Preparation of Silica Nanoparticles from Organic Laboratory Waste of Silica Gel HF_{254} and Their Use as a Highly Efficient Catalyst for the One-Pot Synthesis of 2,3-Dihydro-1*H*-isoindolone Derivatives

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Reaction of an isocyanide with an iminium ion intermediate, formed by reaction between 6-formyl-2,3-dimethoxybenzoic acid and secondary amines (dibenzyl- or benzyl(isopropyl)amine) in the presence of silica nanoparticles (silica NPs, *ca.* 70 nm) proceeds smoothly at room temperature to afford 2,3-dihydro-1*H*-isoindolone derivatives in high yields.

Introduction. – In the past years, combinatorial methods using multicomponent reactions have been closely examined as a fast and convenient solution for the synthesis of diverse classes of compounds [1][2]. Multicomponent reactions (MCRs), defined as one-pot reactions in which at least three functional groups join through covalent bonds, have been steadily gaining importance in synthetic organic chemistry [1–4].

Recently, nanoparticles (NPs) have attracted tremendous attention in catalysis because of their improved efficiency under mild and environmentally benign conditions in the context of 'Green' synthesis [5][6]. Due to their enormously large and highly reactive surface area, NPs have the potential to exhibit superior catalytic activity in comparison to bulk counterparts [7][8].

Here, we report a simple procedure for the preparation of 2,3-dihydro-1*H*-isoindolone derivatives *via* MCR in the presence of silica nanoparticles (silica NPs, *ca.* 70 nm).

Results and Discussion. – As part of our ongoing program to develop efficient and robust methods for the preparation of heterocyclic compounds [9–13], we report here a simple, one-pot, three-component reaction between 6-formyl-2,3-dimethoxybenzoic acid (**1**), secondary amines (dibenzyl- and benzyl(isopropyl)amine) **2**, and isocyanides **3** in the presence of silica NPs at room temperature, leading after 7 h to 2,3-dihydro-1*H*-isoindolone derivatives **4** (*Scheme 1* and *Table 1*).

Silica NPs were prepared from silica gel HF_{254} residues. The morphology and grain size of the silica NPs was investigated by SEM (*Fig. 1*).

Silica NPs were found to catalyze the synthesis of 2,3-dihydro-1*H*-isoindolone derivatives **4** from acid **1**, the secondary amines **2**, and isocyanides **3**, under solvent-free conditions (*Table 1*). We have also used silica gel powder instead of silica NPs in this reaction, but increasing reaction times and decreasing yields of **4** were observed (*Table 2*). The use of just 0.2 g of silica NPs (per mmol of reactants) is sufficient to push

Scheme 1. *Synthesis of Isoindolinone Derivatives* **4** *in the Presence of Silica Nanoparticles* (NPs; see also *Table 1*)

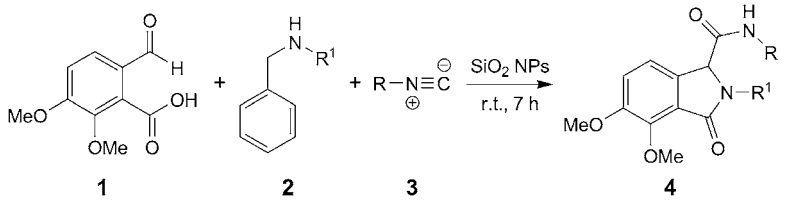


Table 1. *Synthesis of Isoindolinone Derivatives* **4** *in the Presence of Silica Nanoparticles*[a])

	R	R^1	Yield [%][b]) (reaction time: 7 h)
4a	*t*-Bu	$PhCH_2$	94
4b	Cyclohexyl	$PhCH_2$	90
4c	1,1,3,3-Tetramethylbutyl	$PhCH_2$	85
4d	*t*-Bu	i-Pr	92
4e	Cyclohexyl	i-Pr	82
4f	1,1,3,3-Tetramethylbutyl	i-Pr	88

[a]) See *Scheme 1*; 0.2 g of SiO_2 NPs/mmol reactants was applied. [b]) Yield of isolated **4**.

the reaction forward. Higher amounts of silica NPs (0.3 g) did not considerably improve the yields (*Table 2*).

