Reaction of Primary Alkylamines, Heterocumulenes, and Isatoic Anhydride, Catalyzed by Magnetic Fe_3O_4 Nanoparticles in H_2O

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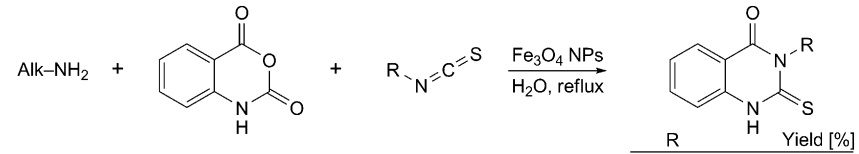
An efficient protocol for the one-pot reaction of isatoic anhydride (=1,2-dihydro-4*H*-3,1-benzoxazine-2,4-dione), primary alkylamines, and heterocumulenes (isothiocyanates and isocyanates) in H_2O catalyzed by magnetically recoverable Fe_3O_4 nanoparticles is described.

Introduction. – The development of efficient and environmentally benign chemical processes using recyclable catalysts is one of the major tasks in organic synthesis [1]. Magnetic nanoparticles are of interest because of their high catalytic activities. Among them, Fe_3O_4 is the most important one [2–7]. Magnetically driven separation makes the recovery of catalysts in a liquid-phase reaction much easier than filtration or centrifugation [8].

As part of our current studies on the development of new routes in organic synthesis [9–12], we describe the use of Fe_3O_4 nanoparticles (NPs) as *Lewis* acid catalyst, for the synthesis of 2,3-dihydro-2-thioxoquinazolin-4(1*H*)-ones *via* a one-pot, three-component reaction of isatoic anhydride (=1,2-dihydro-4*H*-3,1-benzoxazine-2,4-dione) with primary alkylamines and isothiocyanates in H_2O (*Scheme 1*).

Scheme 1



Results and Discussion. – The three-component reaction of $MeNH_2$, isatoic anhydride, and phenylisothiocyanate as a simple model reaction was investigated to optimize the reaction conditions (*Table*). Different amounts of the catalyst were used. As indicated in the *Table*, the best result was obtained with 10 mol-% of Fe_3O_4 NPs, and

the desired product **4b** was obtained in 92% yield. Using a lower amount of catalyst resulted in lower yields, while a higher amount of catalyst and longer reaction times did not affect the yields (*Table*).

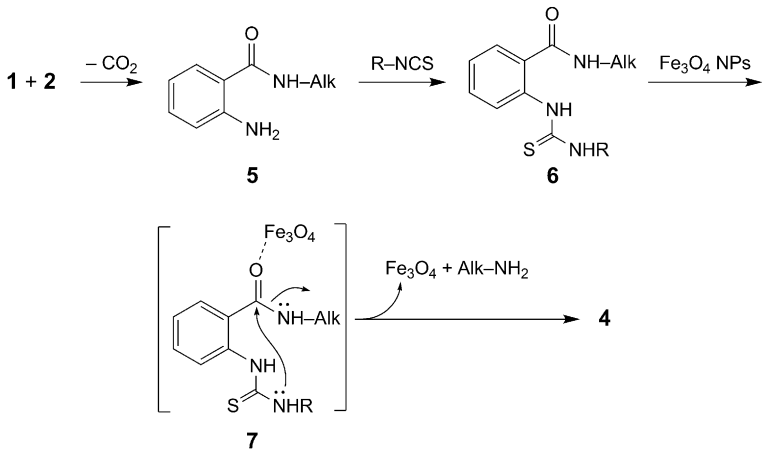
Table. *Model Reaction of $MeNH_2$, Isatoic Anhydride, and Phenyl Isothiocyanate under Various Conditions*

Catalyst (mol-%)	Time [h]	Yield of **4b** [%]
No catalyst	24	trace
ZnO (20)	9	45
Bulk Fe_3O_4 (20)	3	68
Fe_3O_4 NPs (5)	1	87
Fe_3O_4 NPs (10)	1	92
Fe_3O_4 NPs (15)	1	92

After optimization of the reaction conditions, a variety of isothiocyanates and amines were employed under similar reaction conditions to evaluate the scope of the reaction. The results are shown in *Scheme 1*. All reactions proceeded smoothly, and no undesirable side reactions were observed. The isothiocyanates carrying either electron-withdrawing or electron-releasing groups on the aromatic ring were converted to the corresponding 2,3-dihydro-2-thioxoquinazolin-4(1*H*)-one derivatives **4a**–**4f** in good yields.

