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STUDIES USING (*E*)-6-OXO-1-ARYL-4-(2-*N*-PIPERIDINYL)VINYL-1,6-DIHYDROPYRIDAZINE-5-CARBONITRILE

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Abstract – Condensing 1-aryl-4-methyl-1,6-dihydropyridazine-5-carbonitrile with triethyl orthoformate and piperidine afforded the *trans*-enamine **2**. This could be converted into pyrido[3,4-*d*]pyridazine **3** upon treatment with primary aromatic amines. Reacting **2** with hydrazonoyl chlorides **5** afforded **7** rather than **6**. Compound **2** gives also pyrido[3,4-*d*]pyridazine **10** upon treatment with acetic acid and ammonium acetate. Compound **2** afforded *N*-aminopyrido[3,4-*d*]pyridazine **11** upon treatment with hydrazine hydrate. Compound **11** reacted with triethyl orthoformate to give [1,2,4]triazolo[2',3':1,2]pyrido[4,3-*d*]pyridazin-10-one **12** and can be acetylated to **13**. Compound **2** could be coupled with *p*-chlorobenzenediazonium chloride to give the pyridazino[4,5-*d*]pyridazine **17**.

INTRODUCTION

Pyridazine chemistry is one of the most dynamic areas of heterocyclic chemistry. This can be readily realized from large number of recent papers [1-4] and patents [5,6] in this field. In the past two decades we have been involved in programme aimed at developing efficient routes to pyridazinones and condensed pyridazinones.[7-9] Our work in this area has enabled in the past developing routes to thieno[3,4-*d*]pyridazinones, [9-11] phthalazines [8,12] as well as diversity of other condensed pyridazinones.[13,14] Synthetic

routes developed in our laboratories have been extensively utilized by other groups. [15,16] In a previous work[8,17] condensing pyridazinones with dimethylformamide dimethylacetal (DMFDMA) afforded enamines that were utilized for synthesis of pyridopyridazinones. As DMFDMA is expensive and potentially carcinogenic, utility of these enamines received only limited application despite their versatility as precursors to condensed pyridazines. It is occurred to us of value to replace DMFDMA by safer and less expensive reagent.

RESULTS AND DISCUSSION

In the present paper we describe a route for synthesis of piperidenyl enamines **2** and then report their utility as readily obtainable inexpensive starting materials for synthesis of otherwise not readily obtainable condensed pyridazines. Thus reacting **1** with triethyl orthoformate and piperidine in refluxing DMF afforded **2** that has been established to exist in *trans* form based on ^{1}H NMR that revealed *trans* olefinic protons with $J \approx 13$ Hz. We believe that initially piperidine or morpholine **A** and triethyl orthoformate react to yield intermediate, nonvolatile amide acetal **B** that then condenses with **1** to yield **2**. In support of this view **1** was recovered almost unreacted when refluxed with triethl orthoformate in DMF for long time. Although in this synthesis DMF may be carcinogenic it is safer than DMFDMA as it is industrially approved solvent. [18] The enamines **2a,b** gave pyrido[3,4-*d*]pyridazinones **3a,b** upon treatment with *p*-toluidine, and *p*-chloroaniline respectively in refluxing DMF. On the other hand, the reaction of **2b** or **2c** with methyl anthranilate gave the tetracyclic compound **4**. Formation of **4** is a result of further cyclization of the formed intermediate **3c**. Compounds **3a,b** and **4** could be also obtained *via* refluxing **1** with triethyl orthoformate and *p*-toluidine, *p*-chloroaniline, or methyl anthranilate respectively in DMF.

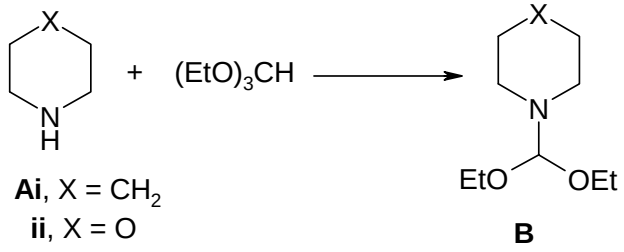
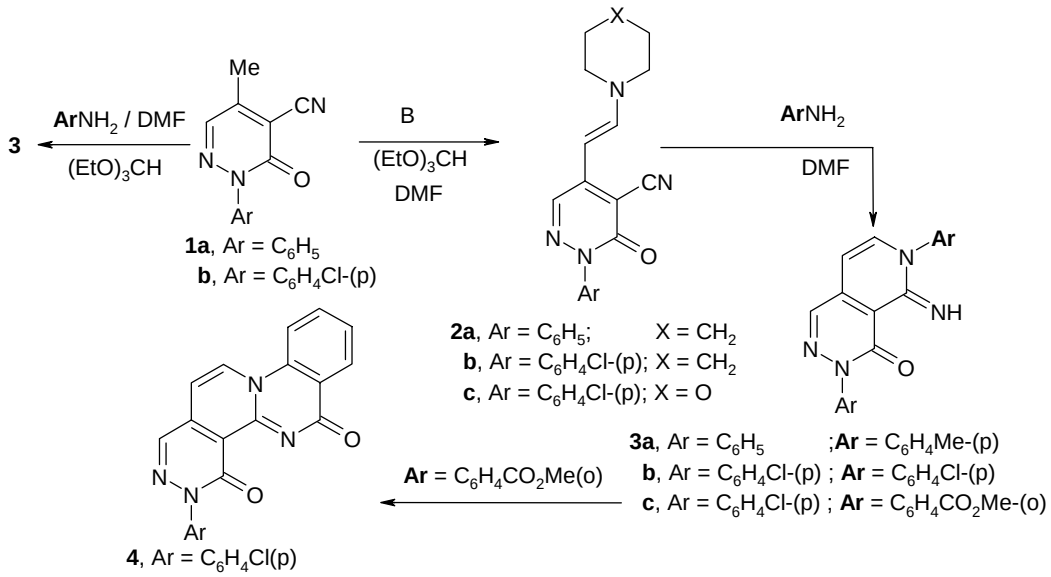


