3,5,5-Trisubstituted Hydantoins from Activated (Benzyloxycarbonylamino)malonic Acids

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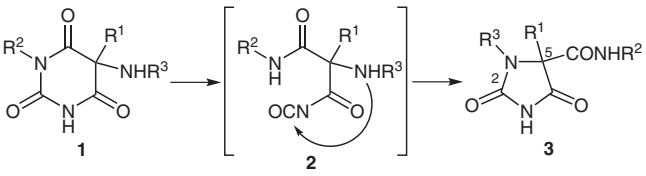
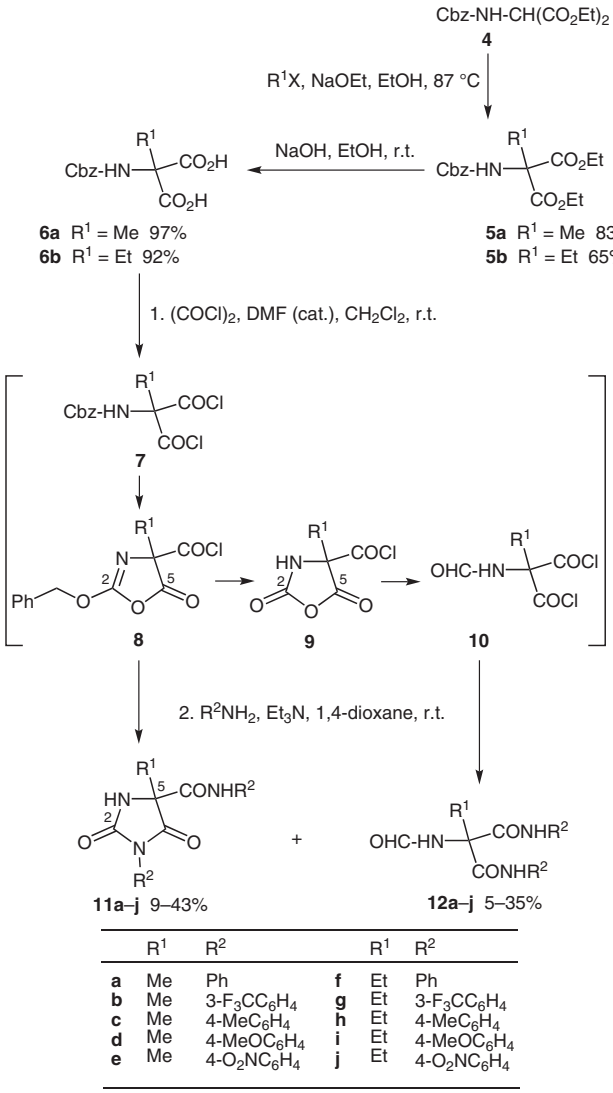
Abstract: Diethyl 2-alkyl-2-(benzyloxycarbonylamino)malonates were saponified, activated with oxalyl chloride, and treated with primary aromatic amines. This gave 3,5-disubstituted hydantoin-5-carboxamides. As second products, 2-alkyl-2-formamido-N^1,N^3-bis(aryl)malonamides were isolated. The formation of both types of products is expected to include a cyclization to 2-alkoxyoxazol-5(4*H*)-ones, acting as precursor for the hydantoins, or a further transformation to *N*-carboxy anhydrides, their chloride-promoted ring opening, and subsequent conversion to give the bis(aryl)malonamides.

Key words: hydantoins, malonic acids, oxazolones, nitrogen heterocycles, ring closure, ring opening

Hydantoins have been the subject of considerable interest in drug discovery because of their wide range of biological activities. With four possible points of diversity, this heterocyclic structure represents a significant molecular scaffold in combinatorial chemistry. Indeed, the reported bioactivities usually arise from the different residues attached to the heterocycle. Moreover, hydantoins are important building blocks for non-natural amino acids through chemical or enzymatic synthesis.[1] Previously, the aminobarbituric acid–hydantoin rearrangement has been reported as an attractive synthetic entry to polysubstituted 5-carbamoylhydantoins.[2] For example, 1,5-disubstituted 5-aminobarbituric acids **1**[2,3] undergo a base-catalyzed ring contraction to 5-carbamoylhydantoins **3** in which the substituent at the carbamoyl moiety originates from the substituent at the N1 nitrogen of the parent barbituric acid (Scheme 1). This elimination–addition process includes an E1cB mechanism and the recyclization of the intermediate **2** due to the nucleophilic attack of the amino group at the isocyanate moiety.[2,4] Besides the attention on 1,5,5-substituted representatives, such as **3**, synthetic efforts to acquire trisubstituted hydantoins have been focused on 1,3,5-substituted derivatives.[5] Herein, we report on a new synthetic entry to 3,5,5-trisubstituted hydantoins **11** (Scheme 2). As in the case of **3**, the N1–C5(CO)–CO portion of **11** originates from an aminomalonic acid precursor.



Scheme 1 Aminobarbituric acid–hydantoin rearrangement[2]



	R^1	R^2		R^1	R^2
a	Me	Ph	**f**	Et	Ph
b	Me	3-$F_3CC_6H_4$	**g**	Et	3-$F_3CC_6H_4$
c	Me	4-MeC_6H_4	**h**	Et	4-MeC_6H_4
d	Me	4-$MeOC_6H_4$	**i**	Et	4-$MeOC_6H_4$
e	Me	4-$O_2NC_6H_4$	**j**	Et	4-$O_2NC_6H_4$

Scheme 2 Synthesis of hydantoins **11** and malonic acid diamides **12**

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The preparation of hydantoins **11** is outlined in Scheme 2. Diethyl 2-aminomalonate was reacted with benzyl chloroformate to provide benzyloxycarbonyl-protected diethyl aminomalonate **4**.[6] Alkylation of **4** with methyl iodide or ethyl bromide afforded **5a** or **5b**, respectively. Malonic ester derivatives **5** were treated with aqueous ethanolic sodium hydroxide solution for four days at room temperature, acidified under cooling, extracted with ethyl acetate and evaporated at room temperature. Under the mild conditions of saponification, decarboxylation could be avoided.

Next, the reactions of malonic acids **6** with oxalyl chloride followed by instantaneous treatment of the activated intermediates with aromatic amines were carried out. The reaction with oxalyl chloride (4.6 equiv) was performed in dichloromethane in the presence of *N*,*N*-dimethylformamide under argon atmosphere. After evaporation of the volatiles, 1,4-dioxane, aniline or a monosubstituted aniline derivative (2 equiv), and triethylamine (2.4 equiv) were added. After a reaction time of 24 hours at room temperature, the products were purified by column chromatography and obtained after recrystallization in 9–43% yield. Products **11** were unambiguously identified as 5-carbamoylhydantoins on the basis of spectroscopic data. Their ^{13}C NMR spectra showed three distinct carbonyl signals at δ = 154–159 (C2), 164–166 (exocyclic CO), and 169–172 (C4), the first and the last being characteristic of the hydantoin scaffold. As expected, multiplets appeared for the diastereotopic methylene protons in the ^{1}H NMR spectra of 5-ethylhydantoins **11f–j**. The structure of the hydantoin **11f** was further confirmed by X-ray crystallography (Figure 1).

