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Synthesis of heterocyclic compounds using cyanoacetic acid hydrazide: synthesis of pyrazolo[3,4-*b*]pyridine and pyrano[3,4-*d*]pyridazine derivatives

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Abstract: The reaction of cyanoacetic acid hydrazide with ethyl benzoylpyruvate and 3-arylhydrazono-2,4-dioxo-4-phenylbutanoates occurs with formation of pyrazolo[3,4-*b*]pyridine-4-carboxylate (**3**) and pyrano[3,4-*d*]pyridazine-1,4-diones (**8a-c**), respectively. The compound **3** reacts with hydrazine hydrate and phenyl isocyanate to afford pyrazolo[3,4-*b*]pyridine derivatives **4** and **5**, respectively. The chemical structure of the compounds has confirmed by analytical, IR, ^{1}H NMR and ^{13}C NMR spectral data.

Keywords: Benzoylpyruvate, Arylhydrazone, Cyanoacetic acid hydrazide, Pyrazolo[3,4-*b*]pyridine-4-carboxylate, Pyrano[3,4-*d*]pyridazine-1,4-dione.

Introduction

Pyrazolopyridines are nitrogen containing 10-π aromatic bicyclic heterocycles. Pyrazolopyridines have continued to attract interest because of their biological activity and structural relationship to indoles, azaindoles and pyrrolopyridines. Five pyrazolopyridine isomers exist as shown in Figure **1** [1]. The isomer of interest for the present study is pyrazolo[3,4-*b*]pyridines.

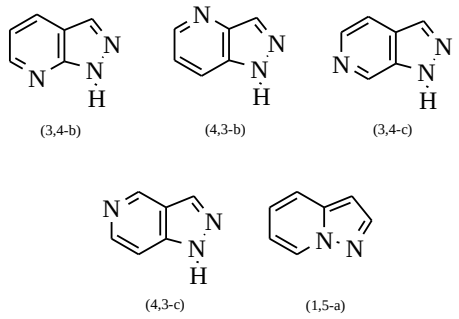

Figure 1: Pyrazolopyridine analogues.

Pyrazolo[3,4-*b*]pyridines comprise a very interesting class of compounds because of their significant biological and pharmacological activities acting as vasodilators, antihypertensive, hypoglycemic, anti-inflammatory, analgesic and antipyretic agents. They have been used in treating thrombocytopenia, erythropenia and pancytopenia. They are also useful for the treatment of depression and obsessive compulsive disorder. They have been also used as platelet aggregation inhibitors [2]. The literature indicates different synthetic approaches to these compounds and mentions two main processes: one route reported for the preparation of pyrazolo[3,4-*b*] pyridines by reaction of 2-chloronicotinonitrile, 2-chloronicotinic acid derivatives or 3-acyl-2-pyridones with some hydrazines [3-6]. And others have been described the condensation of the 5-aminopyrazoles with *α*,*β*-unsaturated compounds [7-12].

Derivatives of pyranopyridazines have received little study in the literature [13-15]. Pyranopyridazine derivatives are an important class of heterocycles which are known as potassium channel openers (PCOs) [16].

We report in this article the preparation of pyrazolo[3,4-*b*]pyridine-4-carboxylate (**3**) and