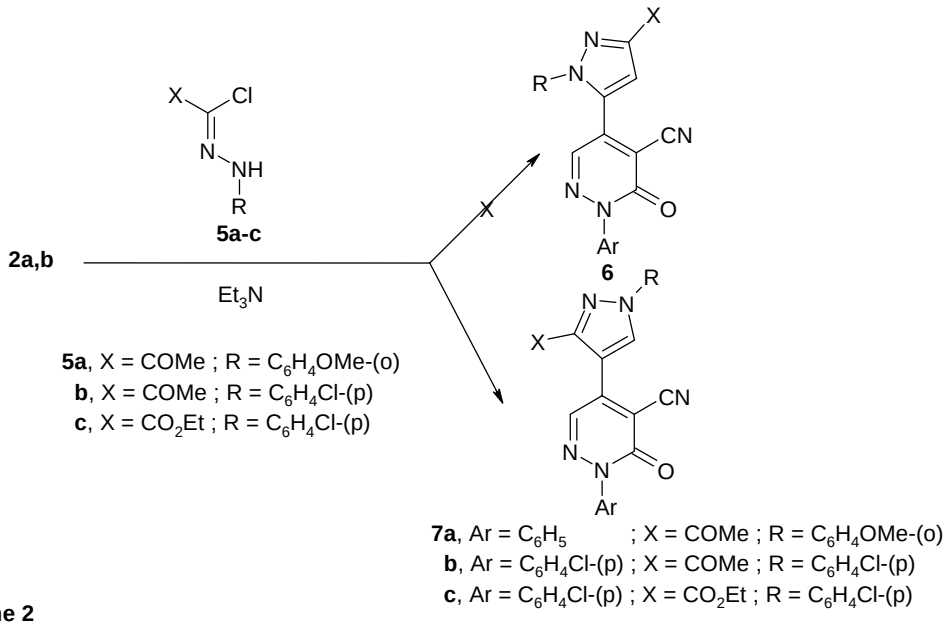
Figure 1

The enamines **2** reacted with hydrazonoyl chlorides **5a-c** in the presence of triethylamine to yield pyrazole derivatives (Scheme 2). The compounds **5** are considered as precursors for nitrile imines. These in situ generated intermediates can react in 1,3-dipolar cycloadditions with the enamines **2**.



Scheme 1

The parent dipole $HC^{+}{=}N{-}NH^{-}$ has a low-lying LUMO and would react with enamines in a LUMO (dipole) – HOMO (dipolarophile) controlled process to give the corresponding cycloadduct, which then aromatized to pyrazoles. On the basis of orbital coefficients and resonance integrals, the frontier orbital theory predicts for this case the regioselective formation of 5-amino-4,5-dihydro-1*H*-pyrazoles as cycloadducts.[19] Application of this theory to the present reaction **2** + **5** would lead after aromatization (elimination of piperidine) to **7**. The cycloaddition of benzonitrile *N*-phenylimine (diphenylnitrilimine) to (*E*)-1-dimethylamino-2-phenylthioethylene, as simple enamine, is, to our best knowledge, the only experimental example of this reaction type.[20] The gerneration of 1,3-diphenyl-4-phenylthio-1*H*-pyrazole confirms the predicted regioselectivity. However, the enamines **2** as well as the nitrile imines **5**, used here, contain electron-withdrawing groups which could change the situation. Therefore we had to take the regioisomers **6** into account.



Scheme 2

The determination of the correct structure was based on 2D-NMR measurements HMQC and HMBC. It turned out that the regioisomers **7** were obtained. Figure 1 shows the complete assignment of all ^{1}H and ^{13}C NMR signals of **7b** and **7c**.

