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Benzofuranyl-pyran-2-ones, -pyridazines, and -pyridones from Naturally Occurring Furochromones (Visnagin and Khellin)

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ABSTRACT: *The novel and versatile enaminones* **2a,b** *were synthesized by treatment of visnaginone methyl ether* **1a** *or khellinone methyl ether* **1b** *with* N,N-*dimethylformamide dimethylacetal. They were reacted with hippuric acid or* N-*acetylglycine to yield benzofuran-5-yl-2H-pyran-2-ones* **3a–d**. *The reaction of* **2a,b** *with cyanoacetamide and malononitrile dimer in sodium ethoxide gave benzofuran-5-yl-pyridones* **4a,b** *and [benzofuran-5-yl-1H-pyridine-2-ylidene] malononitrile* **5a**, *respectively. Refluxing* **2a,b** *with hydrazine hydrate or with hydroxylamine afforded benzofuran-5-yl-1H-pyrazoles* **6a,b** *and benzofuran-5-yl-isoxazoles* **7a,b**, *respectively. Moreover,* **2a,b** *coupled with aryl diazonium salt in the presence of sodium hydroxide to yield 3-(benzofuran-5-yl)-2-aryl-hydrazono-3-oxo-propanals* **8a,b** *which were excellent precursors for the synthesis of pyridazines* **9–12**. © 2003 Wiley Periodicals, Inc. Heteroatom Chem 15:85–91, 2004; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.10219

INTRODUCTION

Benzofuran derivatives are known to have a wide variety of pharmacological activitives [1–6]. Recent development in the field of 2H-pyran-2-one derivatives has shown a high importance in the field of medicinal chemistry. In particular, derivatives of this system represent a new class of HIV protease inhibitors [7,8]. Significant biological activities are also associated with substituted pyridazines [9–12], pyridones [13], pyrazoles [14,15], and isoxazoles [16,17]. In view of these facts and in continuation of our work on the synthesis of heterocyclic compounds derived from the naturally occurring furochromones (visnagin and khellin) of pharmacological interest [18,19], it was worthwhile to synthesize new benzofuran derivatives by incorporating these biogenic moieties.

RESULTS AND DISCUSSION

In the present investigation, 4,6-dimethoxy-5-benzofuranyl methyl ketone (visnaginone methyl ether, **1a**) and 4,6,7-trimethoxy-5-benzofuranyl methyl ketone (khellinone methyl ether, **1b**) were prepared from the naturally occurring visnagin and khellin [20,21], respectively.

Treatment of **1a** or **1b** with *N*,*N*-dimethylformamide dimethylacetal in dry toluene afforded 1-benzofuran-5-yl-3-dimethylamino-propenones **2a,b** in excellent yields. All analytical and spectral data of **2a,b** were in an accord with the suggested structures.

Enaminones **2a,b** have been used as a building block for the synthesis of some heterocyclic compounds. They were reacted with hippuric acid or *N*-acetylglycine in refluxing acetic anhydride to yield benzofuran-5-yl-2H-pyran-2ones **3a–d** respectively. It is assumed that hippuric acid or *N*-acetyl glycine is cyclized into an oxazolone, which then reacted with

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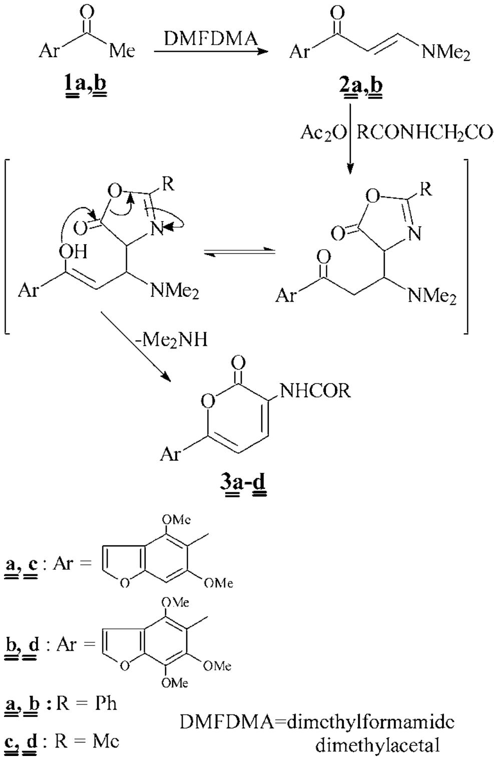
enaminones **2a,b** yielding the final isolable **3a–d** (Scheme 1). The ^{1}H NMR spectra of compounds **3a–d** revealed characteristic doublets for H-4 and H-5 of pyranone ring with $J = 7.5$ Hz.

