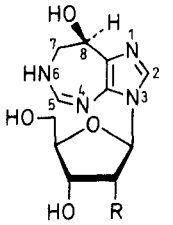
Synthesis of a Novel Ring-Expanded Xanthine Analogue and Several Methyl or Benzyl Derivatives Containing the 5:7-Fused Imidazo[4,5-*e*][1,2,4]triazepine Ring System

Ramachandra S. Hosmane,* Vishweshwar S. Bhadti, Benjamin B. Lim

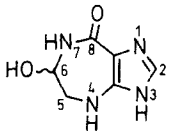
Laboratory for Chemical Dynamics, Department of Chemistry and Biochemistry, University of Maryland Baltimore County, Baltimore, Maryland 21228, USA

Syntheses of 3,4,6,7-tetrahydroimidazo[4,5-*e*][1,2,4]triazepine-5,8-dione (**1a**) and its 3- and/or 7-methyl/benzyl substituted derivatives **1b–1e** are reported. The structure of **1c** is confirmed by single-crystal X-ray diffraction analyses.

5:7-Fused heterocyclic systems are of chemical, biochemical, and pharmaceutical interest. From a chemical standpoint their synthesis, riddled with opportunistic rearrangements,[1-3] have proven interesting and challenging. From a biochemical standpoint they can be regarded as ring-expanded analogous of natural purines,[4] and thus are potentially a rich source of substrates or inhibitors of enzymes of purine metabolism. The naturally occurring nucleoside antibiotics coformycin and pentostatin,[5] and the recently discovered azepinomycin,[6] are members of the 5:7-fused imidazodiazepine family of heterocycles.



Coformycin R = OH
Pentostatin R = H

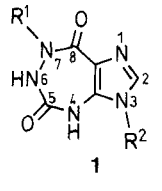


Azepinomycin

Furthermore, nucleosides and nucleotides derived from these heterocycles have been recently shown to possess novel conformational characteristics,[7] and are potential probes for nucleic acid structure and function. Finally, their pharmaceutical significance derives from their structural similarity to the medicinally and commercially successful benzodiazepines.[8] We report here the sythesis of a novel ring-expanded xanthine, **1a**, along with several of its derivatives, **1b–1e**, containing the imidazo[4,5-*e*]-[1,2,4]triazepine ring system.

Whereas cyclic homologues of xanthine and xanthosine bearing imidazo[4,5-*e*][1,4]diazepine **2**,[4,7,9,10] imidazo-[4,5-*d*][1,3]diazepine **3**,[11] and imidazo[4,5-*e*]-[1,3]diazepine **4**[12] ring systems have recently been synthesized, the associated Hückel antiaromaticity (4n π electrons) and the consequent propensity to opportunistic rearrangements render the synthesis of target **1** especially challenging. Indeed, our efforts to synthesize an adenine analogue containing the title heterocyclic system have only resulted in rearrangements.[1-3] Undesired ring-closures and facile rearrangements have also been well documented in the corresponding benzotriazepine systems.[13-17]

In an attempt to synthesize **1f** (Scheme **A**), 5-amino-1-benzylimidazol-4-carbohydrazide (**6**) was prepared by zinc chloride catalyzed reaction of **5** with hydrazine, and subsequently converted to the corresponding phenoxycarbonyl derivative **7**.



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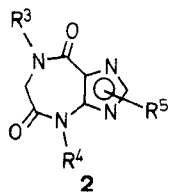

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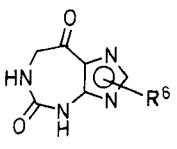

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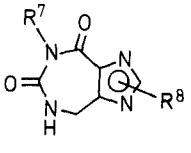
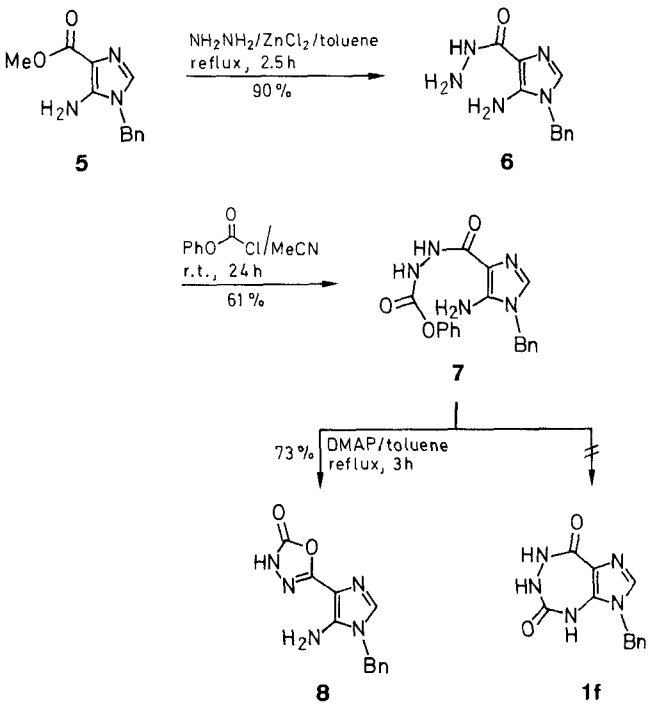


