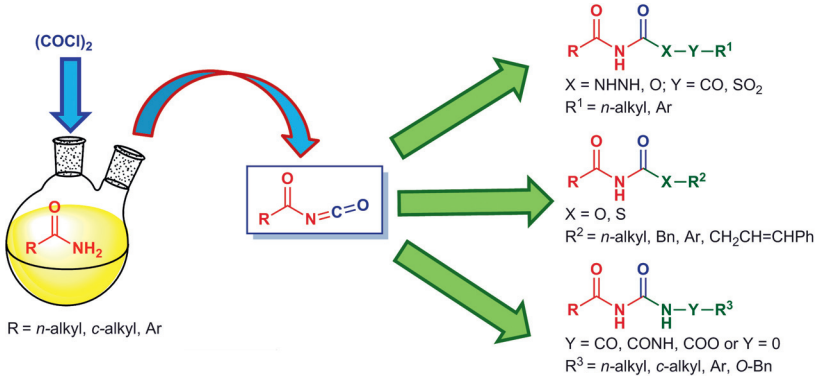
Synthesis A. G. Hernandez et al. Paper

Convenient One-Pot Two-Step Synthesis of Symmetrical and Unsymmetrical Diacyl Ureas, Acyl Urea/Carbamate/Thiocarbamate Derivatives, and Related Compounds

Anolan Garcia Hernandez
Gregory M. Grooms
Abir T. El-Alfy[1]
Jozef Stec[*2]

Chicago State University, College of Pharmacy, Department of Pharmaceutical Sciences, 9501 S. King Drive, Chicago, IL 60628, USA
jstec@ketchum.edu

Dedicated to Professor Richard J. Whitby



Received: 19.12.2016
Accepted after revision: 27.01.2017
Published online: 21.02.2017
DOI: 10.1055/s-0036-1588724; Art ID: ss-2016-m0860-op

Abstract A wide range of chemicals such as amides, hydrazides, amines, alcohols, carbazate, and sulfonate were reacted with acyl isocyanates generated by the reaction of primary amides with oxalyl chloride to give symmetrical and unsymmetrical diacyl urea derivatives, acyl ureas/carbamates/thiocarbamates, and related compounds. This method provides means for convenient one-pot, two-step synthesis of compounds bearing urea, carbamate, and other functional groups from cheap and commercially available starting reagents. It is expected that the results presented in this report will expand the medicinal chemist's toolbox.

Key words bioisostere, acyl isocyanates, symmetrical/unsymmetrical diacyl ureas, acyl ureas, acyl carbamates, acyl thiocarbamates

Carbamate (urethane) **2** and urea **3** functional groups share similarities in structural, electronic, and biologic properties with amide (peptide) bond **1** (Figure 1). Both of these groups are considered to be nonclassical bioisosteres of amide bond, and in the case of urea – hydroxyl group **4** as well (Figure 1).[3] The overall physicochemical properties of carbamate and urea linkers are often decisive not only to the pharmacologic activity but also to the ADME/Tox (absorption, distribution, metabolism, excretion, and toxicity) profile of compounds relevant to medicine and agriculture. Bioisosteric replacement of functional groups is often used to modulate the druggability of lead candidates by improving their potency, selectivity, metabolic stability, pharmacokinetic properties, and safety profile.[4] Accordingly, carbamate and urea motifs are broadly utilized in medicinal chemistry, drug discovery, and development process.

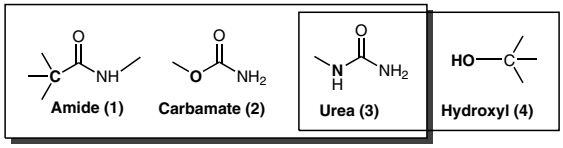


Figure 1 Nonclassical bioisosteres of amide bond: carbamate and urea groups. Urea is also a bioisostere of the hydroxyl group.

Numerous drug molecules approved for the treatment of various diseases contain carbamate moiety (Figure 2).[5] Rivastigmine (**5**), for treatment of mild-to-moderate Alzheimer's disease (AD) dementia and dementia due to Parkinson's disease (PD); the anticonvulsant medication felbamate (**6**); the antibiotic linezolid (**7**); and the anthelmintic agents albendazole (**8**) and mebendazole (**9**) represent only few examples of important medications that con-

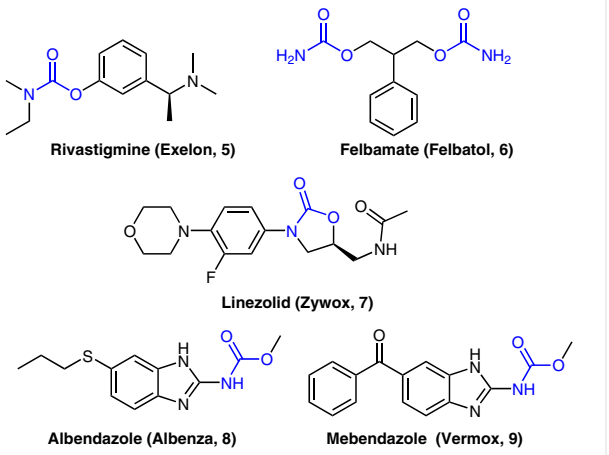


Figure 2 Examples of marketed drugs that contain carbamate moiety

tain a carbamate moiety (Figure 2).[5] Additionally, the use of carbamates in the development of prodrugs cannot be overemphasized. Prodrug strategy is frequently employed to increase the bioavailability of drug molecules and to improve their overall ADME/Tox properties. Representative examples of carbamate-based prodrugs approved for clinical use include the beta blocker bambuterol (**10**) used in the treatment of asthma,[5] the antihistamine agent loratadine (**12**),[6] and the anticancer medication capecitabine (**14**)[7] (Figure 3).

Basic urea (**18**) is the end product of protein metabolism that is excreted in the urine of ureotelic organisms (Figure 4).[8] This chemical group is also present in various therapeutics and agrochemicals. The antineoplastic agent sorafenib (**19**), the anthelmintic drug hetrazan (**20**), and the antipsychotic medication cariprazine (**21**) represent pharmaceuticals containing urea functionality (Figure 4).[9] Cumyluron (**22**) and tebuthiuron (**23**) are herbicides that also possess a urea linker (Figure 4).[9]

Furthermore, close derivatives of urea group such as hydroxyurea (antineoplastic, **24**),[10] nitrosourea in lomustine (anticancer, **25**),[11] sulfonylurea in torsemide (diuretic, **26**),[12] acylated ureas in pheneturide (anticonvulsant, **27**),[13] bromisoval (hypnotic and sedative, **28**),[14] diflubenzuron (insecticide, **29**),[15] and lufenuron (insecticide, **30**)[15b,16] are decisive to the bioactivity of the aforementioned com-