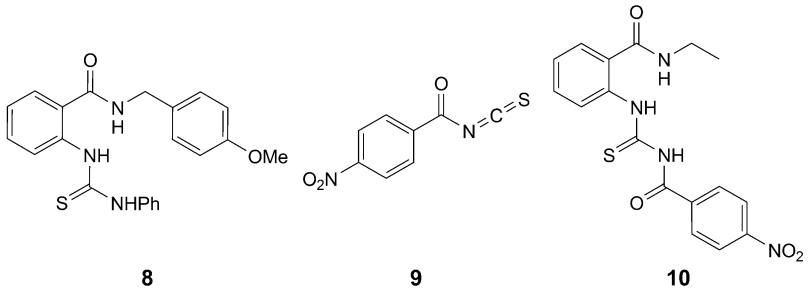
A plausible mechanism for this reaction is proposed in *Scheme 2*. It is conceivable that the Fe_3O_4 NPs are coordinated to the O-atom of the CO groups in different stages of the reaction activating them for the nucleophilic attack of the N-atom. The high surface area-to-volume ratio of Fe_3O_4 NPs is mainly responsible for their catalytic properties [13].

Scheme 2



When the reaction was carried out with bulky alkylamines, the product did not cyclize. For example, the reaction of 4-methoxybenzylamine, isatoic anhydride, and phenylisothiocyanate led to *N*-(4-methoxybenzyl)-2-[(phenylcarbamothioyl)amino]-

benzamide (**8**; *Fig. 1*). The reaction of ethylamine, isatoic anhydride, and 4-nitrobenzoyl isothiocyanate (**9**) led to uncyclized product **10** (*Fig. 1*).

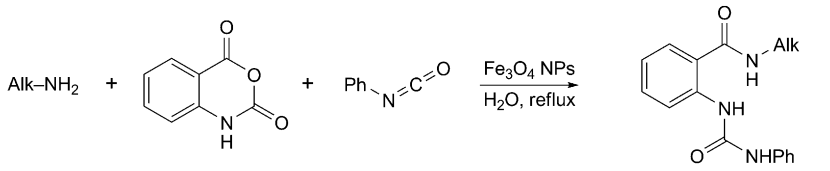


8 **9** **10**

Fig. 1. *Structure of Compounds* **8**–**10**

The reaction of primary alkylamines, isatoic anhydride, and phenylisocyanate led to phenylurea derivatives **12a**–**12c** (*Scheme 3*).

Scheme 3



	R	Yield [%]
12a	Me	93
12b	Et	95
12c	4-MeO–Bn	94

1a Alk = Me
1b Alk = Et
1c Alk = 4-MeO–Bn

2 **11**

Fig. 2 shows the XRD pattern of the Fe_3O_4 NPs. All of the diffraction peaks are in agreement with the JCPDS file of Fe_3O_4 (JCPDS No. 19-0629). The morphology and grain size of the Fe_3O_4 NPs were investigated by SEM (*Fig. 3*). They have spherical morphology including a narrow distribution of sizes, from 32 to 68 nm.

In conclusion, we have developed an efficient method to use Fe_3O_4 NPs as a *Lewis* acid catalyst for the synthesis of 2,3-dihydro-2-thioxoquinazolin-4(1*H*)-ones by a one-pot, three-component condensation of isatoic anhydride with amines and isothiocyanates in H_2O. The Fe_3O_4 NPs would act as a catalyst to activate the substrate molecules. Moreover, the catalyst can be recovered conveniently and reused for at least nine reaction cycles without considerable loss of activity.