The following mechanism for the formation of 5-carbamoylhydantoins **11** is proposed (Scheme 2): Treatment of **6** with oxalyl chloride leads to a malonyl dichloride derivative **7**, which undergoes cyclocondensation to the 2-alkoxyoxazol-5(4*H*)-one **8**.[7] This intermediate reacts at the exocyclic acid chloride group to form the carboxamide moiety, and is furthermore attacked by the aromatic amine at either ring carbon C2 or C5. In the latter case, ring cleavage produces the second carboxamide group of the resulting 2-(benzyloxycarbonylamino)malonic acid diamide. This intermediate undergoes a subsequent ring closure to **11**.[8]

A second product was observed in each of the ten syntheses, and was isolated by column chromatography, recrystallized, and obtained in 5–35% yield. Its structure was assigned as the corresponding 2-formamidomalonic acid diamide **12** (Scheme 2).

Structural assignments of **12a–j** were confirmed by NMR data, which clearly indicated the equivalence of the two carboxamide portions. The formamido group produces two ^{1}H NMR signals at δ = 8.12–8.19 and 8.47–9.43, for the CH and NH resonances, respectively, as assigned by HSQC experiments. If observed at all, ^{3}J(HH) (HCONH) coupling occurred with coupling constants smaller than 2 Hz. This clearly indicates that the N-substituted formamides **12** are present as *Z*-isomers, because for *E*-isomers much larger coupling constants (^{3}J > 10 Hz) have been detected.[9–12] The *E*/*Z* ratio, as determined on the basis of ^{1}H NMR assignments, was reported for several N-monoalkylated formamides, including those with *tert*-alkyl groups. The proportion of the *Z*-isomer was generally higher (≥70%).[10,13] In the case of formanilides, the preference for the *Z*-isomer was less pronounced.[9,12] In contrast to the hydantoins **11**, the methylene protons of the achiral malonic acid diamides **12f–j** are not diastereotopic, and their signals appear as quartets.

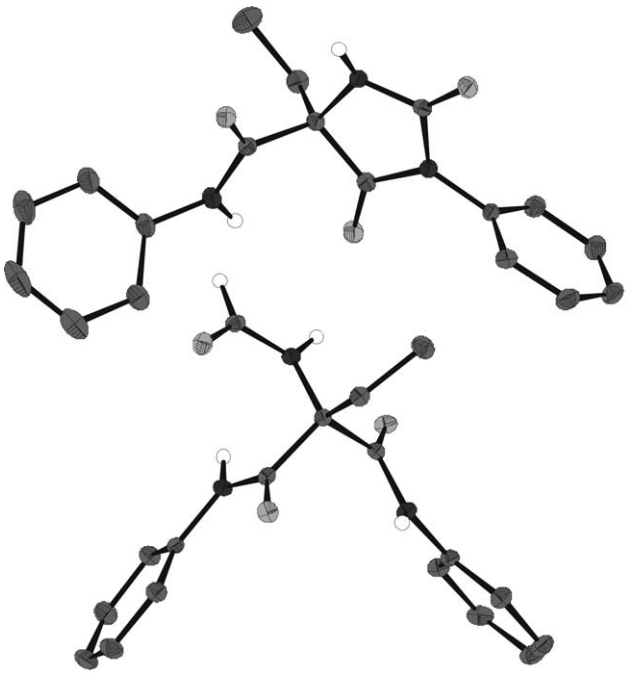


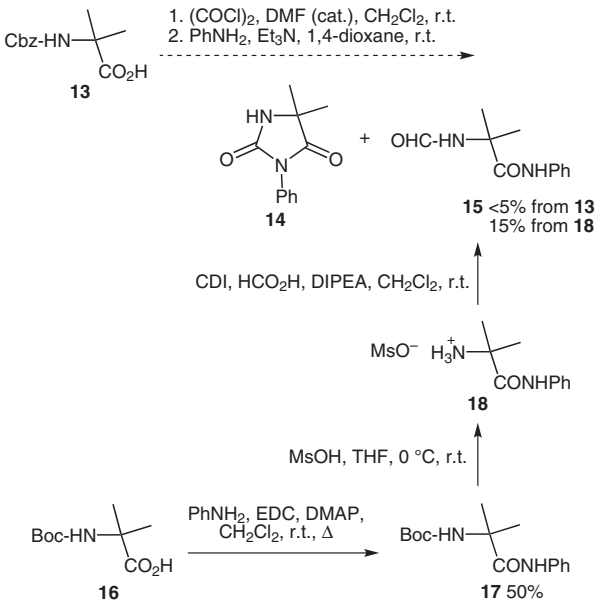
Figure 1 Molecular structure of 5-ethyl-3-phenyl-5-(phenylcarbamoyl)hydantoin (**11f**, top) and 2-ethyl-2-formamido-N^1,N^3-diphenylmalonamide (**12f**, bottom).[14] Hydrogen atoms of the phenyl and ethyl groups have been omitted for clarity. Carbon atoms are shown in gray, oxygen atoms in light gray, nitrogen atoms in dark gray, and hydrogen atoms in white.

A single-crystal X-ray analysis was carried out on the 2-formamidomalonic acid diamide **12f**, as an example, confirming its structure and the *Z*-configuration (Figure 1).

The unexpected formation of products **12** could not be fully rationalized. A possible mechanism is as follows (Scheme 2): In the course of the activation of the malonic acid **6a** or **6b**, the 2-alkoxyoxazol-5(4*H*)-one **8** is formed. The activation of the carboxyl groups by means of oxalyl chloride leads to the release of hydrogen chloride, carbon dioxide, and carbon monoxide.[15] Under these conditions, a chloride-promoted displacement of the benzyl group is operative and the *N*-carboxy anhydride (NCA) **9** is generated.[16] A nucleophilic attack of chloride occurs at the electrophilic C5 carbon of NCA **9**,[17,18] resulting in the reopening of the cyclic anhydride and decarboxylation. The thus generated amino group is formylated, probably by carbon monoxide or due to the action of *N*,*N*-dimethylformamide, activated by oxalyl chloride,[19] to produce **10**. When malonyl dichloride **10** is then exposed to the aro-

matic amine, it can readily react with the amine to form the corresponding 2-formamidomalonic acid diamide **12**.

Next, we addressed the question of whether the hydantoin formation and the formylation reaction would also occur with a benzyloxycarbonyl-protected monocarboxylic acid (Scheme 3). In the 2-aminoisobutyric acid derivative **13**, one carboxyl group of **6a** has been replaced by methyl.



Scheme 3 Synthesis of hydantoin **14** and anilide **15**

Compound **13** was subjected to the treatment with oxalyl chloride, *N*,*N*-dimethylformamide, and aniline (Scheme 3). The reaction mixture was analyzed with respect to the formation of the envisaged products **14** and **15**. Hydantoin **14** and anilide **15** were independently synthesized as follows. Compound **14** was prepared from 2-aminoisobutyric acid and phenyl isocyanate,[20] and **15** was obtained by a route starting from *tert*-butoxycarbonyl-protected 2-aminoisobutyric acid **16**. The N-formylation to **15** was achieved with in situ generated *N*-formylimidazole.[21] For compound **15**, the *Z*-configuration of the formamido group was again ascertained. With authentic samples of **14** and **15** in hand, their presence in the product mixture formed in the reaction of **13** could be verified. After preparative chromatography, the N-formylated product **15** was found in a corresponding fraction and further purified by recrystallization. Compound **15** was at least produced in minor quantities, but the hydantoin **14** could not be identified in the various fractions. The diminished formation of products **14** and **15**, in comparison with **11** and **12** (Scheme 2), may be because of entropic reasons: intermediate **7** provides two electrophilic sites for the ring closure, whereas the acid chloride derived from **13** only one.

