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Synthesis of 3-Hydroxy-6-oxo[1,2,4]triazin-1-yl Alaninamides, a New Class of Cyclic Dipeptidyl Ureas

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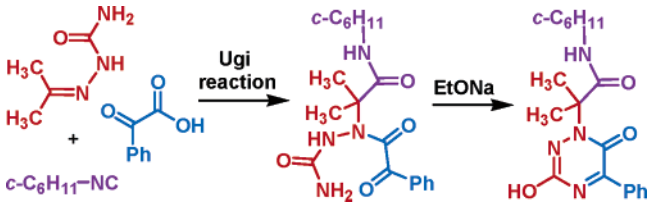

Cyclohexyl or benzyl isocyanide, benzoyl-, or 4-methoxybenzoylformic acid and semicarbazones underwent Ugi reactions in methanol for 3 days to give the Ugi adducts, which were then stirred with sodium ethoxide in ethanol for 12 h to give 3-hydroxy-6-oxo[1,2,4]triazin-1-yl alaninamides. The X-ray diffraction structure of the first example showed the tautomer having the proton in the O2 atom that was fixed in the crystal by packing in dimers with a H-bond distance of 1.9 Å. Selected [1,2,4]triazines were treated with diazomethane for 12 h to get the *O*-methyl derivatives. Both hydroxy and *O*-methyl derivatives obtained by this method constitute a new class of pseudopeptidic [1,2,4]triazines composed of two different amino acids, arylglycine and alanine derivatives, in which the *N*-terminal arylglycine and the peptidic amide nitrogen atoms are bonded through a urea moiety.

Introduction

The design and synthesis of metabolically stable peptide analogues that can either mimic or block the bioactivity of natural peptides or enzymes is an important constituent of bioorganic and medicinal chemistry research. Isosteric replacement of a scissile peptide bond represents a viable and popular approach in the rational design of peptidomimetics.[1] Peptidomimetics find applications as drugs, in protein engineering, and so on. This is evident from the wealth of therapeutically useful peptidomimetic leads incorporating any of the peptide isosteres that are currently available. Between the several types of peptide isosteres known to date, ureidopeptides and azapeptides are useful peptidomimetics. Ureidopeptides[2] are obtained by the insertion of a nitrogen atom between the α-carbon and the carbonyl of the scissile amide bond, therefore, they contain a urea linkage but retain a strong structural resemblance to their cognate peptides, as they differ by the addition of a single backbone atom, being in principle inert to enzymatic hydrolysis. This class of urea pseudopeptides has been successfully used for the creation of active site human immunodeficiency virus (HIV-1) protease inhibitors.[3] On the other hand, azapeptides are peptide analogues in which an α-CH group in a peptide chain is isoelectronically replaced by nitrogen and have displayed considerable biological activity as hormone analogues, protease inhibitors, and active-site titrants.[4] Selected examples are atazanavir,[5] an azapeptide protease inhibitor marketed for HIV treatment, and zoladex,[6] an azapeptide analogue of the peptide hormone luliberin, used for breast and prostate cancer treatment. Indeed, most azapeptides of therapeutic value bear the urea moiety in their structure, because they are conceptually derived from semicarbazone[7] and, of course, both structural

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(1) Venkatesan, N.; Kim, B. H. *Curr. Med. Chem.* **2002**, *9*, 2243−2270.
(2) Semetey, V.; Hemmerlin, C.; Didierjean, C.; Schaffner, A. P.; Giner, A. G.; Aubry, A.; Briand, J. P.; Marraud, M.; Guichard, G. *Org. Lett.* **2001**, *3*, 3843−3846.
(3) (a) Myers, A. C.; Kowalski, J. A.; Lipton, M. A. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5219−5222. (b) Barth, B. S.; Myers, A. C.; Lipton, M. A. *J. Pept. Res.* **2005**, *65*, 352−354.
(4) Zega, A. *Curr. Med. Chem.* **2005**, *12*, 589−597.
(5) Piliero, P. J. *Drugs Today* **2004**, *40*, 901−912.
(6) Zinner, N. R.; Bidair, M.; Centeno, A.; Tomera, K. *Urology* **2004**, *64*, 1177−1181. Mansel, R. E.; Goyal, A.; Preece, P.; Leinster, S.; Maddox, P. R.; Gateley, C.; Kubista, E.; von Fournier, D. *Am. J. Obstet. Gynecol.* **2004**, *191*, 1942−1949.

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motifs, urea and aza-amino acids, can be combined in the same molecule.[8] 1,4,5,6-Tetrahydro-l,2,4-triazin-3(2*H*)ones have been prepared as bridged azapeptides by direct cyclization of linear azapeptides by using ethylene glycol bistriflate.[9] 1,2,4-Triazine-3,6-diones have been prepared in the context of aza-urea peptide mimetics by the reaction of hydrazines with α-lactams.[10] A serious drawback of the synthesis is constituted by reports that some compounds originally assigned as 1,2,4-triazine-3,6-diones were actually 3-aminohydantoins; therefore, the reaction is limited to selected substituted hydrazines.[11] 3-Aminohydantoins and 1,2,4-triazine-3,6-diones have been obtained as amino acid derived urea peptidomimetics, using phoxime resin, amino acids, and substituted hydrazines, followed by cyclization of the intermediate carbamate hydrazide resin, but the cyclization strongly depended on the hydrazine substitution.[12] A single example of 1,2,4-triazine-3,6-dione azapeptide, obtained by a complex route from an α-isocyanatocarboxylic acid derivative, is also known.[13] 1,2,4-Triazine derivatives[14] possess biological activity as selective herbicides[15] and have been screened for in vitro anti-HIV[16] and anti-cancer activities.[17] Remarkable therapeutic tools are tirapazamine (3-amino-1,2,4-benzotriazine 1,4-dioxide), a bioreductive drug in clinical trials as an anticancer agent to kill refractory hypoxic cells of solid tumors,[18] and lamotrigine {3,5-diamino-6-(2,3-dichlorophenyl)[1,2,4]triazine}, a sodium-channel blocker, which is in clinical use as an anticonvulsant.[19] Furthermore, pyrimido-triazines possess significant biological activities, such as the antibiotic fervenuline, reumycine, and toxoflavine derivatives,[20] showing all a pyrimido[5,4-*e*][1,2,4]triazine (7-azapteridine) ring system, and the imidazo[5,1-*f*][1,2,4]triazinone scaffold has recently received attention as the core structure of vardenafil (Levitra), a potent and effective PDE5 inhibitor for the treatment of erectile dysfunction.[21] Despite the broad interest in this class of heterocycles, a short and regioselective route to 1,2,4-triazine-3,6-diones has been lacking. We have recently shown that the sequences of classical Ugi or Passerini isocyanide multicomponent reactions, followed by post-condensation transformations, constitute extremely powerful synthetic tools for the preparation of structurally diverse complex molecules, among them are heterocyclic compounds with elaborate substitution patterns, constrained peptides, and peptide mimetics, which are of great interest in drug discovery programs.[22] As a new contribution of this methodology, we want to report in this paper a new synthesis of pseudopeptidic 1,2,4-triazines by the sequence of a semicarbazone Ugi reaction, followed by a carbamide cyclization and, in selected cases, methylation of the hydroxyl group.

Results and Discussion

Cyclohexyl or benzyl isocyanide **2a**,**b** (1 equiv) and benzoylformic or 4-methoxybenzoylformic acid[23] **3a**,**b** (1 equiv) were added consecutively to a solution of the corresponding semicarbazone **1a**−**e** (1 equiv) in methanol, and the mixture was stirred at room temperature for 3 days until complete precipitation of the Ugi adducts. The resultant solid products **4a**−**i** were then filtered, recrystallized, and characterized by the usual spectroscopic and analytical techniques. In turn, compounds **4a**−**i** (1 equiv) were stirred with sodium ethoxide (1.05 equiv) in ethanol for 12 h. Then the solvent was evaporated, the residue was suspended in isopropyl ether, and the resulting solid was filtered, dissolved in water, and reprecipitated by the addition of acetic acid until acidic pH. Solid products **5a**−**i** were then filtered, recrystallized in dichloromethane/methanol (6:1), and characterized. Selected products, **5b**,**c**,**e**−**g**,**i**, were treated with diazomethane in ether/chloroform, stirred for 12 h, and worked-up to get the *O*-methyl derivatives **6b**,**c**,**e**−**g**,**i**. Scheme 1 and Table 1 show the complete list of reagents, products, and yields.

Semicarbazones have not been previously employed in Ugi four-component condensations, but in our experiments, they reacted smoothly under the usual conditions, in a similar way to the known examples of Ugi reactions employing hydrazones.[24] The Ugi adducts **4a**−**i** were obtained as colorless

(7) See, for example: (a) Melendez, R. E.; Lubell, W. D. *J. Am. Chem. Soc.* **2004**, *126*, 6759−6764. (b) Bondebjerg, J.; Fuglsang, H.; Valeur, K. R.; Kaznelson, D. W.; Hansen, J. A.; Pedersen, R. O.; Krogh, B. O.; Jensen, B. S.; Lauritzen, C.; Petersen, G.; Pedersen, J.; Næruma, L. *Bioorg. Med. Chem.* **2005**, *13*, 4408−4424. (c) Wieczerzak, E.; Drabik, P.; Lankiewicz, L.; Ołdziej, S.; Grzonka, Z.; Abrahamson, M.; Grubb, A.; Brömme, D. *J. Med. Chem.* **2002**, *45*, 4202−4211. (d) Bailey, M. D.; Halmos, T.; Goudreau, N.; Lescop, E.; Llinas-Brunet, M. *J. Med. Chem.* **2004**, *47*, 3788−3799.