Experimental Part

General. All chemicals were obtained commercially and used without further purification. M.p.: *Electrothermal-9100* apparatus. IR Spectra: *Shimadzu-IR-460* spectrometer; $\tilde{\nu}$ in cm^{-1}. ^1H- and ^{13}C-NMR Spectra: *Bruker DRX-500 Avance* instrument at 500.1 and 125.7 MHz, resp., in $CDCl_3$ with TMS as internal standard; δ in ppm, J in Hz. MS: *Finnigan-MAT-8430EI-MS* mass spectrometer; at 70 eV; in m/z (rel. %). Elemental analyses: *Vario EL III CHNOS* elemental analyzer. Scanning electron microscopy (SEM) images: *Stereo Scan XL30 Philip* instrument.

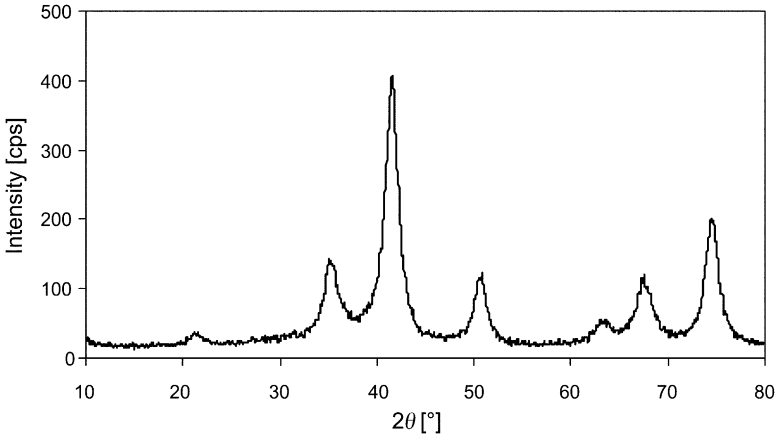


Fig. 2. *XRD Pattern of synthesized Fe_3O_4 nanoparticles*

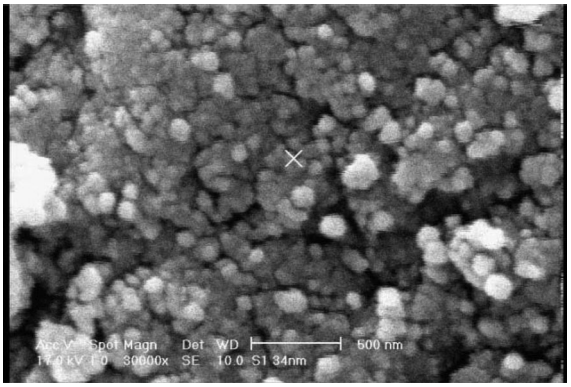


Fig. 3. *SEM Image of the synthesized Fe_3O_4 nanoparticles*

General Procedure. Isatoic anhydride (=1,2-dihydro-4*H*-3,1-benzoxazine-2,4-dione; **2**; 1 mmol), amine **1** (1 mmol), isothiocyanate **3** or phenyl isocyanate **11** (1 mmol), and Fe_3O_4 (0.1 mmol) were mixed in H_2O (5 ml). The mixture was stirred under reflux in an air atmosphere for 1 h. Then, AcOEt (5 ml) was added. The Fe_3O_4 nanoparticles were removed with a magnetic stirring bar. The org. and aq. layers were separated. The org. phase was dried over anh. Na_2SO_4, and the solvent was evaporated under vacuum. Pure products were obtained by recrystallization from EtOH.