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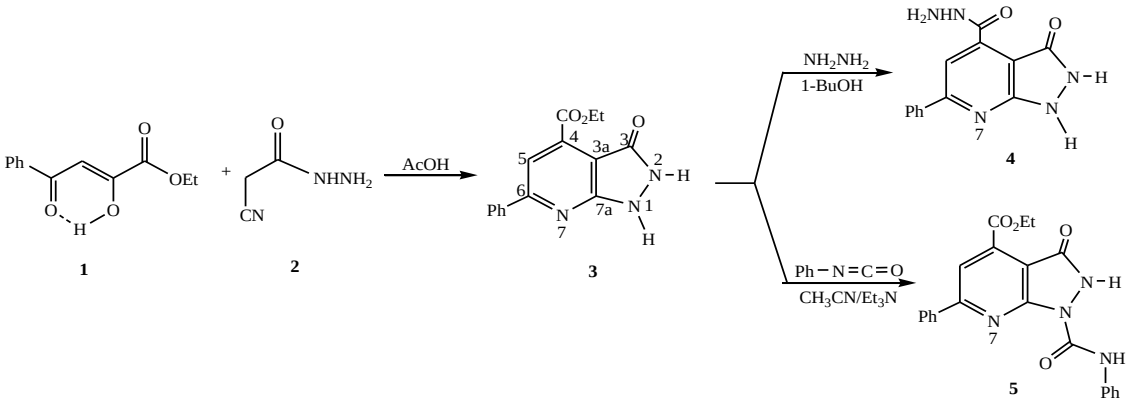
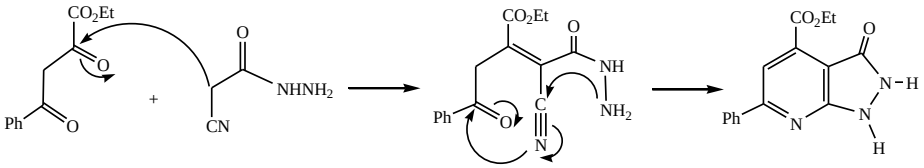
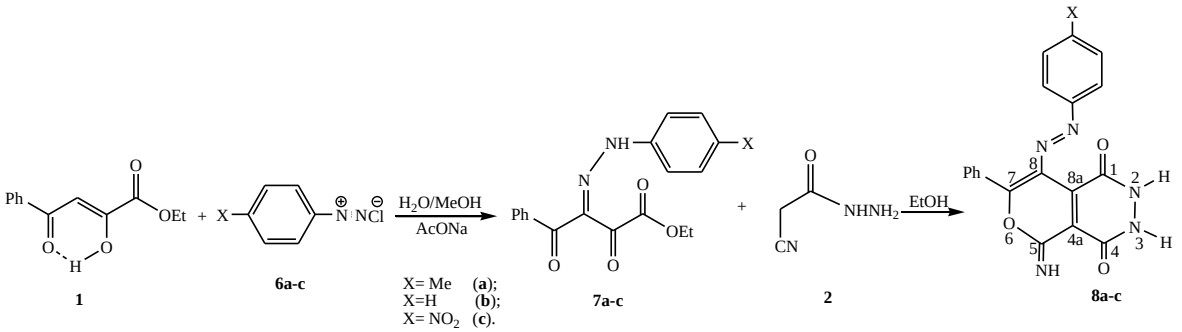
pyrano[3,4-*d*]pyridazine-1,4-diones (**8a-c**) by condensation of the cyanoacetic acid hydrazide with ethyl benzoylpyruvate and 3-arylhydrazono-2,4-dioxo-4-phenylbutanoates (**7a-c**), respectively (Schemes **1** and **3**).



Scheme 1: Synthesis of pyrazolo[3,4-*b*]pyridine-4-carboxylate derivatives.



Scheme 2: Proposed mechanism for the formation of pyrazolo[3,4-*b*]pyridine-4-carboxylate.



Scheme 3: Synthesis of pyrano[3,4-*d*]pyridazine-1,4-dione derivatives.

Results and discussion

*Synthesis of ethyl 6-phenyl-3-oxo-2,3-dihyropyrazolo[3,4-b]pyridine-4-carboxylate (**3**):*

Condensation of the acidic methylene cyanoacetic acid hydrazide with ethyl benzoylpyruvate in glacial acetic acid at 70–80°C afford ethyl 6-phenyl-3-oxo-2,3-dihyropyrazolo[3,4-*b*]pyridine-4-carboxylate (**3**) (Scheme **1**).

Presumably, the reaction mechanism includes formation of alkene from cyanoacetohydrazide and ethyl benzoylpyruvate to give ethyl 2-benzoylmethylene-3-cyano-4-oxo-4-hydrazinobutanoate which then undergoes two of intramolecular ring closure to the final product (Scheme **2**) [17].

