Synthesis of Isoindolo[2,1-*a*]quinazoline-5,11-dione Derivatives *via* the Reductive One-Pot Reaction of *N*-Substituted 2-Nitrobenzamides and 2-Formylbenzoic Acids

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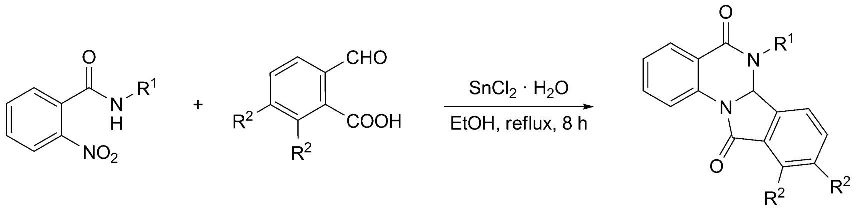
Various isoindolo[2,1-*a*]quinazoline-5,11-dione derivatives **3** were synthesized in good yields by means of the reductive reaction of *N*-substituted 2-nitrobenzamides **1** and 2-formylbenzoic acids **2** in the presence of $SnCl_2 \cdot 2\,H_2O$ under reflux in EtOH (*Scheme*, *Table*). The procedure needed two steps, the reduction of the nitro group of the 2-nitrobenzamide and ring closure by nucleophilic addition of the NH_2 group to both the formyl and carboxylic acid C=O groups.

Introduction. – Isoindolin-1-ones (=2,3-dihydro-1*H*-isoindol-1-ones) and their derivatives exhibit important physiological and chemotherapeutic activities [1]. Also they have shown a wide range of activities including antioxidant [2], antimicrobial [3], and anticancer activity [4]. Some 2-[3-(cyclopentyloxy)-4-methoxyphenyl]isoindolin-1-one derivatives were synthesized and screened for a developed allosteric mGluR1 antagonist by *Park* and co-workers [5]. They are potent inhibitors of TNF-α production in LPS-stimulated RAW264.7 cells.

The 2,3-dihydroquinazolin-4(1*H*)-one-centered compounds play also an important role in organic chemistry, as key structural units in many natural products and important pharmaceuticals [6][7]. A considerable number of 2,3-dihydroquinazolin-4(1*H*)-ones are well-known as antibacterial [8], vasodilatory [9], antispermatogenic [10], antifibrillatory [11], and analgesic [12] agents.

Although isoindolin-1-ones and 2,3-dihydroquinazolin-4(1*H*)-ones individually possess important biological properties, to the best of our knowledge, only a few studies have been published on the synthesis and biological activities of fused isoindoloquinazolinone derivatives [13–19]. Thus, herein, in continuation of our work on the synthesis new heterocycles [20], particularly bioactive compounds [21], we wish to report an efficient route for the synthesis of isoindolo[2,1-*a*]quinazoline-5,11-dione derivatives **3** *via* reaction of 2-nitrobenzamides **1** and 2-formylbenzoic acids **2** in the presence of $SnCl_2 \cdot 2\,H_2O$ under reflux conditions in EtOH (*Scheme*). The reductive reaction of 2-nitrobenzamides in the presence of $SnCl_2$ with diverse substrates has been investigated, and proficient routes for the synthesis of heterocyclic scaffolds have been provided [22–24].

Scheme. *Synthesis of Isoindolo[2,1-*a*]quinazoline-5,11-dione-Derivatives* **3**. For R^1 and R^2, see *Table*.



1 **2** **3**

Results and Discussion. – We began our study with the reaction of *N*-(furan-2-ylmethyl)-2-nitrobenzamide (**1a**) and 2-formylbenzoic acid (**2a**), investigating the influence of different amounts of $SnCl_2 \cdot 2\,H_2O$ and solvents under various conditions with the aim of improving the yield of the product **3a**. It was found that the use of 1 mmol of each starting material **1a** and **2a** and 4 mmol of $SnCl_2 \cdot 2\,H_2O$ in refluxing EtOH gave the optimized conditions, and **3a** was obtained in 85% yield (*Table*).

With these results in hand, reactions were performed with various 2-nitrobenzamides **1** to explore the substrate scope with regard to two 2-formylbenzoic acid derivatives **2a** ($R^2 = H$) and **2b** ($R^2 = MeO$; *Table*). It should be noted that all the reactions reached completion within 8 h, furnishing the products **3a** – **3h** in very good yields.