The reaction of **2a,b** with some active nitriles such as cyanoacetamide and malononitrile dimer in sodium ethoxide was studied. Enaminones **2a,b** were reacted with cyanoacetamide in refluxing ethanolic sodium ethoxide to give 6-benzofuran-5-yl-2-oxo-1,2-dihydro-pyridine-3-carbonitriles **4a,b**. Structures **4a,b** were based on the correct elemental analyses and spectral data. The IR spectra of **4a,b** were compatible with the assigned structures and revealed the amidic carbonyl absorption band at 1685, 1687 cm^{-1} respectively. The ^{1}H NMR of compounds **4a** and **4b** showed the absence of the dimethylamino group and revealed signal at $\delta = 9.90$, 9.95 ppm (br s, NH), respectively. Compound **2a** was also reacted with malononitrile dimer in refluxing ethanolic sodium ethoxide to give 2-[3-cyano-6-(4,6-dimethoxy-benzofuran-5-yl)-1H-pyridine-2-ylidene] malononitrile **5a**. All analytical and spectral data supported the suggested structure. The IR spectra showed absorption band at 2220, 2210 (CN) cm^{-1}.

Moreover, enaminones **2a,b** were reacted with hydrazine hydrate or with hydroxylamine to yield 5-benzofuran-5-yl-1H-pyrazoles **6a,b** and 5-benzofuran-5-yl-isoxazoles **7a,b**, respectively (Scheme 2). It is suggested that the compounds **6a,b** and **7a,b** proceeded via initial substitution of the dimethylamino group, followed by cyclization and elimination of water molecule to afford **6a,b** and **7a,b**. Structures **6a,b** and **7a,b** were established on the correct elemental analyses and spectral data.



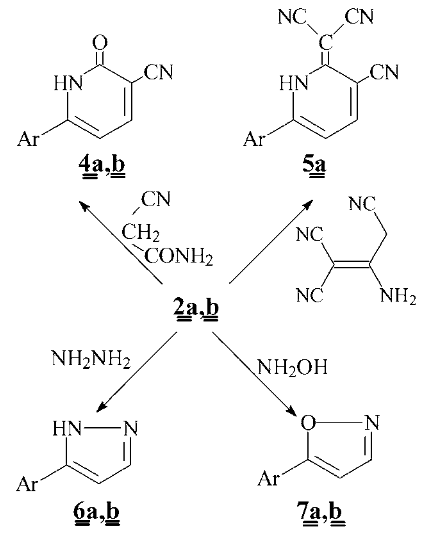
DMFDMA=dimethylformamide dimethylacetal

SCHEME 1

Pyridazines comprise a very interesting class of heteroaromatics because of their significant biological activities [9–12]. So, enaminones **2a,b** coupled with 4-nitrophenyldiazonium salt in the presence of sodium hydroxide to yield 3-(benzofuran-5-yl)-2-[(4-nitrophenyl)-hydrazono]-3-oxo-propanals **8a,b** which are excellent precursors for the synthesis of pyridazine derivatives. Assignment of structures **8a,b** were established on the basis of elemental analyses, IR, ^{1}H NMR, and mass spectra. The ^{1}H NMR spectrum of **8a** showed a singlet at 10.27 ppm, characteristic for the aldehydic group. The mass spectrum of **8a** showed a molecular ion peak at $m/z = 397$.

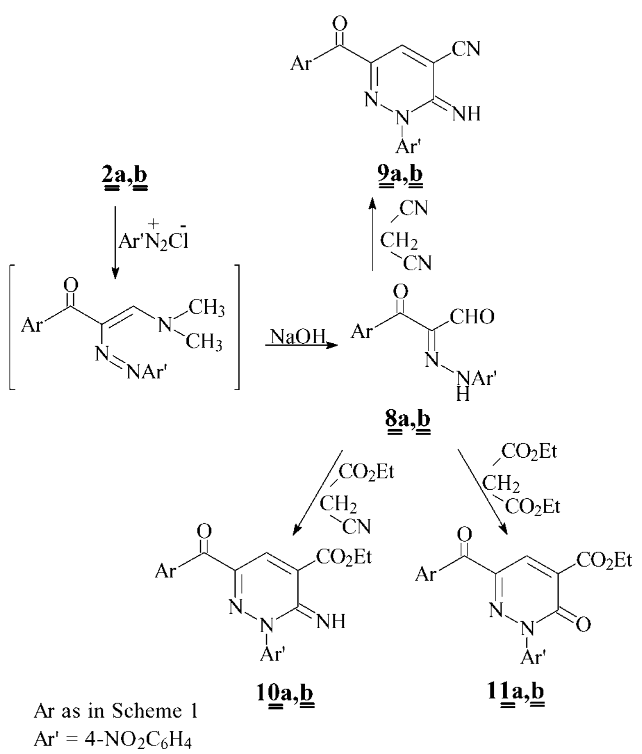
Compounds **8a,b** readily condensed with malononitrile to yield 3-(benzofuran-5-carbonyl)-6-imino-1-(4-nitrophenyl)-1,6-dihydropyridazine-5-carbonitriles **9a,b**.