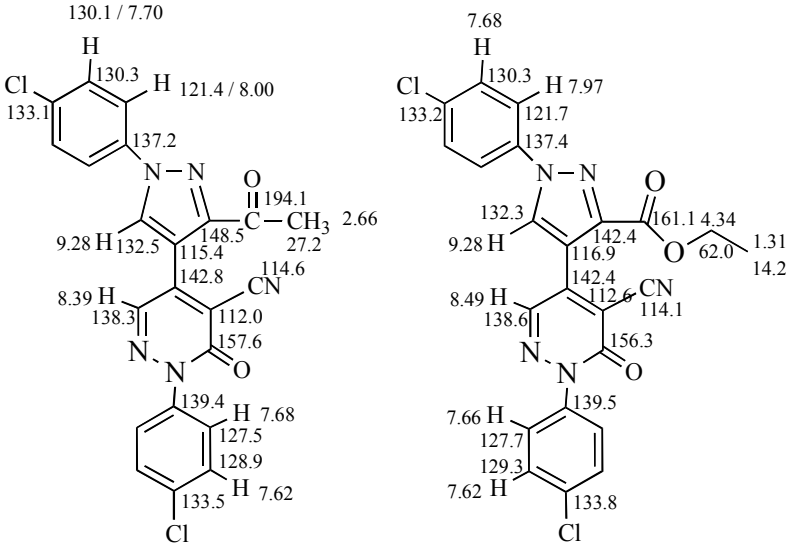


Figure 2: Assignment of the ^{1}H and ^{13}C chemical shifts (δ values measured in CD_3SOCD_3, related to TMS as internal standard).

The decisive difference between the alternative structures **6** and **7** in the HMBC measurement is due to the fact that the pyrazole hydrogen 5-H (δ = 9.28) shows a cross peak which indicates a ^{3}J coupling to C-3 (δ = 148.5 for **7b** and 142.4 for **7c**). The alternative regioisomer **6** would show ^{3}J couplings to the carbonyl carbon atom. The regioselectivity is in accordance with related reactions of hydrazonoyl chlorides with substituted 1-vinylpiperidines.[21,22]

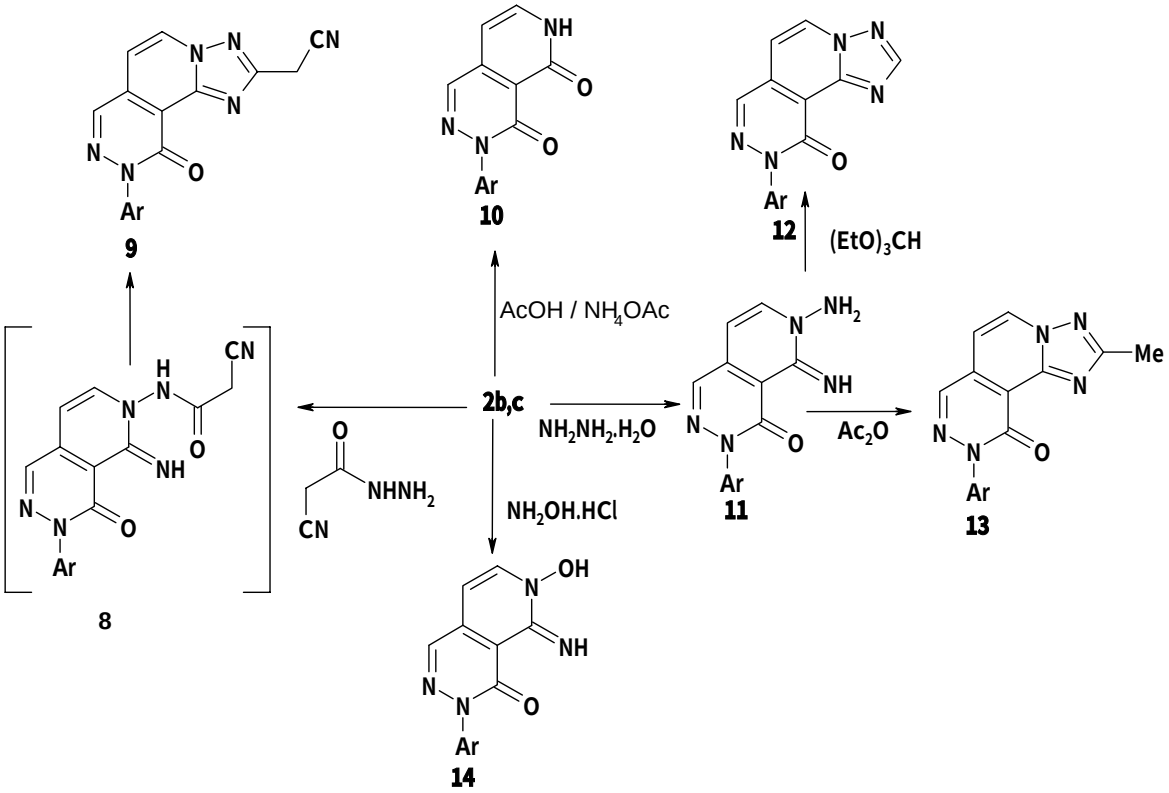
Reacting **2b or c** with cyanoacethydrazide afforded **9** most likely *via* intermediacy of **8**. Compounds **2b,c** could be readily converted into pyridopyridazinone **10** on refluxing acetic acid in presence of ammonium acetate. Also compound **2** reacted with hydrazine hydrate to give *N*-aminopyrido[3,4-*d*]pyridazinone **11**, which then reacted with triethyl orthoformate to yield **12**, and with acetic anhydride to give **13**. The enamine **2b** also reacted with hydroxylamine hydrochloride in presence of sodium acetate to give **14**.