Structure **3** was assigned on the basis of their analytical, IR, ^{1}H NMR and ^{13}C NMR spectra. The IR spectra of compound **3** has shown five characteristic absorption bands at 3451, 3175, 1543, 1690 and 1597 cm^{-1} attributable to three bands for NH, ester C=O and amide C=O, functions, respectively. In the 1H NMR spectra of **3** we have observed a triplet at δ 1.40 for CH_3 protons, a quartet at δ 4.46 for CH_2 protons, a set of multiplet signals integrated for 5 protons at δ 7.50-8.15 ppm for aromatic protons, a singlet at δ 7.93 ppm for CH proton of pyridine and two broad singlet at δ 10.40, 12.73 ppm for NH protons. On shaking the compounds **3** with D_2O, the broad band signals at δ

10.40, 12.73 ppm disappeared. The ^{13}C NMR spectum of **3** revealed two signals at δ 13.82 (CH_3), 62.37 (CH_2) ppm for ethyl, five signals at δ 99.14 (C_{3a}), 112.38 (C_5), 133.21 (C_4), 152.46 (C_6), 152.89 (C_{7a}) and 156.41 (C_3=O) ppm due to the carbons of the pyrazolopyridine, besides four signals at δ 127.06-137.79 ppm attributable to the aromatic carbons and a signal at δ 166.42 ppm for the esteric carbon.

*Synthesis of 6-phenyl-3-oxo-2,3-dihyropyrazolo[3,4-b]pyridine-4-carbohydrazide (**4**) and ethyl 6-phenyl-1-(N-phenylcarbamoyl)-3-oxo-2,3-dihyro-1H-pyrazolo [3,4-b]pyridine-4-carboxylate (**5**):*

Treatment of **3** with hydrazine hydrate in 1-butanol led to the formation of 6-phenyl-3-oxo-2,3-dihyropyrazolo[3,4-b]pyridine-4-carbohydrazide (**4**). Also, compound **3** reacts with phenyl isocyanate in refluxing acetonitrile containing a catalytic amount of triethylamine to yield ethyl 6-phenyl-1-(N-phenylcarbamoyl)-3-oxo-2,3-dihyro-1H-pyrazolo[3,4-b]pyridine-4-carboxylate (**5**) (Scheme **1**). The structures of **4** and **5** were confirmed by analytical, IR, ^{1}H NMR and ^{13}C NMR spectroscopic data. In the ^{1}H NMR and ^{13}C NMR spectra of product **4** the absorptions of ethyl group was absent. The ^{1}H NMR absorptions of the NH_2 and NH groups in **4** are found at about δ 5.73 and 6.31 ppm. IR absorptions of the C=O groups of amidic and ureic **5** are found at about 1624 and 1674 cm^{-1}. Its ^{1}H NMR spectra showed multiplet signals integrated for 10 protons of aromatic ring at δ 7.15-8.24 ppm. In the ^{13}C NMR spectra of **5** we have observed a set of signals for aromatic carbons at δ 119.56-137.80 ppm and a signal at δ 161.34 ppm due to the carbon of the urea C=O.

*Synthesis of 8-arylazo-5-imino-7-phenyl-1,2,3,4-tetrahydro-5H-pyrano[3,4-d]pyridazine-1,4-diones (**8a-c**):*

The ambivalent electrophilic nature of 3-arylhydrazono-2,4-dioxo-4-phenylbutanoates (**7a-c**) resides on the presence of three interrelated carbonyl entities, capable of modulating and accentuating the individual electronic character through inductive and tautomeric effects. Embedded within the framework of the 3-arylhydrazono-2,4-dioxo-4-phenylbutanoates (**7a-c**) are both the structural features of α–keto ester and β–diketon (Figure **2**). As a consequence, the chemistry of 3-arylhydrazono-2,4-dioxo-4-phenylbutanoates (**7a-c**) may be expected to resonate this dual relationship [18].