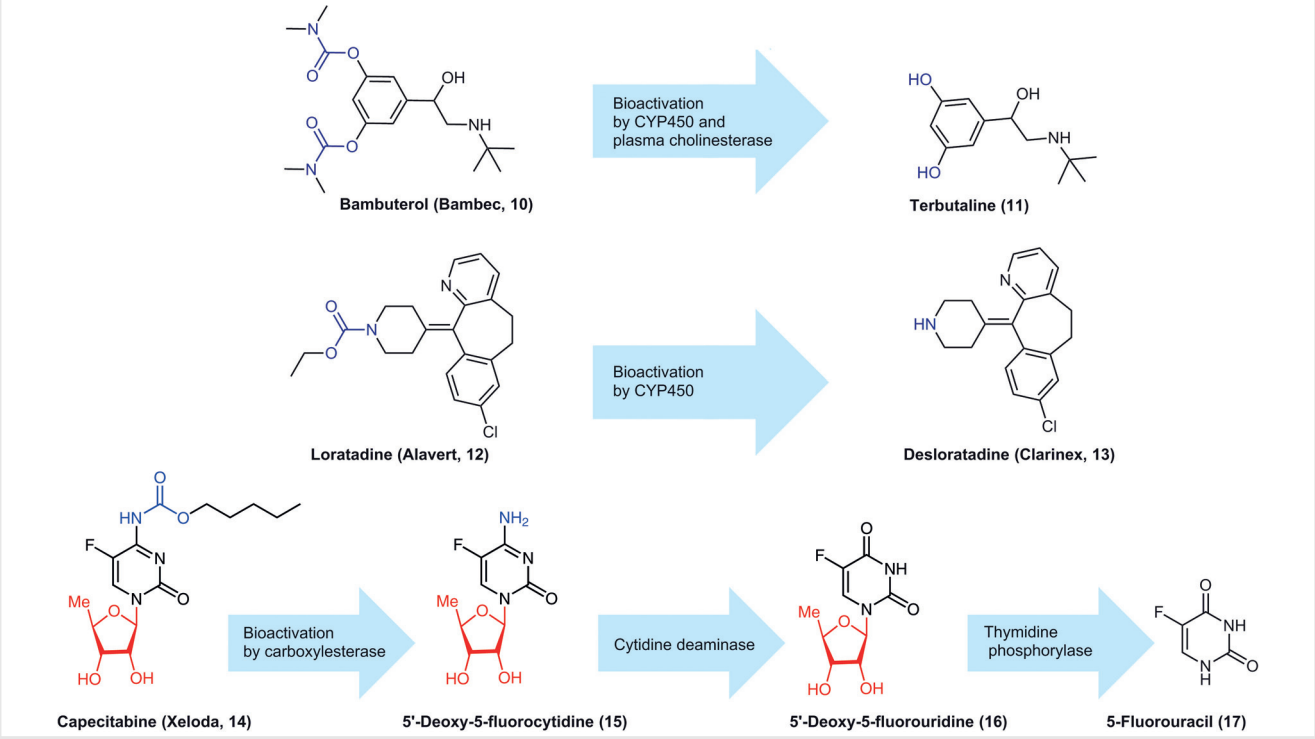


Figure 3 Carbamate group employed in the prodrug strategy

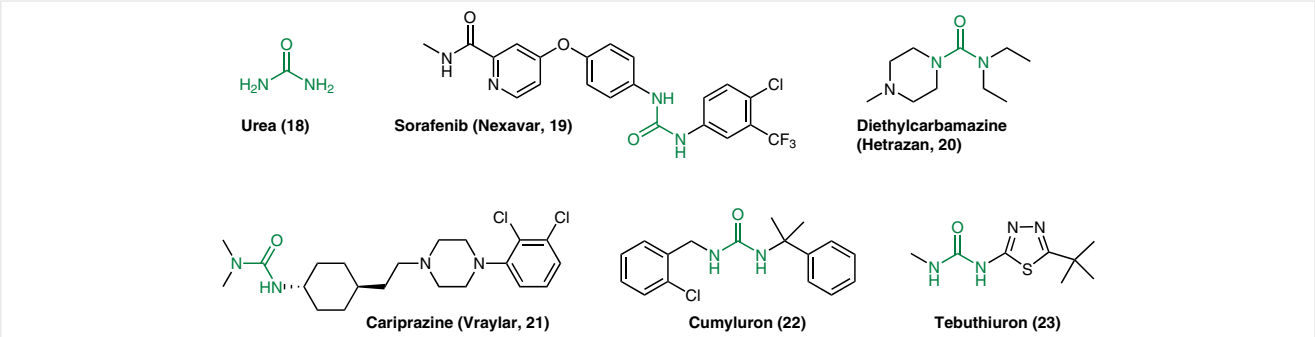


Figure 4 Urea motif present in important medications and agrochemicals

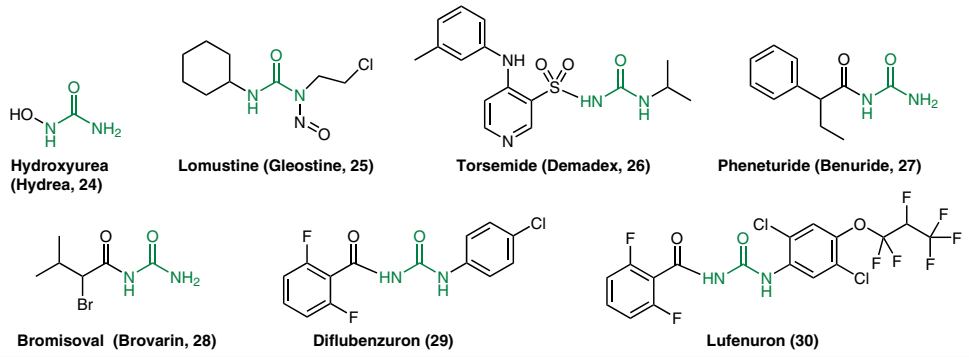


Figure 5 Modified urea group installed in drug molecules and agrochemicals

pounds (Figure 5). Ritonavir (**31**)[17] is an approved antiviral agent that contains both the carbamate and the urea groups (Figure 6).

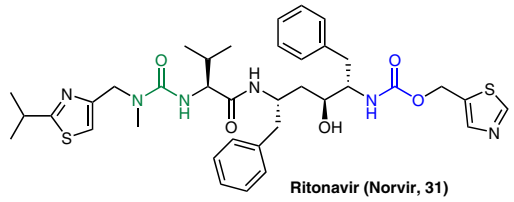
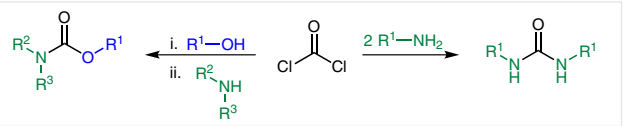
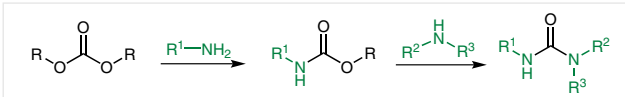


Figure 6 Structure of ritonavir

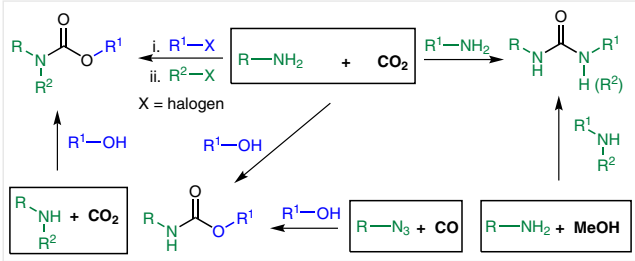
A plethora of synthetic protocols provide means for implementation of carbamate or urea functional groups within organic molecules. One of the oldest methods used to access carbamates and ureas utilizes the harsh reagent phosgene (Scheme 1).[18] Commonly adopted methods for preparation of carbamates and ureas are based on the addition of alcohols and amines, respectively, to isocyanates generated in situ or available commercially (Scheme 2).[5,19] Newer methods utilize milder and less toxic phosgene surrogates, carbonates, formamides, chloroformates, and other reagents (Scheme 3).[20] Most recent synthetic methods employ various metal and non-metal reagents and raw materials such as carbon monoxide, carbon dioxide, and methanol (Scheme 4).[5,21] Conversion of primary aliphatic amines and carbon dioxide to urea derivatives in the absence of solvent and catalyst was also reported.[22]



Scheme 1 Classic method for preparation of carbamates and ureas

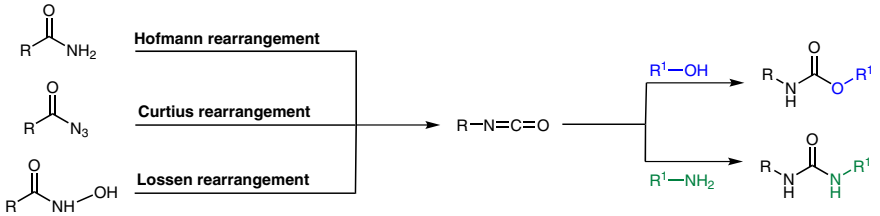


Scheme 3 Synthesis of carbamates and ureas from carbonates as the starting materials



Scheme 4 Exploitation of raw materials in the synthesis of substituted carbamates and ureas

A simple diacetyl urea (ureide) was first prepared nearly one and a half centuries ago by condensation of two equivalents of acetamide with phosgene.[23] Next, a stepwise approach to acyl urea, diacyl urea, and acyl carbamate was developed by reacting ammonia, amide, and alcohol, respectively, with an acyl isocyanate that was generated via

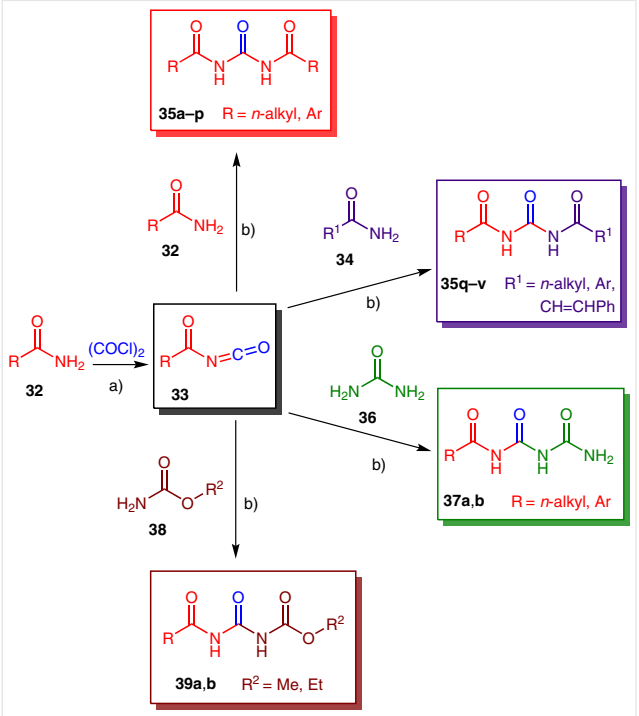


Scheme 2 Isocyanate-based method for the synthesis of carbamates and ureas

reaction of acetyl chloride with the explosive mercury(II) fulminate.[23b,24] Modification[25] of the initial method by replacing phosgene with oxalyl chloride provided diacyl ureas; however, limitation of this method was observed.[23b] Synthesis of symmetrical and unsymmetrical diacyl ureas by the condensation of monoacyl ureas with acyl chlorides and sulfuric acid as the catalyst was reported in 1938.[23b] The use of oxalyl chloride in generating acyl isocyanates from primary amides and their subsequent application to synthesis of acyl ureas, acyl carbamates, and thiocarbamates as well as other compounds was extensively investigated by Speziale and Smith.[26] Symmetrical diaroyl ureas can be prepared by the reaction of urea with aromatic acid esters in the presence of sodium hydride.[27] Alternatively, treatment of urea with excess of acyl chloride in a DMAP–pyridine solution affords a symmetrical diacyl urea derivative.[28] Dye-induced photooxygenation of imidazolin-2-ones also was shown to yield diacyl ureas.[29] Method for the preparation of diacyl ureas for use in agriculture from urea and carboxylic acids was also reported.[30] Metal-catalyzed carbonylation of urea derivatives with aryl halides affords aroyl ureas.[31]

Herein we report optimization and scoping studies on the addition of a wide range of nucleophiles **32**, **34**, **36**, **38**, **40**, **42**, **43**, and **45** to acyl isocyanates **33** generated by the reaction of primary amides **32** with oxalyl chloride (Scheme 5). This method provides means for convenient one-pot, two-step synthesis of symmetrical and unsymmetrical diacyl urea derivatives, acyl ureas/carbamates/thiocarbamates, and related compounds starting from cheap and commercially available reagents (Scheme 5). The obtained compounds are presented in Table 1.

Synthesis of the symmetrical 1,3-diaroyl ureas **35a–o** was efficient and provided the final products in yields ranging from good to excellent (67–92%) (Scheme 5, Table 1). Exception was the thiobenzamide, which did not provide the thio analogue of **35a** (results not shown).[32] Lower yield for the aliphatic diacyl urea **35p** in comparison to aromatic analogues is consistent with findings reported in the literature.[26b] The unsymmetrical acyl ureas **35q–v** were obtained in various yields. The aromatic compounds **35q** and **35s** were obtained in very good yields, similarly to the mixed aromatic-aliphatic counterparts **35u** and **35v**. For compounds **35s**, **35u**, and **35v**, the acyl isocyanates were generated from the corresponding benzamides. When the isocyanate was generated from nicotinamide (**34a**) followed by the addition of benzamide (**32a**), the crude reaction mixture consisted of several products; thus compound **35s** was neither isolated from that reaction nor the reaction for symmetrical 1,3-dinicotinoyl urea was successful. The reaction yield for compound **35r** was slightly decreased due to use of only 1.0 equivalent of *p*-chlorobenzamide. It is noteworthy that the product **35r** is a close analogue of diflubenzuron (**29**). The yield for **35t** was compromised by



Scheme 5 Elaboration of acyl isocyanates **33** obtained from primary amides **32**. *Reagents and conditions*: a) i. **32** (1.0 mmol), anhyd CH_2Cl_2, r.t., 5 min, ii. $(COCl)_2$ (3.0 equiv) reflux 2.5–3 h, iii. r.t., in vacuo solvent evaporation; b) nucleophile **32**, **34**, **36**, or **38** (1.1–1.25 equiv), anhyd toluene, reflux, 2.5–3 h.

difficult purification. In general, the reaction for unsymmetrical diacyl ureas was rather capricious, often accompanied by formation of a small amount of the symmetrical product rendering the need for purification and/or adjustment of equivalents of the nucleophile.