(8) Soth, M. J.; Nowick, J. S. *J. Org. Chem.* **1999**, *64*, 276−281.

(9) Gante, J.; Neunhoeffer, H.; Schmidt, A. *J. Org. Chem.* **1994**, *59*, 6487−6489.

(10) Hoffman, R. V.; Nayyar, N. K. *J. Org. Chem.* **1995**, *60*, 5992−5994 and references therein.

(11) Hoffman, R. V.; Reddy, M. M.; Klumas, C. M.; Cervantes-Lee, F. *J. Org. Chem.* **1998**, *63*, 9128−9130 and references therein.

(12) Hamuro, Y.; Marshall, W. J.; Scialdone, M. A. *J. Comb. Chem.* **1999**, *1*, 163−172.

(13) Burger, K.; Schierlinger, C.; Muetze, K.; Hollweck, W.; Koksch, B. *Liebigs Ann. Chem.* **1994**, *4*, 407−414.

(14) Neunhoeffer, H. In *Comprehensive Heterocyclic Chemistry II*; Katrizky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Elsevier: Oxford, 1996; Vol. 6, Chapter 6.11, pp 507−573.

(15) See, for example, Metribuzin: Landgraf, M. D.; da Silva, S. C.; Rezende, M. O. *Anal. Chim. Acta* **1998**, *368*, 155−164. Metamitron: Ludvik, J.; Riedl, F.; Liska, F.; Zuman, P. *J. Electroanal. Chem.* **1998**, *457*, 177−190. For a review: Abdel-Rahman, R. M. *Pharmazie* **2001**, *56*, 195−204.

(16) (a) Vzorova, A. N.; Bhattacharyyab, D.; Marzillib, L. G.; Compansa, R. W. *Antiviral Res.* **2005**, *65*, 57−67. (b) Al-Etaibi, A.; Makhseed, S.; Al-Awadi, N. A.; Ibrahim, Y. A. *Tetrahedron Lett.* **2005**, *46*, 31−35. (c) For a review, see: Abdel-Rahman, R. M. *Pharmazie* **2001**, *56*, 18−22.

(17) (a) Borzilleri, R. M.; Cai, Z.; Ellis, C.; Fargnoli, J.; Fura, A.; Gerhardt, T.; Goyal, B.; Hunt, J. T.; Mortillo, S.; Qian, L.; Tokarski, J.; Vyas, V.; Wautlet, B.; Zheng, X.; Bhide, R. S. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1429−1433. (b) Borzilleri, R. M.; Zheng, X.; Qian, L.; Ellis, C.; Cai, Z.; Wautlet, B. S.; Mortillo, S.; Jeyaseelan, R.; Kukral, D. W.; Fura, A.; Kamath, A.; Vyas, V.; Tokarski, J. S.; Barrish, J. C.; Hunt, J. T.; Lombardo, L. J.; Fargnoli, J.; Bhide, R. S. *J. Med. Chem.* **2005**, *48*, 3991−4008. (c) Hunt, J. T.; Mitt, T.; Borzilleri, R.; Gullo-Brown, J.; Fargnoli, J.; Fink, B.; Han, W. C.; Mortillo, S.; Vite, G.; Wautlet, B.; Wong, T.; Yu, C.; Zheng, X.; Bhide, R. *J. Med. Chem.* **2004**, *47*, 4054−4059.

(18) (a) Anderson, R. F., Shinde, S. S.; Hay, M. P.; Denny, W. A. *J. Am. Chem. Soc.* **2006**, *128*, 245−249. (b) Anderson, R. F., Shinde, S. S.; Hay, M. P.; Gamage, S. A.; Denny, W. A. *Org. Biomol. Chem.* **2005**, *3*, 2167−2174. (c) Shinde, S. S.; Anderson, R. F.; Hay, M. P.; Gamage, S. A.; Denny, W. A. *J. Am. Chem. Soc.* **2004**, *126*, 7865−7874.

(19) (a) Adam, F. M.; Burton, A. J.; Cardwell, K. S.; Cox, R. A.; Henson, R. A.; Mills, K.; Prodger, J. C.; Schilling, M. B.; Tape, D. T. *Tetrahedron Lett.* **2003**, *44*, 5657−5659. For other potential lead compounds, see: (b) Chambers, M. S.; Atack, J. R.; Carling, R. W.; Collinson, N.; Cook, S. M.; Dawson, G. R.; Ferris, P.; Hobbs, S. C.; O'Connor, D.; Marshall, G.; Rycroft, W.; MacLeod, A. M. *J. Med. Chem.* **2004**, *47*, 5829−5832. (c) Sztanke, K.; Fidecka, S.; Kedzierska, E.; Karczmarzyk, Z.; Pihlaja, K.; Matosiuk, D. *Eur. J. Med. Chem.* **2005**, *40*, 127−134.

(20) See for example: (a) Nagamatsu, T.; Yamasaki, H. *J. Chem. Soc., Perkin Trans. 1* **2001**, 130−137. (b) Wang, H.; Lim, K. L.; Yeo, S. L.; Xu, X.; Sim, M. M.; Ting, A. E.; Wang, Y.; Yee, S.; Tan, Y. H.; Pallen, C. J. *J. Nat. Prod.* **2000**, *63*, 1641−1646.

(21) Heim-Riether, A.; Healy, J. *J. Org. Chem.* **2005**, *70*, 7331−7337 and references therein.

(22) Marcaccini, S.; Torroba, T. In *Multicomponent Reactions*; Zhu, J., Bienaymé, H., Eds.; Wiley-VCH: Weinheim, Germany, 2005; Chapter 2, pp 33−75.

(23) Pirrung, M. C.; Tepper, R. J. *J. Org. Chem.* **1995**, *60*, 2461−2465.

SCHEME 1

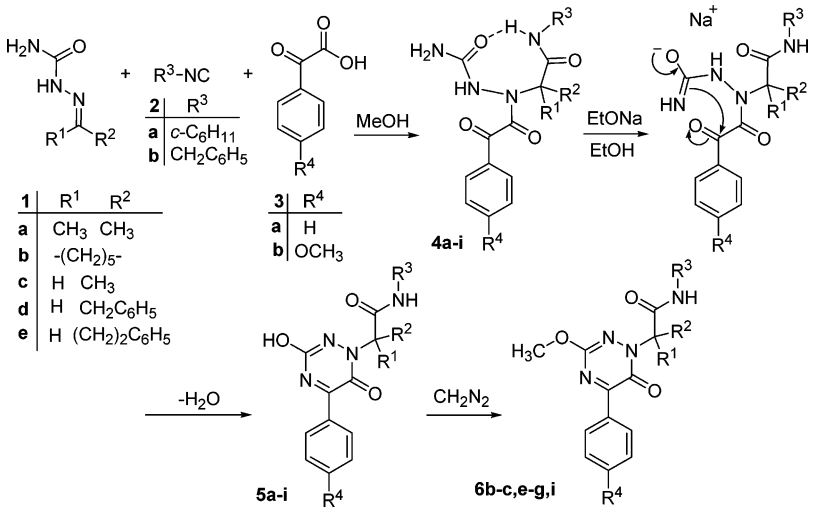

TABLE 1

entry	R^1	R^2	R^3	R^4	**4** (%)	**5** (%)	**6** (%)
a	CH_3	CH_3	*c*-C_6H_{11}	H	50	56	
b	CH_3	CH_3	*c*-C_6H_{11}	OCH_3	48	54	83
c		$-(CH_2)_5-$	*c*-C_6H_{11}	H	55	84	85
d		$-(CH_2)_5-$	*c*-C_6H_{11}	OCH_3	73	54	
e		$-(CH_2)_5-$	$CH_2C_6H_5$	OCH_3	56	85	87
f	H	CH_3	*c*-C_6H_{11}	OCH_3	59	53	86
g	H	$CH_2C_6H_5$	*c*-C_6H_{11}	H	46	84	80
h	H	$CH_2C_6H_5$	*c*-C_6H_{11}	OCH_3	54	64	
i	H	$CH_2CH_2C_6H_5$	*c*-C_6H_{11}	H	55	60	89

crystalline solids, easily characterizable by usual techniques. The different NH groups appeared as distinct peaks in IR at around 3400 and 3300 cm^{-1} and in ^1H NMR at δ 9 (usually two signals) and 6. In the same manner, carbonyl groups were seen as distinct peaks in IR at 1700−1650 cm^{-1} and ^{13}C NMR at δ 150−190. Molecular peaks in mass spectrometry were sometimes missed and, instead, peaks corresponding to ammonia or water loss were found, but molecular formulas were confirmed by microanalyses. Crystals of **4c** were suitable for single-crystal X-ray diffraction measurements. The obtained structure is shown in Figure S1 in the Supporting Information. Structure **4c** showed a hydrogen bond between N(1)H···O(2) having a H-bond distance of 2.1 Å that formed a half-chair eight-membered quasicycle. The packing of the molecules in the crystal was supported by several intermolecular hydrogen bonds between NH amide groups of one molecule and carbonyl groups of the adjacent molecules. This fact probably explains the easy crystallization of the Ugi adducts **4a**−**i** from the reaction mixtures. The crystal structure of **4c** showed molecular disorder of four carbon atoms of the *N*-cyclohexyl group that were located in the middle way between chair and half-chair alternative dispositions.