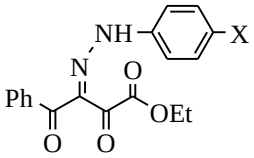
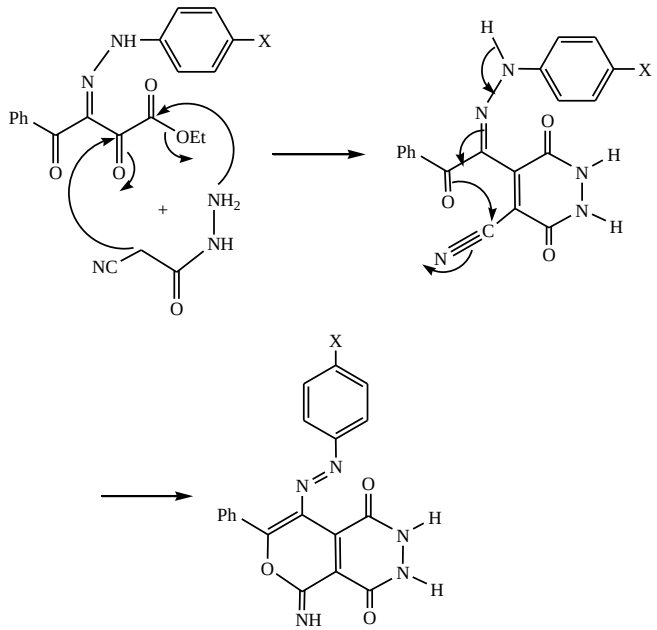


Figure 2: Dual nature of 3-arylhydrazono-2,4-dioxo-4-phenylbutanoates (**7a-c**).

Cyanoacetic acid hydrazide has been reacted with arylhydrazone **7a-c** in ethanol and the annulation involved α-keto ester moiety lead to 8-arylazo-5-imino-7-phenyl-1,2,3,4-tetrahydro-5*H*-pyrano[3,4-*d*]pyridazine-1,4-diones (**8a-c**) (Scheme **3**).

The selection of potentially applicable cyanoacetic acid hydrazide carrying a two-unit linker is wide in terms of a cyclodehydration sequence on 3-arylhydrazono-2,4-dioxo-4-phenylbutanoates (**7a-c**). The product will not be aromatic when condensation involves the β–diketo moiety of the arylhydrazones **7a-c**. This mode of cyclization will only lead to a labile seven-membered. On the other hand, when condensation takes place across the α-keto ester moiety, the resulting annulet may or may not be aromatic. This mode of cyclization leads to a stable six-membered ring which then undergoes an of intramolecular ring closure to the pyrano[3,4-*d*]pyridazine-1,4-diones (Scheme **4**) [17].



Scheme 4: Proposed mechanism for the formation of pyrano[3,4-*d*]pyridazine-1,4-diones.

Structures **8a-c** was confirmed according to their analytical, IR, ^{1}H and ^{13}C NMR spectral data. For example, the IR spectrum of compound **8a** showed

eight characteristic absorption bands at 3430, 3191, 3089, 2927, 1684, 1671, 1623 and 1481 cm^{-1} attributable to the three bands for NH, aliphatic CH, two bands for amidic C=O and two bands for C=N, N=N functions, respectively. In the IR spectra of product **8a** the absorption of cyano group was absent. Its ^1H NMR spectrum displayed three signals at δ 2.42, 5.63 and 9.89 ppm due to the protons of CH_3, C=NH and amidic NH groups, respectively, besides multiplet signals integrated for nine protons at δ 7.30-7.73 ppm (aromatic protons). On shaking the compounds **8a** with D_2O, the broad band signals at δ 5.63 and 9.89 ppm disappeared. The ^{13}C NMR spectrum of **8a** reveled eight signals at δ 20.77 (CH_3), 109.84, 112.88 (C_{4a}, C_{8a}), 144.20 (C_8), 149.78 (C_7), 152.65 (C_5), 155.58, 157.37 (2C=O, amide) ppm, besides eight signals at δ 125.13, 128.10, 129.46, 132.71, 132.82, 134.68, 138.24, 139.71 ppm attributable to the aromatic carbons.

Conclusion

In the present work, it has been shown that cyanoacetic acid hydrazide reacted with each of benzoylpyruvate and arylhydrazones **7a-c** at *β*–keto enol and *α*-keto ester fragments to form cyclocondensation products that were heterocyclic compounds of pyrazolo[3,4-*b*]pyridine-4-carboxylate (**3**) and pyrano[3,4-*d*]pyridazine-1,4-diones (**8a-c**). In addition, we developed preparation of pyrazolo[3,4-*b*]pyridine-4-carboxylate derivatives (**4** and **5**) by conventional procedures in good yields.