Addition of urea (**36**) to isocyanates generated from amides **32a** and **32p** furnished the expected products **37a** and **37b**, respectively (Scheme 5). The reverse reaction was unsuccessful. Compound **37a** was also obtained (87% yield) when two equivalents of benzoyl isocyanate (**33a**; R = Ph, prepared from **32a**) were used with respect to one equivalent of urea, thus indicating that the carbamoylation occurs only at one site of the urea. This result differs from the reported observation relating to the reaction of urea with equimolar amounts of benzoyl isothiocyanate to provide the thio analogue of **37a** along with small quantities of the diadduct.[33] Attempts of reaction of product **37a** with isocyanate **33a** or benzoyl chloride were ineffective, presumably due to insolubility of **37a** in the reaction solvent (results not shown). The concept of dicarbamoylation was further investigated by attempting to generate diisocyanate from 4,5-dichlorophthalamide and further addition of 2 equivalents of benzamide. This reaction failed due to the likely decomposition of the diisocyanate during in vacuo evaporation of dichloromethane.[34] Instead of the desired product,

small amount of compound **35a** (23%) was isolated from this reaction. The reverse approach, namely addition of 4,5-dichlorophthalamide to two equivalents of benzoyl isocyanate (**33a**) also did not occur and the starting material (4,5-dichlorophthalamide) was isolated (73%). This reaction did not proceed, likely due to steric hindrance factors. Addition of succinamide to 2 equivalents of benzoyl isocyanate (**33a**) was unproductive, which supported the initial observation that under the present reaction conditions the dicarbamoylation reaction is apparently ineffective. Conversion of succinamide to the corresponding diisocyanate was not pursued due to the unsatisfactory results for this reaction reported earlier.[34]

Table 1 Structural Formulas of the Reaction Substrates and Final Products

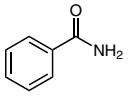
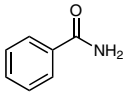
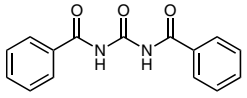
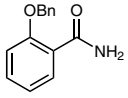
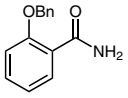
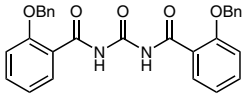
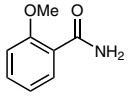
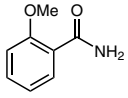
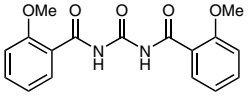
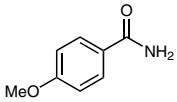
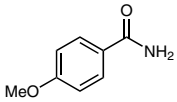
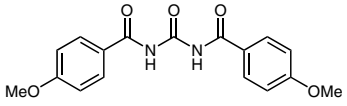
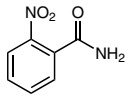
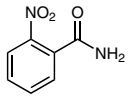
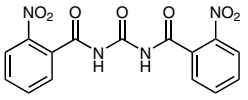
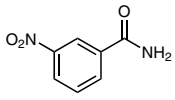
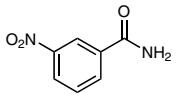
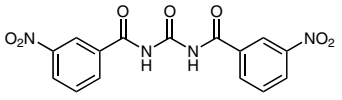
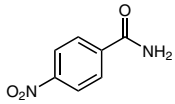
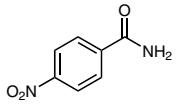
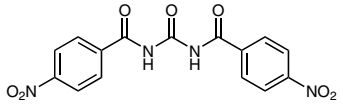
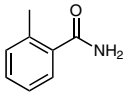
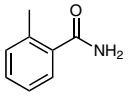
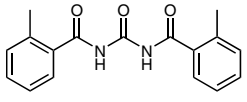
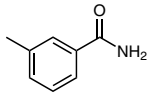
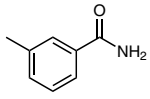
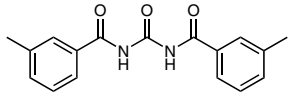
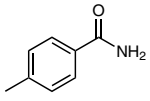
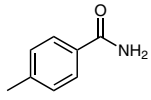
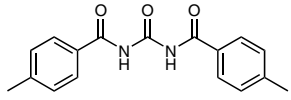
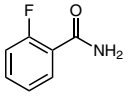
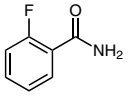
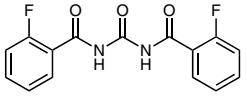
No	Starting amide		Nucleophile		Final product		Yield (%)
1	**32a**		**32a**		**35a**		89
2	**32b**		**32b**		**35b**		85
3	**32c**		**32c**		**35c**		88
4	**32d**		**32d**		**35d**		83[a]
5	**32e**		**32e**		**35e**		70[b]
6	**32f**		**32f**		**35f**		92
7	**32g**		**32g**		**35g**		67
8	**32h**		**32h**		**35h**		83
9	**32i**		**32i**		**35i**		82
10	**32j**		**32j**		**35j**		90
11	**32k**		**32k**		**35k**		93

Table 1 (continued)

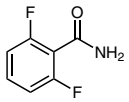
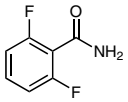
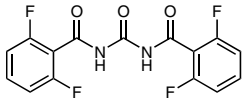
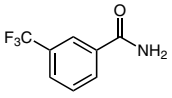
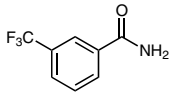
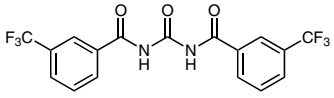
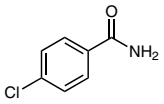
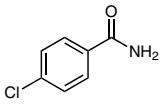
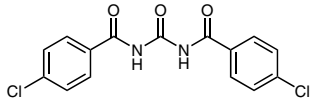
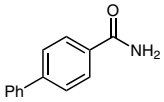
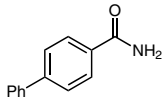
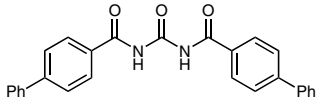
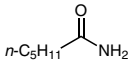
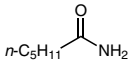
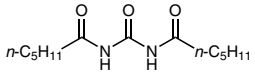
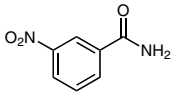
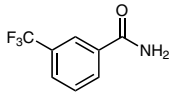
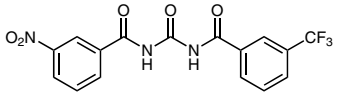
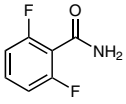
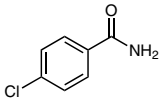
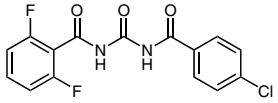
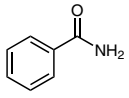
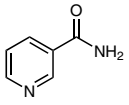
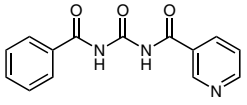
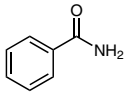
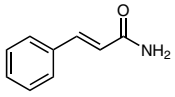
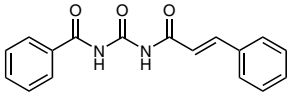
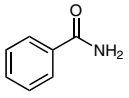
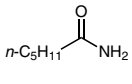
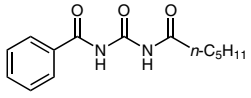
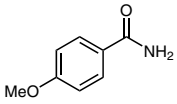
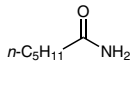
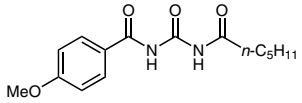
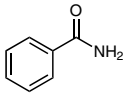
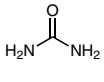
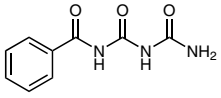
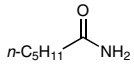
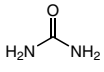
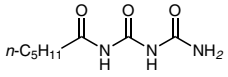
No	Starting amide	Nucleophile	Final product	Yield (%)
12	**32l** 	**32l** 	**35l** 	85
13	**32m** 	**32m** 	**35m** 	68
14	**32n** 	**32n** 	**35n** 	91
15	**32o** 	**32o** 	**35o** 	85
16	**32p** 	**32p** 	**35p** 	60
17	**32f** 	**32m** 	**35q** 	85
18	**32l** 	**32n** 	**35r** 	66[c]
19	**32a** 	**34a** 	**35s** 	88[d]
20	**32a** 	**34b** 	**35t** 	69[e]/16[f]
21	**32a** 	**32p** 	**35u** 	72
22	**32d** 	**32p** 	**35v** 	86
23	**32a** 	**36** 	**37a** 	87[g]
24	**32p** 	**36** 	**37b** 	51[f]

Table 1 (continued)

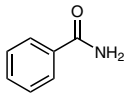
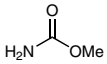
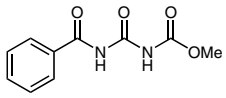
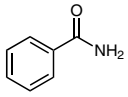
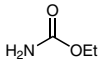
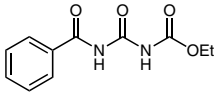
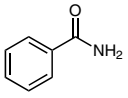
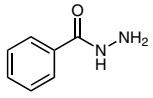
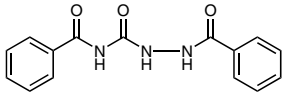
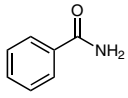
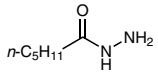
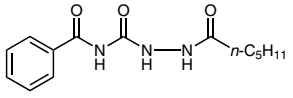
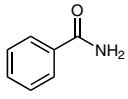
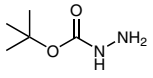
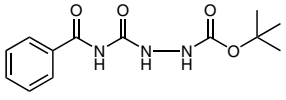
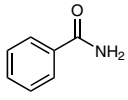
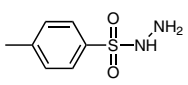
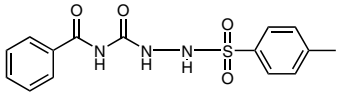
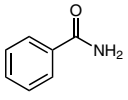
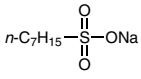
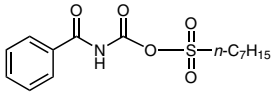
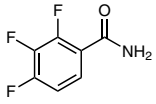
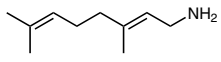
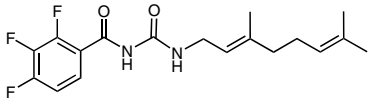
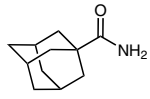
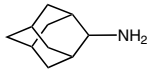
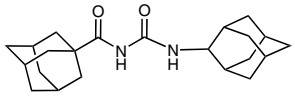
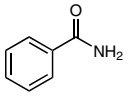
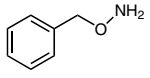
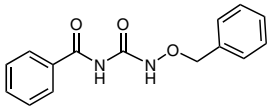
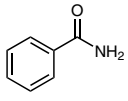
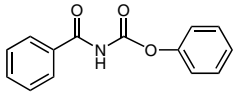
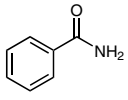
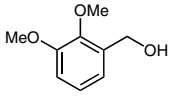
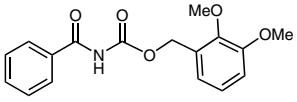
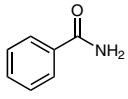
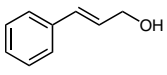
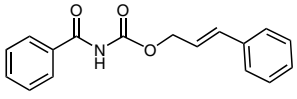
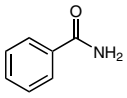
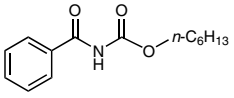
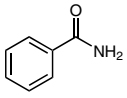
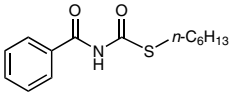
No	Starting amide	Nucleophile	Final product	Yield (%)
25	**32a** 	**38a** 	**39a** 	59[h]
26	**32a** 	**38b** 	**39b** 	55[i]
27	**32a** 	**40a** 	**41a** 	88
28	**32a** 	**40b** 	**41b** 	89[j]
29	**32a** 	**42** 	**41c** 	83
30	**32a** 	**43a** 	**44a** 	73
31	**32a** 	**43b** 	**44b** 	90
32	**32q** 	**45a** 	**46a** 	74[k]/34[f]
33	**32r** 	**45b** 	**46b** 	60[f]
34	**32a** 	**45c** 	**46c** 	78
35	**32a** 	**45d** 	**46d** 	58
36	**32a** 	**45e** 	**46e** 	74[f]
37	**32a** 	**45f** 	**46f** 	79[f]