Moreover, compounds **8a,b** condensed with ethyl cyanoacetate and also with diethyl malonate to afford the pyridazines **10a,b** and **11a,b** respectively (Scheme 3). All analytical and spectral data supported the suggested structures (cf. Experimental section). The phenylhydrazones **8a,b** were reacted with hippuric acid in refluxing acetic anhydride to yield pyridazinones **12a,b** (Scheme 4). Structures



Ar as in Scheme 1

SCHEME 2

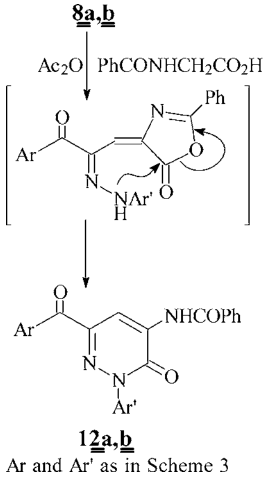


SCHEME 3

12a,b were established on the correct elemental analyses and spectral data.

EXPERIMENTAL

Melting points are uncorrected. Elemental analyses were carried out in the Microanalytical Unit of the Faculty of Science, Cairo University. IR spectra were recorded on a Mattson 5000 FTIR spectrometer. ^{1}H NMR spectra were taken on a Varian-Vx-300 MHz NMR spectrometer using TMS as an internal standard with ($\delta = 0$ ppm). Mass spectra were determined on a GC-MS.QP-1000 (Shimadzu, Japan).



SCHEME 4

*1-(4,6-Dimethoxy- and 4,6,7-trimethoxy-benzofuran-5-yl)-3-dimethylaminopropenones (**2a,b**)*

A mixture of visnaginone methyl ether (**1a**, 2.20 g, 0.01 mol) or khellinone methyl ether (**1b**, 2.50 g, 0.01 mol) and *N,N*-dimethylformamide dimethylacetal (1.78 g, 0.015 mol) in dry toluene (25 ml) was refluxed for 3 h. The crystals which were precipitated after concentration were filtered off, washed with petroleum ether, and crystallized from aqueous ethanol to give:

2a as white crystals; yield, 2.48 g (90%); m.p. 97–98°C; IR (KBr): $\nu = 2955$, 2932 (CH-aliph), 1648 (C=O) cm^{-1}; ^{1}H NMR (CDCl$_3$): $\delta = 2.90$ (s, 6H, —N(CH$_3$)$_2$), 3.82 (s, 3H, OCH$_3$), 4.00 (s, 3H, OCH$_3$), 5.36 (d, 1H, $J = 12.90$ Hz, CH=CH), 6.79 (s, 1H, H-7), 6.82 (d, 1H, $J = 2.3$ Hz, furan H-3), 7.15 (d, 1H, $J = 12.90$ Hz, CH=CH), 7.48 (d, 1H, $J = 2.30$ Hz, furan H-2); MS: $m/z = 275$(M$^+$). Calcd for $C_{15}H_{17}NO_4$ (275.30): C, 65.44; H, 6.22; N, 5.09%. Found: C, 65.60; H, 6.35; N, 5.13%.

2b as white crystals; yield, 2.81 g (92%); m.p. 109–110°C; IR (KBr): $\nu = 2957$, 2934 (CH-aliph), 1649 (C=O) cm^{-1}; ^{1}H NMR (CDCl$_3$): $\delta = 2.91$ (s, 6H, —N(CH$_3$)$_2$), 3.89 (s, 3H, OCH$_3$), 3.95 (s, 3H, OCH$_3$), 4.09 (s, 3H, OCH$_3$), 5.38 (d, 1H, $J = 12.90$ Hz, CH=CH), 6.84 (d, 1H, $J = 2.30$ Hz, furan H-3), 7.18 (d, 1H, $J = 12.90$ Hz, CH=CH), 7.55 (d, 1H, $J = 2.30$ Hz, furan H-2). Calcd for $C_{16}H_{19}NO_5$ (305.33): C, 62.94; H, 6.27; N 4.59%. Found: C, 63.10; H, 6.38; N, 4.50%.