In summary, we have developed a synthetic entry to the new class of 3,5-disubstituted hydantoin-5-carboxamides, thus extending the availability of these promising heterocyclic compounds. Moreover, we have explored an unexpected reaction behavior of aminomalonic acid derivatives when activated with oxalyl chloride. Using the example of 2-(benzyloxycarbonylamino)isobutyric acid, the scope of the reaction was found to be rather narrow, as the monocarboxylic acid derivative did not produce a corresponding hydantoin.

TLC was carried out on Merck aluminum sheets, silica gel 60 F_{254}. Preparative column chromatography was performed on Acros Organics silica gel 60A (0.060–0.200 mm). Melting points were determined on a Büchi 510 oil bath apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were acquired on a Bruker Avance DRX 500 spectrometer operating at 500 MHz for ^{1}H and 125 MHz for ^{13}C. Chemical shifts δ are cited in ppm relative to the signal center by using the solvent peaks of DMSO-d_6 (δ =2.49/39.7) as reference. HRMS (ESI) spectra were recorded on a micrOTOF-Q (Bruker Daltonics) spectrometer. Elemental analyses were carried out with a Vario EL apparatus.

Diethyl 2-(Benzyloxycarbonylamino)malonate (4)

Diethyl 2-aminomalonate hydrochloride (10.6 g, 50 mmol) and Na_2CO_3 (6.36 g, 60 mmol) were dissolved in H_2O (60 mL). The soln was cooled (ice bath) and benzyl chloroformate (8.53 g, 50 mmol) was added. After 2 h, the mixture was allowed to warm to r.t. and stirred overnight. The soln was acidified with 2 M aq HCl to pH 1–2 and extracted with EtOAc (3 × 30 mL). The combined organic layers were dried (Na_2SO_4) and the solvent was removed under reduced pressure. PE (40 mL) was added to the residue and the mixture was heated. When it started boiling, a sufficient amount of EtOAc was added to dissolve the oily material. Na_2SO_4 was added to the soln. After filtration, the soln was kept at –30 °C overnight. The precipitate was collected by suction filtration and dried under reduced pressure.

White solid; yield: 14.62 g (95%); mp 35–36 °C (Lit.[6] 31–32 °C); R_f = 0.64 (PE–EtOAc, 3:1).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.18 (t, J = 7.3 Hz, 6 H, OCH_2CH_3), 4.10–4.21 (m, 4 H, OCH_2CH_3), 4.90 (d, J = 8.2 Hz, 1 H, CONHC*H*), 5.06 (s, 2 H, $PhCH_2O$), 7.29–7.38 (m, 5 H, H_{arom}), 8.24 (d, J = 8.2 Hz, 1 H, CON*H*CH).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 13.95 (OCH_2CH_3), 57.86 (CONH*C*H), 61.77 (OCH_2CH_3), 66.11 ($PhCH_2O$), 127.90, 128.04, 128.48, 136.77 (C_{arom}), 156.01 (OCONH), 166.53 (C*C*OO).

Anal. Calcd for $C_{15}H_{19}NO_6$: C, 58.25; H, 6.19; N, 4.53. Found: C, 58.40; H, 6.07; N, 4.58.

Diethyl 2-Alkyl-2-(benzyloxycarbonylamino)malonates 5; General Procedure

A soln of NaOEt was prepared from Na (460 mg, 20 mmol) and anhyd EtOH (40 mL). Malonate **4** (6.19 g, 20 mmol) and MeI (3.12 g, 1.37 mL, 22 mmol) or EtBr (2.28 g, 1.56 mL, 22 mmol) were added. The soln was stirred at 87 °C for 10 h in an oil bath. CH_2Cl_2 (62 mL), charcoal (0.80 g), silica gel (0.80 g), and Na_2SO_4 (2.1 g) were added. After filtration of the mixture, the solvent was removed under reduced pressure and the oily residue was purified by column chromatography (silica gel, PE–EtOAc, 3:1).

Diethyl 2-(Benzyloxycarbonylamino)-2-methylmalonate (5a)

Colorless oil; yield: 5.40 g (83%); R_f = 0.79 (PE–EtOAc, 3:1).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.14 (t, J = 6.8 Hz, 6 H, OCH_2CH_3), 1.57 (s, 3 H, 2-CH_3), 4.11 (q, J = 6.8 Hz, 4 H, OCH_2CH_3), 5.03 (s, 2 H, $PhCH_2O$), 7.28–7.38 (m, 5 H, H_{arom}), 7.72 (s, 1 H, CONHC).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 13.86 (OCH_2CH_3), 21.68 (2-*C*H_3), 61.71 (OCH_2CH_3), 63.16, 65.71 (C-2, $PhCH_2O$), 127.77, 127.97, 128.43, 136.90 (C_{arom}), 154.93 (OCONH), 168.52 (C*C*OO).

Diethyl 2-(Benzyloxycarbonylamino)-2-ethylmalonate (5b)
Colorless oil; yield: 4.38 g (65%); R_f = 0.80 (PE–EtOAc, 3:1).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 0.76 (t, J = 7.6 Hz, 3 H, 2-CH_2CH_3), 1.12 (t, J = 7.0 Hz, 6 H, OCH_2CH_3), 2.09 (q, J = 7.6 Hz, 2 H, 2-CH_2CH_3), 4.12 (q, J = 7.0 Hz, 4 H, OCH_2CH_3), 5.04 (s, 2 H, $PhCH_2O$), 7.28–7.38 (m, 5 H, H_{arom}), 7.49 (s, 1 H, CONHC).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 7.85 (2-CH_2CH_3), 13.88 (OCH_2CH_3), 26.62 (2-CH_2CH_3), 61.75 (OCH_2CH_3), 65.71, 67.09 (C-2, $PhCH_2O$), 127.67, 127.93, 128.41, 136.89 (C_{arom}), 154.62 (OCONH), 167.63 (CCOO).

2-Alkyl-2-(benzyloxycarbonylamino)malonic Acids 6; General Procedure
A soln of **5a** (1.62 g, 5 mmol) or **5b** (1.69 g, 5 mmol), 2.5 M NaOH (60 mL), and EtOH (20 mL) was stirred at r.t. for 4 d. The soln was cooled (ice bath), acidified with ice-cooled 1 M aq HCl to pH 1–2 and extracted with EtOAc (3 × 30 mL). The combined organic layers were dried (Na_2SO_4). After filtration, the solvent was removed under reduced pressure at r.t. The material was used for the next reaction step without further purification.

2-(Benzyloxycarbonylamino)-2-methylmalonic Acid (6a)
Light-yellow oil; yield: 1.30 g (97%).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.55 (s, 3 H, CH_3), 5.02 (s, 2 H, $PhCH_2O$), 7.12 (s, 1 H, CONHC), 7.28–7.37 (m, 5 H, H_{arom}).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 21.45 (2-CH_3), 62.67, 65.61 (C-2, $PhCH_2O$), 127.66, 127.90, 128.45, 136.93 (C_{arom}), 154.59 (OCONH), 170.34 (CCOO).