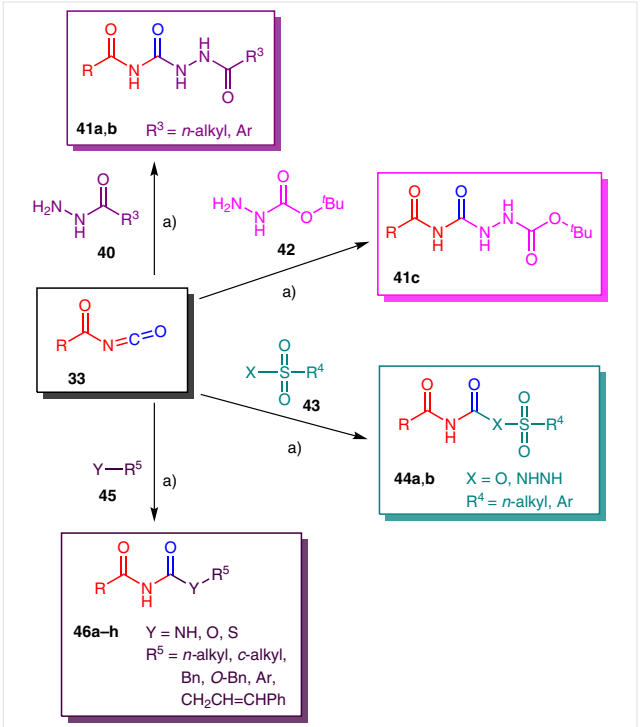
Table 1 (continued)

No	Starting amide		Nucleophile		Final product		Yield (%)
38	**32a**		**45g**	*n*-C_6H_{13}—OH	**46g**		92
39	**32a**		**45h**	*n*-C_6H_{13}—SH	**46h**		90[f]

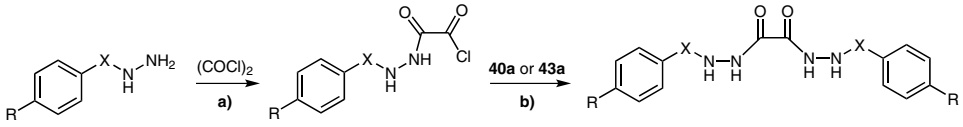
[a] 3 mmol scale reaction.
[b] After purification by crystallization from MeOH.
[c] 1 equivalent of *p*-chlorobenzamide (1 equiv) was used. The isolated crude product was still contaminated with ~5% of *p*-chlorobenzamide as determined by ^{1}H NMR spectroscopy.
[d] Isolated crude product contaminated with ~25% of an unknown by-product as determined by ^{13}C NMR spectroscopy.
[e] Isolated crude product contaminated with cinnamide.
[f] After purification by flash chromatography.
[g] 2 mmol scale reaction with 1.0 equivalent of urea being used.
[h] 2 equivalents of methyl carbamate were used.
[i] Isolated crude product contaminated with ~20% of an unknown by-product as determined by ^{1}H NMR spectroscopy.
[j] Contaminated with ~5% of unknown by-product as determined by ^{1}H NMR spectroscopy.
[k] Isolated crude product contaminated with geranylamine as determined by ^{1}H NMR spectroscopy.

Addition of methyl carbamate (**38a**) and ethyl carbamate (**38b**) to isocyanate **33a** provided products **39a** and **39b**, respectively, in moderate yields and deteriorated purity for **39b** (Scheme 5, Table 1). Reaction of isocyanate **33a** with hydrazides **40a**, and **40b**, *tert*-butyl carbazate (**42**), and *p*-toluenesulfonyl hydrazide **43a** provided in good yields the expected products **41a**,**b**, **41c**, and **44a**, respectively (Scheme 6). Conversion of benzhydrazide (**40a**) to its corresponding isocyanate and subsequent treatment with benzamide resulted in a mixture of products, two of them deemed to be the compounds **41a** and **48a** (entry 27, and Scheme 7). Of note is the fact that the thio analogue of compound **41a**, that is, 1,4-dibenzoylthiosemicarbazide, was previously obtained via reaction of equimolar amounts of hydrazine hydrate with benzoyl isothiocyanate.[35] An interesting outcome was obtained when benzhydrazide (**40a**) and *p*-toluenesulfonyl hydrazide (**43a**) were treated with oxalyl chloride followed by the addition of **40a** and **43a**, respectively (Scheme 7). In both cases, substitution reaction occurred to provide the symmetrical products **48a** and **48b** in good yields (Scheme 7). However, nucleophilic substitution reactions that occur in similar manner with oxalyl chloride are known in the literature.[34,36] In contrast, addition of **40a** to **47b** provided unidentified mixture of products.

Sodium 1-heptanesulfonate (**43b**) readily reacted with **33a** to give the final product **44b** in excellent yield (Scheme 6). Disappointingly, reactions of benzenesulfonamide with **33a** resulted in a mixture of products that was not further analyzed. Other compounds that were unproductively reacted with **33a** include benzoic acid, sodium benzoate, benzhydroxamic acid, dibutyl phosphate, diethyl phosphoramidate, and certain amino acids such as L-serine and L-arginine (results not shown). The unsatisfactory outcome of addition of the amino acids to **33a** is especially disappointing as similar reaction of acyl isothiocyanates with several amino acids has been reported.[37] Reaction of geranyl amine



Scheme 6 Elaboration of acyl isocyanates **33**. *Reagents and conditions*: a) nucleophile **40**, **42**, **43**, or **45** (1.1–1.25 equiv), anhyd toluene, reflux, 2.5–3 h.



Scheme 7 Reaction of oxalyl chloride with hydrazides **40a** and **43a**. *Reagents and conditions*: a) i. **40a** or **43a** (1.0 mmol), anhyd CH_2Cl_2, r.t., 5 min, ii. $(COCl)_2$ (3.0 equiv), reflux 2.5–3 h, iii. r.t., in vacuo solvent evaporation; b) **40a** or **43a** (1.1 equiv), anhyd toluene, reflux, 2–3 h.

(**45a**), 2-adamantylamine (**45b**), and *O*-benzylhydroxylamine (**45c**) with the corresponding isocyanates **33q**, **33r**, **33a** gave the final products **46a–c**, respectively. The significantly lower yield for **46a** pertains to difficult purification of the final product. Addition of various alcohols **45d–g** and a thiol **45h** to **33a** resulted in a range of benzoyl carbamates **46d–g** and benzoyl thiocarbamate (**46h**), respectively. The lower yield for **46d** is assumed to be associated with the lower nucleophilicity of phenol (**45d**) when compared to the other alcohols **45e–g** used in the reaction.

In conclusion, we have reported an optimized synthetic procedure for the synthesis of a wide range of organic molecules **35**, **37**, **39**, **41**, **44**, **46**, **48** possessing diacyl urea; acyl urea, acyl carbamate, acyl thiocarbamate, acyl semicarbazide; and other functional groups. Overall, the reaction is efficient (high yielding) with conversion time of approximately six hours for both steps and straightforward isolation of the crude materials. The isolated products were virtually pure except for a few cases when crystallization or automated flash chromatography purification method was applied. The obtained final products are deemed to share structural similarities with reported agents possessing antibacterial and antiprotozoal activities.[38] Accordingly, the synthetic protocol is currently utilized in the synthesis of compounds suitable for biological investigation. It is believed that the presented results will be of interest to the broader audience of synthetic organic and medicinal chemists.[39]

All reagents were purchased from Sigma-Aldrich and Fisher Scientific. Anhyd toluene was purchased from Sigma-Aldrich whereas anhyd CH_2Cl_2 was obtained by distillation over CaH_2. ^1H NMR and ^{13}C NMR spectra were recorded on a Jeol spectrometer at 400 and 100 MHz, respectively. NMR spectra were reprocessed by ACD/NMR Processor Academic Edition version 12.01. Standard abbreviations were used for indicating multiplicity. HRMS experiments were performed on Agilent 6224 Tof-MS instrument with a mixed chemical ionization/positive electrospray (CI/+ESI) mode. TLC was performed on Merck 60 F254 silica gel plates. Flash chromatography was performed using a Biotage - Isolera™ system with pre-packed silica gel columns (Biotage FLSH SNAP CRT SI 10, 25, or 50 grams).

Synthesis of 35, 37, 39, 41, 44, 46, and 48; General Procedure

The appropriate amide **32a–p**, benzhydrazide (**40a**), or *p*-toluenesulfonyl hydrazide (**43a**) (1.0 mmol, 1.0 equiv) was placed in a Schlenk Kjeldahl reaction flask and the flask was evacuated/argon re-filled three times. Subsequently, anhyd CH_2Cl_2 (25 mL) was added and the mixture was stirred at r.t. for 10 min before dropwise addition of oxalyl chloride (3.0 mmol, 3.0 equiv) followed. The reaction mixture was then stirred at reflux for 2.5–3.0 h before cooling to r.t. and the solvent was evaporated in vacuo. Subsequently, the appropriate nucleophile **32**, **34**, **36**, **38**, **40**, **42**, **43**, or **45** (1.1–1.25 mmol, 1.1–1.25 equiv) was rapidly added and the flask was evacuated/argon re-filled before anhyd toluene (12 mL) was added. The reaction mixture was then stirred at reflux for 2.5–3 h before cooling to r.t. and concentration to about 1/3 of the initial volume on rotavapor. Hexane was added to the residue and the obtained precipitate (often sonicated) was collected by filtration under reduced pressure to yield the crude product. When necessary, the isolated material was purified either by crystallization from MeOH or flash chromatography on silica gel with hexane–EtOAc as the eluent.

***N,N′*-Carbonyldibenzamide (35a)**

Milky-white solid; yield: 240 mg (89%).

^1H NMR (400 MHz, DMSO-d_6): δ = 11.84 (s, 2 H), 7.97–7.92 (dd, *J* = 7.4, 1.4 Hz, 4 H), 7.68–7.63 (t, *J* = 7.4 Hz, 2 H), 7.58–7.52 (t, *J* = 7.4 Hz, 4 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 167.3 (2 C), 149.5 (C), 133.9 (2 × CH), 133.0 (2 C), 129.4 (4 × CH), 128.5 (4 × CH).