*3-Ethyl-2,3-dihydro-2-thioxoquinazolin-4(1*H*)-one* (**4a**). Yield: 0.19 g (95%). White powder. M.p. 246–248°. IR (KBr): 3232, 2965, 1640, 1522, 1339, 1218. ^{1}H-NMR: 1.28 (*t*, *J* = 7.0, Me); 4.55 (*q*, *J* = 7.0, CH_2); 7.35 (*dd*, *J* = 7.9, 1 arom. H); 7.45 (*d*, *J* = 8.1, 1 arom. H); 7.74 (*dd*, *J* = 8.2, 1 arom. H); 8.04 (*d*, *J* = 7.9, 1 arom. H); 11.57 (*s*, NH). ^{13}C-NMR: 12.2 (Me); 42.1 (CH_2); 115.9 (CH); 125.1 (CH); 128.4 (CH); 136.1 (CH); 139.5 (C); 140.5 (C); 160.1 (C=O); 177.1 (C=S). EI-MS: 206 (100, M^+), 166 (27), 145 (13), 119 (25), 92 (16), 77(19). Anal. calc. for $C_{10}H_{10}N_2OS$ (206.05): C 58.23, H 4.89, N 13.58, S 15.55; found: C 57.87, H 5.12, N 13.42, S 15.04.

*2,3-Dihydro-3-phenyl-2-thioxoquinazolin-4(1*H*)-one* (**4b**). Yield: 0.23 g (92%). White powder. M.p. 318–320°. IR (KBr): 3232, 3040, 2935, 1658, 1519, 1405, 1204. ^{1}H-NMR: 7.26 (*d*, *J* = 7.4, 2 arom. H); 7.33

(*dd*, *J* = 7.8, 1 arom. H); 7.39 (*dd*, *J* = 7.3, 1 arom. H); 7.43 – 7.48 (*m*, 3 arom. H); 7.76 (*dd*, *J* = 7.2, 1 arom. H); 7.94 (*d*, *J* = 7.8, 1 arom. H); 13.02 (*s*, NH). ^{13}C-NMR: 115.6 (CH); 116.1 (C); 124.2 (CH); 127.3 (CH); 128.1 (CH); 128.8 (2 CH); 128.9 (2 CH); 135.5 (CH); 139.2 (C); 139.5 (C); 159.7 (C=O); 176.1 (C=S). EI-MS: 254 (100, M^+), 221 (8), 166 (12), 145 (13), 119 (25), 92 (21), 77 (19). Anal. calc. for $C_{14}H_{10}N_2OS$ (254.05): C 66.12, H 3.96, N 11.02, S 12.61; found: C 66.10, H 3.54, N 10.35, S 11.89.

*3-(4-Chlorophenyl)-2,3-dihydro-2-thioxoquinazolin-4(1*H*)-one* (**4c**). Yield: 0.25 g (89%). White powder. M.p. 338 – 340°. IR (KBr) : 3244, 3039, 2939, 1667, 1520, 1404, 1202. ^{1}H-NMR: 7.29 – 7.33 (*m*, 3 arom. H); 7.43 (*d*, *J* = 8.1, 1 arom. H); 7.53 (*d*, *J* = 8.1, 2 arom. H); 7.76 (*dd*, *J* = 7.3, 1 arom. H); 7.94 (*d*, *J* = 7.6, 1 arom. H); 13.07 (*s*, NH). ^{13}C-NMR: 115.7 (CH); 116.1 (C); 124.3 (CH); 127.3 (CH); 128.9 (2 CH); 130.7 (2 CH); 132.6 (C); 135.6 (CH); 138.2 (C); 139.5 (C); 159.7 (C=O); 175.8 (C=S). EI-MS: 290 (5, M^+), 288 (63, M^+), 253 (34), 152 (26), 92 (100), 77 (41). Anal. calc. for $C_{14}H_9ClN_2OS$ (288.01): C 58.23, H 3.14, N 9.70, S 11.10; found: C 57.06, H 3.44, N 9.45, S 11.28.