Coupling **2** with *p*-chlorobenzenediazonium chloride afforded **18**. Intermediacy of **15** -**17** are postulated (cf. scheme 4).

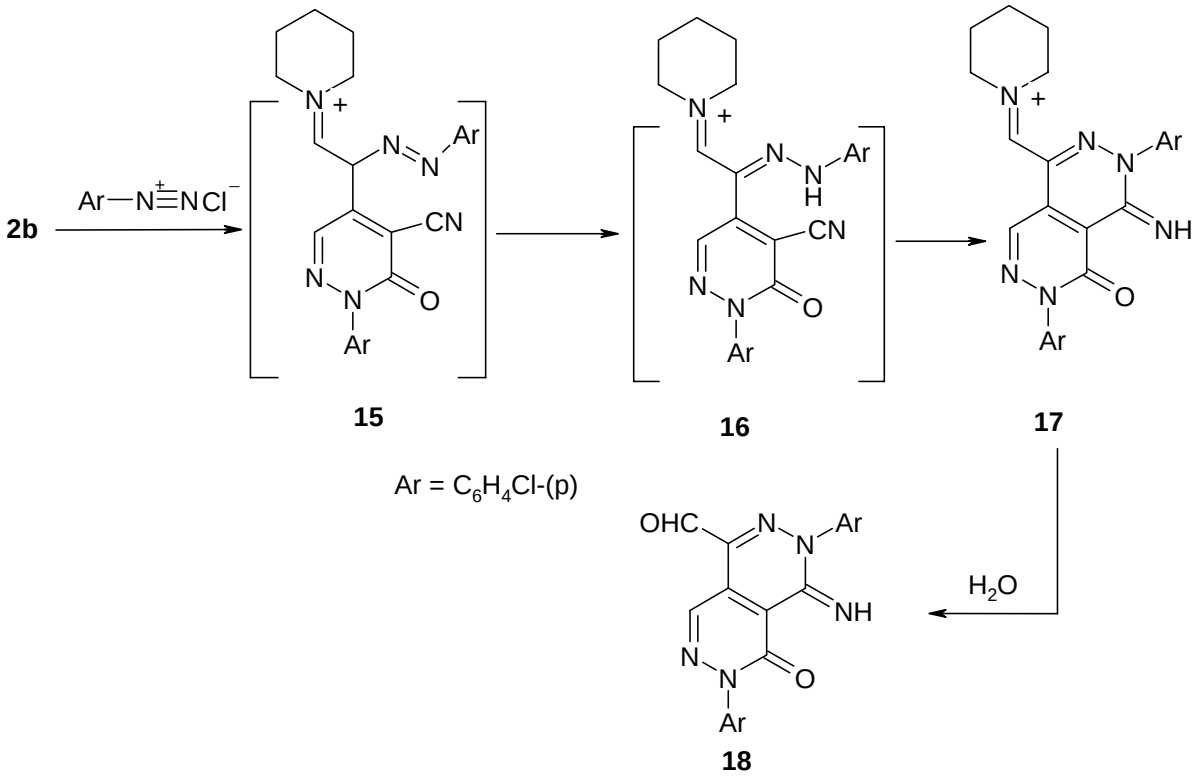
CONCLUSION

The successful replacement of DMFDMA by triethyl orthoformate, secondary or primary amine opened for synthesis of a variety of condensed azoles and azinopyridazines also an easy route to

pyrazolylpyridazines could be developed.



Scheme 3



Scheme 4

EXPERIMENTAL

Melting points were determined on a Stuart melting point apparatus and are uncorrected. The IR spectra were recorded in KBr using a FTIR unit Bruker-vector 22 spectrophotometer. The ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 as solvent at 300 or 400 and 75 MHz respectively on Varian Gemini NMR spectrometer using TMS as internal standard. Chemical shifts are reported in δ units (ppm). Mass spectra were measured on a Shimadzu GMMS -QP-1000 EX mass spectrometer at 70 eV.

General procedures for compounds 2

A mixture of pyridazine **1** (10 mmol), triethyl orthoformate and piperidine was refluxed in DMF (20 mL) for 24 h. The solvent was evaporated under vacuum and the crude product was collected and crystallized from proper solvent.

(*E*)-6-Oxo-1-phenyl-4-(2-piperidin-1-ylvinyl)-1,6-dihydropyridazine-5-carbonitrile (2a)

Recrystallized from EtOH, yield (73%); mp 165-167 ^{o}C. IR (KBr, cm^{-1}): 2206.4 (CN), 1658(CO); ^{1}H NMR (300 MHz, DMSO-d_6): δ: 1.44 (s, 6H, piperidinyl-H), 3.23 (s, 2H, piperidinyl-H), 3.32 (s, 2H, piperidinyl-H), 5.21 (d, 1H, vinyl-H, J = 12.84 Hz), 7.38-7.57 (m, 5H, Ar-H), 8.18 (d, 1H, vinyl-H, J = 12.84 Hz), 8.39 (s, 1H, pyridazine-H); MS (EI): *m/z* (%) = 306 (M^{+}).

Anal. Calcd for $C_{18}H_{18}N_4O$ (306.37): C, 70.57; H, 5.92; N, 18.29. Found: C, 70.38; H, 6.23; N, 18.43.