4

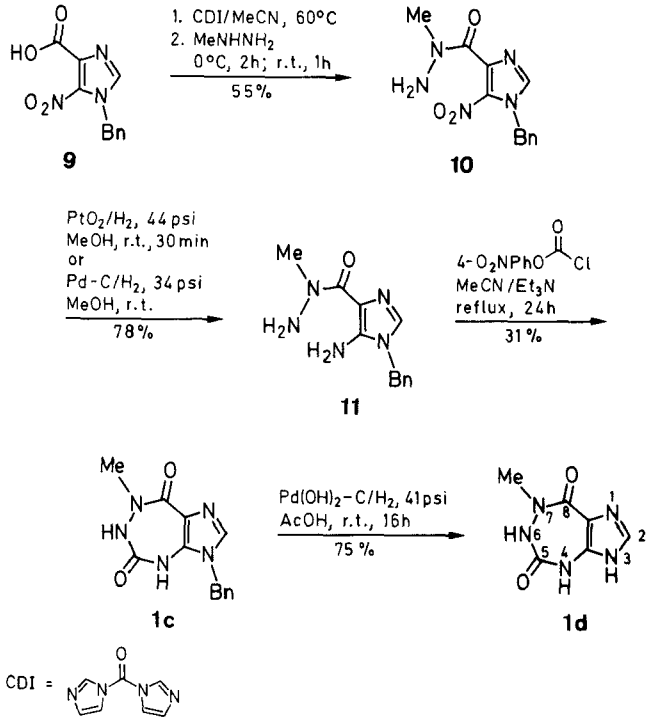
1	R^1	R^2	**1**	R^1	R^2
a	H	H	**d**	Me	H
b	Bn	Bn	**e**	Bn	H
c	Me	Bn	**f**	H	Bn



Scheme A

However, the ring-closure of **7**, catalyzed by 4-dimethylaminopyridine (DMAP), gave instead the substituted

oxadiazolone **8**. Therefore, substituting the carbohydrazide NH with a methyl group as in **11** (Scheme **B**) was envisaged to block the undesired ring-closure.



Scheme **B**

To this end, **11** was prepared from **9** by reaction with 1,1'-carbonyldiimidazole(CDI)/methylhydrazine (to give **10**), followed by hydrogenation over platinum oxide. Ring-closure of **11** to **1c** was effected by reaction with *p*-nitrophenyl chloroformate, in the presence of triethylamine. The structure of **1c** was consistent with its elemental analyses, ^{1}H-NMR and mass spectral data. The UV spectrum of **1c** exhibited two shoulders at 227 and 252 nm in neutral pH, and a significant bathochromic shift in basic pH (λ_{max} = 301 nm).

Single crystal X-ray structure (Figure)[18,19] of **1c** shows the imidazole ring to be planar while the triazepinedione ring is quite distorted from the plane of the imidazole ring. This distortion is due mainly to the large (87.4°) torsional angle, C(12)-N(11)-N(12)-C(13). The lone-pair electrons of the *N*-methyl amide bond are shown to be not fully conjugated to the carbonyl group, the torsional angle between the carbonyl and the methyl group being 8.3°. The three amide bonds of **1c** show three different lengths with N(12)-C(13) being the shortest (1.352 Å) and N(13)-C(13), the longest (1.406 Å).