Experimental

The chemicals were purchased from Merck and used without further purification. Melting points were measured with an Electrothermal 9100 apparatus and are uncorrected. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyzer. These results agreed favorably with the calculated values. Infrared spectra were measured from KBr disk using a FT-IR Perkin Elmer GX spectrometer and frequencies are reported in cm^{-1}. ^1H and ^{13}C NMR spectra ($CDCl_3$ and DMSO-d_6) were recorded on a Bruker Avance spectrometer at 300 and 75 MHz, respectively. Chemical shifts are reported in ppm. Thin-layer chromatography was performed on "Silufol-UV 254" plates

Materials:

Ethyl 2,4-dioxo-4-phenylbutanoate (**1**) was prepared from diethyl oxalate and acetophenone in the presence of sodium ethoxide using of ethanol as the solvent [19]. Cyanoacetic acid hydrazide (**2**) was obtained by careful addition of hydrazine hydrate to ethyl cyanoacetate in ethanol with stirring at 0°C [20].

*Synthesis of Ethyl 6-phenyl-3-oxo-2,3-dihyropyrazolo[3,4-b]pyridine-4-carboxylate (**3**, $C_{15}H_{13}N_3O_3$):*

A mixture of ethyl benzoylpyruvate (**1**) (2.20 g, 10 mmol) and cyanoacetic acid hydrazide (**2**) (0.99 g, 10 mmol) in glacial acetic acid (30 ml) was stirred at 70–80°C for 3 h. The solvent was evaporated, the residue washed with ethanol, dried to give compound **3**.

Yellow crystal (Yield 81%), m.p. 228-230°C; IR (KBr): $\bar{\nu}$ = 3451, 3175 (NH), 1690 (C=O, ester), 1597 (C=O, amide), 1543 (NH) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 1.40 (3H, t, $^3J_{HH}$=7.1 Hz, CH_3), 4.46 (2H, q, $^3J_{HH}$=7.1 Hz, CH_2), 7.50 (1H, t, $^3J_{HH}$=7.4 Hz, CH_{para} of Ph), 7.55 (2H, t, $^3J_{HH}$=7.4 Hz, $2CH_{meta}$ of Ph), 7.93 (1H, s, CH of pyridine), 8.15 (2H, d, $^3J_{HH}$=7.6 Hz, $2CH_{ortho}$ of Ph), 10.40, 12.73 (2H, 2br.s, 2NH, exchangeable with D_2O) ppm; ^{13}C NMR (DMSO-d_6): δ = 13.82 (CH_3), 62.37 (CH_2), 99.14 (C_{3a}), 112.38 (C_5), 127.06 (CH_{ortho} of Ph), 128.85 (CH_{meta} of Ph), 129.77 (CH_{para} of Ph), 133.21 (C_4), 137.79 (C_{ipso} of Ph), 152.46 (C_6), 152.89 (C_{7a}), 156.41 (C=O, amide), 166.42 (C=O, ester) ppm.

Reactions of the compound **1** with each of hydrazine hydrate and phenyl isocyanate:

*6-Phenyl-3-oxo-2,3-dihyropyrazolo[3,4-b]pyridine-4-carbohydrazide (**4**, $C_{13}H_{11}N_5O_2$):*

A mixture of **1** (0.283 g, 1.0 mmol) and hydrazine hydrate (0.200 g, 4.0 mmol) in 1-butanol (10 ml) was refluxed for 4 h. The solid that separated was filtered off and was washed with ethanol to give compound **4**.