HRMS: *m*/*z* $[M]^+$ calcd for $C_{15}H_{12}N_2O_3$: 268.0848; found: 268.0851.

***N,N′*-Carbonylbis[2-(benzyloxy)benzamide] (35b)**

Off-white solid; yield: 410 mg (85%).

^1H NMR (400 MHz, DMSO-d_6): δ = 11.53 (s, 2 H), 7.67 (dd, *J* = 7.8, 1.4 Hz, 2 H), 7.51 (td, *J* = 7.9, 1.6 Hz, 2 H), 7.45–7.43 (m, 4 H), 7.29–7.21 (m, 8 H), 7.04 (t, *J* = 7.7 Hz, 2 H), 5.29 (s, 4 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 166.0 (2 C), 156.6 (2 C), 148.7 (C), 136.8 (2 C), 134.5 (2 C), 131.4 (2 C), 129.0 (4 × CH), 128.5 (2 × CH), 128.0 (4 × CH), 122.6 (2 C), 121.5 (2 × CH), 114.2 (2 × CH), 70.5 (2 × CH_2).

HRMS: *m*/*z* $[M]^+$ calcd for $C_{29}H_{24}N_2O_5$: 480.1685; found: 480.1691.

***N,N′*-Carbonylbis(2-methoxybenzamide) (35c)**

Grey powder; yield: 288 mg (88%).

^1H NMR (400 MHz, DMSO-d_6): δ = 11.57 (s, 2 H), 7.78 (dd, *J* = 7.8, 1.4 Hz, 2 H), 7.56 (td, *J* = 7.8, 1.8 Hz, 2 H), 7.19 (d, *J* = 8.2 Hz, 2 H), 7.07 (t, *J* = 7.6 Hz, 2 H), 3.93 (s, 6 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 165.7 (2 C), 157.8 (2 C), 148.8 (C), 134.8 (2 × CH), 131.5 (2 × CH), 121.8 (2 C), 121.4 (2 × CH), 112.9 (2 × CH), 56.6 (2 × OCH_3).

HRMS: *m*/*z* [M]$^+$ calcd for $C_{17}H_{16}N_2O_5$: 328.1059; found: 328.1064.

***N,N′*-Carbonylbis(4-methoxybenzamide) (35d)**

White powder; yield: 820 mg (83% on a 3.0 mmol scale).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.77 (s, 2 H), 7.96–7.91 (m, 4 H), 7.10–7.05 (m, 4 H), 3.82 (s, 6 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 166.5 (2 C), 163.8 (2 C), 149.7 (C), 130.7 (4 × CH), 124.9 (2 C), 114.7 (4 × CH), 56.1 (2 × OCH_3).

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{17}N_2O_5$: 329.1132; found: 329.1131.

***N,N′*-Carbonylbis(2-nitrobenzamide) (35e)**

White powder; yield: 250 mg (70%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.29 (s, 2 H), 8.19 (d, *J* = 7.8 Hz, 2 H), 7.89–7.84 (m, 2 H), 7.76–7.68 (m, 4 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 168.2 (2 C), 149.4 (C), 145.7 (2 C), 135.4 (2 × CH), 132.0 (2 × CH), 131.8 (2 C), 129.1 (2 × CH), 124.8 (2 × CH).

HRMS: *m*/*z* [M]$^+$ calcd for $C_{15}H_{10}N_4O_7$: 358.0549; found: 358.0551.

***N,N′*-Carbonylbis(3-nitrobenzamide) (35f)**

Off-white powder; yield: 330 mg (92%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.94 (s, 2 H), 8.71 (br s, 2 H), 8.51–8.47 (m, 2 H), 8.34 (m, 2 H), 7.86 (t, *J* = 8.0 Hz, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 165.6 (2 C), 149.2 (C), 148.4 (2 C), 134.7 (2 × CH), 134.6 (2 C), 131.3 (2 × CH), 128.2 (2 × CH), 123.4 (2 × CH).

HRMS: *m*/*z* [M]$^+$ calcd for $C_{15}H_{10}N_4O_7$: 358.0549; found: 358.0547.

***N,N′*-Carbonylbis(4-nitrobenzamide) (35g)**

Off-white powder; yield: 240 mg (67%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.90 (s, 2 H), 8.37 (d, *J* = 8.7 Hz, 4 H), 8.13 (d, *J* = 8.7 Hz, 4 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 166.1 (2 C), 150.6 (2 C), 149.2 (C), 138.6 (2 C), 130.1 (4 × CH), 124.5 (4 × CH).

HRMS: *m*/*z* [M]$^+$ calcd for $C_{15}H_{10}N_4O_7$: 358.0549; found: 358.0552.

***N,N′*-Carbonylbis(2-methylbenzamide) (35h)**

White powder; yield: 245 mg (83%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.40 (s, 2 H), 7.52 (d, *J* = 7.3 Hz, 2 H), 7.41 (t, *J* = 7.3 Hz, 2 H), 7.31–7.25 (m, 4 H), 2.37 (s, 6 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 169.8 (2 C), 149.2 (C), 136.9 (2 C), 134.8 (2 C), 131.7 (2 × CH), 131.6 (2 × CH), 128.0 (2 × CH), 126.4 (2 × CH), 20.1 (2 × CH_3).

HRMS: *m*/*z* [M]$^+$ calcd for $C_{17}H_{16}N_2O_3$: 296.1161; found: 296.1166.

***N,N′*-Carbonylbis(3-methylbenzamide) (35i)**

White crystalline product; yield: 242 mg (82%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.78 (s, 2 H), 7.77 (br s, 2 H), 7.73 (d, *J* = 7.3 Hz, 2H), 7.49–7.40 (m, 4 H), 2.36 (s, 6 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 167.3 (2 C), 149.5 (C), 138.9 (2 C), 134.5 (2 × CH), 133.0 (2 C), 129.3 (2 × CH), 129.0 (2 × CH), 125.6 (2 × CH), 21.4 (2 × CH_3).

HRMS: *m*/*z* [M]$^+$ calcd for $C_{17}H_{16}N_2O_3$: 296.1161; found: 296.1164.

***N,N′*-Carbonylbis(3-methylbenzamide) (35j)**

White crystalline product; yield: 268 mg (90%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.79 (s, 2 H), 7.84 (d, *J* = 8.2 Hz, 4 H), 7.34 (d, *J* = 8.2 Hz, 4 H), 2.35 (s, 6 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 167.1 (2 C), 149.6 (C), 144.3 (2 C), 130.1 (2 C), 130.0 (4 × CH), 128.6 (4 × CH), 21.6 (2 × CH_3).

HRMS: *m*/*z* [M]$^+$ calcd for $C_{17}H_{16}N_2O_3$: 296.1161; found: 296.1166.

***N,N′*-Carbonylbis(2-fluorobenzamide) (35k)**

Milky-white powder; yield: 283 mg (93%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.57 (s, 2 H), 7.76–7.68 (m, 2 H), 7.67–7.57 (m, 2 H), 7.39–7.26 (m, 4 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 164.7 (2 C), 159.8 (2 C, d, $J_{C,F}$ = 252.1 Hz), 148.8 (C), 135.1 (2 × CH, d, $J_{C,F}$ = 8.6 Hz), 131.1 (2 × CH), 125.4 (2 × CH, d, $J_{C,F}$ = 3.8 Hz), 122.4 (2 C, d, $J_{C,F}$ = 12.5 Hz), 117.0 (2 × CH, d, $J_{C,F}$ = 22.1 Hz).

HRMS: *m*/*z* [M]$^+$ calcd for $C_{15}H_{10}F_2N_2O_3$: 304.0659; found: 304.0668.

***N,N′*-Carbonylbis(2,6-difluorobenzamide) (35l)**

Off-white powder; yield: 290 mg (85%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.39 (s, 2 H), 7.59 (m, 2 H), 7.21 (t, *J* = 8.2 Hz, 4 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 161.6 (2 C), 159.2 (2 C, d, $J_{C,F}$ = 250.1 Hz), 159.1 (2 C, d, $J_{C,F}$ = 250.2 Hz), 148.6 (C), 134.0 (2 × CH, t, $J_{C,F}$ = 10.6 Hz), 113.8 (2 C, t, $J_{C,F}$ = 20.1 Hz), 112.8 (4 × CH, d, $J_{C,F}$ = 23.0 Hz).

HRMS: *m*/*z* [M]$^+$ calcd for $C_{15}H_8F_4N_2O_3$: 340.0471; found: 340.0474.

***N,N′*-Carbonylbis[3-(trifluoromethyl)benzamide] (35m)**

White solid; yield: 275 mg (68%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.90 (s, 2 H), 8.24 (br s, 2 H), 8.21 (d, *J* = 7.8 Hz, 2 H), 8.03 (d, *J* = 7.8 Hz, 2 H), 7.81 (t, *J* = 7.8 Hz, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 166.1 (2 C), 149.3 (C), 134.1 (2 C), 132.6 (2 × CH), 130.8 (2 × CH), 130.3 (2 × CH, d, $J_{C,F}$ = 3.9 Hz), 130.1 (2 C, q, $J_{C,F}$ = 32.3 Hz), 125.2 (2 × CH, d, $J_{C,F}$ = 3.8 Hz), 124.3 (2 × CH, q, $J_{C,F}$ = 272.5 Hz).

HRMS: *m*/*z* [M]$^+$ calcd for $C_{17}H_{10}F_6N_2O_3$: 404.0596; found: 404.0598.

***N,N′*-Carbonylbis(4-chlorobenzamide) (35n)**

White crystalline product; yield: 307 mg (91%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.80 (s, 2 H), 7.93 (d, *J* = 8.2 Hz, 4 H), 7.63 (d, *J* = 8.2 Hz, 4 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 166.4 (2 C), 149.4 (C), 138.8 (2 C), 131.8 (2 C), 130.5 (4 × CH), 129.6 (4 × CH).

HRMS: *m*/*z* [M]$^+$ calcd for $C_{15}H_{10}Cl_2N_2O_3$: 336.0068; found: 336.0072.

***N,N′*-Carbonylbis([1,1′-biphenyl]-4-carboxamide) (35o)**

Milky-white solid; yield: 359 mg (85%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.92 (s, 2 H), 8.08–8.04 (m, 4 H), 7.89–7.85 (m, 4 H), 7.76–7.73 (m, 4 H), 7.51–7.46 (m, 4 H), 7.43–7.38 (m, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 167.0 (2 C), 149.6 (C), 145.3 (2 C), 139.2 (2 C), 131.7 (2 C), 129.7 (4 × CH), 129.3 (4 × CH), 129.1 (2 × CH), 127.6 (8 × CH).

HRMS: *m*/*z* [M]$^+$ calcd for $C_{27}H_{20}N_2O_3$: 420.1474; found: 420.1474.

