α-Halogenohydrazides: useful starting material for the synthesis of hydrazinoazapeptides and azauracils

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Abstract: An efficient method for the synthesis of pseudodipeptides, which combines an aza glycine residue with various hydrazinoacid moieties by simple substitution of the halogen of α-halohydrazides, is described. Some of these hydrazinoazapeptides lead to hydrazones by oxidation or to azaaminouracils by cyclization.

Key words: hydrazinohydrazides, hydrazones, hydrazinoazapeptides, azaaminouracils, pseudopeptides.

Résumé : Une méthode de synthèse efficace de pseudopeptides, combinant une unité azaglycine avec divers hydrazinoacides, est décrite. Celle-ci consiste en une simple réaction de substitution de l'halogène de divers α-halohydrazides. Nous montrons également que certains de ces hydrazinoazapeptides peuvent conduire à des hydrazones par oxydation et par cyclisation intramoléculaire à des hétérocyles très peu représentés, les azaaminouracils.

Mots clés : hydrazinohydrazides, hydrazones, hydrazinoazapeptides, azaaminouracils, pseudopeptides.

Introduction

Following our studies on the high lability of the chloro or bromo atom of α-halogenohydrazides **1** (1, 2), which occurs under basic conditions with rapid substitution of the halogen by nucleophiles, we focussed our attention on the reaction of various substituted hydrazines. Here is a full report of the reaction of hydrazines, hydrazides, or carbazates **2** with α-halogenohydrazides **1**, which affords hydrazinoazapeptides **3**, **4**, or azauracils **9**. Such pseudopeptides are interesting since hydrazinopeptides (3), as well as azapeptides (4), are analogues of peptides in which the modification of the amide bond decreases the enzymatic biodegradability (5). Moreover, though azauracils are well known compounds (6), only a few of them are *N*-amino substituted and they have been shown to act as herbicidal agents (7).

Results

α-Hydrazinohydrazides **3** or **4** are readily obtained via a simple procedure that involves stirring the starting α-halogenohydrazides **1** with an excess of nucleophiles **2** (typically 3- to 6-fold excess) at room temperature. The basicity of most of the hydrazine derivatives **2** means that only in the case of the lowest basic hydrazides or carbazates must some additional base (NEt_3) be added to promote the reaction.

Most of the cases we have examined give moderate to good yields (Tables 1 and 2). It is interesting to note that monoalkylated hydrazines **2** react either exclusively (R^3 = Me, CH_2Ph; R^4 = H; only one isomer **4** is observed by ^1H NMR spectra of the crude reaction mixture) or predominantly ($R^3 = CH_2CF_3$; R^4 = H) through the substituted nitrogen, the most nucleophilic one being due to the electron donor substituent (Table 2). In the former case, both isomers **3** and **4**, which can be separated by column chromatography, are formed in the proportion 3:7. The structure **4** was proved by NMR spectroscopy as well as by condensation with an aldehyde or a ketone to give **5** (Scheme 1).

Some exceptions to the general reaction must be noted. (*i*) The use of *N*-aminotriazole **6** affords the triazolium salt **7** instead of the expected α-hydrazino compound (Scheme 2). This structure was confirmed by ^1H NMR spectroscopy; in particular, the CH at 6.75 ppm is in accord with a proton in the α position of a pyridinium salt (8). (*ii*) The reaction with phenylhydrazine **2** (R^3 = Ph, R^4 = H) leads to the corresponding hydrazone **8** (*syn* and *anti*) probably via the oxidation of an α-hydrazino intermediate **3** (Scheme 3). (*iii*) In some cases (Table 3), if the reaction is run in refluxing toluene, the formation of *N*-aminoazauracil **9** was observed even under a nitrogen or argon atmosphere. This reaction probably takes place through the oxidation of the primary α-hydrazinohydrazide **3**. It was possible to isolate **3** at room temperature and to show that the α-hydrazinohydrazide can be oxidized by DDQ to yield the hydrazone **8**, which affords *N*-aminoazauracil **9** by cyclization in the presence of NEt_3 (Scheme 4).