We also used other secondary amines (Et_2NH, piperidine, and benzyl(methyl)amine) in the presence of silica NPs and silica gel powder, but in all cases, several products were observed (TLC investigations). Therefore, the reactions with other than dibenzylamine and benzyl(isopropyl)amine have, according to our experience, no synthetic value.

The structures of compounds **4a**–**4f** were deduced from their IR, and ^{1}H- and ^{13}C-NMR spectra. For example, the IR spectrum (KBr) of **4a** showed a strong adsorption at 3327 cm^{-1}, indicating the presence of NH amide, and sharp bands at 1698 and 1675 cm^{-1} were assigned to the amide CO groups. The ^{1}H-NMR spectrum ($CDCl_3$) of **4a** consisted of a *singlet* for the Me groups (Me_3C, δ(H) 1.13), two *singlet*s for the MeO groups (δ(H) 3.89 and 4.12), an *AM* system for the $PhCH_2$ group (δ(H) 4.46 and

Table 2. *Synthesis of Isoindolone* **4a** *from 6-Formyl-2,3-dimethoxybenzoic Acid* (**1**)*, Dibenzylamine, and* tert-*Butyl Isocyanide under Various Conditions*

Entry	Catalyst[a])	Temp.	Time [h]	Yield [%][b])
1	Silica gel powder (0.2 g)	r.t.	24	48
2	Silica gel powder (0.5 g)	r.t.	24	63
3	Silica gel powder (1 g)	r.t.	24	75
4	Silica gel powder (1.2 g)	r.t.	24	73
5	SiO_2 NPs (0.1 g)	r.t.	7	82
6	SiO_2 NPs (0.2 g)	r.t.	7	94
7	SiO_2 NPs (0.3 g)	r.t.	7	91

[a]) Amount of SiO_2 catalyst per mmol of reactants. [b]) Yields of isolated **4a**.