(*E*)-1-(4-Chlorophenyl)-6-oxo-4-(2-piperidin-1-ylvinyl)-1,6-dihydropyridazine-5-carbonitrile (2b)

Recrystallized from EtOH / dioxane, yield (67%); mp 158-160 ^{o}C. IR (KBr, cm^{-1}): 2212 (CN), 1652 (CO); ^{1}H NMR (400 MHz, DMSO-d_6): δ: 1.64 (s, 6H, piperidinyl-H), 3.45 (m, 4H, piperidinyl-H), 5.36 (d, 1H, vinyl-H, J = 12.93 Hz), 7.51 (d, 2H, Ar-H), 7.58 (d, 2H, Ar-H),8.20 (d, 1H, vinyl-H, J = 12.93 Hz), 8.44 (s, 1H, pyridazine-H); ^{13}C NMR (75 MHz, DMSO-d_6): δ: 24.32, 25.86, 27.26, 46.56, 55.78, 89.86 (vinyl CH), 91.41 (C-CN), 117.18 (CN), 127.98, 129.46, 132.73, 134.73, 140.82 (vinyl CH), 149.16, 152.71, 158.44 (CO); MS (EI): *m/z* (%) = 340 (M^{+}).

Anal. Calcd for $C_{18}H_{17}ClN_4O$ (340.82): C, 63.44; H, 5.03; N, 16.44. Found: C, 63.68; H, 5.37; N, 15.23.

(*E*)-1-(4-Chlorophenyl)-4-(2-morpholin-1-ylvinyl)-6-Oxo-1,6-dihydropyridazine-5-carbonitrile (2c)

Recrystallized from EtOH / dioxane, yield (67%); mp 212-214 ^{o}C. IR (KBr, cm^{-1}): 2223 (CN), 1671 (CO); ^{1}H NMR (400 MHz, DMSO-d_6): δ: 3.51 (s, 4H, morpholin-H), 3.69 (m, 4H, morpholin-H), 5.41 (d, 1H, vinyl-H, J = 13.05 Hz), 7.52 (d, 2H, Ar-H), 7.58 (d, 2H, Ar-H),8.23 (d, 1H, vinyl-H, J = 13.05 Hz), 8.45 (s, 1H, pyridazine-H); ^{13}C NMR (75 MHz, DMSO-d_6): δ: 46.21, 54.02, 67.27, 67.38, 92.81 (vinyl CH), 110.17 (C-CN), 116.89 (CN), 128.02, 129.49, 132.86, 134.65, 140.75 (vinyl CH), 149.13, 152.80, 158.34 (CO); MS (EI): *m/z* (%) = 342 (M^{+}).

Anal. Calcd for $C_{17}H_{15}ClN_4O_2$ (342.79): C, 59.57; H, 4.41; N, 16.34. Found: C, 59.39; H, 4.58; N, 16.23.

General method for preparation of compounds 3a-c

Method A: A mixture of enamine **2a,b** was refluxed with primary aromatic amines in DMF for 6 h. The

solvent was evaporated under vacuum and the crude product was collected and crystallized from EtOH/dioxane mixture.

***Method B*:** A mixture of pyridazine 1 (10 mmol), triethyl orthoformate and primary aromatic amine was refluxed in DMF (20 mL) for 24 h. The solvent was evaporated under vacuum and the crude product was collected and crystallized from proper solvent.

5-Imino-3-phenyl-6-*p*-tolyl-5,6-dihydro-3*H*-pyrido[3,4-*d*]pyridazin-4-one (3a)

Recrystallized from EtOH / dioxane, yield (81%); mp 180-182 ^{o}C. IR (KBr, cm^{-1}): 3258 (NH), 1658 (CO);^{1}H NMR (300 MHz, DMSO-d_6): δ: 2.27 (s, 3H, CH_3), 7.10 (d, 1H, pyridine-H, J = 5.1 Hz), 7.45-7.68 (m, 9H, Ar-H), 8.47 (s, 1H, pyrimidine-H), 8.54 (d, 1H, pyridine-H, J = 5.1 Hz), 11.30 (s, 1H, NH); MS (EI): *m/z* (%) = 328 (M^+).

Anal. Calcd for $C_{20}H_{16}N_4O$ (328.38): C, 73.15; H, 4.91; N, 17.06. Found: C, 73.36; H, 5.13; N, 17.27.

3,6-Bis-(4-chlorophenyl)-5-Imino-5,6-dihydro-3*H*-pyrido[3,4-*d*]pyridazin-4-one (3b)

Recrystallized from EtOH / dioxane, yield (79%); mp 278-280 ^{o}C. IR (KBr, cm^{-1}): 3121 (NH), 1652.3 (C=NH), 1620.8 (CO); ^{1}H NMR (400 MHz, DMSO-d_6): δ: 7.19 (d, 1H, pyridine-H, J = 5.2 Hz), 7.39 (d, 2H, Ar-H), 7.63 (d, 2H, Ar-H), 7.68 (d, 2H, Ar-H), 7.88 (d, 2H, Ar-H), 8.54 (s, 1H, pyrimidine-H), 8.61 (d, 1H, pyridine-H, J = 5.2 Hz), 11.41 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ: 67.38, 79.67, 80.00, 80.33,109.18, 110.46, 122.52, 128.56 129.15, 129.77, 133.59, 139.17, 134. 139.58 (C=NH), 153.72 (CO); MS (EI): *m/z* (%) = 383 (M^+).