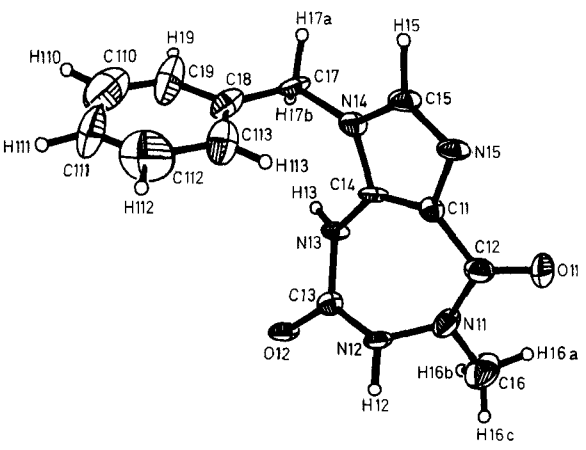
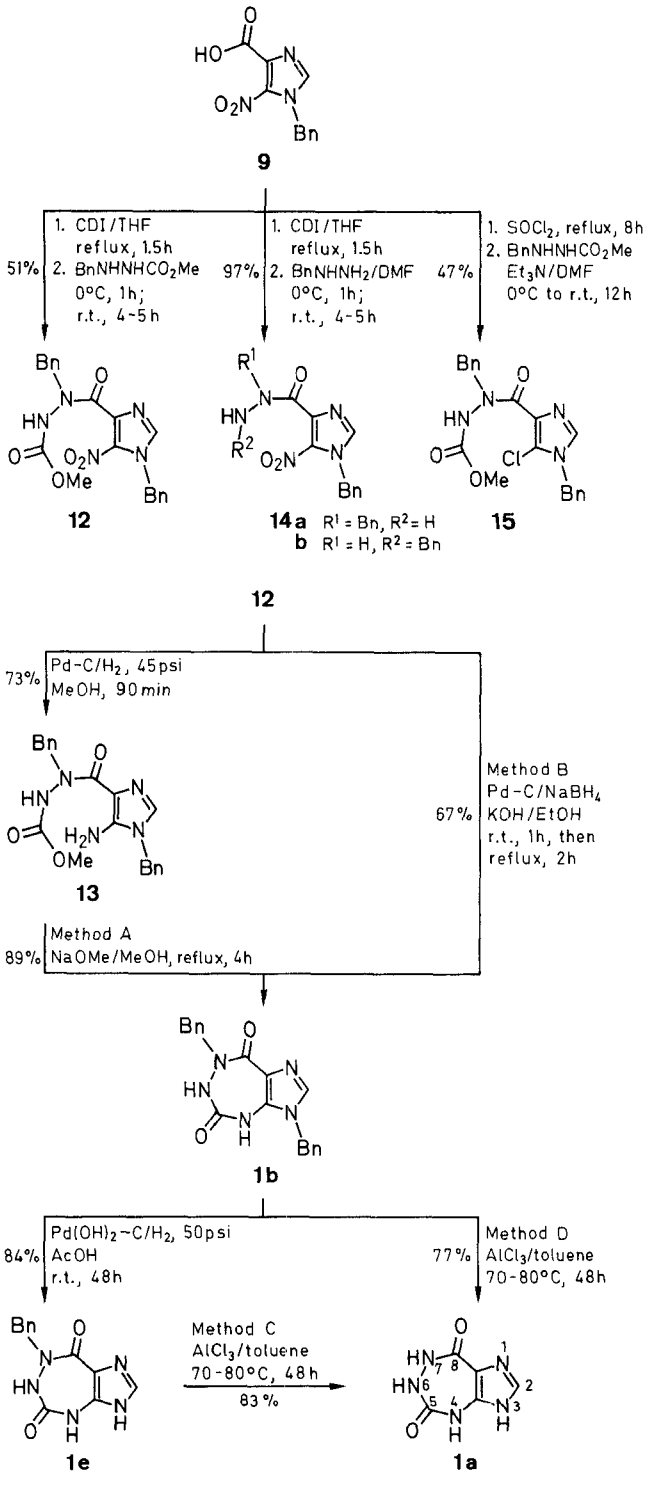


Figure. ORTEP view of **1c** showing the atom numbering scheme and thermal ellipsoids at the 30% probability level.

Compound **1c** was debenzylated by reduction with palladium hydroxide/hydrogen in glacial acetic acid to give



Scheme **C**

1d. However, the *N*-methyl group of **1d** could not be removed by treatment with boron tribromide/xylene or a variety of other dealkylating reagents.

Attempts to prepare **14a** (Scheme **C**), akin to **10**, by reaction of **9** with CDI and benzylhydrazine gave instead the isomeric carbohydrazide **14b**.

Similarly, the reaction of **9** with thionyl chloride and subsequent treatment of the acid chloride with methyl N^2-benzyl carbazate[20] gave **15** instead of the expected **12**. Compound **12** could, however, be obtained by reaction of **9** with CDI and methyl N^2-benzyl carbazate. It is to be noted that the ^{1}H-NMR spectra of **10, 12,** and **15** in deuterated dimethyl sulfoxide exhibited the presence of two isomers each. The isomeric ratio in **12**, as calculated by proton signal intensities, was 1:4. That these isomers are conformers arising from the anticipated restricted rotation about the N–C=O bond of the hydrazide group was verified by variable temperature ^{1}H-NMR studies. Thus, increasing the sample temperature resulted in gradual coalescence of each pair of CH, CH_2, and CH_3 signals as well as sharpening of the NH signal, and at 75 °C each set of signals had collapsed to reveal a single sharp absorption.

Sequential reactions of **12** involving reduction over palladium (to give **13**), cyclization with sodium methoxide/methanol (to **1b**), and debenzylation by hydrogenation over palladium hydroxide gave the monodebenzylated product **1e**. Reduction and ring-closure of **12** to form **1b** was also accomplished in a one-pot reaction, employing palladium on carbon/sodium borohydride/potassium hydroxide in ethanol. Further debenzylation of **1e** to **1a** by catalytic hydrogenation at elevated temperatures or by treatment with sodium naphthalide or boron tribromide/xylene was not successful. Debenzylation was, however, achieved by heating **1e** with aluminum chloride in toluene. With the latter reagent, **1a** could also be obtained directly from **1b**. The ^{1}H-NMR spectrum of **1a** clearly reveals all four NH's, exchangeable with D_2O, at $\delta = 8.3$, 9.0, 9.7, and 12.8, and the imidazole CH at $\delta = 7.7$. The mass spectrum (70 eV) showed the molecular ion peak at $m/z = 167$ (relative intensity 83%), the fragment ion 136 being the base peak. We are currently in the process of preparing the corresponding nucleoside/nucleotide derivatives for further biochemical and biological investigations of the novel heterocyclic ring system.