Lemon yellow powder (Yield 87%), m.p. 279-281°C; IR (KBr): $\bar{\nu}$ = 3435, 3258, 3123 (NH), 1682, 1645 (C=O, amide), 1548 (NH) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 7.49 (1H, t, $^3J_{HH}$=7.4 Hz, CH_{para} of Ph), 7.55 (2H, t, $^3J_{HH}$=7.4 Hz, $2CH_{meta}$ of Ph), 7.94 (1H, s, CH of pyridine), 8.17 (2H, d, $^3J_{HH}$=7.6 Hz, $2CH_{ortho}$ of Ph), 5.73, 6.31, 10.40, 12.73 (5H, 4br.s, NH_2, 3NH, exchangeable with D_2O) ppm; ^{13}C NMR (DMSO-d_6): δ = 100.39 (C_{3a}), 110.36 (C_5), 127.17 (CH_{ortho} of Ph), 128.92 (CH_{meta} of Ph), 129.91 (CH_{para} of Ph), 136.24 (C_4), 138.06 (C_{ipso} of Ph), 153.88 (C_6), 154.53 (C_{7a}), 157.50 (C=O, amide), 163.56 (C=O, hydrazide) ppm.

*Ethyl 6-phenyl-1-(N-phenylcarbamoyl)-3-oxo-2,3-dihyro-1H-pyrazolo[3,4-b]pyridine-4-carboxylate (**5**, $C_{22}H_{18}N_4O_4$):*

A mixture of **1** (0.283 g, 1.0 mmol) and phenyl isocyanate (0.119 g, 1.0 mmol) in acetonitrile (10 ml) containing a few drops of TEA was refluxed for 4 h. The solid that separated was filtered off and was washed with ethanol to give compound **5**.

Lemon yellow powder (Yield 78%), m.p. 233-235°C; IR (KBr): ν = 3412, 3245 (NH), 1721 (C=O, ester), 1675, 1624 (C=O, amide), 1558 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ = 1.39 (3H, t, $^3J_{HH}$=6.9 Hz, CH_3), 4.46 (2H, q, $^3J_{HH}$=6.9 Hz, CH_2), 7.15 (1H, t, $^3J_{HH}$=7.4 Hz, CH_{para} of Ph-NH), 7.42 (2H, t, $^3J_{HH}$=7.4 Hz, $2CH_{meta}$ of Ph-NH), 7.51-7.62 (3H, m, CH_{para} and $2CH_{ortho}$ of Ph), 7.68 (2H, t, $^3J_{HH}$=7.7 Hz, $2CH_{ortho}$ of Ph-NH), 8.18 (1H, s, CH of pyridine), 8.24 (2H, d, $^3J_{HH}$=6.6 Hz, $2CH_{ortho}$ of Ph), 10.85, 12.01 (2H, 2br.s, 2NH, exchangeable with D_2O) ppm; ^{13}C NMR (DMSO-d_6): δ = 13.91 (CH_3), 62.46 (CH_2), 103.89 (C_{3a}), 115.07 (C_5), 119.56, 123.88, 127.55, 129.19, 129.30, 130.79, 136.82, 137.80 (12C of 2Ph), 132.62 (C_4), 146.66 (C_{7a}), 151.17 (C_6), 155.78 (C=O, amide), 161.35 (C=O, urea), 164.84 (C=O, ester) ppm.

*Synthesis of 3-arylhydrazono-2,4-dioxo-4-phenylbutanoates (**7a-c**):*

3-Arylhydrazono-2,4-dioxo-4-phenylbutanoates (**7a-c**) have been prepared by the coupling of benzoylpyruvate with aryldiazonium chlorides (**6a-c**) [21].

*Synthesis of 8-arylazo-5-imino-7-phenyl-1,2,3,4-tetrahydro-5H-pyrano[3,4-d]pyridazine-1,4-dione (**8a-c**). General Procedure:*

A mixture of *cyanoacetohydrazide (**2**)* (0.099 g, 1.0 mmol) and each of 3-arylhydrazono-2,4-dioxo-4-phenylbutanoates (**7a-c**) (1.0 mmol) in ethanol (15ml) was refluxed for 3 h. The solid that separated in each case was filtered off, washed with water and ethanol (4:6) to give **8a-c**, respectively.