Regarding the peptidomimic properties of the resulting compounds **3** and **4**, it appears that a lot of them are interesting pseudopeptidic building blocks that combine an

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Table 1. Yields for compounds **3a–3q.**

Compound	R^1	R^2	R^3	R^4	Yield, %
3a	$pClC_6H_4$	Ph	CO_2Me	H	70
3b	$pMeC_6H_4$	Ph	CO_2Me	H	72
3c	$pMeC_6H_4$	OMe	CO_2Me	H	55
3d	$pMeC_6H_4$	OtBu	CO_2Me	H	60
3e	$pClC_6H_4$	OtBu	CO_2Me	H	82
3f	$pClC_6H_4$	Ph	COPh	H	65
3g	$pMeC_6H_4$	OMe	COPh	H	70
3h	$pClC_6H_4$	OMe	COPh	H	78
3i	$pClC_6H_4$	Ph	CO_2Et	H	69
3j	$pMeC_6H_4$	Ph	CO_2Et	H	71
3k	$pMeC_6H_4$	OMe	CO_2tBu	H	60
3l	$pClC_6H_4$	OMe	CO_2tBu	H	88
3m	$pMeC_6H_4$	OMe	Me	Me	48
3n	$pClC_6H_4$	OMe	Me	Me	44
3o	2,4-$Cl_2C_6H_3$	OMe	$(CH_2)_2O(CH_2)_2$		40
3p	$pMeC_6H_4$	Ph	$(CH_2)_5$		74
3q	$pMeC_6H_4$	OMe	CF_3CH_2	H	27

Table 2. Yields for compounds **4a–4n**.

Compound	R^1	R^2	R^3	Yield
4a	$pClC_6H_4$	OMe	Me	73
4b	$pMeC_6H_4$	OMe	Me	70
4c	$pClC_6H_4$	Ph	Me	68
4d	Et	Ph	Me	68
4e	$pClC_6H_4$	Me	Me	47
4f	$pClC_6H_4$	O*t*Bu	Me	93
4g	$pMeC_6H_4$	O*t*Bu	Me	70
4h	Et	O*t*Bu	Me	70
4i	H	O*t*Bu	Me	76
4j	$pClC_6H_4$	OCH_2Ph	Me	78
4k	$pMeC_6H_4$	OCH_2Ph	Me	60
4l	$pClC_6H_4$	OMe	$PhCH_2$	55
4m	$pMeC_6H_4$	OMe	$PhCH_2$	41
4n	$pMeC_6H_4$	OMe	CF_3CH_2	63

azaglycine residue (ester form) with various hydrazinoarylglycine moieties in racemic form (Scheme 5). Such association of aza aminoacids and hydrazino acids has not been previously reported; moreover, substituted phenylglycine derivatives have been described as potent agonists or antagonists of the glutamate receptors of the central nervous system (9).

It is important to note that although the presence of an additional nitrogen makes their incorporation into peptidic backbones (10) difficult, such pseudodipeptides **(3** and **4)** could be linked to aminoacids (3*b*). For example the *N* extremity could be coupled with the free carboxylic acid function of protected aminoacids or peptides. Alternatively, the Boc-hydrazino (11) or Bz-hydrazino (12) moiety could be deprotected, leading to an hydrazido extremity that could react with isocyano aminoester (13). Of course these two aspects could be combined to integrate the pseudodipeptides into elaborated peptidic analogues. This last promising aspect is under investigation in our laboratory.

Experimental section

General procedures

^1H NMR spectra were recorded at 80 MHz on a Bruker WP 80 or at 300 MHz on a Bruker AM 300 spectrometer and ^{13}C NMR spectra at 75 MHz on a Bruker AM 300 spectrometer with tetramethylsilane as internal reference. Mass spectra were determined with a Varian Mat 311 spectrometer from the Centre Régional de Mesures Physiques de l'Ouest. IR spectra were determined with a Perkin–Elmer 225 or 1420 spectrometer. Elemental analyses were performed by the analytical laboratory, CNRS (Lyon). Melting points were taken with a Kofler hot stage apparatus. α-Halohydrazides **1** (X = Cl or Br) were prepared as previously described (14).

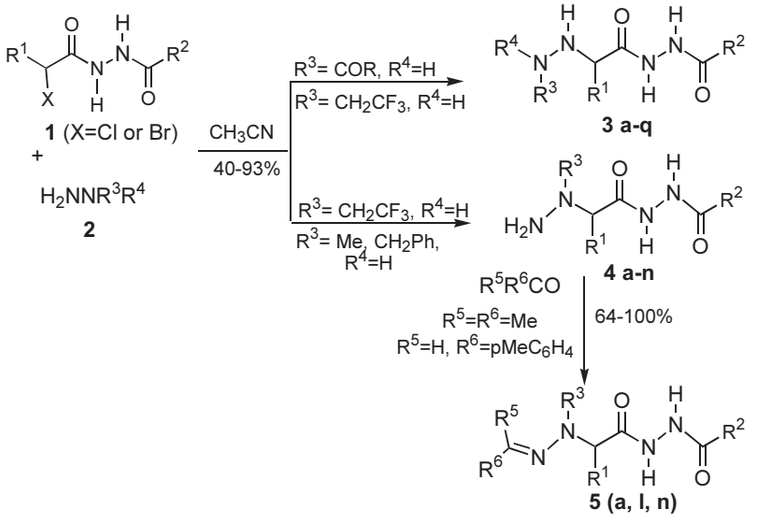
Preparation of hydrazinoazapeptides 3a–3e