Compounds **5a**−**i** were obtained as crystalline yellow solids, characterized by spectroscopy and microanalysis. A coupled NH proton was seen by ^1H NMR at δ 7−8, an OH proton between δ 3−6, and two distinct carbonyl groups were observed by ^{13}C NMR and IR. HRMS showed in all studied cases molecular formulas of **5a**−**i**, corresponding to dehydration and, therefore, cyclization of **4a**−**i**. The obtained dioxo-5-phenyl[1,2,4]triazin-1-ylglycinamide structures could include different tautomers that should be compatible with their spectral and analytical data; therefore, a proper assignation of the right tautomer should need some structural study. Crystals of **5a** were suitable for X-ray diffraction measurements. The obtained structure is shown in Figure S2 in the Supporting Information. Only the tautomer having the proton in the O2 atom was obtained. This tautomer was fixed in the crystal packing by a hydrogen bond between O(2)H···O(3) of two contiguous molecules, packing in fact in tight dimers in close proximity at a H-bond distance of 1.9 Å (See Figure S3 in the Supporting Information). The 1,2,4-thiazine ring in Figure S2 (Supporting Information) was completely planar, showing angles around the N(2) of 124 (N3−N2−CO), 118 (N3−N2−CC), and 118 (CC−N2−CO) degrees, indicating a sp^2 hybridization. A quick search on the CCDC crystallographic database afforded only three examples of partially aliphatic 1,2,4-triazine-3,6-dione derivatives, which were not planar, but a few examples of dehydrogenated 1,2,4-triazine-6-one derivatives[25] showed planarity, indicating that this is a common feature for this type of heterocycle.

The tautomer shown in Figure S2 (Supporting Information) was also proved by chemistry. In fact, by treating selected compounds **5b**,**c**,**e**−**g**,**i** with diazomethane (1.5 equiv) in ether/chloroform, the *O*-methyl derivatives **6b**,**c**,**e**−**g**,**i** were obtained as crystalline yellow solids, easily characterized by the usual techniques. Effectively, the methoxy group from the 1,2,4-thiazine nucleus in the derivatives **6b**,**c**,**e**−**g**,**i** was seen as a neat peak at δ 4 in their ^1H NMR spectra, the NH proton was observed as a coupled signal at δ 6−7, and there was no trace of OH signal. MS, HRMS, and microanalyses confirmed the molecular formulas. Careful comparison between the spectral features of the hydrocarbon backbone of all compounds permitted the assignment of spectral patterns common to all types of structures. Products **5a**−**i**, as well as the methyl derivatives **6b**,**c**,**e**−**g**,**i**, constitute a new class of pseudopeptidic 1,2,4-triazines, composed of two different amino acids, an arylglycine, and several natural, as well as nonnatural, achiral or racemic alanine derivatives, such as alanine (**5f**, **6f**), 2-methylalanine (**5a**,**b**, **6b)**, phenylalanine (**5g**,**h**, **6g**), homophenylalanine (**5i**,

(24) See for example: (a) Marcos, C. F.; Marcaccini, S.; Pepino, R.; Polo, C.; Torroba, T. *Synthesis* **2003**, 691−694. (b) Marcaccini, S.; Pepino, R.; Polo, C.; Pozo, M. C. *Synthesis* **2001**, 85−88.

(25) See for example: (a) Garg, N. A.; Stoltz, B. M. *Tetrahedron. Lett.* **2005**, *46*, 1997−2000. (b) Wade, P. C.; Vogt, B. R.; Toeplitz, B.; Puar, M. S.; Gougoutas, J. Z. *J. Org. Chem.* **1979**, *44*, 88−99.

6i), and 2,3-tetramethylenealanine (**5c**−**e**, **6c**, **6e**). In all cases, both the *N*-terminal arylglycine and the peptidic amide nitrogen atoms are bonded through a urea moiety, giving rise to a new class of cyclic dipeptidyl ureas of high pharmacological interest.

Experimental Section

***N*-Cyclohexyl-2-[*N*′-carbamoyl-*N*-(2-oxo-2-phenylacetyl)hydrazino]isobutyramide 4a.** Cyclohexylisocyanide **2a** (300 mg, 2.75 mmol) and benzoylformic acid **3a** (413 mg, 2.75 mmol) were added consecutively to a solution of acetone semicarbazone **1a** (317 mg, 2.75 mmol) in methanol (5 mL) and stirred for 3 days, and the resulting solid was filtered to give compound **4a** (515 mg, 50%) as colorless crystals (MeOH−CH_2Cl_2, 1:6), mp 229−230 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.37 (s, 1H), 9.25 (s, 1H), 7.85 (m, 2H), 7.72 (m, 1H), 7.56 (m, 2H), 6.35 (m, 2H), 3.63 (m, 1H), 1.72 (m, 4H), 1.50 (m, 4H), 1.29 (m, 8H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 190.5, 171.2, 167.9, 159.5, 134.7, 132.0, 128.8, 127.3, 65.3, 46.8, 32.1, 25.4, 24.5, 21.3; IR (KBr) $\tilde{\nu}$ 3600 and 3222 (NH), 3050, 2928, 1704, 1689, 1674 and 1652 (C═O), 1364, 1226 cm^{-1}; EIMS *m*/*z* 357 (M^+ − 17, 10), 328 (2), 302 (4), 115 (75), 72 (100). Anal. Calcd for $C_{19}H_{26}N_4O_4$: C, 60.95; H, 7.00; N, 14.96. Found: C, 61.04; H, 6.89; N, 14.78.

***N*-Cyclohexyl-2-[*N*′-carbamoyl-*N*-(2-oxo-2-{*p*-methoxy}phenylacetyl)hydrazino]isobutyramide 4b.** Cyclohexylisocyanide **2a** (720 mg, 6.60 mmol) and *p*-methoxybenzoylformic acid **3b**[23] (1.19 g, 6.60 mmol) were added consecutively to a solution of acetone semicarbazone **1a** (760 mg, 6.60 mmol) in methanol (10 mL) and stirred for 3 days, and the resulting solid was filtered to give compound **4b** (1.28 g, 48%) as colorless crystals (MeOH−CH_2Cl_2, 1:6), mp 246−247 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.25 (m, 2H), 7.81 (d, J = 8.8 Hz, 2H), 7.06 (d, J = 8.8 Hz, 2H), 6.27 (s, 2H), 3.86 (s, 3H), 3.61 (m, 1H), 1.76 (m, 2H), 1.67 (m, 2H), 1.45 (m, 4H), 1.27 (m, 8H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 189.0, 171.3, 168.2, 164.2, 159.5, 131.6, 125.0, 114.1, 65.2, 55.7, 46.9, 32.0, 25.4, 23.6, 21.3; IR (KBr) $\tilde{\nu}$ 3332 (br, NH), 2932, 2850, 1774 and 1709 (C═O), 1420, 1380 cm^{-1}; EIMS *m*/*z* 407 (M^+ + 3, 15), 391 (35), 310 (22), 239 (25), 162 (100). Anal. Calcd for $C_{20}H_{28}N_4O_5$: C, 59.39; H, 6.98; N, 13.85. Found: C, 59.51; H, 6.83; N, 13.67.

***N*-Cyclohexyl-1-[*N*′-carbamoyl-*N*-(2-oxo-2-phenylacetyl)hydrazino]cyclohexanecarboxamide 4c.** Cyclohexylisocyanide **2a** (900 mg, 8.24 mmol) and benzoylformic acid **3a** (1.237 g, 8.24 mmol) were added consecutively to a solution of cyclohexanone semicarbazone **1b** (1.279 g, 8.24 mmol) in methanol (15 mL) and stirred for 3 days, and the resulting solid was filtered to give compound **4c** (1.88 g, 55%) as colorless crystals (MeOH−CH_2Cl_2, 1:6), mp 243−244 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.46 (s, 1H), 9.26 (s, 1H), 7.86 (d, 2H, J = 7.5 Hz), 7.73 (d, 1H, J = 7.5 Hz), 7.57 (t, 2H, J = 7.5 Hz), 6.19 (br s, 2H), 3.65 (m, 1H), 2.34 (m, 1H), 1.77 (m, 9H), 1.40 (m, 10H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 191.2, 171.7, 168.9, 160.0, 135.5, 132.6, 129.9, 129.5, 68.3, 47.5, 32.9, 32.3, 30.0, 26.2, 25.4, 24.4, 22.4, 22.3; IR (KBr) $\tilde{\nu}$ 3384 and 3248 (NH), 3085, 2930, 2853, 1697, 1685, 1656 and 1650 (C═O), 1225 cm^{-1}; EIMS *m*/*z* 309 (M^+ − 105, 8), 271 (15), 260 (42), 156 (25), 105 (100), 77 (23). Anal. Calcd for $C_{22}H_{30}N_4O_4$: C, 63.75; H, 7.30; N, 13.52. Found: C, 63.91; H, 7.19; N, 13.39. Crystal data for **4c**: $C_{22}H_{30}N_4O_4$; M = 414.50; monoclinic, P2(1)/c; a = 9.071(2) Å, b = 14.515(3) Å, c = 17.209(4) Å; α = 90°, β = 95.318(5)°, γ = 90°; V = 2256.3(9) Å^3; Z = 4; D_{calc} = 1.220 g cm^{-1}; μ(Mo Kα) = 0.085 mm^{-1}. White needle, (0.20 × 0.10 × 0.10) mm^3, 21 927 measured reflections, 3980 independent (R_{int} = 0.1193), 2003 observed ($I > 2\sigma(I)$), R_1 = 0.1820, and wR_2 = 0.3495 (all data). CCDC 602195.