N,N′-Carbonyldihexanamide (35p)

White powder; yield: 153 mg (60%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.83 (s, 2 H), 2.47–2.44 (m overlapped with DMSO, 4 H), 1.49 (quint, J = 7.3 Hz, 4 H), 1.29–1.15 (m, 8 H), 0.82 (t, J = 6.9 Hz, 6 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 175.5 (2 C), 150.0 (C), 36.9 (2 × CH_2), 31.1 (2 × CH_2), 24.1 (2 × CH_2), 22.4 (2 × CH_2), 14.3 (2 × CH_3).

HRMS: m/z [M]$^+$ calcd for $C_{13}H_{24}N_2O_3$: 256.1787; found: 256.1790.

3-Nitro-*N*-{[3-(trifluoromethyl)benzoyl]carbamoyl}benzamide (35q)

Off-white solid; yield: 325 mg (85%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.93 (br s, 2 H), 8.71 (m, 1 H), 8.48 (m, 1 H), 8.34 (m, 1 H), 8.25 (br s, 1 H), 8.22 (d, J = 7.8 Hz, 1 H), 8.04 (d, J = 7.8 Hz, 1 H), 7.86 (t, J = 8.0 Hz, 1 H), 7.81 (t, J = 7.8 Hz, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 166.2 (C), 165.6 (C), 165.5 (C), 149.3 (C), 148.4 (C), 134.7 (CH, q, $J_{C,F}$ = 4.8 Hz), 134.1 (C), 132.6 (CH), 131.3 (CH), 130.8 (CH), 130.3 (CH, d, $J_{C,F}$ = 2.9 Hz), 130.1 (C, q, $J_{C,F}$ = 32.3 Hz), 128.2 (CH), 125.3 (CH, d, $J_{C,F}$ = 3.8 Hz), 124.3 (C, q, $J_{C,F}$ = 272.2 Hz), 123.4 (CH).

HRMS: m/z [M]$^+$ calcd for $C_{16}H_{10}F_3N_3O_5$: 381.0573; found: 381.0567.

***N*-[(4-Chlorobenzoyl)carbamoyl]-2,6-difluorobenzamide (35r)**

White solid; yield: 222 mg (66%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.66 (br s, 1 H), 11.41 (br s, 1 H), 7.90 (d, J = 8.2 Hz, 2 H), 7.64–7.57 (m, 1 H), 7.61 (d, J = 8.2 Hz, 2 H), 7.23 (t, J = 8.2 Hz, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 166.5 (C), 161.7 (C), 159.2 (2 C, dd, $J_{C,F}$ = 250.7, 7.2 Hz), 149.0 (C), 138.8 (C), 134.0 (CH, t, $J_{C,F}$ = 10.1 Hz), 131.7 (C), 130.6 (2 × CH), 129.9 (2 × CH), 114.0 (C, t, $J_{C,F}$ = 20.6 Hz), 112.9 (2 × CH, d, $J_{C,F}$ = 23.0 Hz).

HRMS: m/z [M]$^+$ calcd for $C_{15}H_9ClF_2N_2O_3$: 338.0270; found: 338.0275.

***N*-(Benzoylcarbamoyl)nicotinamide (35s)**

Off-white solid; yield: 236 mg (88%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.86 (br s, 1 H), 11.83 (br s, 1 H), 9.06 (d, J = 1.8 Hz, 1 H), 8.79 (dd, J = 4.8, 1.6 Hz, 1 H), 8.27 (m, 1 H), 7.95–7.92 (m, 2 H), 7.66 (m, 1 H), 7.61–7.53 (m, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 166.8 (C), 166.7 (C), 154.0 (CH), 149.5 (CH), 149.4 (C), 136.5 (CH), 133.9 (CH), 133.0 (C), 129.5 (2 × CH), 129.0 (C), 128.4 (2 × CH), 124.3 (CH).

HRMS: m/z [M]$^+$ calcd for $C_{14}H_{11}N_3O_3$: 269.0800; found: 269.0812.

***N*-(Cinnamoylcarbamoyl)benzamide (35t)**

White solid; yield: 48 mg (16%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.14 (br s, 1 H), 11.25 (br s, 1 H), 7.89 (d, J = 7.3 Hz, 2 H), 7.79 (d, J = 16.0 Hz, 1 H), 7.68–7.59 (m, 3 H), 7.56 (t, J = 7.6 Hz, 2 H), 7.44 (m, 3 H), 6.92 (d, J = 16.0 Hz, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 167.8 (C), 165.4 (C), 149.7 (C), 145.5 (CH), 134.4 (C), 133.8 (CH), 133.4 (C), 131.5 (CH), 129.7 (2 × CH), 129.6 (2 × CH), 128.9 (2 × CH), 128.1 (2 × CH), 120.0 (CH).

HRMS: m/z [M]$^+$ calcd for $C_{17}H_{14}N_2O_3$: 294.1004; found: 294.1013.

***N*-(Hexanoylcarbamoyl)benzamide (35u)**

White crystalline product; yield: 190 mg (72%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.82 (s, 1 H), 11.02 (s, 1 H), 7.85 (dd, J = 7.6, 1.4 Hz, 2 H), 7.64 (t, J = 7.3 Hz, 1 H), 7.54 (t, J = 7.6 Hz, 2 H), 2.46–4.43 (m overlapped with DMSO, 2 H), 1.53 (quint, J = 7.3 Hz, 2 H), 1.29–1.18 (m, 4 H), 0.83 (t, J = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 176.5 (C), 165.9 (C), 149.5 (C), 133.8 (CH), 133.2 (C), 129.5 (2 × CH), 128.2 (2 × CH), 36.7 (CH_2), 31.1 (CH_2), 24.2 (CH_2), 22.4 (CH_2), 14.3 (CH_3).

HRMS: m/z [M]$^+$ calcd for $C_{14}H_{18}N_2O_3$: 262.1317; found: 262.1324.

***N*-(Hexanoylcarbamoyl)-4-methoxybenzamide (35v)**

White crystalline product; yield: 252 mg (86%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.67 (s, 1 H), 11.04 (s, 1 H), 7.84 (d, J = 8.7 Hz, 2 H), 7.06 (d, J = 9.2 Hz, 2 H), 3.80 (s, 3 H), 2.47–2.44 (m overlapped with DMSO, 2 H), 1.52 (quint, J = 7.3 Hz, 2 H), 1.30–1.20 (m, 4 H), 0.82 (t, J = 6.7 Hz, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 176.3 (C), 165.4 (C), 163.7 (C), 149.7 (C), 130.4 (2 × CH), 125.1 (C), 114.8 (2 × CH), 56.1 (CH_3), 36.7 (CH_2), 31.1 (CH_2), 24.2 (CH_2), 22.4 (CH_2), 14.3 (CH_3).

HRMS: m/z [M]$^+$ calcd for $C_{15}H_{20}N_2O_4$: 292.1423; found: 292.1428.

***N*-(Carbamoylcarbamoyl)benzamide (37a)**

White powder; yield: 360 mg (87%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.34 (br s, 1 H), 10.25 (s, 1 H), 7.92 (dd, J = 7.6, 1.4 Hz, 2 H), 7.62 (t, J = 7.3 Hz, 1 H), 7.50 (t, J = 7.6 Hz, 2 H), 7.45–7.33 (br s, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 168.6 (C), 153.7 (C), 152.5 (C), 133.8 (CH_2), 132.7 (C), 129.2 (2 × CH_2), 128.8 (2 × CH_2).

HRMS: m/z [M]$^+$ calcd for $C_9H_9N_3O_3$: 207.0644; found: 207.0644.

***N*-(Carbamoylcarbamoyl)hexanamide (37b)**

Off-white solid; yield: 102 mg (51%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.84 (s, 1 H), 10.08 (s, 1 H), 7.35 (s, 2 H), 2.33 (t, J = 7.3 Hz, 2 H), 1.48 (quint, J = 7.4 Hz, 2 H), 1.28–1.15 (m, 4 H), 0.82 (t, J = 6.9 Hz, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 176.5 (C), 153.4 (C), 152.4 (C), 36.4 (CH_2), 31.1 (CH_2), 24.3 (CH_2), 22.3 (CH_2), 14.3 (CH_3).

HRMS: m/z [M]$^+$ calcd for $C_8H_{15}N_3O_3$: 201.1113; found: 201.1113.

Methyl (Benzoylcarbamoyl)carbamate (39a)

White solid; yield: 131 mg (59%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.29 (s, 1 H), 10.94 (s, 1 H), 7.88 (d, J = 7.8 Hz, 2 H), 7.62 (t, J = 7.3 Hz, 1 H), 7.51 (s, 2 H), 3.68 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 167.3 (C), 153.1 (C), 149.1 (C), 133.8 (C), 132.9 (CH), 129.3 (2 × CH), 128.5 (2 × CH), 53.4 (OCH_3).

HRMS: m/z [M]$^+$ calcd for $C_{10}H_{10}N_2O_4$: 222.0641; found: 222.0646.

Ethyl (Benzoylcarbamoyl)carbamate (39b)

Off-white solid; yield: 131 mg (55%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.29 (s, 1 H), 10.89 (s, 1 H), 7.88 (d, J = 7.3 Hz, 2 H), 7.65–7.60 (m, 1 H), 7.57–7.49 (m, 2 H), 4.14 (q, J = 7.3 Hz, 2 H), 1.20 (t, J = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 167.4 (C), 152.5 (C), 149.1 (C), 133.8 (CH), 132.9 (CH), 129.3 (2 × CH), 128.5 (2 × CH), 62.3 (OCH_2), 14.6 (CH_3).

HRMS: m/z [M]$^+$ calcd for $C_{11}H_{12}N_2O_4$: 222.0641; found: 222.0646.

N,2-Dibenzoylhydrazine-1-carboxamide (41a)

Pale yellow powder; yield: 248 mg (88%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.07 (s, 1 H), 10.62 (d, *J* = 1.4 Hz, 1 H), 10.13 (d, *J* = 1.4 Hz, 1 H), 7.97 (d, *J* = 7.3 Hz, 2 H), 7.87 (dd, *J* = 7.6, 1.4 Hz, 2 H), 7.62 (t, *J* = 7.3 Hz, 1 H), 7.56 (t, *J* = 7.3 Hz, 1 H), 7.52–7.46 (m, 4 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 168.6 (C), 166.0 (C), 154.3 (C), 133.6 (CH), 132.7 (2 C), 132.5 (CH), 129.1 (2 × CH), 129.0 (2 × CH), 128.8 (2 × CH), 128.1 (2 × CH).

HRMS: *m*/*z* [M]$^+$ calcd for $C_{15}H_{13}N_3O_3$: 283.0957; found: 283.0961.