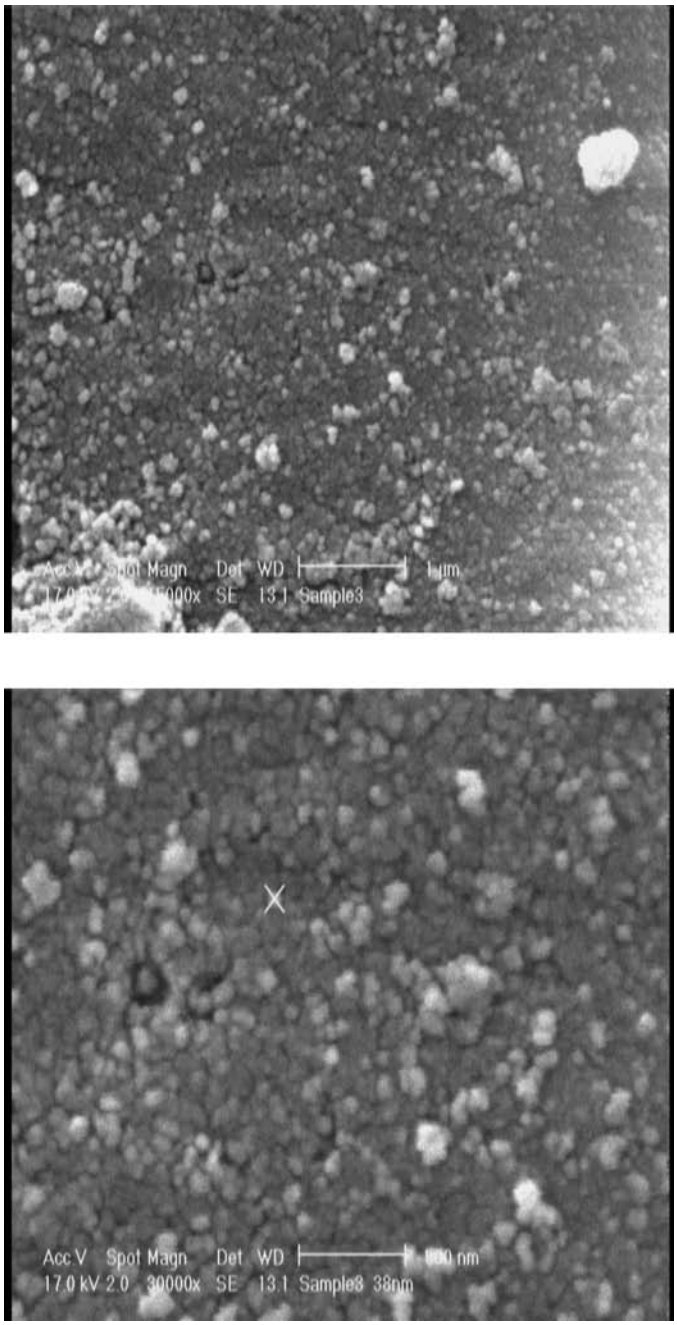
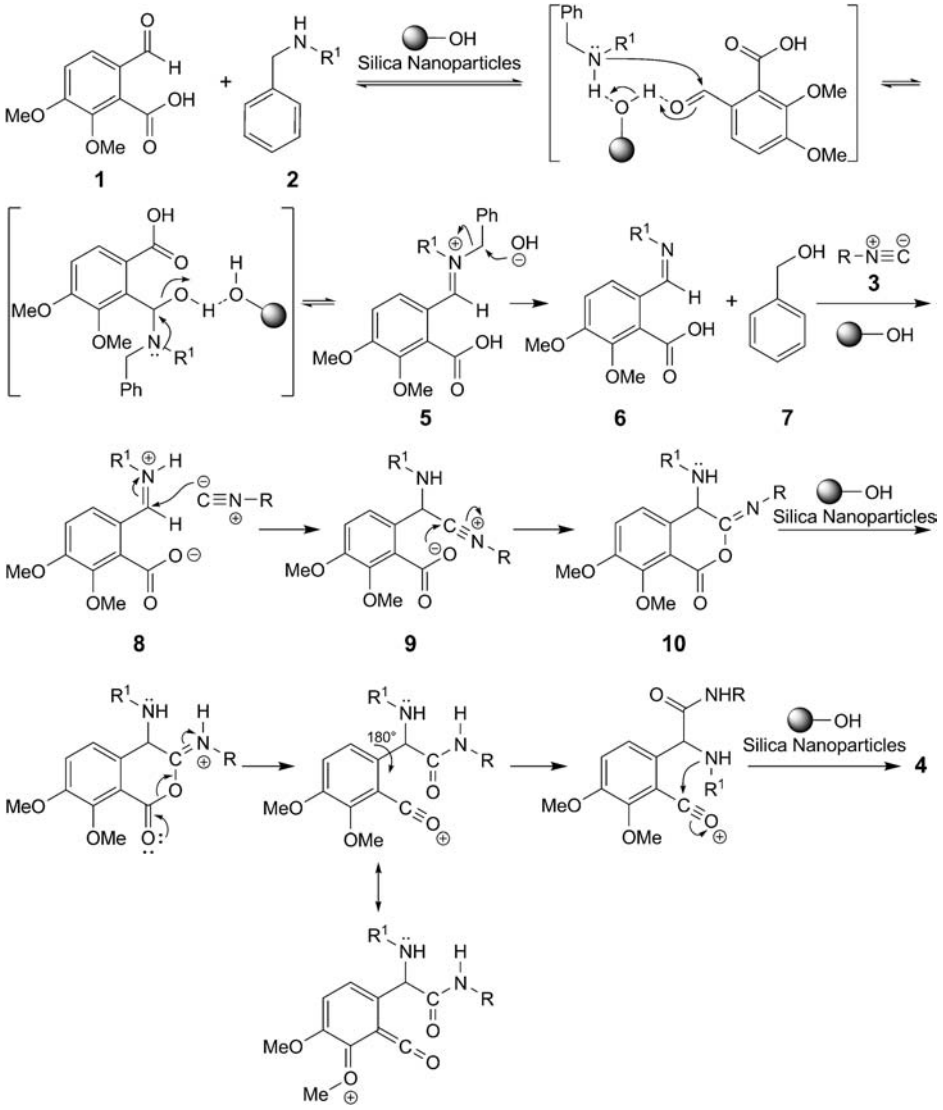