***N*-Cyclohexyl-1-[*N*′-carbamoyl-*N*-(2-oxo-2-{*p*-methoxyphenyl}acetyl)hydrazino]cyclohexanecarboxamide 4d.** Cyclohexylisocyanide **2a** (300 mg, 2.75 mmol) and *p*-methoxybenzoylformic acid **3b**[23] (496 mg, 2.75 mmol) were added consecutively to a solution of cyclohexanone semicarbazone **1b** (427 mg, 2.75) in methanol (5 mL) and stirred for 3 days, and the resulting solid was filtered to give compound **4d** (888 mg, 73%) as colorless crystals (MeOH−CH_2Cl_2, 1:6), mp 236−237 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.43 (d, 1H, J = 7.0 Hz), 9.19 (s, 1H), 7.79 (d, 2H, J = 7.0 Hz), 7.04 (d, 2H, J = 7.0 Hz), 6.13 (br s, 2H), 3.85 (s, 3H), 3.65 (m, 1H), 2.27 (m, 1H), 1.69 (m, 9H), 1.35 (m, 10H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 189.6, 171.9, 169.0, 164.9, 159.8, 132.2, 125.3, 114.6, 68.0, 56.21, 47.4, 32.6, 32.2, 29.6, 25.9, 25.2, 24.2, 22.1; IR (KBr) $\tilde{\nu}$ 3402 and 3266 (NH), 3071, 2941, 2919, 2854, 1698, 1687, 1665 and 1648 (C═O), 1263, 1176 cm^{-1}; EIMS *m*/*z* 445 (M^+ + 1, 4), 426 (8), 383 (6), 340 (10), 300 (55), 290 (72), 135 (100). Anal. Calcd for $C_{23}H_{32}N_4O_5$: C, 62.14; H, 7.26; N, 12.60. Found: C, 62.27; H, 7.15; N, 12.46.

***N*-Benzyl-1-[*N*′-carbamoyl-*N*-(2-oxo-2-{*p*-methoxyphenyl}acetyl)hydrazino]cyclohexanecarboxamide 4e.** Benzylisocyanide **2b** (780 mg, 6.66 mmol) and *p*-methoxybenzoylformic acid **3b**[23] (1.20 g, 6.66 mmol) were added consecutively to a solution of cyclohexanone semicarbazone **1b** (1.034 mg, 6.66 mmol) in methanol (10 mL) and stirred for 3 days, and the resulting solid was filtered to give compound **4e** (1.69 g, 56%) as colorless crystals (MeOH−CH_2Cl_2, 1:6), mp 187−188 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.96 (t, 1H, J = 5.6 Hz), 9.25 (s, 1H), 7.61 (d, J = 8.4 Hz, 2H), 7.31 (m, 5H), 6.85 (m, 2H), 6.12 (br s, 2H), 4.43 (m, 1H), 4.30 (m, 1H), 3.80 (s, 3H), 2.31 (m, 1H), 1.90 (m, 2H), 1.79 (m, 1H), 1.65 (m, 2H), 1.39 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 189.8, 173.1, 169.3, 164.90, 160.0, 140.0, 132.5, 129.0, 128.2, 127.5, 125.4, 114.8, 68.3, 56.37, 43.3, 32.3, 30.0, 25.4, 22.4, 22.3; IR (KBr) $\tilde{\nu}$ 3394 and 3234 (NH), 3071, 2924, 1698, 1661 and 1654 (C═O), 1263, 1173 cm^{-1}; EIMS *m*/*z* 434 (M^+ − 18, 5), 418 (4), 390 (3), 376 (6), 300 (18), 215 (12), 135 (100), 91 (25). Anal. Calcd for $C_{24}H_{28}N_4O_5$: C, 63.70; H, 6.24; N, 12.38. Found: C, 63.57; H, 6.35; N, 12.24.

(±)-*N*-Cyclohexyl-2-[*N*′-carbamoyl-*N*-(2-oxo-2-{*p*-methoxyphenyl}acetyl)hydrazino]propionamide 4f. Cyclohexylisocyanide **2a** (300 mg, 2.75 mmol) and *p*-methoxybenzoylformic acid **3b**[23] (495 mg, 2.75 mmol) were added consecutively to a solution of acetaldehyde semicarbazone **1c** (278 mg, 2.75 mmol) in methanol (5 mL) and stirred for 3 days, and the resulting solid was filtered to give compound **4f** (633 mg, 59%) as colorless crystals (MeOH−CH_2Cl_2, 1:6), mp 214−215 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.50 (br s, 1H), 8.32 (br s, 1H), 7.84 (m, 4H), 6.27 (br s, 2H), 3.84 (s, 3H), 3.59 (m, 1H), 1.71 (m, 4H), 1.28 (m, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 189.6, 172.9, 169.5, 164.6, 164.0, 132.1, 125.7, 114.5, 62.5, 56.0, 47.9, 32.5, 30.9, 25.5, 24.5; IR (KBr) $\tilde{\nu}$ 3440, 3343 and 3289 (NH), 3098, 2941, 2860, 1703, 1687, 1649 and 1611 (C═O), 1252, 1171 cm^{-1}; EIMS *m*/*z* 391 (M^+ + 1, 3), 372 (M − 18, 15), 347 (5), 319 (6), 255 (35), 247 (65), 135 (100). Anal. Calcd for $C_{19}H_{26}N_4O_5$: C, 58.45; H, 6.71; N, 14.35. Found: C, 58.37; H, 6.61; N, 14.21.

(±)-*N*-Cyclohexyl-2-[*N*′-carbamoyl-*N*-(2-oxo-2-phenylacetyl)-hydrazino]-3-phenylpropionamide 4g. Cyclohexylisocyanide **2a** (300 mg, 2.75 mmol) and benzoylformic acid **3a** (413 mg, 2.75 mmol) were added consecutively to a solution of phenylacetaldehyde semicarbazone **1d** (487 mg, 2.75 mmol) in methanol (5 mL) and stirred for 3 days, and the resulting solid was filtered to give compound **4g** (552 mg, 46%) as colorless crystals (MeOH−CH_2Cl_2, 1:6), mp 217−218 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.85 (br s, 0.5H), 8.46 (br s, 0.5H), 8.10 (s, 1H), 7.83 (m, 1H), 7.71 (m, 2H), 7.54 (m, 2H), 7.30 (m, 5H), 6.26 (br s, 2H), 4.82 (s, 0.5H), 4.56 (s, 0.5H), 3.59 (m, 1H, CH), 3.22 (m, 1H), 3.15 (m, 1H), 1.64 (m, 5H), 1.24 (m, 5H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 191.1, 169.72, 159.0, 158.6, 138.1, 135.6, 132.8, 130.0, 129.8, 129.6, 129.1, 127.4, 63.4, 48.0, 34.2, 32.6, 26.0, 24.7; IR (KBr) $\tilde{\nu}$ 3403, 3327 and 3207 (NH), 3071, 2930, 2860, 1703, 1686, 1660 and 1643 (C═O), 1545, 1230, 700 cm^{-1}; EIMS *m*/*z* 419 (M^+ − 17, 6), 393 (3), 331 (5), 293 (31), 230 (48), 104 (100), 91 (26), 77 (28). Anal. Calcd for $C_{24}H_{28}N_4O_4$: C, 66.04; H, 6.47; N, 12.84. Found: C, 66.16; H, 6.33; N, 12.70.