Anal. Calcd for $C_{19}H_{12}Cl_2N_4O$ (383.24): C, 59.55; H, 3.16; N, 14.62. Found: C, 59.32; H, 3.27; N, 14.51.

3-(4-Chlorophenyl)-3*H*-2,3,5,10b-tetrazachrysene-4,6-dione (4)

Recrystallized from EtOH / dioxane, yield (76%); mp >300 ^{o}C. IR (KBr, cm^{-1}): 3077 (NH), 1704 (CO), 1627 (CO); ^{1}H NMR (400 MHz, DMSO-d_6): δ: 7.27 (d, 1H, pyridine-H, J = 7.6 Hz), 7.61-8.0 (m, 8H, Ar-H), 8.38 (d, 1H, pyridine-H, J = 7.6 Hz), 8.55 (s, 1H, pyrimidine-H), 9.06 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ: 107.88, 109.49, 117.59, 118.03, 127.81, 128.93, 129.08, 129.73, 133.51, 134.92, 135.82, 136.70, 137.21, 142.10, 144.12, 148.67, 153.2, 163.4; MS (EI): *m/z* (%) = 374 (M^+).

Anal. Calcd for $C_{20}H_{11}ClN_4O_2$ (374.79): C, 64.10; H, 2.96; N, 14.95. Found: C, 63.82; H, 2.84; N, 14.71.

General procedure for preparation of compounds 7a-c

A mixture of enamines **2a,b** (10 mmol) and hydrazonoyl halides **5a-c** (10 mmol) was refluxed in EtOH in presence of triethylamine (10 mmol) for 6 h, then left over night at rt. The solvent was evaporated under vacuum and the crude product was collected and crystallized from proper solvent.

4-[3-Acetyl-1-(2-methoxyphenyl)-1*H*-pyrazole-5-yl]-6-oxo-1-phenyl-1,6-dihydropyridazine-5-carbonitrile (7a)

Recrystallized from EtOH / dioxane, yield (80%); mp 240-242 ^{o}C.

IR (KBr, cm^{-1}): 2229 (CN), 1690 (CH_3CO), 1666 (CO); ^{1}H NMR (300 MHz, DMSO-d_6): δ: 2.64 (s, 3H,

CH_3CO), 3.91 (s, 3H, OCH_3), 7.19-7.77 (m, 9H, Ar-H), 8.38 (s, 1H, pyridazine-H), 8.89 (s, 1H, triazole-H); MS (EI): m/z (%) = 411 (M^+).

Anal. *Calcd* for $C_{23}H_{17}N_5O_3$ (411.42): C, 67.15; H, 4.16; N, 17.02. Found: C, 67.24; H, 4.07; N, 17.27.

4-[3-Acetyl-1-(4-chlorophenyl)-1*H*-pyrazole-5-yl]-6-oxo-1-(4-chlorophenyl)-1,6-dihydropyridazine-5-carbonitrile (7b)

Recrystallized from EtOH / dioxane, yield (73%); mp 288-290 ^oC.

IR (KBr, cm^{-1}): 2231 (CN), 1689 ($COCH_3$), 1667 (CO).; ^1H NMR (300 MHz, DMSO-d_6): δ: 2.68 (s, 3H, CH_3), 7.63 (d, 2H, Ar-H, *J* = 8.72 Hz), 7.71 (m, 4H, Ar-H), 8.03 (d, 2H, Ar-H, *J* = 8.72 Hz), 8.39 (s, 1H, pyridazine-H), 9.28 (s, 1H, pyrazole-H); ^{13}C NMR (DMSO-d_6): δ: 28.11 (CH_3), 112.81 (C-CN), 114.87 (CN), 116.05, 122.33, 128.45, 129.96, 131.03, 133.54, 133.83, 134.31, 138.16, 139.37, 140.29, 143.40, 149.45, 156.97 (CO), 194.61 ($COCH_3$); MS (EI): m/z (%) = 449 (M^+).

Anal. *Calcd* for $C_{22}H_{13}Cl_2N_5O_2$ (450.29): C, 58.68; H, 2.91; N, 15.55. Found: C, 58.47; H, 3.12; N, 15.76.

1-(4-Chlorophenyl)-4-[1-(4-chlorophenyl)-5-cyano-6-oxo-1,6-dihydropyridazin-4-yl]-*1H*-pyrazole-3-carboxylic acid ester (7c)

Recrystallized from EtOH / dioxane, yield (78%); mp 238-240 ^oC.

IR (KBr, cm^{-1}): 2231 (CN), 1714 (COOEt), 1668 (CO).