Fig. 1. *SEM of the synthesized silica nanoparticles*

4.95, $^2J_{AM} = 14.8$), an amine H-atom (δ(H) 5.35), which was exchangeable with D_2O, two *doublet*s for the isoindolone H-atoms (δ(H) 7.08 and 7.23, $^3J = 8.4$), and a *multiplet* for the aromatic H-atoms (δ(H) 7.25–7.34). The ^{1}H-decoupled ^{13}C-NMR spectrum of **4a** showed 17 distinct resonances, the partial assignment of these resonances is given in the *Exper. Part*. The ^{1}H- and ^{13}C-NMR spectra of **4b**–**4f** were similar to those of **4a**.

Although we have not established the mechanism of the reaction experimentally, a plausible reaction sequence that accounts for the formation of **4** is shown in *Scheme 2*.

Scheme 2. *Proposed Mechanism for the Preparation of Isoindolinone Derivatives* **4** *in the Presence of Silica Nanoparticles*



Thus, condensation of 6-formyl-2,3-dimethoxybenzoic acid (**1**) and secondary amines (dibenzyl- and benzyl(isopropyl)amine) **2** would give the iminium ion intermediate **5**, and this intermediate would give imine **6** and benzyl alcohol (**7**; identified by TLC). Imine **6** would react with the alkyl isocyanide **3** to afford intermediate **8**. This intermediate would cyclize to lactone **10**. And rearrangement of lactone **10** would lead to the isoindolone derivatives **4**.

It may be speculated that the polar amphoteric surface (OH groups of the silica NPs) facilitates the interaction of adsorbed weak acidic and basic components due to stabilization of the corresponding transition states and intermediates by H-bonding. This interaction with the neighboring silanol groups is shown in *Scheme 2* for the first reaction step. Participation of two proximate silanol groups (one as a H-bond donor and the other as a H-bond acceptor) also seems to be plausible.

The recycling potential of silica NPs catalyst was studied by coupling *tert*-butyl isocyanide, **1**, and dibenzylamine in five consecutive cycles. The silica NPs could be recycled and reused by separating it from the mixture through centrifugation, and frequent washing with EtOH and then drying under vacuum to remove the residual solvent. The results show that the yield of product **4a** was only slightly reduced after five runs (*Fig. 2*).

Conclusions. – We have developed an efficient route for the one-pot synthesis of isoindolinone derivatives **4** from simple and readily available alkyl isocyanides **3**, secondary amines (dibenzyl- or benzyl(isopropyl)amine) **2**, and 6-formyl-2,3-dimethoxybenzoic acid (**1**) in the presence of silica NPs (*Scheme 1* and *Table 1*). The ease of