^{1}H-NMR spectra were recorded on either an IBM NR/80 (80 MHz) or a General Electric GN-500 (500 MHz) spectrometer. The reported chemical shift data are relative to TMS, used as an internal reference standard. The 70 eV electron impact (EI) and chemical ionization (CI) mass spectra were recorded either at the School of Pharmacy, University of Maryland at Baltimore, on a Du Pont 21-490 mass spectrometer with a 21-094 data system and an Extranuclear Simulscan GC/MS instrument, or at UMBC on a Hewlett-Packard 5988 A mass spectrometer. Isobutane was the reagent gas employed for the CI mass spectra. The reported mass spectral values are for the EI mode unless otherwise indicated. IR spectra were recorded on a Perkin–Elmer 1420 ratio recording instrument. UV spectra were recorded on either a Carcy 219 UV/Vis or a Gilford Response UV/Vis spectrophotometer. Elemental microanalyses were performed by Atlantic Microlab, Inc., Norcross, Georgia. Melting points were determined on a Thomas–Hoover capillary melting point apparatus and are uncorrected. X-ray crystal structure analyses were performed[18] at the Department of Chemistry, Southern Methodist University, Dallas, Texas. Dry solvents were prepared as follows: MeOH, Et_2O, toluene, and xylene were distilled over Na metal; MeCN was distilled from CaH_2, followed by distillation from P_2O_5; DMF and DMSO were distilled at reduced pressure from CaH_2; THF was first dried over KOH and then distilled from $LiAlH_4$. All dry solvents were stored over 3 or 4 Å molecular sieves.

5-Amino-1-benzylimidazol-4-carbohydrazide (6):
A suspension of 5-amino-1-benzyl-4-carbomethoxyimidazole[21] (**5**; 1.0 g, 4.3 mmol), $ZnCl_2$ (0.11 g, 0.86 mmol), and $NH_2NH_2 \cdot H_2O$ (2.1 mL, 43.2 mmol) in dry toluene (40 mL) is heated to reflux for 2.5 h and cooled to r.t. The mixture is decanted and the remaining semi-solid triturated with EtOH. The resulting solid is filtered to give **6**; yield: 900 mg (90%); mp 200–202 °C (Lit.[17] mp 200–201 °C).

N^1-Phenoxycarbonyl-N^2-(5-amino-1-benzyl-4-imidazolylcarbonyl)hydrazine (7):
To a solution of phenyl chloroformate (0.25 mL, 2.0 mmol) in dry MeCN (25 mL), is added **6** (300 mg, 1.3 mmol) portionswise over 5 min. The mixture is stirred at r.t. for 24 h. The separated solid (the HCl salt of **7**) is filtered and washed with MeCN, and neutralized with sat. aq $NaHCO_3$ to give **7** as a colorless solid: yield: 280 mg (61%); mp 240–242 °C.

$C_{18}H_{17}N_5O_3$	calc.	C 61.52	H 4.88	N 19.93
(351.4)	found	61.42	4.98	19.96.

IR (KBr): $\nu = 1730\ cm^{-1}$ (C=O).

^{1}H-NMR (DMSO-d_6): $\delta = 5.37$ (s, 2, CH_2), 7.06–7.42 (m, 10, $2C_6H_5$), 8.1 (br s, 2, NH_2, exchangeable with D_2O), 8.6 (s, 1, CH), 9.79 (s, 1, NH, exchangeable with D_2O).

5-(5-Amino-1-benzyl-4-imidazolyl)-1,3,4-oxadiazol-2(3*H*)-one (8):
A mixture of **7** (280 mg, 0.79 mmol) and DMAP (200 mg, 1.6 mmol) is heated to reflux in dry toluene (20 mL) for 3 h. The mixture is cooled to r.t. when a solid precipitate separated. It is filtered and purified by flash chromatography on a column of silica gel (20 g, 40 μm), packed with $CHCl_3$, and using a $CHCl_3$/acetone (1:1) mixture as the eluting solvent. The appropriate fractions are pooled and evaporated, and the solid residue is recrystallized from MeCN to give **8** as colorless crystals; yield: 150 mg (73%); mp 206–208 °C.

$C_{12}H_{11}N_5O_2$	calc.	C 55.06	H 4.43	N 26.76
(257.3)	found	55.08	4.40	26.80.

IR (KBr): $\nu = 1770\ cm^{-1}$ (C=O).

^{1}H-NMR (DMSO-d_6): $\delta = 5.14$ (s, 2, CH_2), 5.62 (s, 2, NH_2, exchangeable with D_2O), 7.15–7.39 (m, 6, CH, C_6H_5), 11.96 (s, 1, NH, exchangeable with D_2O).

MS: $m/z = 257$ (M^+, 100%).

N^2-Methyl-N^2-(1-benzyl-5-nitro-4-imidazolylcarbonyl)hydrazine (10):
A mixture of **9** (1 g, 4 mmol) and 1,1'-carbonyldiimidazole (CDI, 680 mg, 5.26 mmol) is warmed in dry MeCN (25 mL) until the solution became clear. The mixture is cooled to 0 °C. and to the cooled solution is added $MeNHNH_2$ (0.4 mL, 7.5 mmol). The mixture is stirred for 2 h at 0 °C and 1 h at r.t. The mixture is decanted from a thick oil which separated and the decanted solution is evaporated to dryness on a rotary evaporator. Trituration of the residue with water gives **10**, which is recrystallized from H_2O; yield: 610 mg (55%); mp 142–144 °C.