*2,3-Dihydro-3-(4-methylphenyl)-2-thioxoquinazolin-4(1*H*)-one* (**4d**). Yield: 0.34 g (94%). White powder. M.p. 318 – 320°. IR (KBr): 3233, 3033, 2928, 2350, 1657, 1519, 1403, 1201. ^{1}H-NMR: 2.35 (*s*, Me); 7.12 (*d*, *J* = 7.8, 2 arom. H); 7.25 (*d*, *J* = 7.8, 2 arom. H); 7.32 (*dd*, *J* = 7.6, 1 arom. H); 7.43 (*d*, *J* = 8.2, 1 arom. H); 7.76 (*dd*, *J* = 7.6, 1 arom. H); 7.93 (*d*, *J* = 7.8, 1 arom. H); 13.01 (*s*, NH). ^{13}C-NMR: 20.7 (Me); 115.6 (CH); 116.1 (C); 124.2 (CH); 127.3 (CH); 128.6 (2 CH); 129.3 (2 CH); 135.5 (CH); 136.6 (C); 137.3 (C); 139.5 (C); 159.7 (C=O); 176.1 (C=S). EI-MS: 268 (13, M^+), 253 (48), 133 (24), 92 (100), 77 (35). Anal. calc. for $C_{15}H_{12}N_2OS$ (268.07): C 67.14, H 4.51, N 10.44, S 11.95; found: C 66.18, H 4.35, N 10.15, S 11.73.

*2,3-Dihydro-3-(4-nitrophenyl)-2-thioxoquinazolin-4(1*H*)-one* (**4e**). Yield: 0.27 g (90%). Yellow powder. M.p. 330 – 332°. IR (KBr): 3239, 3112, 2930, 2349, 1661, 1523, 1412, 1344. ^{1}H-NMR: 7.35 (*dd*, *J* = 7.6, 1 arom. H); 7.45 (*d*, *J* = 8.2, 1 arom. H); 7.65 (*d*, *J* = 8.6, 2 arom. H); 7.79 (*dd*, *J* = 7.6, 1 arom. H); 7.96 (*d*, *J* = 7.8, 1 arom. H); 8.34 (*d*, *J* = 8.6, 2 arom. H); 13.16 (*s*, NH). ^{13}C-NMR: 115.8 (CH); 116.2 (C); 124.2 (2 CH); 124.4 (CH); 127.3 (CH); 130.9 (2 CH); 135.7 (CH); 139.6 (C); 145.2 (C); 147.1 (C); 159.6 (C=O); 175.3 (C=S). EI-MS: 299 (17, M^+), 253 (54), 164 (45), 92 (100), 77 (28). Anal. calc. for $C_{14}H_9N_3O_3S$ (299.04): C 56.18, H 3.03, N 14.04, S 10.71; found: C 55.32, H 2.94, N 13.75, S 11.43.

*3-(2,4-Dichlorophenyl)-2,3-dihydro-2-thioxoquinazolin-4(1*H*)-one* (**4f**). Yield: 0.29 g (92%). White powder. M.p. 254 – 256°. IR (KBr): 3243, 2936, 1659, 1511, 1398, 1202. ^{1}H-NMR: 7.40 (*dd*, *J* = 7.7, 1 arom. H); 7.50 – 7.59 (*m*, 3 arom. H); 7.68 (*s*, 1 arom. H); 7.82 (*dd*, *J* = 7.8, 1 arom. H); 8.07 (*d*, *J* = 7.8, 1 arom. H); 11.90 (*s*, NH). ^{13}C-NMR: 115.1 (CH); 115.5 (C); 124.1 (CH); 127.4 (CH); 127.7 (CH); 128.9 (CH); 131.9 (CH); 133.1 (C); 133.9 (C); 135.4 (CH); 135.6 (C); 139.3 (C); 158.5 (C=O); 175.4 (C=S). EI-MS: 321 (2, M^+), 287 (100), 178 (37), 119 (38), 92 (12). Anal. calc. for $C_{14}H_8Cl_2N_2OS$ (321.97): C 52.03, H 2.49, N 8.67, S 9.92; found: C 54.05, H 3.08, N 8.15, S 9.35.