The structures of compounds **3a** – **3h** were elucidated from their elemental analysis, mass, IR, and ^{1}H-, and ^{13}C-NMR spectra.

The reaction proceeded in two steps, first the reduction of the NO_2 group of **1** and then ring closure by nucleophilic addition of the NH_2 group to both the CHO and COOH groups of **2**.

In conclusion, we developed the direct preparation of isoindolo[2,1-*a*]quinazoline-5,11-dione derivatives **3** in a one-pot reductive reaction of *N*-substituted 2-nitrobenzamides **1** and 2-formylbenzoic acids **2**. Availability of the starting materials, one-pot procedure, and high yield provide a very useful route to construct differently substituted isoindolo[2,1-*a*]quinazoline-5,11-diones.

We gratefully acknowledge the partial financial support from the Medicinal Sciences Research Council of the Tehran University and the *Iran National Science Foundation* (*INSF*).

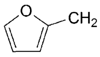
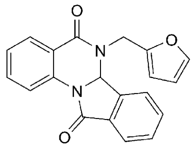
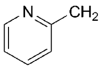
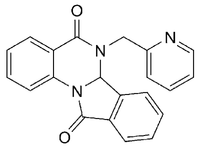
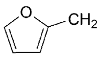
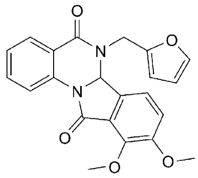
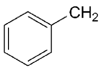
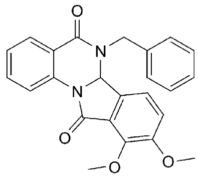
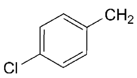
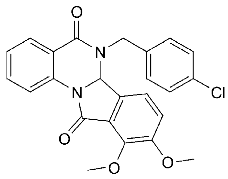
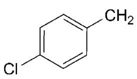
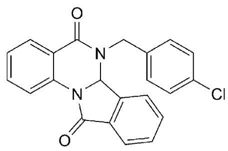
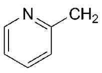
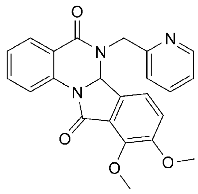
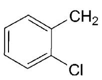
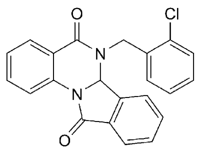
Experimental Part

General. M.p.: *Kofler* hot-stage apparatus; uncorrected. IR Spectra: *Shimadzu-470* spectrophotometer; in KBr; $\tilde{\nu}$ in cm^{-1}. ^{1}H- and ^{13}C-NMR Spectra: *Bruker FT-500*; $CDCl_3$ solns.; δ in ppm rel. to Me_4Si as internal standard, *J* in Hz. MS: *Agilent-Technology* (*HP*) mass spectrometer, ionization potential 70 eV; in *m/z*. Elemental analysis: *VarioEL CHNS* mode (*Elementar Analysensystem GmbH*).

*Isoindolo[2,1-*a*]quinazoline-5,11-dione Derivatives* **3**: *Typical Procedure.* A soln. of 2-nitrobenzamide **1** (1 mmol), 2-formylbenzoic acid **2** (1 mmol), and $SnCl_2 \cdot H_2O$ (4 mmol) in EtOH (8 ml) was stirred under reflux for 8 h. The reaction was quenched with 3% HCl soln. (15 ml) and the resulting mixture filtered. The crude product was purified by recrystallization from $EtOH/H_2O$ 4 : 1: pure **3**.

*6-(Furan-2-ylmethyl)-6,6a-dihydroisoindolo[2,1-*a*]quinazoline-5,11-dione* (**3a**) [18]. White crystals. M.p. 166 – 168°. IR: 1721, 1668, 1602, 1488. ^{1}H-NMR: 8.04 – 7.38 (*m*, 8 arom. H); 7.53 (*d*, *J* = 3.0, 1 H, fur);

Table. *Synthesis of Isoindolo[2,1-*a*]quinazoline-5,11-dione Derivatives* **3**

R^1 in 2-Nitrobenzamide **1**	R^2	Product		Yield [%][a])
	H		**3a** [18]	85
	H		**3b**	90
	MeO		**3c** [25]	80
	MeO		**3d**	80
	MeO		**3e**	80
	H		**3f** [14]	85
	MeO		**3g**	80
	H		**3h**	85