$C_{12}H_{13}N_5O_3$	calc.	C 52.36	H 4.76	N 25.45
(275.3)	found	52.46	4.79	25.44

IR (KBr): $\nu = 1670\ cm^{-1}$ (C=O).

^{1}H-NMR (DMSO-d_6) (two isomers): $\delta = 2.96$, 3.15 (s, 3, NCH_3), 5.2, 4.74 (s, 2, NH_2, exchangeable with D_2O), 5.59 (s, 2, CH_2), 7.14–7.40 (m, 5, C_6H_5), 8.32, 8.26 (s, 1, CH of imidazole).

MS: $m/z = 275$ (M^+, 5%).

N^2-Methyl-N^2-(5-amino-1-benzyl-4-imidazolylcarbonyl)hydrazine (11):

To a solution of **10** (1 g, 3.6 mmol) in MeOH (35 mL) is added $PtO_2 \cdot H_2O$ (20 mg, 0.08 mmol), and the mixture is shaken in a Parr hydrogenator (44 psi, H_2) for 30 min. The resulting suspension is filtered through a pad of Celite and the filtrate rotary evaporated to dryness. The solid **11** is collected by trituration with Et_2O and recrystallized from toluene; yield: 700 mg (78%); mp 155–157 °C.

$C_{12}H_{15}N_5O$	calc.	C 58.76	H 6.16	N 28.56
(245.3)	found	59.04	6.20	28.42

^{1}H-NMR (DMSO-d_6): δ = 3.32 (s, 3, CH_3), 5.09 (s, 2, CH_2), 5.6 (br s, 2, NH_2, exchangeable with D_2O), 6.06 (s, 2, NH_2, exchangeable with D_2O), 7.21–7.32 (m, 6, C_6H_5 and imidazole CH).

MS: m/z = 245 (M^+, 16%), 200 (62).

The above reduction can also be carried out by hydrogenation at 34 psi over 10% Pd–C in MeOH to obtain **11** in a quantitative yield.

3-Benzyl-7-methyl-3,4,6,7-tetrahydroimidazo[4,5*e*][1,2,4]triazepine-5,8-dione (1c):

A solution of **11** (100 mg, 0.4 mmol), Et_3N (0.12 mL, 0.86 mmol), and *p*-nitrophenyl chloroformate (85 mg, 0.42 mmol) in dry MeCN (15 mL) is stirred for 1 h under N_2, then is heated at reflux for 24 h. The resulting solution is purified on a 2 mm Chromatotron plate using a mixture of $CHCl_3$/MeOH (9:1) as eluent. The desired UV-absorbing fractions are collected and evaporated to dryness on a rotary evaporator to obtain a solid. This solid is triturated with MeCN, filtered, and recrystallized from a mixture of EtOH/H_2O/MeCN (1:1:1) to give **1c**; yield: 35 mg (31%); mp 212–215 °C.

$C_{13}H_{13}N_5O_2$	calc.	C 57.55	H 4.83	N 25.82
(271.3)	found	57.70	4.94	25.95

IR (KBr): ν = 1650, 1705 cm^{-1} (C=O).

UV (MeOH): λ_{max} = 227 (sh), 252 (sh); (pH 11) 252, 301 nm.

^{1}H-NMR (DMSO-d_6): δ = 3.11 (s, 3, CH_3), 5.26 (s, 2, CH_2), 7.13–7.36 (m, 5, C_6H_5), 7.59 (s, 1, CH), 8.49 (s, 1, NH, exchangeable with D_2O), 10.06 (br s, 1, NH, exchangeable with D_2O).

MS: m/z = 271 (M^+, 11%), 226 (11), 200 (7).

7-Methyl-3,4,6,7-tetrahydroimidazo[4,5-*e*][1,2,4]triazepine-5,8-dione (1d):

A mixture of **1c** (100 mg, 0.37 mmol) and 20% $Pd(OH)_2$–C (80 mg) in glacial AcOH (15 mL) is hydrogenated at 41 psi for 16 h in a Parr hydrogenator. The mixture is filtered through a pad of Celite and evaporated to dryness on a rotary evaporator. The colorless solid residue is recrystallized from H_2O to yield **1d**; yield: 50 mg (75%); mp > 270 °C.

$C_6H_7N_5O_2$	calc.	C 39.78	H 3.90	N 38.66
(181.2)	found	39.69	4.16	38.81

IR (KBr): ν = 1650, 1710 cm^{-1}.

^{1}H-NMR(DMSO-d_6): δ = 3.09 (s, 3, CH_3), 7.61 (s, 1, imidazole CH), 8.41 (s, 1, amide NH, exchangeable with D_2O), 9.84 (s, 1, amide NH, exchangeable with D_2O), 12.79 (br s, 1, imidazole NH, exchangeable with D_2O).

