{21}H_{16}N_4O_2$ C, 70.77; H, 4.53; N, 15.72. Found C, 70.89; H, 4.12; N, 15.42 %

Ethyl 3-(4-methoxyphenyl)-6-oxo-2-propionyl-5,6-dihydro-3*H*-pyridazino[1,6-a]quinazoline-4-carboxylate (8b). Green crystal (yield 82%, 3.5 g), mp 174-175 °C; ir (KBr): ν_{max} 3445 (NH), 1697, 1665 cm^{-1} (CO); ms (70 eV) m/z 433 (M^+, 24.3%) (360, 40%); ^1H nmr (300 MHz, DMSO-d_6): 0.97 (t, 3H, *J* = 8.4 Hz, CH_3), 1.16 (t, 3H, *J* = 8.0 Hz, CH_3), 2.97 (q, 2H, *J* = 8.4 Hz, CH_2), 3.67 (s, 3H, CH_3), 4.10 (q, 2H, *J* = 8.0 Hz, CH_2), 5.07 (s, 1H, CH), 6.81 (d, 2H, *J* = 9.45 Hz, Ar-H),), 7.1 (d, 2H, *J* = 9.45

Hz, Ar-H), 7.38-7.43 (m, 1H Ar-H), 7.82-8.02 (m, 3H Ar-H), 11.66 (brs, 1H, NH), ^{13}C nmr (75 MHz; DMSO-d_6): 198.3, 167.9, 158.4, 157.3, 148.4, 141.6, 140.8, 135.9, 134.3, 129.0x2, 127.3, 124.8, 115.5, 115.3, 114.0x2, 79.8, 60.3, 55.0, 33.6, 30.3, 14.0, 7.8. *Anal.* calcd. for $C_{24}H_{23}N_3O_5$ C, 66.50; H, 5.35; N, 9.69. Found C, 66.74; H, 5.28; N, 10.02 %

2-(4'-Chloro-phenyl)-5-ethyl-3-oxo-2,3-dihydro-pyridazine-4-carbonitrile (9). A mixture of **3a** (0.01 mol), and cyanoacetic acid ethyl ester (0.01 mol) were treated with ammonium acetate (2 g), and acetic acid (15 ml) then refluxed for 15 min. The solvent was then evaporated under reduced pressure and the residue poured into water. The product was collected by filtration and crystallized from ethanol, dark orange crystal, (yield 71%, 1.8 g) mp 132-133 °C, ir (KBr): ν_{max} 2234 (CN), 1659 cm^{-1} (CO); ms (70 eV) m/z 259 (M^+, 32%) (111, 100%); ^{1}H nmr (300 MHz, DMSO-d_6): 1.28 (t, 3H, *J* = 7.6 Hz, CH_3), 2.77 (q, 2H, *J* = 7.6 Hz, CH_2), 7.32 (d, 2H, *J* = 8.2 Hz, Ar-H), 7.43 (d, 2H, *J* = 8.2 Hz, Ar-H), 8.31 (s, 1H, CH). *Anal.* calcd. for $C_{13}H_{10}ClN_3O$. C, 60.12; H, 3.88; N, 16.18. Found C, 60.44; H, 3.51; N, 15.79 %

7-Amino-2-(4'-chloro-phenyl)-5-methyl-2*H*-thieno[3,4-*d*]-pyridazin-1-one (10). A mixture of **9** (0.01 mol), and elemental sulfur (0.01 mol) in dioxane (15 ml) and piperidine (0.5 ml) was refluxed for 5 hrs then poured onto water. The product was collected by filtration and crystallized from ethanol, pale brown crystal, (yield 62 %, 1.8 g); m.p. 212-213 °C, ir (KBr): ν_{max} 3406, 3304 (NH_2), 1661 cm^{-1} (CO); ms (70 eV) m/z: 291 (M^+, 35%), (258, 100%); ^{1}H nmr (400 MHz, DMSO-d_6): 2.44 (s, 3H, CH_3), 7.37 (brs, 2H, NH_2), 7.47 (d, 2H, *J* = 8.7 Hz, Ar-H), 7.55 (d, 2H, *J* = 8.7 Hz, Ar-H), 8.04 (s, 1H, CH). *Anal.* calcd. for $C_{13}H_{10}ClN_3OS$ C, 53.52; H, 3.45; N, 14.40; S, 10.99. Found C, 53.46; H, 3.46; N, 14.14; S, 10.82 %

General procedure 12, 14, 16, 17. A suspension of **10** (0.01 mol) in dioxan (15 ml) and acetic acid (2 ml) was treated with maleic anhydride, acrylonitrile, enaminone **15** [25] or with ethyl propiolate (0.01 mol). The reaction mixture was refluxed for 6 hrs then poured into water. The solid product was collected by filtration and recrystallized from dioxan to yield **12**, **14**, **16** and **17**, respectively