(±)-*N*-Cyclohexyl-2-[*N*′-carbamoyl-*N*-(2-oxo-2-{*p*-methoxyphenyl}acetyl)hydrazino]-3-phenylpropionamide 4h. Cyclohexylisocyanide **2a** (300 mg, 2.75 mmol) and *p*-methoxybenzoylformic acid **3b**[23] (495 mg, 2.75 mmol) were added consecutively to a solution of phenylacetaldehyde semicarbazone **1d** (487 mg, 2.75 mmol) in methanol (5 mL) and stirred for 3 days, and the resulting solid was filtered to give compound **4h** (693 mg, 54%) as colorless crystals (MeOH−CH_2Cl_2, 1:6), mp 230−232 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.85 (br s, 0.5H), 8.40 (br s, 0.5H), 8.05 (s, 1H), 7.77 (m, 1H), 7.68 (m, 2H), 7.28 (m, 5H), 7.03 (m, 2H), 6.22 (br s, 2H), 4.78 (s, 0.5H), 4.49 (s, 0.5H), 3.84 (s, 3H), 3.76 (m, 1H), 3.15 (m, 2H), 1.61 (m, 5H), 1.20 (m, 5H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 189.4, 169.9, 164.8, 158.9, 158.4, 137.7, 132.2, 129.7, 128.9, 127.0, 125.2, 114.7, 63.2, 56.2, 48.0, 34.2, 32.3, 25.7, 24.6; IR (KBr) $\tilde{\nu}$ 3397, 3332, 3256, 3196 (NH), 3033, 2930, 2854, 1687, 1665 and 1600 (C═O), 1257, 1176 cm^{-1}; EIMS *m*/*z* 449 (M^+ − 17, 6), 423 (2), 323 (8), 230 (72), 135 (100). Anal. Calcd for $C_{25}H_{30}N_4O_5$: C, 64.36; H, 6.48; N, 12.01. Found: C, 64.49; H, 6.56; N, 11.88.

(±)-*N*-Cyclohexyl-2-[*N*′-carbamoyl-*N*-(2-oxo-2-phenylacetyl)-hydrazino]-4-phenylbutyramide 4i. Cyclohexylisocyanide **2a** (229 mg, 2.10 mmol) and benzoylformic acid **3a** (315 mg, 2.10 mmol) were added consecutively to a solution of 3-phenylpropionaldehyde semicarbazone **1e** (402 mg, 2.10 mmol) in methanol (5 mL) and stirred for 3 days, and the resulting solid was filtered to give compound **4i** (520 mg, 55%) as colorless crystals (MeOH−CH_2Cl_2, 1:6), mp 198−199 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 7.90 (triplet of doublets, J = 7.0, 1.2 Hz, 2H), 7.64 (m, 1H), 7.49 (triplet of doublets, J = 7.0, 1.2 Hz, 2H), 7.18 (m, 5H), 4.50 (t, J = 7.4 Hz, 1H), 3.69 (m, 1H), 3.30 (s, 1H), 3.26 (s, 3H), 2.71 (m, 2H), 2.12 (m, 2H), 1.88 (m, 2H), 1.76 (m, 2H), 1.60 (m, 1H), 1.31 (m, 5H); ^{13}C NMR (100 MHz, CD_3OD) δ 191.8, 182.3, 171.3, 154.8, 142.1, 136.1, 134.0, 130.6, 130.0, 129.7, 129.6, 127.4, 63.7, 48.0, 33.8, 33.6, 31.6, 26.7, 26.1; IR (KBr) $\tilde{\nu}$ 3424, 3348 and 3310 (NH), 2936, 2854, 1730, 1692, 1676 and 1638 (C═O), 1230, 714 cm^{-1}; EIMS *m*/*z* 433 (M^+ − 17, 6), 432 (M^+ − 18, 17), 328 (100), 279 (21), 216 (88), 190 (37), 104 (63), 91 (58). Anal. Calcd for $C_{25}H_{30}N_4O_4$: C, 66.65; H, 6.71; N, 12.44. Found: C, 66.57; H, 6.62; N, 12.31.

***N*-Cyclohexyl-2-(3-hydroxy-6-oxo-5-phenyl-6*H*-[1,2,4]triazin-1-yl)isobutyramide 5a.** Isobutyramide **4a** (200 mg, 0.53 mmol) was stirred at room temperature with sodium ethoxide (from Na, 13 mg, 0.56 mmol) in ethanol (5 mL) for 12 h. Then the solvent was evaporated, the residue was treated with isopropyl ether (5 mL), and the resulting solid was filtered and dissolved in water (5 mL). The solution was acidified with acetic acid until pH = 4, and the resulting solid was filtered to give **5a** (106 mg, 56%) as yellow crystals (MeOH−CH_2Cl_2, 1:6), mp 215−216 °C; ^{1}H NMR (400 MHz, acetone-d_6) δ 8.54 (d, J = 7.2 Hz, 2H), 7.57 (t, J = 7.2 Hz, 1H), 7.47 (t, J = 7.2 Hz, 2H), 6.87 (d, J = 8.0 Hz, 1H), 3.68 (m, 1H), 2.09 (s, 1H), 1.82 (m, 2H), 1.64 (m, 2H), 1.62 (s, 6H), 1.27 (m, 2H), 1.10 (m, 4H); ^{13}C NMR (100 MHz, acetone-d_6) δ 172.0, 164.0, 154.6, 154.3, 135.8, 133.7, 131.8, 129.7, 69.3, 50.2, 34.25, 27.2, 26.8, 25.2; IR (KBr) $\tilde{\nu}$ 3377 (NH, OH), 2931, 2853, 1653 and 1554 (C═O), 1218 cm^{-1}; EIMS *m*/*z* 356 (M^+, 55), 258 (8), 231 (86), 202 (22), 175 (25), 104 (100); HRMS (EI) calcd for $C_{19}H_{24}N_4O_3$, 356.1848; found, 356.1848. Anal. Calcd for $C_{19}H_{24}N_4O_3$: C, 64.03; H, 6.79; N, 15.72. Found: C, 64.15; H, 6.65; N, 15.61. Crystal data for **5a**: $C_{19}H_{24}N_4O_3$; M = 356.42; monoclinic, P2(1)/n, a = 11.367(4) Å, b = 15.514(5) Å, c = 11.871(4) Å; α = 90°, β = 116.880(4)°, γ = 90°; V = 1867.2(11) Å^3; Z = 4; D_{calc} = 1.268 gcm^{-1}; μ(Mo Kα) = 0.088 mm^{-1}. Yellow prism, (0.20 × 0.20 × 0.20) mm^3, 18 241 measured reflections, 3472 independent (R_{int} = 0.0723), 2047 observed ($I > 2\sigma(I)$), R_1 = 0.1321, and wR_2 = 0.2488 (all data). CCDC 602196.

***N*-Cyclohexyl-2-(3-hydroxy-6-oxo-5-(*p*-methoxyphenyl)-6*H*-[1,2,4]triazin-1-yl)isobutyramide 5b.** Isobutyramide **4b** (200 mg, 0.49 mmol) was stirred at room temperature with sodium ethoxide (from Na, 12 mg, 0.52 mmol) in ethanol (5 mL) for 12 h. Then the solvent was evaporated, the residue was treated with isopropyl ether (5 mL), and the resulting solid was filtered and dissolved in water (5 mL). The solution was acidified with acetic acid until pH = 4, and the resulting solid was filtered to give **5b** (104 mg, 54%) as yellow crystals (MeOH−CH_2Cl_2, 1:6), mp 109−110 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.49 (d, J = 8.8 Hz, 2H), 7.8 (d, J = 8.4 Hz, 1H), 7.34 (d, J = 8.8 Hz, 1H), 7.06 (d, J = 8.8 Hz, 2H), 6.26 (br s, 1H), 3.85 (s, 3H), 3.50 (m, 1H), 1.64 (m, 4H), 1.52 (s, 6H), 1.19 (m, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.7, 164.9, 163.3, 161.53, 152.9, 132.6, 126.8, 114.4, 67.6, 56.1, 48.7, 32.9, 26.0, 25.7, 24.6; IR (KBr) $\tilde{\nu}$ 3462, 3359, (NH, OH), 2930, 2860, 1660 and 1611 (C═O), 1556, 1269, 1182 cm^{-1}; EIMS *m*/*z* 386 (M^+, 21), 261 (65), 162 (64), 134 (100). Anal. Calcd for $C_{20}H_{26}N_4O_4$: C, 62.16; H, 6.78; N, 14.50. Found: C, 62.25; H, 6.69; N, 14.39.

***N*-Cyclohexyl-1-(3-hydroxy-6-oxo-5-phenyl-6*H*-[1,2,4]triazin-1-yl)cyclohexanecarboxamide 5c.** Cyclohexanecarboxamide **4c** (500 mg, 1.21 mmol) was stirred at room temperature with sodium ethoxide (from Na, 29 mg, 1.27 mmol) in ethanol (10 mL) for 12 h. Then the solvent was evaporated, the residue was treated with isopropyl ether (10 mL), and the resulting solid was filtered and dissolved in water (10 mL). The solution was acidified with acetic acid until pH = 4, and the resulting solid was filtered to give **5c** (403 mg, 84%) as yellow crystals (MeOH−CH_2Cl_2, 1:6), mp 230−231 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 8.37 (d, J = 7.2 Hz, 2H), 7.51 (q, J = 7.2 Hz, 1H), 7.42 (t, J = 7.2 Hz, 2H), 3.63 (m, 1H), 3.26 (s, 2H), 2.42 (m, 2H), 2.02 (m, 2H), 1.66 (m, 10H), 1.26 (m, 4H), 1.12 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 173.8, 164.7, 154.7, 154.4, 135.1, 133.4, 131.3, 129.3, 71.9, 50.5, 33.6, 32.6, 26.7, 26.6, 26.5, 23.3; IR (KBr) $\tilde{\nu}$ 3358 and 3063 (OH, NH), 2932, 2852, 1629 (C═O), 1579, 1560, 1541, 1208 cm^{-1}; EIMS *m*/*z* (396, M^+, 75), 271 (100), 208 (20), 190 (55), 104 (92); HRMS (EI) calcd for $C_{22}H_{28}N_4O_3$, 396.2161; found, 396.2158. Anal. Calcd for $C_{22}H_{28}N_4O_3$: C, 66.64; H, 7.12; N, 14.13. Found: C, 66.75; H, 7.05; N, 14.03.