^1H NMR (400 MHz, DMSO-d_6): δ: 1.31 (t, 3H, CH_3, *J* = 6.9 Hz), 4.36 (q, 2H, CH_2, *J* = 6.9 Hz), 7.63 (d, 2H, Ar-H, *J* = 9 Hz), 7.67-7.71 (m, 4H, Ar-H), 7.96 (d, 2H, Ar-H, *J* = 9 Hz), 8.48 (s, 1H, pyridazine-H), 9.28 (s, 1H, pyrazole-H);^{13}C NMR (DMSO-*d6*): δ: 13.82 (CH_3), 61.44 (CH_2), 112.18 (C-CN), 113.66 (CN), 116.46, 121.26, 127.21, 128.84, 129.82, 131.96, 132.73, 137.05, 138.22, 139.14, 141.87, 142, 155.8 (CO), 160.59 (COOEt); MS (EI): m/z (%) = 480 (M^+).

Anal. *Calcd* for $C_{23}H_{15}Cl_2N_5O_3$ (480.31): C, 57.52; H, 3.15; N, 14.58. Found: C, 57.29; H, 3.35; N, 14.73.

[9-(4-chlorophenyl)-10-oxo-4,9,10-trihydro[1,2,4]triazolo[2',3':1,2]pyrido[4,3-*d*]pyridazine-2-yl]-acetonitrile (9)

A mixture of enamine **2b** (10 mmol), and cyanoacet hydrazide was refluxed in DMF (20 mL) for 5 h. The solvent was evaporated under vacuum and the crude product was collected and crystallized from EtOH / DMF (5:1).

Yield (68%); mp > 300 ^oC. IR (KBr, cm^{-1}): 2211 (CN), 1657 (CO); ^1H NMR (300 MHz, DMSO-d_6): δ: 2.43 (s, 2H, CH_2), 7.55 (d, 1H, pyridine-H, *J* = 8.7 Hz), 7.60-7.68 (m, 4H, Ar-H), 7.82 (s, 1H, pyridazine-H), 8.70 (d, 1H, pyridine-H, *J* = 8.7 Hz); MS (EI): *m/z* (%) = 336 (M^+).

Anal. Calcd for $C_{16}H_9ClN_6O$ (336.74): C, 57.07; H, 2.69; N, 24.96. Found: C, 57.58; H, 2.93; N, 25.21.

3-(4-Chlorophenyl-3*H*,6*H*-pyrido[3,4-*d*]pyridazine-4,5-dione (10)

The enamine **2b** (10 mmol) was refluxed in AcOH (20 mL) in presence of ammonium acetate for 2 h.

The solvent was evaporated under vacuum and the crude product was collected and crystallized from EtOH / DMF (5:1).

Yield (79%); mp > 300 °C. IR (KBr, cm^{-1}): 3383 (NH), 1657 (CO), 1579 (CONH); ^{1}H NMR (300 MHz, DMSO-d_6): δ: 6.48 (d, 1H, pyridine-H, J = 6.6 Hz), 6.85 (d, 2H, Ar-H), 7.81 (d, 1H, pyridine-H, J = 6.6 Hz), 8.23 (s, 1H, pyridazine-H), 8.58 (d, 2H, Ar-H), 12.07 (br s, 1H, NH, D_2O exchangeable); MS (EI): *m/z* (%) = 273 (M^+).

Anal. Calcd for $C_{13}H_8ClN_3O_2$ (273.68): C, 57.05; H, 2.95; N, 15.35. Found: C, 57.26; H, 3.12; N, 15.46.

6-Amino-3-(4-chlorophenyl)-5-imino-5,6-dihydro-3*H*-pyrido[3,4-*d*]pyridazin-4-one (11)

A mixture of enamine **2b** (10 mmol), and hydrazine hydrate (20 mmol) was refluxed in EtOH (20 mL) for 5 h. The solvent was evaporated under vacuum and the crude product was collected and crystallized from EtOH / dioxane (2:1).

Yield (76%); mp 228-230 °C. IR (KBr, cm^{-1}): 3286 (NH), 3128 and 3075 (NH_2), 1660 (CO); ^{1}H NMR (300 MHz, DMSO-d_6): δ: 6.17 (d, 1H, pyridine-H, J = 7.2 Hz), 6.34 (br s, 2H, NH_2), 7.47-7.71 (m, 5H, Ar-H and NH), 7.77 (d, 1H, pyridine-H, J = 7.2 Hz), 8.37 (s, 1H, pyridazine-H); MS (EI): *m/z* (%) = 287 (M^+).

Anal. Calcd for $C_{13}H_{10}ClN_5O$ (287.71): C, 54.27; H, 3.50; N, 24.34. Found: C, 54.36; H, 3.63; N, 24.13.

9-(4-Chlorophenyl)-4,9,10-trihydro[1,2,4]triazolo[2',3':1,2]pyrido[4,3-*d*]pyridazine-10-one (12)

A mixture of 11 (10 mmol), and triethyl orthoformate (20 mmol) was refluxed in DMF (20 mL) for 5 h. The solvent was evaporated under vacuum and the crude product was collected and crystallized from EtOH / DMF (2:1).