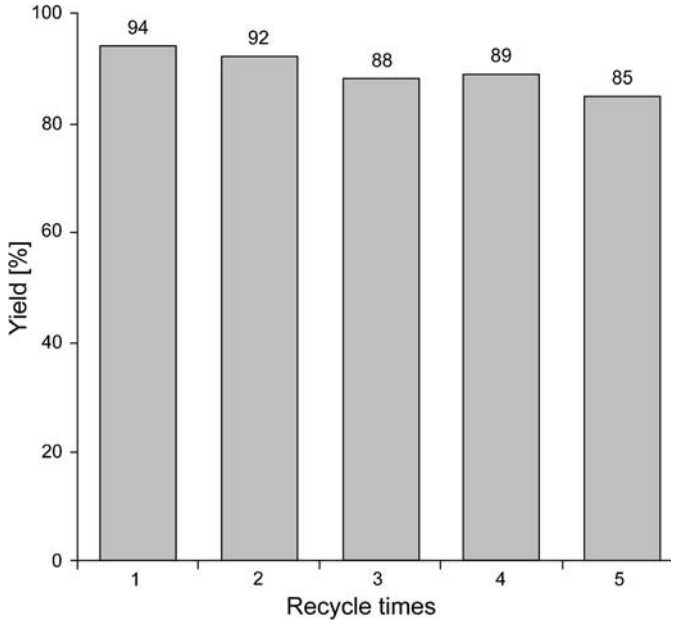


Fig. 2. *Development of the yield after several recycling cycles of the catalyst*

work-up and the high yields of the products make this procedure a useful addition to the library of modern synthetic methods. Furthermore, this solid-state reaction (*i.e.*, solvent-free reaction) has many advantages: reduced pollution, low costs, and simplicity in process and handling. These factors are especially important for industrial synthesis.

Experimental Part

General. Freshly distilled solvents were used, and anh. solvents were dried according to *Perrin* and *Armarego* [14]. IR Spectra (KBr): *Jasco 6300 FT-IR* spectrometer. ^{1}H- and ^{13}C-NMR spectra ($CDCl_3$): *BRUKER DRX-250 AVANCE* spectrometer at 250.0 and 62.5 MHz, resp. Elemental analyses: *Heraeus CHN-O-Rapid* analyzer. The samples were characterized with a scanning electron microscope (SEM) (*Philips XL 30*) with gold coating.

Preparation of Silica Nanoparticles from Organic Laboratory Waste of Silica Gel HF_{254}. Silica gel *HF_{254}* residues (5 g) were heated at 500° for 1 h. The sample was heated at reflux in 2M HCl for 24 h. The mixture was filtered, and the residue was washed with dist. H_2O for several times, until the filtrate was free from acid. The acid-leached silica was dried in an oven at 100° for 1 h and then heated in a furnace at 700° for 2 h. The morphology and grain size of the silica NPs was investigated by SEM (*Fig. 1*).

General Procedure for the Synthesis of Isoindolinones **4**. Silica nanoparticles (0.2 g) were added to a mixture of *6-formyl-2,3-dimethoxybenzoic acid* (**1**; 1 mmol), secondary amine (dibenzyl- or benzyl(isopropyl)amine) (**2**; 1 mmol), and isocyanide **3** (1 mmol) at r.t., followed by 7 h of stirring. After completion of the reaction, flash column chromatography (petroleum ether/AcOEt 5:2) of the residue gave **4**.

2-Benzyl-N-*(*tert-*butyl)-2,3-dihydro-4,5-dimethoxy-3-oxo-1*H-*isoindole-1-carboxamide* (**4a**). Colorless oil. IR: 3327, 2971, 1698, 1675, 1544, 1494, 1270. ^{1}H-NMR: 1.13 (*s*, Me_3C); 3.89, 4.12 (2*s*, 2 MeO); 4.46, 4.95 (*AM*, $^2J_{AM} = 14.8$, PhCH_2); 4.63 (*s*, CH); 5.35 (*s*, NH); 7.08, 7.23 (2*d*, $^3J = 8.4$, 2 CH of isoindolone); 7.25–7.34 (*m*, 5 arom. H). ^{13}C-NMR: 28.3 (Me_3C); 46.5 (PhCH_2); 51.4 (Me_3C); 56.6, 62.5 (2 MeO); 64.7 (CH); 117.1, 117.7 (2 CH of isoindolone); 122.6, 134.5, 148.4, 153.1 (4 C of isoindolone), 128.0, 128.7, 129.0 (5 CH of Ph), 136.8 (C of Ph), 166.9 (2 C=O of amides). Anal. calc. for $C_{22}H_{26}N_2O_4$: C 69.09, H 6.85, N 7.32; found: C 69.01, H 6.81, N 7.37.