*5-Imino-8-(4-methylphenylazo)-7-phenyl-1,2,3,4-tetrahydro-5H-pyrano[3,4-d]pyridazine-1,4-dione (**8a**, $C_{20}H_{15}N_5O_3$):*

Reddish-orange powder (Yield 81%), m.p. 273-275°C; IR (KBr): ν = 3430, 3191, 3089 (NH), 2927 (CH, aliphatic), 1684, 1671 (2C=O, amide), 1623 (C=N), 1481 (N=N) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ = 2.42 (3H, s, CH_3), 5.63 (1H, br.s, C=NH, exchangeable with D_2O), 7.30 (2H, d, $^3J_{HH}$=8.2 Hz, $2CH_{ortho}$ of Ph-CH_3), 7.45 (2H, t, $^3J_{HH}$=7.3 Hz, $2CH_{meta}$ of Ph), 7.49 (1H, t, $^3J_{HH}$=7.3 Hz, CH_{para} of Ph), 7.55 (2H, d, $^3J_{HH}$=8.2 Hz, $2CH_{ortho}$ of Ph-N=N), 7.73 (2H, d, $^3J_{HH}$=7.0 Hz, $2CH_{ortho}$ of Ph), 9.89 (2H, br.s, 2NH, exchangeable with D_2O) ppm; ^{13}C NMR (DMSO-d_6): δ = 20.77 (CH_3), 109.84, 112.88 (C_{4a}, C_{8a}), 125.13, 128.10, 129.46, 132.71, 132.82, 134.68, 138.24, 139.71 (12C of 2Ph), 144.20 (C_8), 149.78 (C_7), 152.65 (C_5), 155.58, 157.37 (2C=O, amide) ppm.

*5-Imino-7-phenyl-8-phenylazo-1,2,3,4-tetrahydro-5H-pyrano[3,4-d]pyridazine-1,4-dione (**8b**, $C_{19}H_{13}N_5O_3$):*

Reddish-brown powder (Yield 73%), m.p. 270-272°C; IR (KBr): ν = 3453, 3185, 3107 (NH), 1686, 1674 (2C=O, amide), 1627 (C=N), 1492 (N=N) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ = 5.63 (1H, br.s, C=NH, exchangeable with D_2O), 7.45 (2H, t, $^3J_{HH}$=7.3 Hz, $2CH_{meta}$ of Ph), 7.49 (1H, t, $^3J_{HH}$=7.3 Hz, CH_{para} of Ph), 7.49 (2H, t, $^3J_{HH}$=7.6 Hz, $2CH_{metha}$ of Ph-N=N), 7.53 (1H, t, $^3J_{HH}$=7.9 Hz, CH_{para} of Ph-N=N), 7.72 (2H, d, $^3J_{HH}$=7.0 Hz, $2CH_{ortho}$ of Ph), 7.95 (2H, d, $^3J_{HH}$=7.9 Hz, $2CH_{ortho}$ of Ph-N=N), 9.86 (2H, 2br.s, 2NH, exchangeable with D_2O) ppm.

*5-Imino-8-(4-nitrophenylazo)-7-phenyl-1,2,3,4-tetrahydro-5H-pyrano[3,4-d]pyridazine-1,4-dione (**8c**, $C_{19}H_{12}N_6O_5$):*

Brown powder (Yield 79%), m.p. 313-315°C; IR (KBr): ν = 3442, 3173, 3096 (NH), 1687, 1675 (2C=O, amide), 1619 (C=N), 1520, 1337 (NO_2), 1485 (N=N) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ = 5.65 (1H, br.s, C=NH, exchangeable with D_2O), 7.47 (2H, t, $^3J_{HH}$=7.2 Hz, $2CH_{meta}$ of Ph), 7.54 (1H, t, $^3J_{HH}$=7.2 Hz, CH_{para} of Ph), 7.72 (2H, d, $^3J_{HH}$=7.0 Hz, $2CH_{ortho}$ of Ph), 7.97 (2H, d, $^3J_{HH}$=8.9 Hz, $2CH_{ortho}$ of Ph-N=N), 8.42 (2H, d, $^3J_{HH}$=8.9 Hz, $2CH_{ortho}$ of Ph-NO_2), 9.88 (2H, 2br.s, 2NH, exchangeable with D_2O) ppm.

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