Yield (78%); mp 338-340 °C. IR (KBr, cm^{-1}): 1665 (CO); ^{1}H NMR (400 MHz, DMSO-d_6): δ: 7.62 (d, 1H, pyridine-H, J = 8.16), 7.68-7.72 (m, 4H, Ar-H), 8.72 (s, 1H, pyridazine-H), 8.81 (s, 1H, triazole-H), 9.38 (d, 1H, pyridine-H, J = 8.16); ^{13}C NMR (100 MHz , DMSO-d_6): δ: 112.15, 117.49, 128.90, 129.76, 133.1, 133.44, 135.28, 137.63, 141.42, 147.42, 155.86, 156.48 (CO); MS (EI): *m/z* (%) = 297 (M^+).

Anal. Calcd for $C_{14}H_8ClN_5O$ (297.71): C, 56.48; H, 2.71; N, 23.52. Found: C, 56.65; H, 2.84; N, 23.39.

9-(4-Chlorophenyl)-2-methyl-4,9,10-trihydro[1,2,4]triazolo[2',3':1,2]pyrido[4,3-*d*]pyridazine-10-one (13)

Compound **11** (10 mmol) was refluxed in acetic anhydride (20 mL) for 5 h. The solvent was evaporated under vacuum and the crude product was collected and crystallized from EtOH / DMF (5:1).

Yield (72%); mp 316-318 °C. IR (KBr, cm^{-1}): 1665 (CO); ^{1}H NMR (400 MHz, DMSO-d_6): δ: 2.58 (s, 3H, CH_3), 7.55 (d, 2H, Ar-H), 7.61 (d, 1H, pyridine-H, J = 6.9 Hz), 7.70 (d, 2H, Ar-H), 8.68 (s, 1H, pyridazine-H), 9.24 (d, 1H, pyridine-H, J = 6.9 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ: 19.58 (CH_3), 111.24, 116.58, 128.76, 129.72, 133.36, 134.70, 137.71, 141.42, 148.07, 155.87, 163.36, 165.94 (CO); MS (EI): *m/z* (%) = 311 (M^+).

Anal. Calcd for $C_{15}H_{10}ClN_5O$ (311.73): C, 57.80; H, 3.23; N, 22.47. Found: C, 57.63; H, 3.54; N, 22.74.

3-(4-Chlorophenyl)-6-hydroxy-5-imino-5,6-dihydro-3*H*-pyrido[3,4-*d*]pyridazin-4-one (14)

A mixture of enamine **2b** (10 mmol), and hydroxylamine hydrochloride (30 mmol) was refluxed in DMF (20 mL) in presence sodium acetate (0.5 g) for 5 h. The solvent was evaporated under vacuum and the crude product was collected and crystallized from EtOH / dioxane (1:1).

Yield (74%); mp 303-305 ^oC. IR (KBr, cm^{-1}): 3397 (NH), 3238 (OH), 1649 (CO); ^1H NMR (400 MHz, DMSO-d_6): δ: 7.13 (d, 1H, pyridine-H, J = 6.72), 7.61 (d, 2H, Ar-H), 7.65 (d, 2H, Ar-H), 7.92 (s, 1H, pyridazine-H), 8.46 (s, 1H, NH), 8.49 (br s, 1H, OH, D_2O exchangeable), 8.58 (d, 1H, pyridine-H, J = 6.72); ^{13}C NMR (100 MHz, DMSO-d_6): δ: 108.77, 127.69, 128.95, 129.69, 133.29, 138.81, 141.01,142.11, 142.47, 150.95, 160 (CO); MS (EI): *m/z* (%) = 288 (M^+).

Anal. Calcd for $C_{13}H_{19}ClN_4O_2$ (288.70): C, 54.09; H, 3.14; N, 19.41. Found: C, 54.33; H, 3.25; N, 19.67.

3,6-Bis-(4-chlorophenyl)-4-imino-5-oxo-3,4,5,6-tetrahydropyridazino[4,5-*d*]pyridazine-1-carbaldehyde (18)

A cold solution of aryldiazonium salt (10 mmol) was prepared by adding a solution of sodium nitrite (0.7 g into 10 mL H_2O) to a cold solution of arylamine hydrochloride (10 mmol of arylamine in 5 mL concentrated HC1) with stirring. The resulting solution of aryldiazonium salt was then added to a cold solution of enamine **2b** in EtOH (50 mL) containing sodium acetate (2 g). The reaction mixture was stirred for 1 h. The solid product so formed was collected by filtration and crystallized from dioxane.

Yield (83%); mp 298-300 ^oC. IR (KBr, cm^{-1}): 3254 (NH), 1666 (CO); ^1H NMR (400 MHz, DMSO-d_6): δ: 7.62-7.69 (m, 8H, Ar-H), 9.17 (s, 1H, pyridazine-H), 9.63 (s, 1H, NH, D_2O exchangeable), 10.16 (s, 1H, CHO); ^{13}C NMR (100 MHz, DMSO-d_6): δ: 121.34, 127.18, 128.76, 129.23, 129.98, 133.64, 134.06, 134.34, 134.94, 140.51, 141.68, 146.07, 152.95 (C=NH), 159.18 (CO), 190.54 (CHO); MS (EI): *m/z* (%) = 412 (M^+).

Anal. Calcd for $C_{19}H_{11}Cl_2N_5O_2$ (412.24): C, 55.36; H, 2.69; N, 16.99. Found: C, 55.53; H, 2.92; N, 17.32.

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