***N*-Benzoyl-2-hexanoylhydrazine-1-carboxamide (41b)**

White crystalline product; yield: 246 mg (89%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.98 (s, 1 H), 10.04 (d, *J* = 2.3 Hz, 1 H), 10.00 (d, *J* = 1.8 Hz, 1 H), 7.93 (d, *J* = 7.3 Hz, 2 H), 7.60 (t, *J* = 7.5 Hz, 1 H), 7.48 (t, *J* = 7.5 Hz, 2 H), 2.10 (t, *J* = 7.3 Hz, 2 H), 1.49 (quint, *J* = 7.2 Hz, 2 H), 1.29–1.16 (m, 4 H), 0.82 (t, *J* = 6.9 Hz, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 171.5 (C), 168.5 (C), 153.7 (C), 133.5 (CH), 132.7 (C), 129.1 (2 × CH), 128.8 (2 × CH), 33.5 (CH_2), 31.3 (CH_2), 25.2 (CH_2), 22.4 (CH_2), 14.4 (CH_3).

HRMS: *m*/*z* [M]$^+$ calcd for $C_{14}H_{19}N_3O_3$: 277.1426; found: 277.1422.

***tert*-Butyl 2-(Benzoylcarbamoyl)hydrazine-1-carboxylate (41c)**

White powder; yield: 231 mg (83%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.91 (s, 1 H), 9.72 (s, 1 H), 8.97 (s, 1 H), 7.92 (d, *J* = 7.8 Hz, 2 H), 7.60 (t, *J* = 7.3 Hz, 1 H), 7.48 (t, *J* = 7.6 Hz, 2 H), 1.38 (s, 9 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 168.5 (C), 155.8 (C), 154.7 (C), 133.5 (CH), 132.7 (C), 129.1 (2 × CH), 128.8 (2 × CH), 80.0 (C), 28.6 (3 × CH_3).

HRMS: *m*/*z* [M]$^+$ calcd for $C_{13}H_{17}N_3O_4$: 279.1219; found: 279.1225.

***N*-Benzoyl-2-tosylhydrazine-1-carboxamide (44a)**

White powder; yield: 242 mg (73%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.93 (s, 1 H), 9.92 (s, 2 H), 7.87 (d, *J* = 7.3 Hz, 2 H), 7.70 (d, *J* = 8.2 Hz, 2 H), 7.59 (t, *J* = 7.6 Hz, 1 H), 7.48–7.44 (m, 2 H), 7.37 (d, *J* = 8.2 Hz, 2 H), 2.35 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 168.6 (C), 153.6 (C), 144.3 (C), 135.9 (C), 133.7 (CH), 132.3 (C), 130.2 (2 × CH), 129.1 (2 × CH), 128.8 (2 × CH), 128.2 (2 × CH), 21.6 (CH_3).

HRMS: *m*/*z* [M]$^+$ calcd for $C_{15}H_{15}N_3O_4S$: 333.0783; found: 333.0787.

Benzoylcarbamic Heptane-1-sulfonic Anhydride (44b)

White solid; yield: 293 mg (90%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.84 (s, 1 H), 7.94 (dd, *J* = 8.5, 1.1 Hz, 2 H), 7.65 (m, 1 H), 7.57–7.53 (m, 2 H), 2.33–2.29 (m, 2 H), 1.52–1.45 (m, 2 H), 1.25–1.19 (m, 8 H), 0.81 (t, *J* = 6.9 Hz, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 167.3 (C), 149.5 (C), 133.9 (CH), 133.0 (C), 129.4 (2 × CH), 128.5 (2 × CH), 52.1 (SO_2CH_2), 31.7 (CH_2), 29.1 (CH_2), 28.9 (CH_2), 25.7 (CH_2), 22.6 (CH_2), 14.5 (CH_3).

HRMS: *m*/*z* [M]$^+$ calcd for $C_{15}H_{21}NO_5S$: 327.1140; found: 327.1138.

(*E*)-*N*-[(3,7-Dimethylocta-2,6-dien-1-yl)carbamoyl]-2,3,4-trifluorobenzamide (46a)

White solid; yield: 122 mg (34%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.81 (s, 1 H), 8.22 (t, *J* = 5.3 Hz, 1 H), 7.50–7.36 (m, 2 H), 5.18 (t, *J* = 6.6 Hz, 1 H), 5.03 (t, *J* = 6.9 Hz, 1 H), 3.76 (t, *J* = 6.2 Hz, 2 H), 2.04–1.92 (m, 4 H), 1.61–1.59 (m, 6 H), 1.52 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 164.4 (C), 152.9 (C), 152.6 (C, ddd, $J_{C,F}$ = 252.1, 9.6, 2.9 Hz), 149.0 (C, ddd, $J_{C,F}$ = 254.6, 10.5, 3.4 Hz), 139.4 (C, dt, $J_{C,F}$ = 250.2, 15.6 Hz), 138.5 (C), 131.5 (C), 125.3 (CH, dd, *J* = 8.6, 3.8 Hz), 124.4 (CH), 121.5 (C, overlapped d, $J_{C,F}$ = 2.9 Hz), 121.4 (CH), 113.5 (CH, dd, $J_{C,F}$ = 17.7, 3.4 Hz), 39.4 (CH_2), 37.5 (CH_2), 26.4 (CH_2), 26.0 (CH_3), 18.1 (CH_3), 16.5 (CH_3).

HRMS: *m*/*z* [M]$^+$ calcd for $C_{18}H_{21}F_3N_2O_2$: 354.1555; found: 354.1557.

***N*-[(Adamantan-2-yl)carbamoyl]adamantane-1-carboxamide (46b)**

White powder; yield: 212 mg (60%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.05 (s, *J* = 7.8 Hz, 1 H), 8.19 (s, 1 H), 3.99 (d, *J* = 8.2 Hz, 1 H), 2.06 (br s, 3 H), 1.93–1.82 (m, 16 H), 1.76–1.60 (m, 10 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 179.8 (C), 153.2 (C), 54.1 (CH), 41.9 (C), 38.6 (3 × CH_2), 37.6 (CH_2), 37.1 (2 × CH_2), 36.3 (3 × CH_2), 32.2 (2 × CH), 32.0 (2 × CH), 28.0 (3 × CH), 27.3 (CH), 27.2 (CH).

HRMS: *m*/*z* [M]$^+$ calcd for $C_{22}H_{32}N_2O_2$: 356.2464; found: 356.2459.

***N*-[(Benzyloxy)carbamoyl]benzamide (46c)**

White powder; yield: 210 mg (78%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.99 (s, 1 H), 10.84 (s, 1 H), 7.89 (d, *J* = 7.3 Hz, 2 H), 7.59 (t, *J* = 7.3 Hz, 1 H), 7.46 (t, *J* = 7.8 Hz, 2 H), 7.43–7.29 (m, 5 H), 4.87 (s, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 167.8 (C), 153.8 (C), 136.3 (C), 133.4 (CH), 132.6 (C), 129.4 (2 × CH), 129.0 (2 × CH), 128.9 (3 × CH), 128.8 (2 × CH), 77.9 (CH_2).

HRMS: *m*/*z* [M]$^+$ calcd for $C_{15}H_{14}N_2O_3$: 270.1004; found: 270.1008.

Phenyl Benzoylcarbamate (46d)

Off-white solid; yield: 140 mg (58%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.47 (s, 1 H), 7.92 (dd, *J* = 7.3, 1.4 Hz, 2 H), 7.61 (tt, *J* = 7.6, 1.4 Hz, 1 H), 7.49 (t, *J* = 7.6 Hz, 2 H), 7.45–7.40 (m, 2 H), 7.29–7.19 (m, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 166.5 (C), 150.5 (C), 150.4 (C), 135.5 (C), 133.4 (CH), 130.1 (2 × CH), 129.0 (4 × CH), 126.5 (CH), 122.4 (2 × CH).

HRMS: *m*/*z* [M]$^+$ calcd for $C_{14}H_{11}NO_3$: 241.0739; found: 241.0743.

2,3-Dimethoxybenzyl Benzoylcarbamate (46e)

White solid; yield: 233 mg (74%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.02 (s, 1 H), 7.84–7.81 (m, 2 H), 7.56 (tt, *J* = 7.4, 1.4 Hz, 1 H), 7.46–7.43 (m, 2 H), 7.08–6.98 (m, 3 H), 5.15 (s, 2 H), 3.78 (s, 3 H), 3.74 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 166.4 (C), 152.9 (C), 152.0 (C), 147.4 (C), 133.7 (C), 133.1 (CH), 129.8 (C), 128.9 (4 × CH), 124.5 (CH), 121.9 (CH), 113.8 (CH), 62.5 (CH_2), 60.9 (OCH_3), 56.3 (OCH_3).

HRMS: *m*/*z* [M]$^+$ calcd for $C_{17}H_{17}NO_5$: 315.1107; found: 315.1108.

Cinnamyl Benzoylcarbamate (46f)

Off-white solid; yield: 224 mg (79%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.03 (s, 1 H), 7.84 (m, 2 H), 7.57 (tt, J = 7.6, 1.4 Hz, 1 H), 7.49–7.41 (m, 4 H), 7.32 (t, J = 7.6 Hz, 2 H), 7.24 (tt, J = 7.3, 2.3 Hz, 1 H), 6.74 (d, J = 16.0 Hz, 1 H) 6.39 (dt, J = 15.9, 6.0 Hz, 1 H), 4.78 (dd, J = 6.2, 1.2 Hz, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 166.4 (C), 152.0 (C), 136.4 (C), 134.0 (CH), 133.8 (C), 133.1 (CH), 129.3 (2 × CH), 128.9 (2 × CH), 128.9 (2 × CH), 128.6 (CH), 127.0 (2 × CH), 124.1 (CH), 65.8 (CH_2).

HRMS: m/z [M]$^+$ calcd for $C_{17}H_{15}NO_3$: 281.1052; found: 281.1056.

Hexyl Benzoylcarbamate (46g)

White solid; yield: 229 mg (92%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.11 (br s, 1 H), 7.86–7.78 (m, 2 H), 7.57 (tt, J = 7.6, 1.6 Hz, 1 H), 7.49–7.44 (m, 2 H), 4.21 (t, J = 6.9 Hz, 2 H), 1.71–1.64 (m, 2 H), 1.40–1.23 (m, 6 H), 0.87 (t, J = 6.9 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.9 (C), 151.2 (C), 133.1 (C), 133.1 (CH), 129.0 (2 × CH), 127.7 (2 × CH), 66.7 (OCH_2), 31.5 (CH_2), 28.6 (CH_2), 25.5 (CH_2), 22.6 (CH_2), 14.1 (CH_3).

HRMS: m/z [M]$^+$ calcd for $C_{14}H_{19}NO_3$: 249.1365; found: 249.1366.

***S*-Hexyl Benzoylcarbamothioate (46h)**

White solid; yield: 238 mg (90%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.68 (s, 1 H), 7.88 (dd, J = 8.5, 1.1 Hz, 2 H), 7.59 (m, 1 H), 7.47 (t, J = 7.6 Hz, 2 H), 2.79 (t, J = 7.3 Hz, 2 H), 1.52 (quint, J = 7.3 Hz, 2 H), 1.35–1.23 (m, 6 H), 0.82 (t, J = 6.7 Hz, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 170.6 (C), 166.8 (C), 133.5 (CH), 132.7 (C), 129.1 (2 × CH), 128.8 (2 × CH), 31.3 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 28.5 (CH_2), 22.5 (CH_2), 14.5 (CH_3).