***N*-Cyclohexyl-1-(3-hydroxy-6-oxo-5-{*p*-methoxyphenyl}-6*H*-[1,2,4]triazin-1-yl)cyclohexanecarboxamide 5d.** Cyclohexanecarboxamide **4d** (500 mg, 1.12 mmol) was stirred at room temperature with sodium ethoxide (from Na, 27 mg, 1.17 mmol) in ethanol (10 mL) for 12 h. Then the solvent was evaporated, the residue was treated with isopropyl ether (10 mL), and the resulting solid was filtered and dissolved in water (10 mL). The solution was acidified with acetic acid until pH = 4, and the resulting solid was filtered to give **5d** (258 mg, 54%) as yellow crystals (MeOH−CH_2Cl_2, 1:6), mp 163−164 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 8.46 (d, J = 9.2 Hz, 2H), 7.29 (br d, J = 8.4 Hz, 1H), 6.93 (d, J = 9.2 Hz, 2H), 3.80 (s, 3H), 3.60 (m, 1H), 3.24 (s, 1H), 2.38 (m, 2H), 1.99 (m, 2H), 1.62 (m, 12H), 1.23 (m, 2H), 1.1 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 174.2, 174.1, 165.1, 163.6, 154.97, 133.7, 127.8, 114.9, 71.9, 56.2, 50.7, 33.8, 32.8, 26.9, 26.8, 26.7, 23.5; IR (KBr) $\tilde{\nu}$ 3435 and 3381 (OH, NH), 2936, 2860, 1660 and 1605 (C═O), 1551, 1263, 1181 cm^{-1}; EIMS *m*/*z* 426 (M^+, 20), 328 (5), 301 (93), 220 (40), 134 (100); HRMS (EI) calcd for $C_{23}H_{30}N_4O_4$, 426.2267; found, 426.2280. Anal. Calcd for $C_{23}H_{30}N_4O_4$: C, 64.77; H, 7.09; N, 13.14. Found: C, 64.65; H, 7.16; N, 13.06.

***N*-Benzyl-1-(3-hydroxy-6-oxo-5-{*p*-methoxyphenyl}-6*H*-[1,2,4]-triazin-1-yl)cyclohexanecarboxamide 5e.** Cyclohexanecarboxamide **4e** (500 mg, 1.10 mmol) was stirred at room temperature with sodium ethoxide (27 mg, 1.17 mmol) in ethanol (10 mL) for 12 h. Then the solvent was evaporated, the residue was treated with isopropyl ether (10 mL), and the resulting solid was filtered and dissolved in water (10 mL). The solution was acidified with acetic acid until pH = 4, and the resulting solid was filtered to give **5e** (407 mg, 85%) as yellow crystals (MeOH−CH_2Cl_2, 1:6), mp 99−100 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.51 (d, J = 9.0 Hz, 2H), 8.08 (br t, J = 6.0 Hz, 1H), 7.23 (d, J = 4.5 Hz, 4H), 7.18 (quintet, J = 4.5 Hz, 1H), 7.06 (d, J = 9.0 Hz, 2H), 4.22 (d, J = 6.0 Hz, 2H), 3.85 (s, 3H), 3.40 (v br s, 1H), 2.42 (br d, J = 13.6 Hz, 2H), 1.98 (m, 2H), 1.52 (m, 6H); ^{13}C NMR (100 MHz, DMSO-

d_6) δ 171.5, 162.4, 160.6, 152.9, 152.6, 139.9, 131.9, 127.9 126.8, 126.3, 126.2, 113.5, 69.7, 55.4, 42.2, 30.8, 24.9, 21.6; IR (KBr) $\tilde{\nu}$ 3375 (NH, OH), 2930, 2860, 1660 and 1611 (C═O), 1557, 1263, 1182 cm^{-1}; EIMS *m*/*z* 434 (M$^+$, 14), 376 (3), 328 (4), 300 (100), 216 (35), 134 (63), 91 (51); HRMS (EI) calcd for $C_{23}H_{30}N_4O_4$, 426.2267; found, 426.2280. Anal. Calcd for $C_{24}H_{26}N_4O_5$: C, 64.77; H, 7.09; N, 13.14. Found: C, 64.65; H, 7.16; N, 13.06.

(±)-*N*-Cyclohexyl-2-(3-hydroxy-6-oxo-5-{*p*-methoxyphenyl}-6*H*-[1,2,4]triazin-1-yl)propionamide 5f. Propionamide **4f** (200 mg, 0.51 mmol) was stirred at room temperature with sodium ethoxide (from Na, 12 mg, 0.52 mmol) in ethanol (5 mL) for 12 h. Then the solvent was evaporated, the residue was treated with isopropyl ether (5 mL), and the resulting solid was filtered and dissolved in water (10 mL). The solution was acidified with acetic acid until pH = 4, and the resulting solid was filtered to give **5f** (101 mg, 53%) as yellow crystals (MeOH−CH_2Cl_2, 1:6), mp 210−211 °C; ^{1}H NMR (400 MHz, acetone-d_6) δ 8.70 (d, *J* = 9.1 Hz, 2H), 7.06 (br s, 1H), 7.05 (d, *J* = 9.1 Hz, 2H), 5.39 (q, *J* = 7.1 Hz, 1H), 3.91 (s, 3H), 3.66 (m, 1H), 2.84 (br s, 1H), 1.79 (m, 2H), 1.66 (m, 2H), 1.57 (m, 1H), 1.54 (d, *J* = 7.1 Hz, 3H), 1.28 (m, 2H), 1.13 (m, 3H); ^{13}C NMR (100 MHz, acetone-d_6) δ 169.6, 165.3, 162.6, 156.5, 155.0, 134.3, 128.4, 115.4, 56.9, 51.6, 48.7, 34.4, 27.3, 26.7, 16.9; IR (KBr) $\tilde{\nu}$ 3294 (OH, NH), 2941, 2865, 1660 (C═O), 1611, 1589, 1556, 1252, 845 cm^{-1}; EIMS *m*/*z* 372 (M$^+$, 25), 293 (5), 274 (5), 247 (100), 204 (25), 134 (95). Anal. Calcd for $C_{19}H_{24}N_4O_6$: C, 61.28; H, 6.50; N, 15.04. Found: C, 61.14; H, 6.62; N, 14.91.

(±)-*N*-Cyclohexyl-2-(3-hydroxy-6-oxo-5-phenyl-6*H*-[1,2,4]triazin-1-yl)-3-phenylpropionamide 5g. Phenylpropionamide **4g** (200 mg, 0.46 mmol) was stirred at room temperature with sodium ethoxide (11 mg, 0.48 mmol) in ethanol (5 mL) for 12 h. Then the solvent was evaporated, the residue was treated with isopropyl ether (5 mL), and the resulting solid was filtered and dissolved in water (5 mL). The solution was acidified with acetic acid until pH = 4, and the resulting solid was filtered to give **5g** (162 mg, 84%) as yellow crystals (MeOH−CH_2Cl_2, 1:6), mp 220−221 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.31 (d, *J* = 8.4 Hz, 2H), 7.83 (d, *J* = 7.8 Hz, 1H), 7.57 (q, *J* = 7.8 Hz, 1H), 7.48 (t, *J* = 7.8 Hz, 2H), 7.18 (m, 4H), 7.13 (m, 1H), 5.55 (dd, *J* = 10.5 Hz, *J* = 4.8 Hz, 1H), 3.57 (m, 1H), 3.42 (dd, *J* = 14.0 Hz, *J* = 4.8 Hz, 1H), 3.26 (dd, *J* = 14.0 Hz, *J* = 10.5 Hz, 1H), 3.34 (br s, 1H), 1.69 (m, 4H), 1.55 (m, 1H), 1.19 (m, 5H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 166.5, 161.7, 152.80, 152.5, 137.5, 133.4, 132.3, 129.7, 128.8, 128.2, 128.1, 126.3, 61.6, 48.2, 35.1, 32.2, 30.7, 24.7; IR (KBr) $\tilde{\nu}$ 3289 (OH, NH), 3076, 2936, 2860, 1671 and 1643 (C═O), 1573, 1426, 1280, 704 cm^{-1}; EIMS *m*/*z* 420 (M$^+$ + 2, 30), 419 (M$^+$ + 1, 27), 418 (M$^+$, 13), 335 (5), 293 (25), 230 (65), 104 (100). Anal. Calcd for $C_{24}H_{26}N_4O_3$: C, 68.88; H, 6.26; N, 13.39. Found: C, 68.95; H, 6.15; N, 13.29.