2-(Benzyloxycarbonylamino)-2-ethylmalonic Acid (6b)
Light-yellow oil; yield: 1.30 g (92%).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 0.73 (t, J = 7.4 Hz, 3 H, 2-CH_2CH_3), 2.10 (q, J = 7.4 Hz, 2 H, 2-CH_2CH_3), 5.03 (s, 2 H, $PhCH_2O$), 6.85 (s, 1 H, CONHC), 7.28–7.37 (m, 5 H, H_{arom}).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 8.01 (2-CH_2CH_3), 25.67 (2-CH_2CH_3), 65.60, 66.75 (C-2, $PhCH_2O$), 127.54, 127.89, 128.46, 136.96 (C_{arom}), 154.24 (OCONH), 169.57 (CCOO).

5-Alkyl-3-aryl-5-(arylcarbamoyl)hydantoins 11 and 2-Alkyl-2-formamido-*N*^{1},*N*^{3}-bis(aryl)malonamides 12; General Procedure
Malonic acid **6a** (1.34 g, 5 mmol) or **6b** (1.41 g, 5 mmol) was dissolved in anhyd CH_2Cl_2 (100 mL), and four drops of DMF were added. Oxalyl chloride (2.92 g, 2.00 mL, 23 mmol) was added and the soln was stirred at r.t. under argon atmosphere until the evolution of gas had ceased, approximately after 30–60 min. The solvent was removed under reduced pressure and the residue was diluted with anhyd 1,4-dioxane (20 mL). An argon atmosphere was again introduced. A mixture of Et_3N (1.21 g, 1.67 mL, 12 mmol), anhyd 1,4-dioxane (5 mL), and the appropriate amine [aniline (1.40 g, 1.37 mL, 15 mmol), 3-aminobenzotrifluoride (2.42 g, 1.88 mL, 15 mmol), *p*-toluidine (1.61 g, 1.65 mL, 15 mmol), *p*-anisidine (1.85 g, 15 mmol), or 4-nitroaniline (2.07 g, 15 mmol)] was prepared. This mixture was injected through a septum over a period of 30 min. The soln was stirred at r.t. for 24 h. The precipitated [Et_3NH]Cl was removed by suction filtration and the filtrate was evaporated to dryness. The oily residue was purified by column chromatography (silica gel, PE–EtOAc, 1:1). The corresponding fractions were combined and the solvents were removed under reduced pressure. Et_2O was added to the residues, and after storage at –30 °C for 2 h, the precipitates were collected by suction filtration and dried under reduced pressure to provide the corresponding products **11** and **12** from each reaction.

5-Methyl-3-phenyl-5-(phenylcarbamoyl)hydantoin (11a)
White solid; yield: 0.14 g (9%); mp 147–148 °C; R_f = 0.64 (PE–EtOAc, 1:1).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.73 (s, 3 H, CH_3), 7.09–7.13 (m, 1 H, H_{arom}), 7.31–7.35 (m, 2 H, H_{arom}), 7.38–7.43 (m, 3 H, H_{arom}), 7.47–7.50 (m, 2 H, H_{arom}), 7.63–7.65 (m, 2 H, H_{arom}), 8.96 (s, 1 H, NH), 9.92 (s, 1 H, 5-CONH).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 21.68 (CH_3), 65.39 (C-5), 120.95, 124.40, 126.98, 128.15, 128.70, 128.83, 132.08, 138.24 (C_{arom}), 155.12 (C-2), 165.25 (5-CONH), 171.29 (C-4).

HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{17}H_{15}N_3O_3$: 332.1006; found: 332.1000.

5-Methyl-3-[3-(trifluoromethyl)phenyl]-5-{[3-(trifluoromethyl)phenyl]carbamoyl}hydantoin (11b)
White solid; yield: 0.54 g (24%); mp 170–171 °C; R_f = 0.82 (PE–EtOAc, 1:1).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.76 (s, 3 H, CH_3), 7.46–7.49 (m, 1 H, H_{arom}), 7.59 (t, J = 7.9 Hz, 1 H, H_{arom}), 7.73–7.80 (m, 3 H, H_{arom}), 7.89 (br s, 1 H, H_{arom}), 7.97–8.00 (m, 1 H, H_{arom}), 8.07 (br s, 1 H, H_{arom}), 9.12 (s, 1 H, NH), 10.23 (s, 1 H, 5-CONH).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 21.41 (CH_3), 65.56 (C-5), 117.01 (q, ^3J = 3.9 Hz, C_{arom}), 120.79 (q, ^3J = 3.6 Hz, C_{arom}), 123.61 (q, ^3J = 3.8 Hz, C_{arom}), 123.93 (q, ^1J = 270.7 Hz, CF_3), 124.18 (q, ^1J = 270.6 Hz, CF_3), 124.39 (C_{arom}), 124.83 (q, ^3J = 3.7 Hz, C_{arom}), 129.49 (q, ^2J = 31.5 Hz, C_{arom}), 129.59 (q, ^2J = 32.0 Hz, C_{arom}), 130.08 (C_{arom}), 130.20 (C_{arom}), 130.94 (C_{arom}), 132.81 (C_{arom}), 139.04 (C_{arom}), 154.69 (C-2), 165.63 (5-CONH), 170.74 (C-4).

Anal. Calcd for $C_{19}H_{13}F_6N_3O_3$: C, 51.25; H, 2.94; N, 9.44. Found: C, 51.65; H, 2.98; N, 9.08.

5-Methyl-3-(4-methylphenyl)-5-[(4-methylphenyl)carbamoyl]hydantoin (11c)
Off-white solid; yield: 0.20 g (12%); mp 185–186 °C; R_f = 0.71 (PE–EtOAc, 1:1).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.71 (s, 3 H, 5-CH_3), 2.26, 2.36 (each s, 6 H, CH_3Ph), 7.12–7.14 (m, 2 H, H_{arom}), 7.28 (s, 4 H, H_{arom}), 7.50–7.53 (m, 2 H, H_{arom}), 8.90 (s, 1 H, NH), 9.83 (s, 1 H, 5-CONH).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 20.58, 20.83 (CH_3Ph), 21.69 (5-CH_3), 65.33 (C-5), 120.96, 126.85, 129.07, 129.31, 129.50, 133.40, 135.74, 137.67 (C_{arom}), 155.25 (C-2), 165.10 (5-CONH), 171.42 (C-4).

Anal. Calcd for $C_{19}H_{19}N_3O_3$: C, 67.64; H, 5.68; N, 12.46. Found: C, 67.47; H, 5.60; N, 12.21.

3-(4-Methoxyphenyl)-5-[(4-methoxyphenyl)carbamoyl]-5-methylhydantoin (11d)
White solid; yield: 0.34 g (18%); mp 157–158 °C; R_f = 0.38 (PE–EtOAc, 1:1).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.70 (s, 3 H, 5-CH_3), 3.72, 3.78 (each s, 6 H, CH_3OPh), 6.88–6.92 (m, 2 H, H_{arom}), 7.00–7.04 (m, 2 H, H_{arom}), 7.29–7.33 (m, 2 H, H_{arom}), 7.51–7.55 (m, 2 H, H_{arom}), 8.86 (s, 1 H, NH), 9.79 (s, 1 H, 5-CONH).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 21.63 (5-CH_3), 55.31, 55.51 (CH_3OPh), 65.24 (C-5), 113.82, 114.10, 122.54, 124.66, 128.40, 131.27, 155.41, 156.04 (C_{arom}), 158.90 (C-2), 164.96 (5-CONH), 171.57 (C-4).