9-Amino-2-(4'-chloro-phenyl)-5-methyl-2*H*-furo[3,4-*g*]-phthalazine-1,6,8-trione (12). Yellow crystal, (yield 64%, 2.3 g); mp 230-231 °C, ir (KBr): ν_{max} 3448, 3321 (NH_2), 1717, 1654 cm^{-1} (CO); ms (70 eV) m/z: 355 (M^+, 100%), (283, 64%); ^{1}H nmr (300 MHz, DMSO-d_6): 2.7 (s, 3H, CH_3), 7.50-7.68 (m, 4H, Ar-H), 8.40 (brs, 2H, NH_2), 8.75 (s, 1H, CH). *Anal.* calcd. for $C_{17}H_{10}ClN_3O_4$ C, 57.40; H, 2.83; N, 11.81. Found C, 57.17; H, 2.75; N, 11.47 %

5-Amino-3-(4'-chloro-phenyl)-8-methyl-4-oxo-3,4-dihydro-phthalazine-6-carbonitrile (14). Yellow solid, (yield 66%, 2.0 g); m.p. 285-286 °C, ir (KBr): ν_{max} 3431, 3316 (NH_2), 2211 (CO), 1654 cm^{-1} (CO); ms (70 eV) m/z 310 (M^+, 100%), (291, 84%);^{1}H nmr (300 MHz, DMSO-d_6): 2.44 (s, 3H, CH_3), 7.55-7.63 (m, 4H, Ar-H), 7.79 (s, 1H, CH), 7.82 (brs, 2H, NH_2), 8.49 (s, 1H, CH). *Anal.* calcd. for $C_{16}H_{11}ClN_4O$ C, 61.84; H, 3.57; N, 18.03. Found C, 61.38; H, 3.31; N, 18.32 %

2-(4'-Chloro-phenyl)-5-methyl-7-(3-oxo-3-thiophen-2-yl-propenylamino)-2*H*-thieno[3,4-*d*]pyridazin-1-one (16). Dark red solid, (yield 61%, 2.6 g); mp 216-217 °C, ir (KBr): ν_{max} 3437 (NH), 1689, 1658 cm^{-1} (CO); ms (70 eV) m/z : 427 (M^+, 42%), (315, 10%), (111, 100%);^{1}H nmr (300 MHz, DMSO-d_6): 2.63 (s, 3H, CH_3), 6.21 (d, 1H, *J* = 8.1 Hz, CH), 7.21 (t, 1H, *J* = 4.2 Hz, CH), 7.33-7.40 (m, 1H, CH), 7.51 (d, 2H, *J* = 10.1 Hz, Ar-H), 7.61 (d, 2H, *J* = 10.1 Hz, Ar-H), 7.89-7.93 (m, 2H, CH), 8.26 (s, 1H, CH), 13.03 (d, 1H, *J* = 12.3, NH), ^{13}C nmr (100 MHz; DMSO-d_6): 182.7, 161.2, 156.9, 148.8, 145.3, 142.8, 142.7, 139.5, 134.4, 133.7, 130.7, 128.5x2, 128.1, 127.0, 126.4x2, 109.5, 97.0, 11.9. *Anal.* calcd. for $C_{20}H_{14}ClN_3O_2S_2$ C, 56.13; H, 3.30; N, 9.82; S, 14.99. Found C, 56.26; H, 3.13; N, 9.78; S, 15.20 %

Ethyl 3-[3-(4'-chloro-phenyl)-7-methyl-4-oxo-3,4-dihydro-thieno[3,4-*d*]pyridazin-5-ylamino]-acrylate (17). Dark green solid, (yield 67%, 2.6 g) mp 199-200 °C, ir (KBr): ν_{max}: 3430 (NH), 1685, 1645 cm^{-1} (CO); ms (70 eV) m/z 389 (M^+, 42%), (316, 21%), (291, 100%); ^{1}H nmr (400 MHz, DMSO-d_6): 1.21 (t, 3H, *J* = 6.3 Hz, CH_3) 2.28 (s, 3H, CH_3), 4.09 (q, 2H, *J* = 6.3 Hz, CH_2), 5.03 (d, 0 .5 H, *J* = 7.3 Hz, CH), 5.65 (d, 0 .5 H, *J* = 12.2 Hz, CH), 8.08 (d, 0 .5 H, *J* = 7.3 Hz, CH), 8.30 (d, 0 .5H, *J* = 12.2 Hz, CH), 8.38 (s, 1H, CH), 7.48-7.62 (m, 4H, Ar-H), 10.97 (brs, 1H, NH), ^{13}C nmr (100 MHz; DMSO-d_6): 173.0, 161.0, 155.1, 152.0, 140.5, 140.4, 133.7, 132.6, 129.7x2, 129.6, 129.1x2, 128.8, 118.0, 25.7, 22.1, 16.0. *Anal.* calcd. for $C_{18}H_{16}ClN_3O_3S$ C, 55.45; H, 4.14; N, 10.78; S, 8.22. Found C, 55.14; H, 4.05; N, 11.08; S, 8.68 %

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