(±)-*N*-Cyclohexyl-2-(3-hydroxy-6-oxo-5-{*p*-methoxyphenyl}-6*H*-[1,2,4]triazin-1-yl)-3-phenylpropionamide 5h. Phenylpropionamide **4h** (500 mg, 1.07 mmol) was stirred at room temperature with sodium ethoxide (from Na, 26 mg, 1.13 mmol) in ethanol (10 mL) for 12 h. Then the solvent was evaporated, the residue was treated with isopropyl ether (10 mL), and the resulting solid was filtered and dissolved in water (10 mL). The solution was acidified with acetic acid until pH = 4, and the resulting solid was filtered to give **5h** (307 mg, 64%) as yellow crystals (MeOH−CH_2Cl_2, 1:6), mp 172−173 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 8.39 (d, *J* = 9.2 Hz, 2H), 7.16 (m, 4H), 7.08 (m, 1H), 6.92 (d, *J* = 9.2 Hz, 2H), 5.58 (dd, *J* = 10.0, 5.5 Hz, 1H), 3.81 (s, 3H), 3.61 (m, 1H), 3.41 (dd, *J* = 13.8, 5.5 Hz, 1H), 3.34 (dd, *J* = 13.8, 10.0 Hz, 1H), 1.69 (m, 6H), 1.26 (m, 2H), 1.13 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 169.8, 165.0, 163.0, 155.2, 155.1, 138.4, 133.6, 130.3, 129.4, 127.8, 127.5, 114.7, 63.7, 56.0, 50.4, 36.9, 33.5, 26.6, 23.1; IR (KBr) $\tilde{\nu}$ 3395 and 3180 (NH, OH), 3084, 2929, 2853, 1691 and 1660 (C═O), 1585, 1250, 1165 cm^{-1}; EIMS *m*/*z* 448 (M$^+$, 48), 323 (12), 230 (100), 219 (35), 134 (50); HRMS (EI) calcd for $C_{25}H_{28}N_4O_4$, 448.2111; found, 448.2126. Anal. Calcd for $C_{25}H_{28}N_4O_4$: C, 66.95; H, 6.29; N, 12.49. Found: C, 67.13; H, 6.36; N, 12.36.

(±)-*N*-Cyclohexyl-2-(3-hydroxy-6-oxo-5-phenyl-6*H*-[1,2,4]triazin-1-yl)-4-phenylbutyramide 5i. 4-Phenylbutyramide **4i** (200 mg, 0.44 mmol) was stirred at room temperature with sodium ethoxide (from Na, 11 mg, 0.47 mmol) in ethanol (5 mL) for 12 h. Then the solvent was evaporated, the residue was treated with isopropyl ether (5 mL), and the resulting solid was filtered and dissolved in water (5 mL). The solution was acidified with acetic acid until pH = 4, and the resulting solid was filtered to give **5i** (115 mg, 60%) as yellow crystals (MeOH−CH_2Cl_2, 1:6), mp 97−98 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.45 (d, *J* = 7.5 Hz, 2H), 7.76 (d, *J* = 7.5 Hz, 1H), 7.62 (t, *J* = 7.5 Hz, 1H), 7.54 (t, *J* = 7.5 Hz, 2H), 7.25 (t, *J* = 7.5 Hz, 2H), 7.17 (d, *J* = 7.5 Hz, 3H), 5.20 (t, *J* = 7.5 Hz, 1H), 3.54 (m, 1H), 3.35 (br s, 1H), 2.56 (t, *J* = 7.5 Hz, 2H), 2.35 (q, *J* = 7.5 Hz, 2H), 1.66 (m, 4H), 1.54 (m, 1H), 1.18 (m, 5H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 167.0, 161.7, 153.1, 152.8, 141.0, 133.6, 132.2, 129.9, 128.3, 128.2, 128.1, 125.8, 60.3, 48.0, 35.8, 32.1, 31.0, 30.7, 24.7; IR (KBr) $\tilde{\nu}$ 3305 (NH, OH), 2935, 2859, 1664 and 1555 (C═O), 1224, 707 cm^{-1}; EIMS *m*/*z* 432 (M$^+$, 15), 328 (100), 279 (25), 216 (93), 190 (48), 104 (75), 91 (84); HRMS (EI) calcd for $C_{25}H_{28}N_4O_3$, 432.2161; found, 432.2188. Anal. Calcd for $C_{25}H_{28}N_4O_3$: C, 69.42; H, 6.53; N, 12.95. Found: C, 69.31; H, 6.45; N, 12.86.

***N*-Cyclohexyl-2-[3-methoxy-5-(4-methoxyphenyl)-6-oxo-6*H*-[1,2,4]triazin-1-yl]isobutyramide 6b.** An ethereal solution of diazomethane (8.2 mg, 0.20 mmol in diethyl ether), freshly prepared from *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide and titrated as it has been described,[26] was added to a suspension of isobutyramide **5b** (50 mg, 0.13 mmol) in chloroform (15 mL) at 0 °C, and the mixture was stirred for 12 h at room temperature until a homogeneous solution was obtained. Then the solvent was evaporated to give **6b** (43 mg, 83%) as yellow crystals (MeOH−CH_2Cl_2, 1:6), mp 226−227 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (d, *J* = 8.5 Hz, 2H), 6.92 (d, *J* = 8.5 Hz, 2H), 5.48 (d, *J* = 7.8 Hz, 1H), 3.95 (s, 3H), 3.86 (s, 3H), 3.80 (m, 1H), 1.72 (s, 6H), 1.68 (m, 4H), 1.34 (m, 4H), 1.14 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 163.5, 162.1, 153.2, 132.8, 128.7, 125.8, 113.7, 67.8, 63.9, 55.4, 48.6, 32.9, 25.5, 24.9, 23.8; IR (KBr) $\tilde{\nu}$ 3419 (NH), 2920, 2850, 1651 (C═O), 1235, 1164 cm^{-1}; EIMS *m*/*z* 400 (M$^+$, 43), 376 (6), 275 (100), 246 (55), 232 (34), 134 (46). Anal. Calcd for $C_{21}H_{28}N_4O_4$: C, 62.98; H, 7.05; N, 13.99. Found: C, 63.11; H, 6.94; N, 13.88.

***N*-Cyclohexyl-1-(3-methoxy-6-oxo-5-phenyl-6*H*-[1,2,4]triazin-1-yl)cyclohexanecarboxamide 6c.** An ethereal solution of diazomethane (16 mg, 0.38 mmol in diethyl ether), freshly prepared from *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide,[26] was added to a suspension of cyclohexanecarboxamide **5c** (100 mg, 0.25 mmol) in chloroform (30 mL) at 0 °C, and the mixture was stirred for 12 h at room temperature until a homogeneous solution was obtained. Then the solvent was evaporated to give **6c** (88 mg, 85%) as yellow crystals (MeOH−CH_2Cl_2, 1:6), mp 164−165 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 8.38 (doublet of triplets, *J* = 7.2, 1.5 Hz, 2H), 7.54 (triplet of triplets, *J* = 7.2, 1.5 Hz, 1H), 7.44 (triplet of doublets, *J* = 7.2, 1.5 Hz, 2H), 7.37 (d, *J* = 8.1 Hz, 1H), 3.95 (s, 3H), 3.64 (m, 1H), 2.47 (m, 2H), 2.05 (m, 2H), 1.77 (m, 2H), 1.69 (m, 8H), 1.59 (m, 2H), 1.27 (m, 2H), 1.14 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 173.7, 173.6, 165.0, 154.6, 134.9, 133.6, 131.3, 129.3, 72.2, 56.0, 50.6, 33.6, 32.5, 26.7, 26.6, 26.4, 23.3; IR (KBr)

(26) Recent examples of the preparation and titration of diazomethane are: (a) Gaucher, A.; Dutot, L.; Barbeau, O.; Hamchaoui, W.; Wakselman, M.; Mazaleyrat, J. P. *Tetrahedron: Asymmetry* **2005**, *16*, 857−864. (b) Bug, T.; Hartnagel, M.; Schlierf, C.; Mayr, H. *Chem.—Eur. J.* **2003**, *9*, 4068−4076. (c) Brown, E.; Dhal, R.; Papin, N. *Tetrahedron* **1995**, *51*, 13061−13072. A general procedure and safety indications can be found in: (d) Furniss, B. S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R. *Vogel's Textbook of Practical Organic Chemistry*, 5th edition; Longman Group: Harlow, U.K., 1989; p 430 (safety indications), p 431 (preparation of *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide), and pp 432−433 (preparation of diazomethane).

$\tilde{\nu}$ 3296 (NH), 2926, 2853, 1646 (C═O), 1582, 1561, 1368, 1226 cm^{-1}; EIMS *m*/*z* 410 (M^+, 15), 312 (10), 299 (15), 285 (100), 256 (32), 208 (75), 204 (93), 189 (28); HRMS (EI) calcd for $C_{23}H_{30}N_4O_3$, 410.2318; found, 410.2310. Anal. Calcd for $C_{23}H_{30}N_4O_3$: C, 67.29; H, 7.37; N, 13.65. Found: C, 67.21; H, 7.28; N, 13.58.