General Procedure for **3a–d**

A mixture of **2a** (2.75 g, 0.01 mol) or **2b** (3.05 g, 0.01 mol) and hippuric acid (1.79 g, 0.01 mol) or *N*-acetylglycine (1.17 g, 0.01 mol) was heated at 90°C in acetic anhydride (30 ml) for 4 h. Acetic anhydride was evaporated under reduced pressure and the product obtained was triturated with ethanol. The solid that formed was filtered off, dried, and crystallized from ethanol to give **3a–d**:

N-[6-(4,6-Dimethoxy-benzofuran-5-yl)-2-oxo-2H-pyran-3-yl]-benzamide (**3a**) as pale yellow crystals; yield, 3.33 g (85%); m.p. 165–166°C; IR (KBr): $\nu = 3400$(NH), 2945 (CH-aliph), 1709, 1661 (CO) cm^{-1}; ^{1}H NMR (CDCl$_3$): $\delta = 3.82$ (s, 3H, OCH$_3$), 4.05 (s, 3H, OCH$_3$), 6.40 (d, 1H, $J = 7.50$ Hz, pyranone H-5), 6.80 (s, 1H, H-7), 6.88 (d, 1H, $J = 2.3$ Hz, furan H-3), 7.40–7.90 (m, 6H, 5Ar-H, furan H-2), 8.50 (d, 1H, $J = 7.50$ Hz, pyranone H-4), 8.75 (br s, 1H, NH); MS: $m/z = 391(M^+)$. Calcd for $C_{22}H_{17}NO_6$ (391.37): C, 67.51; H, 4.38; N, 3.58%. Found: C, 67.63; H, 4.50; N, 3.69%.

N-[6-(4,6,7-Trimethoxy-benzofuran-5-yl)-2-oxo-2H-pyran-3-yl]-benzamide (**3b**) as pale yellow crystals; yield, 3.50 g (83%); m.p. 115–117°C; IR (KBr): $\nu = 3403$(NH), 2940 (CH-aliph), 1707, 1764 (CO) cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 3.85$ (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 4.10 (s, 3H, OCH_3), 6.45 (d, 1H, $J = 7.50$ Hz, pyranone H-5), 6.90 (d, 1H, $J = 2.30$ Hz, furan H-3), 7.50–7.90 (m, 6H, 5Ar-H, furan H-2), 8.53 (d, 1H, $J = 7.50$ Hz, pyranone H-4), 8.75 (br s, 1H, NH). Calcd for $C_{23}H_{19}NO_7$ (421.40): C, 65.55; H, 4.54; N, 3.32%. Found: C, 65.68; H, 4.38; N, 3.40%.

N-[6-(4,6-Dimethoxy-benzofuran-5-yl)-2-oxo-2H-pyran-3-yl]-acetamide (**3c**) as white crystals; yield, 2.70 g (82%); m.p. 200–202°C; IR (KBr): $\nu = 3321$ (NH), 2937 (CH-aliph), 1706, 1674 (CO) cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 2.21$ (s, 3H, $COCH_3$), 3.80 (s, 3H, OCH_3), 4.03 (s, 3H, OCH_3), 6.32 (d, 1H, $J = 7.50$ Hz, pyranone H-5), 6.79 (s, 1H, H-7), 6.87 (d, 1H, $J = 2.30$ Hz, furan H-3), 7.49 (d, 1H, $J = 2.30$ Hz, furan H-2), 8.00 (br s, 1H, NH), 8.32 (d, 1H, $J = 7.50$ Hz, pyranone H-4). Calcd for $C_{17}H_{15}NO_6$ (329.30): C, 62.00; H, 4.59; N, 4.25%. Found: C, 62.13; H, 4.72; N, 4.32%.

N-[6-(4,6,7-Trimethoxy-benzofuran-5-yl)-2-oxo-2H-pyran-3-yl]-acetamide (**3d**) as white crystals; yield, 2.87 g (80%), m.p. 160–162°C; IR (KBr): $\nu = 3327$(NH), 2947 (CH-aliph), 1709, 1680 (CO) cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 2.21$ (s, 3H, $COCH_3$), 3.82 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 4.12 (s, 3H, OCH_3), 6.34 (d, 1H, $J = 7.50$ Hz, pyranone H-5), 6.89 (d, 1H, $J = 2.30$ Hz, furan H-3), 7.52 (d, 1H, $J = 2.30$ Hz, furan H-2), 8.05 (br s, 1H, NH), 8.34 (d, 1H, $J = 7.50$ Hz, pyranone H-4). Calcd for $C_{18}H_{17}NO_7$ (359.33): C, 60.17; H, 4.77; N, 3.90%. Found: C, 60.28; H, 4.88; N, 3.96%.