6.63 (*s*, CH); 6.32 (*t*, *J* = 3.0, 1 H, fur); 6.14 (*d*, *J* = 3.0, 1 H, fur); 5.11 (*d*, *J* = 16.8, 1 H, CH_2); 4.76 (*d*, *J* = 16.8, 1 H, CH_2). ^{13}C-NMR: 164.3; 163.0; 150.4; 142.3; 138.1; 136.6; 133.6; 130.6; 128.6; 133.1; 126.1; 125.1; 124.2; 121.4; 119.9; 119.8; 110.5; 107.4; 70.2; 45.0. MS: 330 (M^+), 249, 235, 207, 179. Anal. calc. for $C_{20}H_{14}N_2O_3$ (330.34): C 72.72, H 4.27, N 8.48; found: C 72.52, H 4.39, N 8.37.

*6,6a-Dihydro-6-(pyridin-2-ylmethyl)isoindolo[2,1-*a*]quinazoline-5,11-dione* (**3b**): White crystals. M.p. 212 – 214°. IR: 1721, 1660, 1597. ^{1}H-NMR: 8.49 – 7.23 (*m*, 12 arom. H); 6.81 (*s*, CH); 5.26 (*d*, *J* = 17.2, 1 H, CH_2); 4.90 (*d*, *J* = 17.2, 1 H, CH_2). ^{13}C-NMR: 164.3; 163.3; 156.7; 149.0; 138.1; 136.9; 136.8; 133.5; 132.8; 131.9; 130.5; 128.6; 125.9; 125.0; 124.1; 122.2; 121.2; 119.9; 119.8; 70.6; 47.5. MS: 341 (M^+), 249, 207, 93. Anal. calc. for $C_{21}H_{15}N_3O_2$ (341.36): C 73.89, H 4.43, N 12.31; found: C 73.67, H 4.61, N 12.50.

*6-(Furan-2-ylmethyl)-6,6a-dihydro-9,10-dimethoxyisoindolo[2,1-*a*]quinazoline-5,11-dione* (**3c**) [25]: White crystals. M.p. 181 – 183°. IR: 1731, 1660, 1601. ^{1}H-NMR: 8.01 – 7.36 (*m*, 6 arom. H); 7.56 (*d*, *J* = 2.0, 1 H, fur); 6.46 (*s*, CH); 6.36 (*dd*, *J* = 3.0, 2.0, 1 H, fur); 6.17 (*d*, *J* = 3.0, 1 H, fur); 5.06 (*d*, *J* = 16.7, 1 H, CH_2); 4.64 (*d*, *J* = 16.7, 1 H, CH_2); 3.91 (*s*, MeO); 3.88 (*s*, MeO). ^{13}C-NMR: 162.9; 162.5; 153.8; 150.5; 147.1; 142.3; 136.7; 133.4; 130.3; 128.5; 124.9; 123.8; 121.6; 120.2; 120.0; 117.4; 110.6; 107.3; 69.0; 61.7; 56.4; 47.2. MS: 390 (M^+), 295, 280, 252, 224. Anal. calc. for $C_{22}H_{18}N_2O_5$ (390.39): C 67.69, H 4.65, N 7.18; found: C 67.50, H 4.75, N 7.35.

*6-Benzyl-6,6a-dihydro-9,10-dimethoxyisoindolo[2,1-*a*]quinazoline-5,11-dione* (**3d**): White crystals. M.p. 197 – 200°. IR: 1709, 1655, 1601, 1491. ^{1}H-NMR: 8.05 – 7.07 (*m*, 11 arom. H); 6.54 (*s*, CH); 5.06 (*d*, *J* = 16.9, 1 H, CH_2); 4.90 (*d*, *J* = 16.9, 1 H, CH_2); 3.86 (*s*, MeO); 3.81 (*s*, MeO). ^{13}C-NMR: 163.2; 162.4; 153.6; 146.9; 137.3; 136.8; 133.3; 130.2; 128.6; 128.4; 126.6; 126.0; 125.0; 123.8; 121.5; 120.2; 120.1; 117.3; 69.1; 61.7; 56.3; 45.5. MS: 400 (M^+), 296, 252, 224, 179, 152. Anal. calc. for $C_{24}H_{20}N_2O_4$ (400.43): C 71.99, H 5.03, N 7.00; found: C 72.15, H 5.22, N 7.10.