Anal. Calcd for $C_{19}H_{19}N_3O_5$: C, 61.78; H, 5.18; N, 11.38. Found: C, 62.11; H, 5.20; N, 10.98.

5-Methyl-3-(4-nitrophenyl)-5-[(4-nitrophenyl)carbamoyl]hydantoin (11e)
Yellow solid; yield: 0.48 g (24%); mp 208–209 °C; R_f = 0.49 (PE–EtOAc, 1:1).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.78 (s, 3 H, CH_3), 7.79–7.83 (m, 2 H, H_{arom}), 7.93–7.97 (m, 2 H, H_{arom}), 8.23–8.27 (m, 2 H, H_{arom}), 8.35–8.39 (m, 2 H, H_{arom}), 9.23 (s, 1 H, NH), 10.46 (s, 1 H, 5-CONH).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 21.50 (CH_3), 65.64 (C-5), 120.62, 124.18, 124.80, 127.21, 137.77, 143.19, 144.35, 146.28 (C_{arom}), 154.18 (C-2), 165.82 (5-CONH), 170.38 (C-4).

Anal. Calcd for $C_{17}H_{13}N_5O_7$: C, 51.13; H, 3.28; N, 17.54. Found: C, 50.78; H, 3.55; N, 17.02.

5-Ethyl-3-phenyl-5-(phenylcarbamoyl)hydantoin (11f)
White solid; yield: 0.37 g (23%); mp 142–144 °C; R_f = 0.75 (PE–EtOAc, 1:1).

The product was recrystallized from PE–EtOAc; this gave crystals for X-ray analysis.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 0.92 (t, J = 7.4 Hz, 3 H, CH_2CH_3), 2.10–2.18 (m, 1 H, CH_2CH_3), 2.22–2.30 (m, 1 H, CH_2CH_3), 7.09–7.13 (m, 1 H, H_{arom}), 7.31–7.43 (m, 5 H, H_{arom}), 7.46–7.51 (m, 2 H, H_{arom}), 7.62–7.65 (m, 2 H, H_{arom}), 9.01 (s, 1 H, NH), 9.85 (s, 1 H, 5-CONH).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 7.63 (CH_2CH_3), 27.99 (CH_2CH_3), 69.49 (C-5), 120.95, 124.41, 126.89, 128.25, 128.71, 128.96, 131.93, 138.18 (C_{arom}), 155.40 (C-2), 164.58 (5-CONH), 170.50 (C-4).

Anal. Calcd for $C_{18}H_{17}N_3O_3$: C, 66.86; H, 5.30; N, 13.00. Found: C, 67.01; H, 5.72; N, 13.06.

5-Ethyl-3-[3-(trifluoromethyl)phenyl]-5-{[3-(trifluoromethyl)phenyl]carbamoyl}hydantoin (11g)
White solid; yield: 0.99 g (43%); mp 63–64 °C; R_f = 0.87 (PE–EtOAc, 1:1).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 0.94 (t, J = 7.4 Hz, 3 H, CH_2CH_3), 2.15–2.31 (m, 2 H, CH_2CH_3), 7.46–7.49 (m, 1 H, H_{arom}), 7.59 (t, J = 8.0 Hz, 1 H, H_{arom}), 7.73–7.81 (m, 3 H, H_{arom}), 7.83–7.85 (m, 1 H, H_{arom}), 7.97–8.00 (m, 1 H, H_{arom}), 8.08 (br s, 1 H, H_{arom}), 9.23 (s, 1 H, NH), 10.16 (s, 1 H, 5-CONH).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 7.66 (CH_2CH_3), 27.98 (CH_2CH_3), 69.63 (C-5), 117.04 (q, ^3J = 3.7 Hz, C_{arom}), 120.79 (q, ^3J = 3.6 Hz, C_{arom}), 123.40 (q, ^3J = 3.7 Hz, C_{arom}), 123.87 (q, ^1J = 270.6 Hz, CF_3), 124.18 (q, ^1J = 270.7 Hz, CF_3), 124.43 (C_{arom}), 124.92 (q, ^3J = 3.7 Hz, C_{arom}), 129.70 (q, ^2J = 32.0 Hz, C_{arom}), 129.71 (q, ^2J = 31.5 Hz, C_{arom}), 130.05 (C_{arom}), 130.33 (C_{arom}), 130.78 (C_{arom}), 132.61 (C_{arom}), 138.97 (C_{arom}), 154.88 (C-2), 164.84 (5-CONH), 169.98 (C-4).

Anal. Calcd for $C_{20}H_{15}F_6N_3O_3$: C, 52.30; H, 3.29; N, 9.15. Found: C, 52.56; H, 3.67; N, 9.16.

5-Ethyl-3-(4-methylphenyl)-5-[(4-methylphenyl)carbamoyl]hydantoin (11h)
Off-white solid; yield: 0.44 g (25%); mp 168–170 °C; R_f = 0.80 (PE–EtOAc, 1:1).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 0.91 (t, J = 7.4 Hz, 3 H, CH_2CH_3), 2.07–2.15 (m, 1 H, CH_2CH_3), 2.20–2.28 (m, 1 H, CH_2CH_3), 2.26, 2.33 (each s, 6 H, CH_3Ph), 7.12–7.14 (m, 2 H, H_{arom}), 7.23–7.29 (m, 4 H, H_{arom}), 7.50–7.53 (m, 2 H, H_{arom}), 8.94 (s, 1 H, NH), 9.77 (s, 1 H, 5-CONH).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 7.62 (CH_2CH_3), 20.59, 20.83 (CH_3Ph), 27.96 (CH_2CH_3), 69.42 (C-5), 120.96, 126.76, 129.09, 129.35, 129.43, 133.42, 135.68, 137.80 (C_{arom}), 155.54 (C-2), 164.44 (5-CONH), 170.61 (C-4).

Anal. Calcd for $C_{20}H_{21}N_3O_3$: C, 68.36; H, 6.02; N, 11.96. Found: C, 68.15; H, 6.12; N, 11.65.

5-Ethyl-3-(4-methoxyphenyl)-5-[(4-methoxyphenyl)carbamoyl]hydantoin (11i)
Off-white solid; yield: 0.38 g (20%); mp 152–153 °C; R_f = 0.53 (PE–EtOAc, 1:1).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 0.90 (t, J = 7.4 Hz, 3 H, CH_2CH_3), 2.06–2.15 (m, 1 H, CH_2CH_3), 2.19–2.27 (m, 1 H, CH_2CH_3), 3.72, 3.78 (each s, 6 H, CH_3OPh), 6.88–6.92 (m, 2 H, H_{arom}), 7.00–7.04 (m, 2 H, H_{arom}), 7.25–7.29 (m, 2 H, H_{arom}), 7.51–7.55 (m, 2 H, H_{arom}), 8.91 (s, 1 H, NH), 9.73 (s, 1 H, 5-CONH).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 7.64 (CH_2CH_3), 27.92 (CH_2CH_3), 55.33, 55.53 (CH_3OPh), 69.35 (C-5), 113.83, 114.23, 122.55, 124.52, 128.31, 131.23, 155.70, 156.06 (C_{arom}), 158.97 (C-2), 164.30 (5-CONH), 170.76 (C-4).