General Procedure for the Reaction of **2a,b** *with Active Methylene Compounds to Form* **4a,b** *and* **5a**

Sodium ethoxide solution (0.23 g sodium metal in 25 ml absolute ethanol) was added with stirring to a mixture of **2a** (2.75 g, 0.01 mol) or **2b** (3.05 g, 0.01 mol) and cyanoacetamide or malononitrile dimer (0.01 mol) in absolute ethanol (25 ml). The reaction mixture was refluxed for 3 h, then poured into cooled water (50 ml) and neutralized with diluted hydrochloric acid. The precipitate that formed was filtered off, dried, and crystallized from ethanol to give:

6-(4,6-Dimethoxy-benzofuran-5-yl)-2-oxo-1,2-dihydro-pyridine-3-carbonitrile (**4a**) as yellow crystals; yield, 2.52 g (85%); m.p. 128–130°C; IR (KBr): $\nu = 3342$ (NH), 2940(CH-aliph), 2207(CN), 1685(C=O), 1619 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 3.85$ (s, 3H, OCH_3), 4.10 (s, 3H, OCH_3), 6.80 (d, 1H, $J = 2.00$ Hz, pyridone H-5), 6.83 (s, 1H, H-7), 6.88 (d, 1H, $J = 2.30$ Hz, furan H-3), 7.50 (d, 1H, $J = 2.30$ Hz, furan H-2), 7.52 (d, 1H, $J = 2.00$ Hz, pyridone H-4), 9.90 (br s, 1H, NH); MS: $m/z = 296$ (M^+). Calcd for $C_{16}H_{12}N_2O_4$ (296.28): C, 64.86; H, 4.08; N, 9.46%. Found: C, 64.71; H, 3.95; N 9.52%.

6-(4,6,7-Trimethoxy-benzofuran-5-yl)-2-oxo-1,2-dihydro-pyridine-3-carbonitrile (**4b**) as yellow crystals; yield, 2.68 g (82%); m.p. 118–120°C; IR (KBr): $\nu = 3339$ (NH), 2943 (CH-aliph), 2210 (CN), 1687 (C=O), 1620 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 3.83$ (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 4.12 (s, 3H, OCH_3), 6.83 (d, 1H, $J = 2.00$ Hz, pyridone H-5), 6.90 (d, 1H, $J = 2.30$ Hz, furan H-3), 7.55 (d, 1H, $J = 2.30$ Hz, furan H-2), 7.59 (d, 1H, $J = 2.00$ Hz, pyridone H-4), 9.95 (br s, 1H, NH). Calcd for $C_{17}H_{14}N_2O_5$ (326.30): C, 62.57; H, 4.32; N, 8.59%. Found: C, 62.42; H, 4.20; N, 8.65%.

*2-[3-Cyano-6-(4,6-dimethoxy-benzofuran-5-yl)-1H-pyridine-2-ylidene]malononitrile (***5a***)*

Yellow crystals; yield, 2.06 g (60%); m.p. 171–173°C; IR (KBr): $\nu = 3387$ (NH), 2945 (CH-aliph), 2220, 2210(CN), 1619 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta =$ 3.83 (s, 3H, OCH_3), 4.06 (s, 3H, OCH_3), 6.78 (s, 1H, H-7), 6.80 (d, 1H, $J = 2.00$ Hz, pyridine H-5), 6.87 (d, 1H, $J = 2.30$ Hz, furan H-3), 7.52 (d, 1H, $J = 2.30$ Hz, furan H-2), 7.54 (d, 1H, $J = 2.00$ Hz, pyridine H-4), 8.90 (br s, 1H, NH); MS: $m/z = 344$ (M^+). Calcd for $C_{19}H_{12}N_4O_3$ (344.32): C, 66.28; H, 3.51; N, 16.27%. Found: C, 66.43; H, 3.65; N, 16.20%.

*5-(4,6-Dimethoxy and 4,6,7-trimethoxy-benzofuran-5-yl)-1H-pyrazoles (***6a,b***)*

A mixture of **2a** (2.75 g, 0.01 mol) or **2b** (3.05 g, 0.01 mol) and hydrazine monohydrate (0.50 g, 0.01 mol) in absolute ethanol (25 ml) was refluxed for 2 h, then the solvent was concentrated to about 10 ml, diluted with water and left to cool. The precipitate which formed was filtered off, dried, and crystallized from ether-petroleum ether to give:

6a as white crystals; yield, 2.27 g (93%); m.p. 120–122°C; IR (KBr): $\nu = 3315$ (NH), 2940 (CH-aliph), 1620 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 3.94$ (s, 3H, OCH_3), 4.01 (s, 3H, OCH_3), 6.85 (d, 1H, $J =$ 2.00 Hz, pyrazole H-4), 6.88 (s, 1H, H-7), 6.90 (d, 1H, $J = 2.30$ Hz, furan H-3), 7.50 (d, 1H, $J = 2.30$ Hz, furan H-2), 7.65 (d, 1H, $J = 2.00$ Hz, pyrazole H-3), 11.10 (br s, 1H, NH). Calcd for $C_{13}H_{12}N_2O_3$ (244.25):

C, 63.93; H, 4.95; N, 11.47%. Found: C, 63.75; H, 4.82; N, 11.40%.