HRMS: m/z [M]$^+$ calcd for $C_{14}H_{19}NO_2S$: 265.1136; found: 265.1127.

***N*^{r1},*N*^{r2}-Dibenzoyloxalohydrazide (48a)**

Pale yellow solid; yield: 251 mg (77%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.82 (s, 2 H), 10.49 (s, 2 H), 7.86 (dd, J = 7.7, 1.8 Hz, 4 H), 7.57 (t, J = 7.3 Hz, 2 H), 7.49 (t, J = 7.6 Hz, 4 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 165.7 (2 C), 159.1 (2 C), 132.7 (2 C), 132.5 (2 × CH), 129.1 (4 × CH), 128.0 (4 × CH).

HRMS: m/z [M]$^+$ calcd for $C_{16}H_{14}N_4O_4$: 326.1015; found: 326.1010.

***N*^{r1},*N*^{r2}-Bis[(4-methylphenyl)sulfonyl]ethanedihydrazide (48b)**

Milky-white solid; yield: 400 mg (94%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.82 (d, J = 2.8 Hz, 2 H), 9.90 (d, J = 3.2 Hz, 2 H), 7.60 (d, J = 8.2 Hz, 4 H), 7.32 (d, J = 7.8 Hz, 4 H), 2.34 (s, 6 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 158.6 (2 C), 143.9 (2 C), 136.8 (2 C), 129.9 (4 × CH), 128.1 (4 × CH), 21.6 (2 × CH_3).

HRMS: m/z [M]$^+$ calcd for $C_{16}H_{18}N_4O_6S_2$: 426.0668; found: 426.0673.

Acknowledgment

All authors acknowledge CSU COP (summer research training for AGH and GMG) and CSU CTRE (Seed Grant) for generous financial support of this project. The unlimited access to the NMR facility (JEOL 400) in the Department of Chemistry at CSU is acknowledged. Sarah Cramer is acknowledged for the assistance with analyzing the NMR spectra.

References

(1) Current address: University of South Carolina, S. o. M. G., Greenville, SC 29605, USA.
(2) Current address: Marshall B. Ketchum University, C. o. P., Department of Pharmaceutical Sciences, 2575 Yorba Linda Blvd., Fullerton, CA 82831, USA. Phone: +1 7148725711; jstec@ketchum.edu.
(3) Patani, G. A.; LaVoie, E. J. *Chem. Rev.* **1996**, *96*, 3147.
(4) Silverman, R. B.; Holladay, M. W. *The Organic Chemistry of Drug Design and Drug Action*; Academic Press: San Diego, **2014**, 62.
(5) Ghosh, A. K.; Brindisi, M. *J. Med. Chem.* **2015**, *58*, 2895.
(6) Simplício, A. L.; Clancy, J. M.; Gilmer, J. F. *Molecules* **2008**, *13*, 519.
(7) Blum, J. L. *Oncologist* **2001**, *6*, 56.
(8) Tymoczko, J. L.; Berg, J. M.; Stryer, L. *Biochemistry: A Short Course*; W. H. Freeman and Company: New York, **2015**, 526.
(9) Bogolubsky, A. V.; Moroz, Y. S.; Mykhailiuk, P. K.; Granat, D. S.; Pipko, S. E.; Konovets, A. I.; Doroschuk, R.; Tolmachev, A. *ACS Comb. Sci.* **2014**, *16*, 303.
(10) Roche, V. F. In *Foye's Principles of Medicinal Chemistry*; Lemke, T. L.; Williams, D. A.; Roche, V. F.; Zito, S. W., Eds.; Walters Kluwer Health/Lippincott Williams & Wilkins: Baltimore, **2013**, 1243.
(11) (a) Ishikawa, S.; Mochizuki, M. *Genes Environ.* **2007**, *29*, 1. (b) Roche, V. F. In *Foye's Principles of Medicinal Chemistry*; Lemke, T. L.; Williams, D. A.; Roche, V. F.; Zito, S. W., Eds.; Walters Kluwer Health/Lippincott Williams & Wilkins: Baltimore, **2013**, 1215.
(12) Harvison, P. J.; Rankin, G. O. In *Foye's Principles of Medicinal Chemistry*; Lemke, T. L.; Williams, D. A.; Roche, V. F.; Zito, S. W., Eds.; Walters Kluwer Health/Lippincott Williams & Wilkins: Baltimore, **2013**, 740.
(13) Gallagher, B. B. In *Anticonvulsants*; Vida, J., Ed.; Academic Press: New York, **1977**, 42.
(14) Saam, E. US Patent 914518A, **1909**.
(15) (a) Diflubenzuron. WHO Specifications and Evaluations for Public Health Pesticides; **2006**; http://www.who.int/whopes/quality/diflubenzuron_eval_march_2006.pdf. (b) Pete, U. D.; Zade, C. M.; Bhosale, J. D.; Tupe, S. G.; Chaudhary, P. M.; Dikundwar, A. G.; Bendre, R. S. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 5550.
(16) *Lufenuron. FAO Specifications and Evaluations for Agricultural Pesticides*; **2008**; http://www.fao.org/fileadmin/templates/agphome/documents/Pests_Pesticides/Specs/Lufenuron08.pdf.
(17) Woster, P. M. In *Foye's Principles of Medicinal Chemistry*; Lemke, T. L.; Williams, D. A.; Roche, V. F.; Zito, S. W., Eds.; Walters Kluwer Health/Lippincott Williams & Wilkins: Baltimore, **2013**, 1298.
(18) (a) Babad, H.; Zeiler, A. G. *Chem. Rev.* **1973**, *73*, 75. (b) Bigi, F.; Maggia, R.; Sartori, G. *Green Chem.* **2000**, *2*, 140. (c) Kreye, O.; Mutlua, H.; Meier, M. A. R. *Green Chem.* **2013**, *15*, 1431.
(19) (a) Dubé, P.; Nathel, N. F.; Vetelino, M.; Couturier, M.; Aboussafy, C. L.; Pichette, S.; Jorgensen, M. L.; Hardink, M. *Org. Lett.* **2009**, *11*, 5622. (b) El Dine, T. M.; Chapron, S.; Duclos, M.-C.; Duguet, N.; Popowycz, F.; Lemaire, M. *Eur. J. Org. Chem.* **2013**, 5445.
(20) (a) Zadeh, E. H. G.; Abo-Dya, N. E.; Sotuyo, A. C.; Ghiviriga, I.; Hall, C. D. *Tetrahedron Lett.* **2013**, *54*, 5467. (b) Spyropoulos, C.; Kokotos, C. G. *J. Org. Chem.* **2014**, *79*, 4477. (c) Han, C.; Porco, J. A. Jr. *Org. Lett.* **2007**, *9*, 1517.
(21) (a) Yoshida, M.; Hara, N.; Okuyama, S. *Chem. Commun.* **2000**, 151. (b) Kim, S. H.; Hong, S. H. *Org. Lett.* **2016**, *18*, 212. (c) Sun, D.-L.; Ye, J.-H.; Fang, Y.-X.; Chao, Z.-S. *Ind. Eng. Chem. Res.* **2016**,

55, 64. (d) Shi, F.; Deng, Y.; SiMa, T.; Peng, J.; Gu, Y.; Qiao, B. *Angew. Chem. Int. Ed.* **2003**, *42*, 3257. (e) Díaz, D. J.; Darko, A. K.; McElwee-White, L. *Eur. J. Org. Chem.* **2007**, 4453.
(22) Wu, C.; Cheng, H.; Liu, R.; Wang, Q.; Hao, Y.; Yua, Y.; Zhao, F. *Green Chem.* **2010**, *12*, 1811.
(23) (a) Schmidt, E. *J. Prakt. Chem.* **1872**, *5*, 63. (b) Stoughton, R. W.; Diacylureas, I. *J. Org. Chem.* **1938**, *2*, 514.
(24) (a) Scholl, R. *Ber. Dtsch. Chem. Ges.* **1890**, *23*, 3516. (b) Meyer, V.; Jacobson, P. *Lehrbuch der Organischen Chemie: Allgemeiner Theil*; Veit & Comp: Leipzig, **1893**, 1013–1014. (c) Bayer & Co. German Patent 286 760, **1913**; *Chem. Abstr.* **1916**, *10*, 1579
(25) Bornwater, J. T. *Rec. Trav. Chim. Pays-Bas* **1912**, *31*, 105.
(26) (a) Speziale, A. J.; Smith, L. R. *J. Org. Chem.* **1962**, *27*, 3742. (b) Speziale, A. J.; Smith, L. R.; Fedder, J. E. *J. Org. Chem.* **1965**, *30*, 4306. (c) Speziale, A. J.; Smith, L. R. US Patent 3213135, **1965**. (d) Speziale, A. J.; Smith, L. R. *Org. Synth.* **1966**, *46*, 16. (e) Speziale, A. J.; Smith, L. R. *J. Org. Chem.* **1963**, *28*, 1805. (f) Speziale, A. J.; Smith, L. R.; Fedder, J. E. *J. Org. Chem.* **1965**, *30*, 4303. (g) Smith, L. R.; Speziale, A. J.; Fedder, J. E. *J. Org. Chem.* **1969**, *34*, 633.
(27) Wolfe, J. F.; Trimitsis, G. B. *Can. J. Chem.* **1969**, *47*, 2097.
(28) Kanji Kubo, K.; Moriy, A. *Chem. Lett.* **2005**, *34*, 1250.
(29) Chawla, H. M.; Pathak, M. *Tetrahedron* **1990**, *46*, 1331.
(30) Dean, F. W. US Patent 6448440 B1, **2004**.
(31) Bjerglund, K.; Lindhardt, A. T.; Skrydstrup, T. *J. Org. Chem.* **2012**, *77*, 3793.
(32) Cohen, V. I. *J. Org. Chem.* **1974**, *39*, 3043.
(33) Basyouni, M. N.; El-Khamry, A.-M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 3728.
(34) Otohiko, T.; Tadashi, I.; Masashi, T. *Tetrahedron* **1968**, *24*, 2583.
(35) (a) Hoggarth, E. *J. Chem. Soc.* **1949**, 1160. (b) Durant, G. J. *J. Chem. Soc. C* **1967**, 92.
(36) (a) Nenitzescu, C. D.; Necsoiu, I.; Zalman, M. *Comun. Acad. Rep. Populare Romine* **1958**, *8*, 659; *Chem. Abstr.* **1959**, *53*, 17092. (b) McDonald, R. *J. Org. Chem.* **1959**, *24*, 1580.
(37) Elmore, D. T.; Ogle, J. R. *J. Chem. Soc.* **1958**, 1141.
(38) Stec, J.; Huang, Q.; Pieroni, M.; Kaiser, M.; Fomovska, A.; Mui, E.; Witola, W.; Bettis, S.; McLeod, R.; Brun, R.; Kozikowski, A. P. *J. Med. Chem.* **2012**, *55*, 3088.
(39) Roughley, S. D.; Jordan, A. M. *J. Med. Chem.* **2011**, *54*, 3451.