*6-(4-Chlorobenzyl)-6,6a-dihydro-9,10-dimethoxyisoindolo[2,1-*a*]quinazoline-5,11-dione* (**3e**): White crystals. M.p. 180 – 182°. IR: 1725, 1658, 1605, 1490. ^{1}H-NMR: 8.04 – 7.07 (*m*, 10 arom. H); 6.53 (*s*, CH); 4.97 (*s*, CH_2); 3.86 (*s*, MeO); 3.82 (*s*, MeO). ^{13}C-NMR: 163.2; 162.4; 153.7; 147.0; 136.7; 136.5; 133.3; 131.1; 130.2; 128.6; 128.3; 127.9; 125.0; 123.7; 121.6; 120.2; 120.1; 117.3; 69.1; 61.7; 56.3; 45.0. MS: 434 (M^+), 436 ($[M+2]^+$), 295, 280, 252, 125. Anal. calc. for $C_{24}H_{19}ClN_2O_4$ (434.87): C 66.29, H 4.40, N 6.44; found: C 66.44, H 4.55, N 6.65.

*6-(4-Chlorobenzyl)-6,6a-dihydroisoindolo[2,1-*a*]quinazoline-5,11-dione* (**3f**) [14]: White crystals. M.p. 180 – 182°. IR: 1718, 1661, 1605, 1491. ^{1}H-NMR: 8.05 – 7.07 (*m*, 12 arom. H); 6.71 (*s*, CH); 5.08 (*d*, *J* = 17.2, 1 H, CH_2); 5.01 (*d*, *J* = 17.2, 1 H, CH_2). ^{13}C-NMR: 164.3; 163.3; 137.9; 136.6; 136.5; 133.5; 132.9; 131.7; 131.1; 130.5; 128.6; 128.2; 127.8; 126.1; 125.1; 124.1; 119.9; 70.2; 45.1. MS: 374 (M^+), 376 ($[M+2]^+$), 280, 235, 167, 149. Anal. calc. for $C_{22}H_{15}ClN_2O_2$ (374.82): C 70.50, H 4.03, N 7.47; found: C 69.95, H 4.20, N 7.50.

*6,6a-Dihydro-9,10-dimethoxy-6-(pyridin-2-ylmethyl)isoindolo[2,1-*a*]quinazoline-5,11-dione* (**3g**): White crystals. M.p. 210 – 212°. IR: 1725, 1658, 1602, 1590. ^{1}H-NMR: 8.50 – 7.12 (*m*, 10 arom. H); 6.64 (*s*, CH); 5.22 (*d*, *J* = 17.2, 1 H, CH_2); 4.82 (*d*, *J* = 17.2, 1 H, CH_2); 3.82 (*s*, MeO); 3.89 (*s*, MeO). ^{13}C-NMR: 163.2; 162.5; 156.7; 153.7; 149.0; 147.0; 137.0; 136.9; 133.3; 130.3; 128.5; 124.9; 123.9; 122.2; 121.4; 121.3; 120.1; 117.2; 69.5; 61.7; 56.3; 47.2. MS: 401 (M^+), 309, 225, 190, 69. Anal. calc. for $C_{23}H_{19}N_3O_4$ (401.41): C 68.82, H 4.77, N 10.47; found: C 69.05, H 4.85, N 10.55.

*6-(2-Chlorobenzyl)-6,6a-dihydroisoindolo[2,1-*a*]quinazoline-5,11-dione* (**3h**): White crystals. M.p. 185 – 188°. IR: 1709, 1686, 1602, 1490. ^{1}H-NMR: 8.23 – 7.05 (*m*, 12 arom. H); 6.37 (*s*, CH); 5.27 (*d*, *J* = 17.5, 1 H, CH_2); 5.04 (*d*, *J* = 17.5, 1 H, CH_2). ^{13}C-NMR: 164.9; 164.2; 137.4; 137.0; 133.9; 133.6; 132.7; 132.4; 132.1; 130.6; 129.8; 129.5; 128.4; 127.2; 126.8; 125.4; 124.9; 124.8; 120.3; 120.0; 70.7; 44.7. MS: 374 (M^+), 376 ($[M+2]^+$), 280, 235, 149. Anal. calc. for $C_{24}H_{19}ClN_2O_4$ (374.82): C 70.50, H 4.03, N 7.47; found: C 70.77, H 4.32, N 6.60.

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