6b as white crystals; yield, 2.52 g (92%); m.p. 62–64°C; IR (KBr): $\nu = 3309$ (NH), 2944 (CH-aliph), 1618 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 3.81$ (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 4.15 (s, 3H, OCH_3), 6.88 (d, 1H, $J = 2.00$ Hz, pyrazole H-4), 6.90 (d, 1H, $J = 2.30$ Hz, furan H-3), 7.58 (d, 1H, $J = 2.30$ Hz, furan H-2), 7.66 (d, 1H, $J = 2.00$ Hz, pyrazole H-3), 11.12 (br s, 1H, NH). Calcd for $C_{14}H_{14}N_2O_4$ (274.27): C, 61.31; H, 5.14; N, 10.21%. Found: C, 61.45; H, 5.27; N, 10.30%.

*5-(4,6-Dimethoxy and 4,6,7-trimethoxy-benzofuran-5-yl)-isoxazoles (**7a,b**)*

A solution of hydroxylamine hydrochloride (0.695 g, 0.01 mol) in a least amount of water was added to a suspension of **2a** (2.75 g, 0.01 mol) or **2b** (3.05 g, 0.01 mol) in ethanol (25 ml). The reaction mixture was refluxed for 2 h, then the solvent was concentrated to about 10 ml, diluted with water and left to cool. The precipitate or oil that formed was separated, dried, and crystallized from petroleum ether (40–60) to give:

7a as white crystals; yield, 2.26 g (92%); m.p. 70–72°C; IR (KBr): $\nu = 2937$ (CH-aliph), 1608 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 3.84$ (s, 3H, OCH_3), 4.00 (s, 3H, OCH_3), 6.43 (d, 1H, $J = 2.00$ Hz, isoxazole H-4), 6.85 (s, 1H, H-7), 6.89 (d, 1H, $J = 2.30$ Hz, furan H-3), 7.51 (d, 1H, $J = 2.30$ Hz, furan H-2), 8.32 (d, 1H, $J = 2.00$ Hz, isoxazole H-3). Calcd for $C_{13}H_{11}NO_4$ (245.23): C, 63.67; H, 4.52; N, 5.71%. Found: C, 63.51; H, 4.40; N, 5.65%.

7b as oil; yield, 2.48 (90%); IR (neat): $\nu = 2939$ (CH-aliph), 1610 (C=N) cm^{-1}. ^{1}H NMR ($CDCl_3$): $\delta =$ 3.82 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 4.10 (s, 3H, OCH_3), 6.49 (d, 1H, $J = 2.00$ Hz, isoxazole H-4), 6.89 (d, 1H, $J = 2.30$ Hz, furan H-3), 7.59 (d, 1H, $J = 2.30$ Hz, furan H-2), 8.34 (d, 1H, $J = 2.00$ Hz, isoxazole H-3). Calcd for $C_{14}H_{13}NO_5$ (275.26): C, 61.09; H, 4.76; N, 5.09%. Found: C, 61.25; H, 4.60; N, 5.00%.

*3-(4,6-Dimethoxy and 4,6,7-trimethoxy-benzofuran-5-yl)-2-[(4-nitrophenyl)hydrazono]-3-oxo-propanals (**8a,b**)*

A cold solution of aryldiazonium salt (0.01 mol) was prepared by adding a solution of sodium nitrite (1.00 g into 10 ml H_2O) to a cold solution of 4-nitroaniline hydrochloride (1.38 g, 0.01 mol of 4-nitroaniline in 5 ml concentrated HCl) with stirring. The resulting solution of the aryldiazonium salt was then added to a cold solution of **2a** (2.75 g, 0.01 mol) or **2b** (3.05 g, 0.01 mol) in ethanol (50 ml) containing sodium hydroxide (0.015 mol, in 5 ml H_2O). The reaction mixture was stirred at room temperature for 3 h. The precipitate that formed was filtered off, dried, and crystallized from ethanol to give:

8a as pale brown crystals; yield, 2.98 g (75%); m.p. 166–168°C; IR (KBr): $\nu = 3455$ (NH), 2940 (CH-aliph), 1661 (C=O), 1620 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 3.78$ (s, 3H, OCH_3), 4.03 (s, 3H, OCH_3), 6.84 (s, 1H, H-7), 6.89 (d, 1H, $J = 2.30$ Hz, furan H-3), 7.15–8.16 (m, 6H, 4Ar-H, furan H-2, NH), 10.27 (s, 1H, CHO), MS: $m/z = 397$ (M^+). Calcd for $C_{19}H_{15}N_3O_7$ (397.34): C, 57.43; H, 3.81; N, 10.58%. Found: C, 57.60; H, 3.65; N, 10.50%.