Anal. Calcd for $C_{20}H_{21}N_3O_5$: C, 62.65; H, 5.52; N, 10.96. Found: C, 62.62; H, 5.57; N, 10.85.

5-Ethyl-3-(4-nitrophenyl)-5-[(4-nitrophenyl)carbamoyl]hydantoin (11j)
Light-yellow solid; yield: 0.53 g (26%); mp 112–114 °C; R_f = 0.64 (PE–EtOAc, 1:1).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 0.93 (t, J = 7.4 Hz, 3 H, CH_2CH_3), 2.16–2.33 (m, 2 H, CH_2CH_3), 7.76–7.80 (m, 2 H, H_{arom}), 7.94–7.98 (m, 2 H, H_{arom}), 8.23–8.27 (m, 2 H, H_{arom}), 8.34–8.38 (m, 2 H, H_{arom}), 9.34 (s, 1 H, NH), 10.38 (s, 1 H, 5-CONH).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 7.60 (CH_2CH_3), 20.10 (CH_2CH_3), 69.74 (C-5), 120.67, 124.32, 124.81, 127.19, 137.51, 143.22, 144.30, 146.39 (C_{arom}), 154.42 (C-2), 165.07 (5-CONH), 169.67 (C-4).

Anal. Calcd for $C_{18}H_{15}N_5O_7$: C, 52.30; H, 3.66; N, 16.94. Found: C, 52.23; H, 4.12; N, 16.29.

2-Formamido-2-methyl-*N*^{1},*N*^{3}-diphenylmalonamide (12a)
White solid; yield: 0.08 g (5%); mp 169–171 °C; R_f = 0.57 (PE–EtOAc, 1:3).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.78 (s, 3 H, CH_3), 7.06–7.11 (m, 2 H, H_{arom}), 7.28–7.33 (m, 4 H, H_{arom}), 7.56–7.60 (m, 4 H, H_{arom}), 8.14 (d, J = 1.6 Hz, 1 H, *H*CONH), 8.71 (br s, 1 H, HCON*H*), 9.93 (s, 2 H, 2-CONH).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 22.11 (CH_3), 63.27 (C-2), 120.71, 124.17, 128.73, 138.35 (C_{arom}), 162.04 (HCONH), 168.23 (2-CONH).

HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{17}H_{17}N_3O_3$: 334.1162; found: 334.1168.

2-Formamido-2-methyl-*N*^{1},*N*^{3}-bis[3-(trifluoromethyl)phenyl]malonamide (12b)
White solid; yield: 0.47 g (21%); mp 140–141 °C; R_f = 0.73 (PE–EtOAc, 1:3).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.81 (s, 3 H, CH_3), 7.42–7.45 (m, 2 H, H_{arom}) 7.55 (t, J = 8.1 Hz, 2 H, H_{arom}), 7.86–7.89 (m, 2 H, H_{arom}), 8.08 (br s, 2 H, H_{arom}), 8.16 (s, 1 H, *H*CONH), 8.80 (s, 1 H, HCON*H*), 10.20 (s, 2 H, 2-CONH).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 21.81 (CH_3), 63.68 (C-2), 116.84 (q, ^3J = 3.7 Hz, C_{arom}), 120.53 (q, ^3J = 3.7 Hz, C_{arom}), 124.22 (q, ^1J = 270.6 Hz, CF_3), 124.27 (C_{arom}), 129.51 (q, ^2J = 31.5 Hz, C_{arom}), 130.04 (C_{arom}), 139.22 (C_{arom}), 162.12 (HCONH), 168.39 (2-CONH).

Anal. Calcd for $C_{19}H_{15}F_6N_3O_3$: C, 51.01; H, 3.38; N, 9.39. Found: C, 51.10; H, 3.65; N, 9.15.

2-Formamido-2-methyl-*N*^{1},*N*^{3}-bis(4-methylphenyl)malonamide (12c)
Off-white solid; yield: 0.33 g (19%); mp 131–132 °C; R_f = 0.66 (PE–EtOAc, 1:3).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.76 (s, 3 H, 2-CH_3), 2.24 (s, 6 H, CH_3Ph), 7.10–7.12 (m, 4 H, H_{arom}), 7.43–7.46 (m, 4 H, H_{arom}), 8.13 (s, 1 H, *H*CONH), 8.66 (s, 1 H, HCON*H*), 9.85 (s, 2 H, 2-CONH).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 20.56 (CH_3Ph), 22.17 (2-CH_3), 63.11 (C-2), 120.74, 129.10, 133.17, 135.83 (C_{arom}), 161.96 (HCONH), 168.10 (2-CONH).

Anal. Calcd for $C_{19}H_{21}N_3O_3$: C, 67.24; H, 6.24; N, 12.38. Found: C, 66.53; H, 6.36; N, 12.21.

2-Formamido-*N*^{1},*N*^{3}-bis(4-methoxyphenyl)-2-methylmalonamide (12d)
White solid; yield: 0.28 g (15%); mp 151–153 °C; R_f = 0.43 (PE–EtOAc, 1:3).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.76 (s, 3 H, 2-CH_3), 3.71 (s, 6 H, CH_3OPh), 6.86–6.90 (m, 4 H, H_{arom}), 7.44–7.49 (m, 4 H, H_{arom}), 8.12 (s, 1 H, *H*CONH), 8.61 (s, 1 H, HCON*H*), 9.79 (s, 2 H, 2-CONH).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 22.13 (2-CH_3), 55.34 (*C*H_3OPh), 62.95 (C-2), 113.87, 122.38, 131.40, 155.96 (C_{arom}), 161.85 (HCONH), 167.95 (2-CONH).

Anal. Calcd for $C_{19}H_{21}N_3O_5$: C, 61.45; H, 5.70; N, 11.31. Found: C, 60.90; H, 5.72; N, 11.19.

2-Formamido-2-methyl-*N*^{1},*N*^{3}-bis(4-nitrophenyl)malonamide (12e)
Light-yellow solid; yield: 0.65 g (32%); mp 218–219 °C; R_f = 0.41 (PE–EtOAc, 1:3).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.82 (s, 3 H, CH_3), 7.88–7.92 (m, 4 H, H_{arom}) 8.18 (s, 1 H, *H*CONH), 8.20–8.24 (m, 4 H, H_{arom}), 8.92 (s, 1 H, HCON*H*), 10.44 (s, 2 H, 2-CONH).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 21.70 (CH_3), 64.13 (C-2), 120.33, 124.85, 142.96, 144.61 (C_{arom}), 162.38 (HCONH), 168.56 (2-CONH).

Anal. Calcd for $C_{17}H_{15}N_5O_7$: C, 50.88; H, 3.77; N, 17.45. Found: C, 51.02; H, 3.91; N, 17.03.

2-Ethyl-2-formamido-*N*^{1},*N*^{3}-diphenylmalonamide (12f)
White solid; yield: 0.55 g (34%); mp 189–190 °C; R_f = 0.67 (PE–EtOAc, 1:3).