N-*(4-Methoxybenzyl)-2-[(phenylcarbamothioyl)amino]benzamide* (**8**). Yield: 0.38 g (97%). White powder. M.p. 154 – 156°. IR (KBr): 3333, 3182, 3022, 1616, 1518, 1254. ^{1}H-NMR: 3.77 (*s*, MeO); 4.44 (*d*, *J* = 5.9, CH_2); 6.88 (*d*, *J* = 8.6, 2 arom. H); 7.13 (*dd*, *J* = 7.7, 1 arom. H); 7.23 (*dd*, *J* = 7.4, 1 arom. H); 7.27 (*d*, *J* = 8.6, 2 arom. H); 7.39 – 7.46 (*m*, 3 arom. H); 7.52 (*d*, *J* = 7.7, 2 arom. H); 7.67 (*d*, *J* = 7.8, 1 arom. H); 8.05 (*s*, NH); 8.54 (*d*, *J* = 7.8, 1 arom. H); 9.49 (*s*, NH); 10.99 (*s*, NH). ^{13}C-NMR: 43.5 (CH_2); 55.6 (MeO); 114.7 (CH); 124.4 (CH); 125.5 (2 CH); 126.1 (CH); 126.6 (CH); 128.2 (2 CH); 129.8 (2 CH); 130.1 (2 CH); 131.3 (CH); 131.9 (C); 136.4 (C); 139.5 (C); 140.7 (C); 160.1 (C); 169.1 (C=O); 181.1 (C=S). EI-MS: 391 (1, M^+), 298 (12), 272 (11), 253 (70), 135 (95), 121 (86), 93 (100), 77 (70). Anal. calc. for $C_{22}H_{21}N_3O_2S$ (391.14): C 67.50, H 5.41, N 10.73, S 8.19; found: C 66.71, H 5.73, N 9.95, S 7.62.

N-*Ethyl-2-{[(4-nitrobenzoyl)carbamothioyl]amino}benzamide* (**10**). Yield: 0.33 g (91%). Yellow powder. M.p. 202 – 204°. IR (KBr): 3439, 2929, 2349, 1639, 1524. ^{1}H-NMR: 1.23 (*t*, *J* = 7.3, Me); 3.46 – 3.51 (*m*, CH_2); 6.18 (*s*, NH); 7.32 (*dd*, *J* = 7.5, 1 arom. H); 7.50 – 7.54 (*m*, 2 arom. H); 8.12 (*d*, *J* = 8.6, 2 arom. H); 8.29 (*d*, *J* = 8.1, 1 arom. H); 8.36 (*d*, *J* = 8.6, 2 arom. H); 9.19 (*s*, NH); 13.11 (*s*, NH). ^{13}C-NMR: 14.7 (Me); 34.9 (CH_2); 124.1 (2 CH); 126.8 (CH); 126.9 (CH); 127.1 (CH); 129.1 (CH); 129.3 (C); 130.7 (2 CH); 136.4 (C); 137.3 (C); 150.6 (C); 163.6 (C=O); 167.2 (C=O); 178.3 (C=S). EI-MS: 372 (1, M^+), 166 (20), 150 (100), 120 (36), 104 (39), 92 (37). Anal. calc. for $C_{17}H_{16}N_4O_4S$ (372.09): C 54.83, H 4.33, N 15.04, S 8.61; found: C 55.12, H 4.78, N 14.61, S 8.05.

N-*Methyl-2-[(phenylcarbamoyl)amino]benzamide* (**12a**). 0.25 g (93%). Yield: White powder. M.p. 318 – 320°. IR (KBr): 3272, 3089, 1686, 1596, 1513, 1444, 1295, 1216. ^{1}H-NMR: 2.90 (*d*, *J* = 4.7, Me); 6.97