***N*-Benzyl-1-[3-methoxy-5-(4-methoxyphenyl)-6-oxo-6*H*-[1,2,4]-triazin-1-yl)cyclohexanecarboxamide 6e.** An ethereal solution of diazomethane (15 mg, 0.36 mmol in diethyl ether), freshly prepared from *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide,[26] was added to a suspension of cyclohexanecarboxamide **5e** (100 mg, 0.23 mmol) in chloroform (30 mL) at 0 °C, and the mixture was stirred at room temperature for 12 h until a homogeneous solution was obtained. Then the solvent was evaporated to give **6e** (90 mg, 87%) as yellow crystals (MeOH−CH_2Cl_2, 1:6), mp 127−129 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.63 (d, J = 8.2 Hz, 2H), 7.26 (m, 5H), 6.94 (d, J = 8.2 Hz, 2H), 6.23 (t, J = 5.2 Hz, 1H), 4.48 (d, J = 5.2, 2H), 3.93 (s, 3H), 3.88 (s, 3H), 2.65 (m, 2H), 2.11 (m, 2H), 1.72 (m, 2H), 1.60 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 163.5, 162.4, 153.5, 153.0, 138.2, 132.8, 128.5, 127.6, 127.2, 125.7, 113.6, 71.0, 55.4, 55.2, 43.6, 31.3, 25.2, 22.1; IR (KBr) $\tilde{\nu}$ 3412 (NH), 2939, 2849, 1689 (C═O), 1601, 1549, 1510, 1258, 1172 cm^{-1}; EIMS *m*/*z* 448 (M^+, 22), 314 (100), 286 (12), 233 (53), 134 (26), 96 (28), 91 (39). Anal. Calcd for $C_{25}H_{28}N_4O_4$: C, 66.95; H, 6.29; N, 12.49. Found: C, 67.11; H, 6.18; N, 12.36.

(±)-*N*-Cyclohexyl-2-[3-methoxy-5-(4-methoxyphenyl)-6-oxo-6*H*-[1,2,4]triazin-1-yl]propionamide 6f. An ethereal solution of diazomethane (8 mg, 0.19 mmol in diethyl ether), freshly prepared from *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide,[26] was added to a suspension of propionamide **5f** (45 mg, 0.12 mmol) in chloroform (15 mL), and the mixture was stirred for 12 h at room temp until a homogeneous solution was obtained. Then the solvent was evaporated to give **6f** (40 mg, 86%) as yellow crystals (MeOH−CH_2Cl_2, 1:6), mp 175−176 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.66 (d, J = 9.0 Hz, 2H), 6.96 (d, J = 9.0 Hz, 2H), 6.24 (br d, J = 7.1 Hz, 1H), 5.45 (q, J = 7.0 Hz, 1H), 3.94 (s, 3H), 3.88 (s, 3H), 3.75 (m, 1H), 1.85 (m, 2H), 1.64 (d, J = 7.0 Hz, 3H), 1.60 (m, 2H), 1.32 (m, 2H), 1.13 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.7, 163.7, 153.7, 153.5, 141.7, 132.8, 125.8, 113.8, 57.0, 55.5, 48.4, 47.4, 32.8, 25.4, 24.6, 14.7; IR (KBr) $\tilde{\nu}$ 3269 (NH), 2937, 2854, 1648 (C═O), 1607, 1576, 1548, 1259, 1179 cm^{-1}; EIMS *m*/*z* 386 (M^+, 25), 304 (3), 289 (3), 261 (100), 232 (22), 141 (53), 135 (62), 113 (54). Anal. Calcd for $C_{20}H_{26}N_4O_4$: C, 62.16; H, 6.78; N, 14.50. Found: C, 62.07; H, 6.68; N, 14.43.

(±)-*N*-Cyclohexyl-2-(3-methoxy-6-oxo-5-phenyl-6*H*-[1,2,4]triazin-1-yl)-3-phenylpropionamide 6g. An ethereal solution of diazomethane (16 mg, 0.38 mmol in diethyl ether), freshly prepared from *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide,[26] was added to a suspension of propionamide **5g** (105 mg, 0.25 mmol) in chloroform (30 mL) at 0 °C, and the mixture was stirred for 12 h at room temp until a homogeneous solution was obtained. Then the solvent was evaporated to give **6g** (87 mg, 80%) as yellow crystals (MeOH−CH_2Cl_2, 1:6), mp 156−157 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.45 (d, J = 7.8 Hz, 2H), 7.56 (t, J = 7.8 Hz, 1H), 7.45 (t, J = 7.8 Hz, 2H), 7.22 (m, 5H), 6.16 (br d, J = 7.6 Hz, 1H), 5.62 (dd, J = 8.7, 6.8 Hz, 1H), 3.99 (s, 3H), 3.71 (m, 1H), 3.57 (dd, J = 14.5, 6.8 Hz, 1H), 3.47 (dd, J = 14.5, 8.7 Hz, 1H), 1.79 (m, 2H), 1.59 (m, 3H), 1.30 (m, 2H), 1.08 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5, 163.0, 153.5, 153.2, 136.6, 133.0, 130.3, 129.1, 129.0, 128.6, 128.3, 126.8, 62.5, 55.7, 48.5, 32.7, 25.4, 24.6; IR (KBr) $\tilde{\nu}$ 3313 (NH), 2931, 2849, 1687 (C═O), 1634, 1549, 1262, 699 cm^{-1}; EIMS *m*/*z* 432 (M^+, 5), 307 (15), 278 (5), 230 (100), 203 (20), 104 (32), 91 (45). Anal. Calcd for $C_{25}H_{28}N_4O_3$: C, 69.42; H, 6.53; N, 12.95. Found: C, 69.51; H, 6.61; N, 12.87.

(±)-*N*-Cyclohexyl-2-(3-methoxy-6-oxo-5-phenyl-6*H*-[1,2,4]triazin-1-il)-4-phenylbutyramide 6i. An ethereal solution of diazomethane (15 mg, 0.36 mmol in diethyl ether), freshly prepared from *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide,[26] was added to a suspension of propionamide **5i** (100 mg, 0.23 mmol) in chloroform (50 mL) at 0 °C, and the mixture was stirred for 12 h at room temperature until a homogeneous solution was obtained. Then the solvent was evaporated to give **6i** (91 mg, 89%) as yellow crystals (MeOH−CH_2Cl_2, 1:6), mp 114−115 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.51 (d, J = 7.5 Hz, 1H), 8.45 (d, J = 7.5 Hz, 1H), 7.57 (q, J = 7.5 Hz, 1H), 7.48 (sextet, J = 7.5 Hz, 2H), 7.15 (m, 5H), 6.37 (br d, J = 7.5 Hz, 1H), 5.32 (t, J = 7.0 Hz, 1H), 3.96 (s, 3H), 3.73 (m, 1H), 2.69 (m, 2H), 2.56 (m, 2H), 1.87 (m, 2H), 1.62 (m, 4H), 1.21 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.1, 163.0, 154.3, 153.6, 140.4, 133.0, 130.4, 130.3, 128.4, 128.3, 128.2, 126.2, 61.2, 55.6, 48.5, 32.6, 32.3, 30.1, 25.3, 24.6; IR (KBr) $\tilde{\nu}$ 3419 (NH); 2928, 2854, 1651 (C═O), 1557, 1454, 1230 cm^{-1}; EIMS *m*/*z* 446 (M^+, 24), 342 (48), 243 (22), 230 (67), 204 (53), 188 (21), 104 (47), 91 (100). Anal. Calcd for $C_{26}H_{30}N_4O_3$: C, 69.93; H, 6.77; N, 12.55. Found: C, 70.07; H, 6.88; N, 12.46.

Crystal Structure Determination for Compounds 4c and 5a. A suitable crystal was mounted on a glass fiber. X-ray measurements were made using a Bruker SMART CCD area-detector diffractometer with Mo Kα radiation (λ = 0.710 73 Å).[27] Intensities were integrated[28] from several series of exposures, each exposure covering 0.3° in ω, and the total data set being a sphere. Absorption corrections were applied based on multiple and symmetry-equivalent measurements.[29] The structure was solved by direct methods and refined by least squares on weighted F^2 values for all reflections.[30] All nonhydrogen atoms were assigned anisotropic displacement parameters and refined without positional constraints. All hydrogen atoms were constrained to ideal geometries and refined with fixed isotropic displacement parameters. Refinement proceeded smoothly to give the residuals shown in Table 1. Complex neutral-atom scattering factors were used.[31]

CCDC 602195 and 602196 contain the crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax, (+44)1223336033; and e-mail, deposit@ccdc.cam.uk).

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Supporting Information Available: Crystallographic information file (CIF) and X-ray diffraction structures of **4c** and **5a** and X-ray diffraction structures of H-bond dimers of **5a** in the solid state. This material is available free of charge via the Internet at http://pubs.acs.org.

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(27) *SMART*; diffractometer control software; Bruker Analytical X-ray Instruments, Inc.: Madison, WI, 1998.

(28) *SAINT*; integration software; Siemens Analytical X-ray Instruments, Inc.: Madison, WI, 1994.

(29) Sheldrick, G. M. *SADABS*; A program for absorption correction with the Siemens SMART system; University of Göttingen: Germany, 2001.

(30) *SHELXTL*, version 5.1; program system; Bruker Analytical X-ray Instruments, Inc.: Madison, WI, 1998.

(31) *International Tables for Crystallography*; Kluwer: Dordrecht, 1992; Vol. C.