MS: m/z = 181 (M^+, 79%), 152 (40), 136 (100)

N^1-Methoxycarbonyl-N^2-benzyl-N^2-(1-benzyl-5-nitro-4-imidazolylcarbonyl)hydrazine (12):

A mixture of **9** (3.7 g, 15.0 mmol) and CDI (3.6 g, 22.2 mmol) in dry THF (20 mL) is heated at reflux, under N_2, for ≃ 1.5 h to form a clear solution. The solution is cooled in an ice-bath, treated with methyl N^2-benzyl carbazate[20] (4.0 g, 22.2 mmol), and the mixture is stirred at r.t. for 4–5 h. The solvent is removed *in vacuo*, the residue dissolved in EtOAc, and the solution washed successively with a sat. $NaHCO_3$ solution and H_2O. The solution is dried (Na_2SO_4), filtered, and the filtrate rotary evaporated to dryness. The residue, after washing with Et_2O, is triturated with *i*-PrOH when a solid separated. The solid, **12** (2.2 g), is filtered, dried, and recrystallized from *i*-PrOH. The filtrate is chromatographed on a silica gel column, using $CHCl_3$/EtOAc (7:3) as the eluting solvent to recover additional 0.9 g of **12**; combined yield: 3.1 g (51%); mp 139–141 °C.

$C_{20}H_{19}N_5O_5$	calc.	C 58.62	H 4.68	N 17.10
(409.4)	found	58.79	4.72	17.01

IR (KBr): ν = 1675, 1745 cm^{-1} (C=O).

^{1}H-NMR (DMSO-d_6) (two conformers); *major*: δ = 3.53 (s, 3, OCH_3), 4.88 (br s, 2, CH_2 of side-chain benzyl), 5.68 (s, 2, CH_2 of imidazole benzyl), 7.1–7.5 (m, 10, two Ph–H), 8.35 (s, 1, imidazole CH), 9.85 (br s, 1, NH, exchangeable with D_2O); *minor*: δ = 3.68 (s, 3, OCH_3), 4.65 (s, 2, CH_2 of side-chain benzyl), 5.68 (s, 2, imidazole benzyl), 7.1–7.5 (m, 10, two Ph–H), 8.40 (s, 1, imidazole CH), 9.25 (br s, 1, NH, exchangeable with D_2O).

N^1-Methoxycarbonyl-N^2-benzyl-N^2-(5-amino-1-benzyl-4-imidazolylcarbonyl)hydrazine (13):

To a solution of **12** (0.25 g, 0.61 mmol) in MeOH (30 mL) is added Pd–C (10%) (50 mg), and the mixture is hydrogenated at 45 psi for 90 min. The catalyst is filtered off, and the filtrate is evaporated to dryness. The residue is triturated with a mixture of Et_2O and *i*-PrOH, and the solid separated is filtered, dried, and recrystallized from *i*-PrOH to obtain **13** as colorless crystals; yield: 0.17 g (73%); mp 141–143 °C.

$C_{20}H_{21}N_5O_3$	C 63.31	H 5.58	N 18.46.	
(379.4)	63.37	5.58	18.36	

IR (KBr): ν = 1740, 1720 cm^{-1} (C=O).

^{1}H-NMR (DMSO-d_6): δ = 3.5 (s, 3, OCH_3), 5.1 (s, 4, two CH_2), 6.2 (s, 2, NH_2, exchangeable with D_2O), 7.4–7.1 (m, 11, Ph–H + imidazole CH), 9.2 (br s, 1, NH, exchangeable with D_2O).

N^1-Benzyl-N^2-(1-benzyl-5-nitroimidazolyl-4-carbonyl)hydrazine (14b):

To a suspension of **9** (1.0 g, 4.0 mmol) in dry THF (15 mL), under N_2, is added CDI (0.8 g, 4.9 mmol), and the mixture is heated to form a clear solution (≃ 1 h). The mixture is cooled in an ice-bath and treated with a solution of $BnNHNH_2$, freshly prepared from $BnNHNH_2 \cdot 2HCl$ (1.05 g, 5.4 mmol) by treatment with 80% NaH (0.2 g, 6.7 mmol) in DMF (12 mL). The mixture is stirred for 1 h in the ice-bath, allowed to come to r.t., and then stirred for 1 h. The solvents are removed *in vacuo*, the residue triturated with ice-water, and the mixture allowed to stand overnight in a refrigerator. The separated solid is filtered, washed with H_2O, dried, and recrystallized from EtOH to give **14b**; yield: 1.36 g (97%); mp 131–133 °C.

^{1}H-NMR (DMSO-d_6): δ = 3.28 (br s, 1, NH, exchangeable with D_2O), 3.97 (s, 2, CH_2 of side-chain benzyl), 5.53 (s, 2, CH_2 of imidazole benzyl), 7.1–7.4 (m, 10, Ph-H), 8.26 (s, 1, CH), 9.89 (br s, 1, NH, exchangeable with D_2O).