8b as pale brown crystals; yield, 3.29 g (77%); m.p. 127–129°C; IR (KBr): $\nu = 3444$ (NH), 2944 (CH-aliph), 1667(C=O), 1621 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 3.80$ (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 4.15 (s, 3H, OCH_3), 6.84 (s, 1H, H-7), 6.90 (d, 1H, $J =$ 2.30 Hz, furan H-3), 7.16–8.19 (m, 6H, 4Ar-H, furan H-2, NH), 10.29 (s, 1H, CHO). Calcd for $C_{20}H_{17}N_3O_8$ (427.36): C, 56.21; H, 4.01; N, 9.83%. Found: C, 56.38; H, 4.16; N, 9.75%.

*3-(4,6-Dimethoxy and 4,6,7-trimethoxy-benzofuran-5-carbonyl)-6-imino-1-(4-nitrophenyl)-1,6-dihydropyridazine-5-carbonitriles (**9a,b**)*

A mixture of **8a** (3.97 g, 0.01 mol) or **8b** (4.27 g, 0.01 mol), malononitrile (0.66 g, 0.01 mol), and a few drops of piperidine in absolute ethanol (30 ml) was refluxed for 5 h. The crystals which were precipitated after concentration were filtered off, dried, and recrystallized from ethanol to give:

9a as brown crystals; yield, 3.25 g (73%); m.p. 198–200°C; IR (KBr): $\nu = 3391$ (NH), 2941(CH-aliph), 2205(CN), 1668 (C=O), 1618 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 3.81$ (s, 3H, OCH_3), 4.02 (s, 3H, OCH_3), 6.67 (s, 1H, H-7), 6.88 (d, 1H, $J = 2.30$ Hz, furan H-3), 7.16–8.25 (m, 6H, 4Ar-H, furan H-2, pyridazine H-4), 9.98 (br s, 1H, NH); MS, $m/z =$ 445 (M^+). Calcd for $C_{22}H_{15}N_5O_6$ (445.38): C, 59.33; H, 3.39; N, 15.72%. Found: C, 59.18; H, 3.25; N, 15.63%.

9b as brown crystals; yield, 3.38 g (71%); m.p. 150–152°C; IR (KBr): $\nu = 3380$ (NH), 2943 (CH-aliph), 2207(CN), 1670 (C=O), 1619 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 3.89$ (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 4.13 (s, 3H, OCH_3), 6.90 (d, 1H, $J = 2.30$ Hz, furan H-3), 7.15–8.25 (m, 6H, 4Ar-H, furan H-2, pyridazine H-4), 10.05 (br s, 1H, NH). Calcd for $C_{23}H_{17}N_5O_7$ (475.41): C, 58.11; H, 3.60; N, 14.73%. Found: C, 58.30; H; 3.75; N, 14.65%.

*3-(4,6-Dimethoxy and 4,6,7-trimethoxy-benzofuran-5-carbonyl)-6-imino-1-(4-nitrophenyl)-1,6-dihydropyridazine-5-carboxylic acid ethyl ester (***10a,b***)*

A mixture of **8a** (3.97 g, 0.01 mol) or **8b** (4.27 g, 0.01 mol), ethyl cyanoacetate (1.13 g, 0.01 mol), and a few drops of piperidine in dioxane (30 ml) was refluxed for 5 h. The reaction mixture was concentrated and poured into crushed ice. The solid that formed was filtered off, dried, and crystallized from ethanol to give:

10a as brown crystals; yield, 3.54 (72%); m.p. 124–126°C; IR (KBr): $\nu = 3372$ (NH), 2940 (CH-aliph), 1732 (ester C=O), 1671 (C=O), 1620 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 1.27$ (t, 3H, CH_2-$\underline{CH_3}$), 3.82 (s, 3H, OCH_3), 4.03 (s, 3H, OCH_3), 4.30 (q, 2H, $\underline{CH_2}$-CH_3), 6.69 (s, 1H, H-7), 6.89 (d, 1H, $J = 2.30$ Hz, furan H-3), 7.20–8.40 (m, 6H, 4Ar-H, furan H-2, pyridazine H-4), 8.70 (br s, 1H, NH). Calcd for $C_{24}H_{20}N_4O_8$ (492.44): C, 58.54; H, 4.09; N, 11.38%. Found: C, 58.36; H, 4.25; N, 11.29%.

10b as brown crystals; yield, 3.66 g (70%); m.p. 90–92°C; IR (KBr): $\nu = 3375$ (NH), 2945(CH-aliph), 1734 (ester C=O), 1675 (C=O), 1621 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 1.30$ (t, 3H, CH_2-$\underline{CH_3}$), 3.80 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 4.09 (s, 3H, OCH_3), 4.32 (q, 2H, $\underline{CH_2}$-CH_3), 6.90 (d, 1H, $J = 2.30$ Hz, furan H-3), 7.21–8.45 (m, 6H, 4Ar-H, furan H-2, pyridazine H-4), 8.72 (br s, 1H, NH). Calcd for $C_{25}H_{22}N_4O_9$ (522.46): C, 57.47; H, 4.24; N, 10.72%. Found: C, 57.60; H, 4.38; N, 10.80%.