(*dd*, *J* = 7.6, 2 arom. H); 7.26 (*dd*, *J* = 7.8, 2 arom. H); 7.40 (*dd*, *J* = 8.4, 1 arom. H); 7.63–7.64 (*m*, 3 arom. H); 7.89 (*s*, NH); 8.48 (*d*, *J* = 8.4, 1 arom. H); 8.96 (*s*, NH); 10.68 (*s*, NH). ^{13}C-NMR: 26.6 (Me); 119.6 (2 CH); 120.7 (C); 121.2 (CH); 121.5 (CH); 122.8 (CH); 127.9 (CH); 129.4 (2 CH); 132.4 (CH); 141.2 (C); 141.9 (C); 153.3 (C=O); 170.2 (C=O). EI-MS: 269 (8, M^+), 177 (18), 150 (53), 120 (33), 93 (100). Anal. calc. for $C_{15}H_{15}N_3O_2$ (269.12): C 66.90, H 5.61, N 15.60; found: C 65.71, H 5.78, N 14.87.

N-*Ethyl-2-[(phenylcarbamoyl)amino]benzamide* (**12b**). Yield: 0.27 g (95%). White powder. M.p. 204–206°. IR (KBr): 3274, 3084, 2349, 1518, 1447, 1295, 1224. ^{1}H-NMR: 1.21 (*t*, *J* = 7.2, Me); 3.38–3.44 (*m*, CH_2); 6.95 (*dd*, *J* = 7.9, 2 arom. H); 7.26 (*dd*, *J* = 7.7, 2 arom. H); 7.41 (*dd*, *J* = 8.1, 1 arom. H); 7.62–7.65 (*m*, 3 arom. H); 7.92 (*s*, NH); 8.48 (*d*, *J* = 8.3, 1 arom. H); 8.96 (*s*, NH); 10.67 (*s*, NH). ^{13}C-NMR: 14.8 (Me); 35.1 (CH_2); 119.6 (2 CH); 120.9 (C); 121.2 (CH); 121.5 (CH); 122.8 (CH); 128.1 (CH); 129.3 (2 CH); 132.3 (CH); 141.2 (C); 142.1 (C); 153.3 (C=O); 169.6 (C=O). EI-MS: 283 (15, M^+), 191 (22), 164 (46), 120 (37), 93 (100). Anal. calc. for $C_{16}H_{17}N_3O_2$ (283.13): C 67.83, H 6.05, N 14.83; found: C 67.14, H 5.43, N 13.92.

N-*(4-Methoxybenzyl)-2-[(phenylcarbamoyl)amino]benzamide* (**12c**). Yield: 0.35 g (94%). White powder. M.p. 178–180°. IR (KBr): 3255, 3084, 2928, 1689, 1609, 1526, 1445, 1306, 1239. ^{1}H-NMR: 3.76 (*s*, MeO); 4.54 (*d*, *J* = 5.9, CH_2); 6.90 (*d*, *J* = 8.7, 2 arom. H); 6.99 (*dd*, *J* = 7.5, 2 arom. H); 7.26–7.32 (*m*, 4 arom. H); 7.43 (*dd*, *J* = 8.6, 1 arom. H); 7.64 (*d*, *J* = 7.7, 2 arom. H); 7.73 (*d*, *J* = 7.9, 1 arom. H); 8.36 (*s*, NH); 8.50 (*d*, *J* = 8.5, 1 arom. H); 9.01 (*s*, NH); 10.68 (*s*, NH). ^{13}C-NMR: 43.5 (CH_2); 55.6 (MeO); 114.8 (CH); 119.7 (2 CH); 120.8 (C); 121.5 (CH); 121.7 (CH); 123.1 (2 CH); 128.3 (CH); 129.5 (2 CH); 129.7 (2 CH); 132.1 (C); 132.7 (CH); 141.3 (C); 142.3 (C); 153.4 (C=O); 160.1 (C); 169.8 (C=O). EI-MS: 375 (1, M^+), 282 (22), 256 (25), 136 (79), 121 (100), 93 (70), 77 (23). Anal. calc. for $C_{22}H_{21}N_3O_3$ (375.16): C 70.38, H 5.64, N 11.19; found: C 69.10, H 5.12, N 10.34.

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