The product was recrystallized from EtOAc to obtain crystals for X-ray analysis.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 0.83 (t, *J* = 7.5 Hz, 3 H, CH_2CH_3), 2.36 (q, *J* = 7.5 Hz, 2 H, CH_2CH_3), 7.07–7.11 (m, 2 H, H_{arom}), 7.28–7.33 (m, 4 H, H_{arom}), 7.56–7.59 (m, 4 H, H_{arom}), 8.16 (d, *J* = 1.3 Hz, 1 H, *H*CONH), 8.53 (br s, 1 H, HCON*H*), 9.96 (s, 2 H, 2-CONH).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 8.07 (CH_2CH_3), 26.84 (CH_2CH_3), 67.02 (C-2), 120.91, 124.26, 128.71, 138.20 (C_{arom}), 161.78 (HCONH), 167.52 (2-CONH).

Anal. Calcd for $C_{18}H_{19}N_3O_3$: C, 66.45; H, 5.89; N, 12.91. Found: C, 66.31; H, 6.01; N, 12.71.

2-Ethyl-2-formamido-*N*^{1},*N*^{3}-bis[3-(trifluoromethyl)phenyl]malonamide (12g)
White solid; yield: 0.57 g (25%); mp 141–143 °C; R_f = 0.77 (PE–EtOAc, 1:3).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 0.83 (t, *J* = 7.4 Hz, 3 H, CH_2CH_3), 2.39 (q, *J* = 7.4 Hz, 2 H, CH_2CH_3), 7.42–7.45 (m, 2 H, H_{arom}) 7.55 (t, *J* = 8.0 Hz, 2 H, H_{arom}), 7.88–7.91 (m, 2 H, H_{arom}), 8.08 (br s, 2 H, H_{arom}), 8.17 (d, *J* = 1.0 Hz, 1 H, *H*CONH), 8.64 (br s, 1 H, HCON*H*), 10.22 (s, 2 H, 2-CONH).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 7.95 (CH_2CH_3), 26.44 (CH_2CH_3), 67.39 (C-2), 116.97 (q, ^3J = 3.7 Hz, C_{arom}), 120.58 (q, ^3J = 3.5 Hz, C_{arom}), 124.16 (q, ^1J = 270.6 Hz, CF_3), 124.40 (C_{arom}), 129.45 (q, ^2J = 31.5 Hz, C_{arom}), 129.98 (C_{arom}), 139.03 (C_{arom}), 161.81 (HCONH), 167.62 (2-CONH).

Anal. Calcd for $C_{20}H_{17}F_6N_3O_3$: C, 52.07; H, 3.71; N, 9.11. Found: C, 52.16; H, 3.76; N, 8.78.

2-Ethyl-2-formamido-*N*^{1},*N*^{3}-bis(4-methylphenyl)malonamide (12h)
Off-white solid; yield: 0.54 g (31%); mp 156–158 °C; R_f = 0.72 (PE–EtOAc, 1:3).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 0.81 (t, *J* = 7.4 Hz, 3 H, CH_2CH_3), 2.24 (s, 6 H, CH_3Ph), 2.34 (q, *J* = 7.4 Hz, 2 H, CH_2CH_3), 7.09–7.12 (m, 4 H, H_{arom}) 7.42–7.46 (m, 4 H, H_{arom}), 8.15 (d, *J* ≈ 1.2 Hz, 1 H, *H*CONH), 8.47 (d, *J* ≈ 1.2 Hz, 1 H, HCON*H*), 9.87 (s, 2 H, 2-CONH).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 8.07 (CH_2CH_3), 20.56 (*C*H_3Ph), 26.88 (CH_2CH_3), 66.88 (C-2), 120.93, 129.08, 133.27, 135.68 (C_{arom}), 161.73 (HCONH), 167.39 (2-CONH).

Anal. Calcd for $C_{20}H_{23}N_3O_3$: C, 67.97; H, 6.56; N, 11.89. Found: C, 67.82; H, 6.55; N, 11.57.

2-Ethyl-2-formamido-*N*^{1},*N*^{3}-bis(4-methoxyphenyl)malonamide (12i)
Off-white solid; yield: 0.30 g (16%); mp 142–144 °C; R_f = 0.50 (PE–EtOAc, 1:3).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 0.81 (t, *J* = 7.4 Hz, 3 H, CH_2CH_3), 2.34 (q, *J* = 7.4 Hz, 2 H, CH_2CH_3), 3.71 (s, 6 H, CH_3OPh), 6.85–6.89 (m, 4 H, H_{arom}), 7.44–7.48 (m, 4 H, H_{arom}), 8.15 (d, *J* ≈ 1.1 Hz, 1 H, *H*CONH), 8.43 (d, *J* ≈ 1.1 Hz, 1 H, HCON*H*), 9.81 (s, 2 H, 2-CONH).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 8.05 (CH_2CH_3), 26.73 (CH_2CH_3), 55.33 (*C*H_3OPh), 66.77 (C-2), 113.84, 122.53, 131.24, 156.00 (C_{arom}), 161.62 (HCONH), 167.23 (2-CONH).

Anal. Calcd for $C_{20}H_{23}N_3O_5$: C, 62.33; H, 6.01; N, 10.90. Found: C, 61.99; H, 5.92; N, 10.78.

2-Ethyl-2-formamido-*N*^{1},*N*^{3}-bis(4-nitrophenyl)malonamide (12j)
Light-yellow solid; yield: 0.73 g (35%); mp 132–134 °C; R_f = 0.41 (PE–EtOAc, 1:3).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 0.85 (t, *J* = 7.4 Hz, 3 H, CH_2CH_3), 2.38 (q, *J* = 7.4 Hz, 2 H, CH_2CH_3), 7.89–7.93 (m, 4 H, H_{arom}) 8.19 (d, *J* ≈ 1.1 Hz, 1 H, *H*CONH), 8.20–8.24 (m, 4 H, H_{arom}), 8.74 (d, *J* ≈ 1.1 Hz, 1 H, HCON*H*), 10.47 (s, 2 H, 2-CONH).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 8.01 (CH_2CH_3), 26.67 (CH_2CH_3), 67.75 (C-2), 120.59, 124.81, 143.08, 144.39 (C_{arom}), 162.09 (HCONH), 167.85 (2-CONH).

Anal. Calcd for $C_{18}H_{17}N_5O_7$: C, 51.92; H, 4.36; N, 16.82. Found: C, 51.87; H, 4.41; N, 16.51.

Reaction of 13 with Oxalyl Chloride, *N*,*N*-Dimethylformamide, and Aniline
Isobutyric acid **13** (1.19 g, 5 mmol) was dissolved in anhyd CH_2Cl_2 (100 mL), and four drops of DMF were added. Oxalyl chloride (2.92 g, 2.00 mL, 23 mmol) was added and the soln was stirred at r.t. under an argon atmosphere for 30 min. The solvent was removed under reduced pressure and the residue was diluted with anhyd 1,4-dioxane (20 mL). An argon atmosphere was again introduced. A mixture of Et_3N (1.21 g, 1.67 mL, 12 mmol), anhyd 1,4-dioxane (5 mL), and aniline (1.40 g, 1.37 mL, 15 mmol) was prepared. This mixture was injected through a septum over a period of 30 min. The soln was stirred at r.t. for 24 h. The precipitated [Et_3NH]Cl was removed by suction filtration and the filtrate was evaporated to dryness. Four fractions were obtained from the oily residue after column chromatography (silica gel, PE–EtOAc, 1:2). An appropriate fraction (R_f ≈ 0.56) was analyzed by ^{1}H and ^{13}C NMR, but did not contain notable amounts of hydantoin **14**. A further fraction (R_f ≈ 0.19) contained the anilide **15**. Pure material of **15** (5 mg) was obtained by recrystallization (*n*-hexane–EtOAc).