2-Benzyl-N-*cyclohexyl-2,3-dihydro-4,5-dimethoxy-3-oxo-1*H-*isoindole-1-carboxamide* (**4b**). Colorless oil. IR: 3292, 3084, 2976, 1695, 1677, 1490, 1268. ^{1}H-NMR: 0.79–1.79 (2*m*, 5 CH_2 of cyclohexyl); 3.57–3.69 (*m*, CH of cyclohexyl); 3.86, 4.06 (2*s*, 2 MeO); 4.25, 5.14 (*AM*, $^2J_{AM} = 14.8$, PhCH_2); 4.70 (*s*, CH); 5.74 (*d*, $^3J = 8.0$, NH); 7.05, 7.21 (2*d*, $^3J = 8.2$, 2 CH of isoindolone); 7.23–7.45 (*m*, 5 arom. H). ^{13}C-NMR: 24.8, 24.8 (2 $CH_2(\beta)$ of cyclohexyl); 25.3 ($CH_2(\gamma)$ of cyclohexyl); 32.5, 32.7 (2 $CH_2(\alpha)$ of cyclohexyl); 46.0 (PhCH_2); 48.6 (CH of cyclohexyl); 56.6, 62.4 (2 MeO); 63.4 (CH); 117.0, 117.8 (2 CH of isoindolone); 122.6, 134.2, 147.1, 153.1 (4 C of isoindolone); 128.0, 128.6, 129.0 (5 CH of Ph); 136.4 (C of Ph); 166.9, 168.0 (2 C=O of amides). Anal. calc. for $C_{24}H_{28}N_2O_4$: C 70.57, H 6.91, N 6.86; found: C 70.49, H 6.95, N 6.89.

2-Benzyl-2,3-dihydro-4,5-dimethoxy-3-oxo-N-*(1,1,3,3-tetramethylbutyl)-1*H-*isoindole-1-carboxamide* (**4c**). Colorless oil. IR: 3369, 3030, 2946, 1699, 1674, 1461, 1253, 1223. ^{1}H-NMR: 0.77 (*s*, Me_3C); 1.16, 1.27 (2*s*, Me_2CNH); 1.59 (*s*, CH_2CMe_3); 3.89, 4.10 (2*s*, 2 MeO); 4.39, 5.04 (*AM*, $^2J_{AM} = 14.5$, PhCH_2); 4.64 (*s*, CH); 5.44 (*s*, NH); 7.08, 7.25 (2*d*, $^3J = 8.2$, 2 CH of isoindolone); 7.26–7.42 (*m*, 5 arom. H). ^{13}C-NMR: 28.0, 28.7 (Me_2CCH_2); 31.2 (Me_3C); 31.3 (Me_3C); 46.4 (PhCH_2); 52.0 (Me_3CCH_2); 55.5 (Me_2CCH_2); 56.7, 62.4 (2 MeO); 64.7 (CH); 117.1, 118.0 (2 CH of isoindolone); 122.3, 134.3, 148.5, 152.9 (4 C of isoindolone); 128.0, 128.7, 129.0 (5 CH of Ph); 136.6 (C of Ph); 168.3, 173.4 (2 C=O of amides). Anal. calc. for $C_{26}H_{34}N_2O_4$: C 71.21, H 7.81, N 6.39; found: C 71.27, H 7.77, N 6.33.