*3-(4,6-Dimethoxy and 4,6,7-trimethoxy-benzofuran-5-carbonyl)-1-(4-nitro-phenyl)-6-oxo-1,6-dihydropyridazine-5-carboxylic acid ethyl ester (***11a,b***)*

A mixture of **8a** (3.97 g, 0.01 mol) or **8b** (4.27 g, 0.01 mol), and diethyl malonate (1.60 g, 0.01 mol) in pyridine (30 ml) was refluxed for 4 h. The solvent was evaporated under reduced pressure and the product obtained was triturated with ethanol. The solid that formed was filtered off, dried, and crystallized from ethanol to give:

11a as brown crystals; yield, 3.45 g (70%); m.p. 132–134°C; IR (KBr): $\nu = 2943$(CH-aliph), 1740 (ester C=O), 1670 (C=O), 1620 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 1.32$ (t, 3H, CH_2-$\underline{CH_3}$), 3.83 (s, 3H, OCH_3), 4.05 (s, 3H, OCH_3), 4.42 (q, 2H, $\underline{CH_2}$-CH_3), 6.68 (s, 1H, H-7), 6.89 (d, 1H, $J = 2.30$ Hz, furan H-3), 7.20–8.40 (m, 6H, 4Ar-H, furan H-2, pyridazine H-4); Calcd for $C_{24}H_{19}N_3O_9$ (493.42): C, 58.42; H, 3.88; N, 8.52%. Found: C, 58.25; H, 3.70; N, 8.62%.

11b as brown crystals; yield, 3.61 g (69%); m.p. 98–100°C. IR (KBr): $\nu = 2947$ (CH-aliph), 1744 (ester C=O), 1672 (C=O), 1621 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 1.35$ (t, 3H, CH_2-$\underline{CH_3}$), 3.82 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 4.12 (s, 3H, OCH_3), 4.43 (q, 2H, $\underline{CH_2}$-CH_3), 6.90 (d, 1H, $J = 2.30$ Hz, furan H-3), 7.21–8.40 (m, 6H, 4Ar-H, furan H-2, pyridazine H-4). Calcd for $C_{25}H_{21}N_3O_{10}$ (523.45): C, 57.36; H, 4.04; N, 8.03%. Found: C, 57.20; H, 4.20; N, 8.12%.

*N-[3-(4,6-Dimethoxy and 4,6,7-trimethoxy-benzofuran-5-carbonyl)-1-(4-nitrophenyl)-6-oxo-1,6-dihydropyridazin-5-yl]-benzamide (***12a,b***)*

A mixture of **8a** (3.97 g, 0.01 mol) or **8b** (4.27 g, 0.01 mol), and hippuric acid (1.79 g, 0.01 mol) in acetic anhydride (30 ml) was refluxed for 4 h. Acetic anhydride was evaporated under reduced pressure and the product obtained was triturated with ethanol. The solid that formed was filtered off, dried, and crystallized from ethanol to give:

12a as yellow crystals; yield, 4.38 g (81%); m.p. 196–198°C; IR (KBr): $\nu = 3400$ (NH), 2941 (CH-aliph), 1690, 1670 (CO), 1617 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 3.78$ (s, 3H, OCH_3), 4.00 (s, 3H, OCH_3), 6.81 (s, 1H, H-7), 6.87 (d, 1H, $J = 2.30$ Hz, furan H-3), 7.20–8.25 (m, 11H, 9Ar-H, furan H-2, pyridazine H-4), 9.00 (br s, 1H, NH). Calcd for $C_{28}H_{20}N_4O_8$ (540.48): C, 62.22; H, 3.73; N, 10.37%. Found: C, 62.40; H, 3.58; N, 10.42%.

12b as yellow crystals; yield, 4.56 g (80%); m.p. 140–142°C; IR (KBr): $\nu = 3405$(NH), 2945 (CH-aliph), 1695, 1672 (CO), 1618 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 3.80$ (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 4.02 (s, 3H, OCH_3), 6.89 (d, 1H, $J = 2.30$ Hz, furan H-3), 7.25–8.27 (m, 11H, 9 Ar-H, furan H-2, pyridazine H-4), 9.05 (br s, 1H, NH). Calcd for $C_{29}H_{22}N_4O_9$ (570.51): C, 61.05; H, 3.89; N, 9.82%. Found: C, 61.20; H, 3.75; N, 9.74%.

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