N^1-Methoxycarbonyl-N^2-benzyl-N^2-(1-benzyl-5-chloro-4-imidazolylcarbonyl)hydrazine (15):

A mixture of **9** (2.0 g, 8.1 mmol) and $SOCl_2$ (20 mL) is heated to reflux for 8 h. $SOCl_2$ is removed *in vacuo*, and the remaining traces are distilled off by azeotroping with toluene (2 × 5 mL). The residue is dissolved in dry DMF (10 mL), and the solution is carried into an ice-cold solution of methyl N^2-benzyl carbazate[20] (1.84 g, 10.2 mmol) and Et_3N (5 mL) in DMF (10 mL). The mixture is stirred overnight at r.t., the solvent removed *in vacuo*, the residue suspended in ice-water (200 mL), and the mixture allowed to stand for 12 h. After decanting the aqueous layer, the residual gummy mass is triturated successively with hexane and Et_2O, and allowed to stand in Et_2O (30 mL) for several hours. The solid obtained is filtered, dried, and recrystallized from *i*-PrOH to give **15**; yield: 1.5 g (47%); mp 112–114 °C.

$C_{20}H_{19}ClN_4O_3$	calc.	C 60.22	H 4.80	N 14.05
(398.9)	found	60.44	4.81	13.98

IR (KBr): ν = 3180 (NH), 1740, 1655 cm^{-1} (C=O).

^{1}H-NMR (DMSO-d_6) (two conformers); *major*: δ = 3.52 (s, 3, OCH_3), 4.70 (br s, 2, CH_2 of side-chain benzyl), 5.25 (s, 2, CH_2 of imidazole benzyl), 7.1–7.4 (m, 10, Ph–H), 8.0 (s, 1, CH), 9.85 (br

s, 1, NH, exchangeable with D_2O); *minor:* δ = 3.58 (s, 3, OCH_3), 5.12 (br s, 2, CH_2 of side-chain benzyl), 5.28 (s, 2, CH_2 of imidazole benzyl), 7.1–7.4 (m, 10, Ph–H), 8.09 (s, 1, CH), 9.49 (br s, NH, exchangeable with D_2O).

3,7-Dibenzyl-3,4,6,7-tetrahydroimidazo[4,5-*e*][1,2,4]triazepine-5,8-dione (1b):

Method A: (Ring-closure of **13**): To a solution of NaOMe, freshly prepared from Na (100 mg, 4.3 mg atom) in anhydrous MeOH (30 mL), is added **13** (0.49 g, 1.3 mmol). The mixture is heated to reflux for 4 h, cooled, and evaporated to dryness on a rotary evaporator. The residue is dissolved in H_2O (15 mL) and the solution is neutralized with dil. AcOH. The separated solid is filtered, washed with H_2O, dried, and recrystallized from *i*-PrOH to give **1b**; yield: 0.4 g (89%); mp > 230°C.

$C_{19}H_{17}N_5O_2$	calc.	C 65.70	H 4.93	N 20.16
(347.4)	found	65.82	4.99	20.08

IR (KBr): ν = 1710, 1655 cm^{-1} (C=O).

UV (MeOH): λ_{max} = 231 (sh, log ε 4.04), 256 (sh, log ε 3.83); (pH 0.5) 236.5 (log ε 4.01); (pH 11) 252 (log ε 4.11), 307 (log ε 3.61) nm.

^{1}H-NMR (DMSO-d_6): δ = 4.8 (s, 2, CH_2 of 7-ring benzyl), 5.2 (s, 2, CH_2 of imidazole benzyl), 7.1–7.3 (m, 10, Ph-H), 7.6 (s, 1, imidazole CH), 8.5 (s, 1, N^6H, exchangeable with D_2O), 10 (s, 1, N^4H, exchangeable with D_2O).

Method B: (Reduction and Ring-Closure of **12**): A slow stream of N_2 is passed through a suspension of 10% Pd–C (200 mg) in EtOH (30 mL). $NaBH_4$ (0.63 g, 16.5 mmol) is added, followed by a solution of **12** (3.0 g, 7.3 mmol) in ethanolic 85% KOH (100 mL, 7.26 g, 110 mmol) dropwise over a period of 10 min. The mixture is stirred for 1 h at r.t. while maintaining a steady stream of N_2 through the solution, and the heated to reflux for 2 h. It is cooled, filtered through Celite, and then filtrate is evaporated to dryness *in vacuo*. The residue is dissolved in ice-water (100 mL), filtered through Celite, and the filtrate is acidified to pH 6.5–6.0 with glacial AcOH. the precipitated solid is filtered, washed with H_2O, dried, and recrystallized from *i*-PrOH to give **1b**; yield: 1.7 g (67%). Spectral data and TLC behavior of this solid are identical to that of **1b** obtained by Method A described above.

7-Benzyl-3,4,6,7-tetrahydroimidazo[4,5-*e*][1,2,4]triazepine-5,8-dione (1e):

To a solution of **1b** (3.2 g, 9.2 mmol) in glacial AcOH (100 mL) is added 20% $Pd(OH)_2$-C (300 mg), and the mixture is hydrogenated at 50 psi for 48 h. The catalyst is filtered off and the filtrate is rotary evaported to dryness. The residue is triturated with a mixture of *i*-PrOH/Et_2O (1:1) and the solid separated is filtered, washed with *i*-PrOH/Et_2O, dried, and recrystallized from *i*-PrOH to give **1e**; yield: 2.0 g (84%); mp > 230°C.