N-*(*tert-*Butyl)-2,3-dihydro-4,5-dimethoxy-2-(1-methylethyl)-3-oxo-1*H-*isoindole-1-carboxamide* (**4d**). Colorless oil. IR: 3382, 2973, 2933, 1692, 1652, 1540, 1457, 1232. ^{1}H-NMR: 1.22 (*s*, Me_3C); 1.28, 1.34 (*m*, 2 Me_2CH); 3.86, 4.05 (2*s*, 2 MeO); 4.37 (*m*, Me_2CH); 4.77 (*s*, CH); 5.27 (*s*, NH); 7.05, 7.23 (2*d*, $^3J =$ 8.0, 2 CH of isoindolone). ^{13}C-NMR: 20.4, 20.6 (Me_2CH); 28.3 (Me_3C); 45.9 (Me_2CH); 51.4 (Me_3C); 56.6, 62.3 (2 MeO); 63.0 (CH); 117.0, 117.4 (2 CH of isoindolone); 123.3, 135.0, 146.8, 153.0 (4 C of

isoindolone); 168.5 (2 C=O of amides). Anal. calc. for $C_{18}H_{26}N_2O_4$: C 64.65, H 7.84, N 8.38; found: C 64.59, H 7.81, N 8.34.

N-*Cyclohexyl-2,3-dihydro-4,5-dimethoxy-2-(1-methylethyl)-3-oxo-1*H-*isoindole-1-carboxamide* (**4e**). Colorless oil. IR: 3365, 2934, 1855, 1695, 1663, 1451, 1269. ^{1}H-NMR: 1.00–1.60 (2*m*, 5 CH_2 of cyclohexyl); 1.28, 1.34 (*m*, 2 Me_2CH); 3.60–3.68 (*m*, CH of cyclohexyl); 3.87, 4.07 (2*s*, 2 MeO); 4.39 (*sept.*, $^3J = 6.8$, Me_2CH); 4.89 (*s*, CH); 5.63 (*d*, $^3J = 7.8$, NH); 7.06, 7.22 (2*d*, $^3J = 8.2$, 2 CH of isoindolone). ^{13}C-NMR: 20.4 (Me_2CH); 24.7, 24.8 (2 $CH_2(\beta)$ of cyclohexyl); 25.3 ($CH_2(\gamma)$ of cyclohexyl); 32.6 (2 $CH_2(\alpha)$ of cyclohexyl); 45.9 (Me_2CH); 48.5 (CH of cyclohexyl); 56.6, 62.2 (2 MeO); 62.4 (CH); 117.0, 117.6 (2 CH of isoindolone); 123.3, 134.9, 146.8, 153.0 (4 C of isoindolone); 168.6, 168.7 (2 C=O). Anal. calc. for $C_{20}H_{28}N_2O_4$: C 66.64, H 7.83, N 7.77; found: C 66.57, H 7.86, N 7.73.

*2,3-Dihydro-4,5-dimethoxy-2-(1-methylethyl)-3-oxo-*N-*(1,1,3,3-tetramethylbutyl)-1*H-*isoindole-1-carboxamide* (**4f**). Colorless oil. IR: 3324, 2955, 1677, 1660, 1480, 1269. ^{1}H-NMR: 0.70 (*s*, Me_3C); 1.21, 1.35 (*m*, 2 Me_2CH); 1.35 (*s*, Me_2C); 1.68 (*s*, Me_3CCH_2); 3.85, 4.02 (2*s*, 2 MeO); 4.32 (*sept.*, $^3J = 6.8$, Me_2CH); 4.75 (*s*, CH); 5.59 (*s*, NH); 7.06, 7.22 (2*d*, $^3J = 8.2$, 2 CH of isoindolone). ^{13}C-NMR: 20.45, 20.50 (Me_2CH); 27.8, 28.9 (Me_2CCH_2); 31.14 (Me_3C); 31.3 (Me_3C); 46.0 (Me_2CH); 52.5 (Me_3CCH_2); 55.5 (Me_2CCH_2); 56.7, 62.3 (2 MeO); 63.2 (CH); 117.0, 117.8 (2 CH of isoindolone); 123.4, 134.8, 146.9, 152.9 (4 C of isoindolone); 167.8, 168.5 (2 C=O). Anal. calc. for $C_{22}H_{34}N_2O_4$: C 67.66, H 8.78, N 7.17; found: C 67.54, H 8.73, N 7.20.

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