5,5-Dimethyl-3-phenylimidazolidine-2,4-dione (14)
2-Aminoisobutyric acid (516 mg, 5 mmol) was dissolved in 2 M aq NaOH (5 mL), and PhNCO (1.79 g, 1.63 mL, 15 mmol) was added.

The mixture was stirred at r.t. for 1 h. The precipitated *N*,*N*′-diphenylurea was collected by filtration and the filtrate was acidified with 2 M aq HCl to pH 1. The resulting precipitate was collected by filtration and suspended in 2 M aq HCl (50 mL). The reaction mixture was stirred at reflux for 2 h. The aqueous suspension was extracted with CH_2Cl_2 (3 × 50 mL). The soln was dried (Na_2SO_4) and evaporated.

White solid; yield: 0.66 g (65%); mp 164–167 °C (Lit.[20] 168–170 °C); R_f = 0.49 (PE–EtOAc, 1:1), R_f = 0.56 (PE–EtOAc, 1:2).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.39 [s, 6 H, C(CH_3)$_2$], 7.34–7.39 (m, 3 H, H-2, H-4, H-6), 7.44–7.48 (m, 2 H, H-3, H-5), 8.50 (s, 1 H, NH).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 24.88 [C(*C*H$_3$)$_2$], 57.83 [*C*(CH$_3$)$_2$], 126.87, 127.83, 128.77, 132.34 (C$_{arom}$), 154.32 (C-2), 176.53 (C-4).

Anal. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.33; H, 5.84; N, 13.12.

2-(*tert*-Butoxycarbonylamino)-*N*-phenylisobutyramide (17)

Aniline (1.12 g, 1.10 mL, 12 mmol) was dissolved in anhyd CH_2Cl_2 (50 mL). Then, **16** (1.22 g, 6 mmol), EDC (1.02 g, 1.16 mL, 6.60 mmol) and DMAP (37 mg, 0.30 mmol) were added. The reaction mixture was stirred at r.t. for 72 h and refluxed for 6 h. After evaporation of the solvent, the resulting solid was suspended in H_2O and extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with 10% $KHSO_4$ (30 mL), sat. $NaHCO_3$ (2 × 30 mL), H_2O (30 mL), and brine (30 mL). The solvent was dried (Na_2SO_4) and evaporated. The product was purified by column chromatography (silica gel, PE–EtOAc, 1:2).

White solid; yield: 0.83 g (50%); mp 157–160 °C; R_f = 0.79 (PE–EtOAc, 1:1).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.35–1.37 [m, 15 H, C(CH_3)$_3$, C(CH_3)$_2$], 6.86 (br s, 1 H, N*H*Ph), 6.99–7.02 (m, 1 H, H-4), 7.24–7.28 (m, 2 H, H-3, H-5), 7.58–7.59 (m, 2 H, H-2, H-6), 9.34 [s, 1 H, N*H*C(CH$_3$)$_2$].

^{13}C NMR (125 MHz, DMSO-d_6): δ = 25.16 [C(*C*H$_3$)$_2$], 28.22 [C(*C*H$_3$)$_3$], 56.56 [*C*(CH$_3$)$_2$], 78.34 [*C*(CH$_3$)$_3$], 120.02, 123.07, 128.48, 139.51 (C$_{arom}$), 154.40 [*C*OOC(CH$_3$)$_3$], 173.40 (*C*ONHPh).

Anal. Calcd for $C_{15}H_{22}N_2O_3$: C, 64.73; H, 7.97; N, 10.06. Found: C, 64.83; H, 8.38; N, 11.23.

***N*-Phenylisobutyramide-2-aminium Methanesulfonate (18)**

Compound **17** (835 mg, 3 mmol) was dissolved in anhyd THF (15 mL). Under ice cooling, anhyd methanesulfonic acid (1.73 g, 1.17 mL, 18 mmol) was added, and the mixture was stirred at r.t. overnight. The precipitate was collected by filtration, washed with cold EtOAc and PE and dried.

White solid; yield: 0.60 g (73%); mp 180–198 °C; R_f = 0.11 (PE–EtOAc, 1:1).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.59 [s, 6 H, C(CH_3)$_2$], 2.30 (s, 3 H, $CH_3SO_3^-$), 7.12–7.15 (m, 1 H, H-4), 7.34–7.38 (m, 2 H, H-3, H-5), 7.60–7.62 (m, 2 H, H-2, H-6), 8.22 (s, 3 H, NH_3^+), 9.88 (s, 1 H, N*H*Ph).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 23.50 [C(*C*H$_3$)$_2$], 57.23 [*C*(CH$_3$)$_2$], 120.69, 124.56, 128.93, 138.10 (C$_{arom}$), 170.35 (*C*ONHPh).

Anal. Calcd for $C_{11}H_{18}N_2O_4S$: C, 48.16; H, 6.61; N, 10.21. Found: C, 47.33; H, 6.92; N, 10.90.

2-Formamido-*N*-phenylisobutyramide (15)

1,1′-Carbonyldiimidazole (CDI; 178 mg, 1.1 mmol) was dissolved in anhyd CH_2Cl_2 (2.2 mL), and formic acid (51 mg, 42 μL, 1.1 mmol) was added. The mixture was stirred at r.t. for 10 min. Compound **18** (274 mg, 1 mmol) was suspended in anhyd CH_2Cl_2 (25 mL), and DIPEA (129 mg, 174 μL, 1.00 mmol) was added. Both mixtures were combined and stirred at r.t. for 3 h. After evaporation of the solvent, the resulting solid was suspended in H_2O (50 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with 10% aq $KHSO_4$ (2 × 30 mL), sat. aq $NaHCO_3$ (2 × 30 mL), H_2O (30 mL), and brine (30 mL). The solvent was dried (Na_2SO_4) and evaporated. The crude product was recrystallized from EtOAc.

White solid; yield: 30 mg (15%); mp 184–186 °C; R_f = 0.13 (PE–EtOAc, 1:1); R_f = 0.19 (PE–EtOAc, 1:2).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.45 [s, 6 H, C(CH_3)$_2$], 7.01–7.04 (m, 1 H, H-4), 7.25–7.29 (m, 2 H, H-3, H-5), 7.57–7.60 (m, 2 H, H-2, H-6), 7.97 (d, ^3J = 1.9 Hz, 1 H, *H*CONH), 8.19 (br s, 1 H, HCON*H*), 9.36 (s, 1 H, N*H*Ph).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 25.10 [C(*C*H$_3$)$_2$], 56.29 [*C*(CH$_3$)$_2$], 120.35, 123.37, 128.48, 139.23 (C$_{arom}$), 172.49 [*C*OC(CH$_3$)$_2$], 161.03 (HCO).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_{14}N_2O_2$: 229.0947; found: 229.0948.

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