$C_{12}H_{11}N_5O_2$	calc.	C 56.03	H 4.31	N 27.22
(257.3)	found	56.09	4.32	27.15

IR (KBr): ν = 1735, 1720 cm^{-1} (C=O).

UV (MeOH): λ_{max} = 205 (log ε 4.16), 258 (log ε 3.62), 272.5 (sh, log ε 3.48); (pH 0.5) 209 (log ε 3.81), 228.5 (log ε 3.79), 250.5 (log ε 3.65); (pH 13) 212.5 (log ε 4.55), 288.5 (log ε 3.48) nm.

^{1}H-NMR (DMSO-d_6): δ = 4.8 (s, 2, CH_2), 7.3 (s, 5, Ph–H), 7.6 (s, 1, CH), 8.4 (br s, 1, NH, exchangeable with D_2O).

MS (CI): m/z = 258 ($M^+ + 1$, 100%).

3,4,6,7-Tetrahydroimidazo[4,5-*e*][1,2,4]triazepine-5,8-dione (1a):

Method A: (Debenzylation of **1e**): To a suspension of **1e** (2.0 g, 7.8 mmol) in dry toluene (50 mL) is added anhydr. $AlCl_3$ (5.18 g, 38.9 mmol), and the mixture is heated, under N_2, at 70–80°C for 48 h. The solvent is removed *in vacuo*, and the residue triturated with ice-water. The solid separated is filtered, washed with H_2O, and dried. The dry solid is washed successively with Et_2O, MeOH, CH_2Cl_2, and dried to give **1a**; yield: 1.0 g (77%); mp > 250°C. The compound is insoluble in most of the common low-boiling organic solvents or H_2O. A small sample was recrystallized from DMSO/MeOH for elemental microanalyses.

$C_5H_5N_5O_2$	calc.	C 35.93	H 3.02	N 41.90
(167.1)	found	36.17	3.01	41.74

IR (KBr): ν = 1740, 1675 cm^{-1} (C=O).

UV (MeOH): λ_{max} = 227.9 (sh), 257 (sh); (pH 12) 285 nm.

^{1}H-NMR (DMSO-d_6): δ = 7.7 (s, 1, CH), 8.3 (d, 1, N^6H, exchangeable with D_2O), 9.0 (d, 1, N^7H, exchangeable with D_2O), 9.7 (s, 1, N^4H, exchangeable with D_2O), 12.8 (s, 1, imidazole NH, exchangeable with D_2O).

MS: m/z = 167 (M^+, 83%), 136 (100), 109, 81, 69, 54.

Method B: (Didebenzylation of **1b**): To a suspension of **1b** (0.5 g, 1.44 mmol) in dry toluene (30 mL) is added anhydr. $AlCl_3$ (1.0 g, 7.5 mmol), and the mixture is heated at 70–80°C for 48 h. The solvent is removed *in vacuo*, and the residue triturated with ice-water. The solid that separated is filtered and dried. The dried solid is successively washed with Et_2O, CH_2Cl_2, and MeOH, and dried to give **1a**; yield: 0.2 g (83%). Spectral data of this compound were identical to those of **1a** obtained by Method A above.

Single Crystal X-ray Diffraction Analyses[18,19] of Compound 1c:

Data were collected on a Nicolet R_{3m}/V diffractometer at r.t., using graphite monochromated Mo K_α (λ = 0.71073 Å) radiation. The unit cell dimensions were obtained by a least-squares fit of 25 centered reflections in the range of $10° < 2\theta < 25°$. Intensity data were collected by using a $\theta/2\theta$ scan type in the range of $3° < 2\theta < 45°$. Three standard reflections monitored after every 100 reflections did not show 25% change in intensity during data collections. Intensities were corrected for decay and Lorentz polarization effects but not for absorption. The structure was solved and all non-hydrogen atoms were found by using results of SHELXTL-PLUS.[22] After several cycles of refinements using SHELXTL-PLUS and SHELX76[23] the positions of hydrogen atoms were located on difference Fourier maps, and included in the final refinement with isotropic thermal parameters, and with geometrical constraints for CH_2 and CH protons. Refinement proceeded to converge by minimizing the function $\Sigma w(|F_o| - |F_c|)^2$, where the weight, w, is $\sigma(F)^{-2}$. The discrepancy indices $R = \Sigma||F_o| - |F_c||/\Sigma|F_o|$, and $R_w = [\Sigma w(|F_o| - |F_c|)^2/\Sigma w(|F_o|)^2]^{1/2}$ are presented below.

Crystallographic Data for Compound 1c:[19]

$C_{13}H_{13}N_5O_2$, space group P_1, triclinic, a = 11.906(4) Å, b = 14.007(5) Å, c = 18.446(7) Å, α = 87.81(3)°, β = 89.63(3)°, Γ = 78.29 (3)°, V = 3010(2) Å^3, μ (Mo K_α) = 0.08 mm^{-1}. Number of unique reflections = 7695, reflections with $I \geq 3\sigma(I)$ = 4383; R = 0.1185, R_w = 0.1186.

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