A mixture of α-halohydrazide **1** (8 mmol), methylhydrazinocarboxylate **2** ($R^3 = CO_2Me$, $R^4 = H$) (32 mmol), and NEt_3 (32 mmol) was stirred for 16 h in CH_3CN (50 mL). After removal of the solvent under reduced pressure, the residue was diluted in CH_2Cl_2 (100 mL), and the organic layer was washed with an aqueous solution of HCl (100 mL) and water (100 mL) and then dried (Na_2SO_4). Evaporation afforded the α-hydrazinohydrazide **3**.

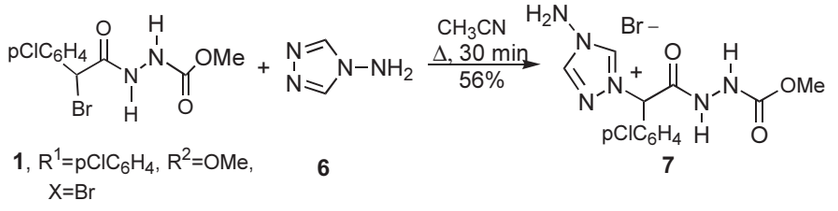
3a *(R^1 = pClC_6H_4, $R^2 = Ph$, $R^3 = CO_2Me$, $R^4 = H$)*: Yield 70%, mp 144°C ($CHCl_3$–Et_2O). IR (Nujol), ν: 3270, 3200, 3100, 1695, 1655 cm^{-1}. ^1H NMR (80 MHz, DMSO-d_6), δ: 3.57 (s, 3 H), 4.72 (s, 1 H), 5.27 (br, 1 H), 7.45–7.95 (m, 9 H), 8.45 (br, 1 H), 10.12 (s, 1 H), 10.40 (s, 1 H). Anal. calcd. for $C_{17}H_{17}N_4O_4Cl$: C 54.18, H 4.52, N 14.87, Cl 9.43%; found: C 54.41, H 4.82, N 15.08, Cl 9.36%.

3b *(R^1 = pMeC_6H_4, $R^2 = Ph$, $R^3 = CO_2Me$, $R^4 = H$)*: Yield 72%, mp 105°C ($CHCl_3$–Et_2O). IR (Nujol), ν: 3220, 1720, 1685, 1645 cm^{-1}. ^1H NMR (80 MHz, DMSO-d_6), δ: 2.30 (s, 3 H), 3.57 (s, 3 H), 4.65 (s, 1 H), 5.12 (br, 1 H), 7.10–7.92 (m, 9 H), 8.42 (br, 1 H), 10.02 (br, 1 H), 10.40 (br, 1 H). Anal. calcd for $C_{18}H_{20}N_4O_4$: C 60.66, H 5.65, N 15.72%; found: C 60.31, H 5.73, N 15.14%.

Scheme 1.



Scheme 2.



Scheme 3.

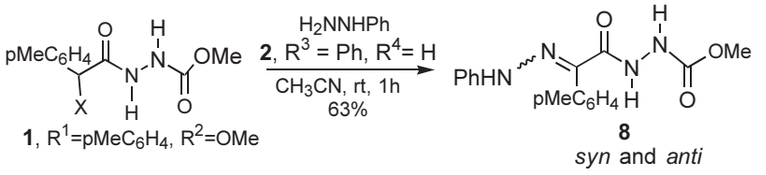


Table 3. Yields for compounds **9a–9d**.

Compound	R^1	R^2	R^3	Yield, %
9a	pClC$_6$H$_4$	Ph	OMe	61
9b	pMeC$_6$H$_4$	Ph	OMe	40
9c	mClC$_6$H$_4$	Me	OMe	42
9d	pClC$_6$H$_4$	Me	OMe	40

3c *(R^1 = pMeC_6H_4, R^2 = OMe, R^3 = CO_2Me, R^4 = H)*: Yield 55%, mp 99°C ($CHCl_3$–Et_2O). IR (Nujol), ν: 3340, 3305, 3270, 1760, 1740, 1710, 1650 cm^{-1}. ^{1}H NMR (80 MHz, $CDCl_3$ + CF_3CO_2H), δ: 2.37 (s, 3 H), 3.80 (s, 6 H), 5.30 (s, 1 H), 7.30 (s, 4 H). Anal. calcd. for $C_{13}H_{18}N_4O_5$: C 49.36, H 5.70, N 17.72%; found: C 50.35, H 5.63, N 18.24%.

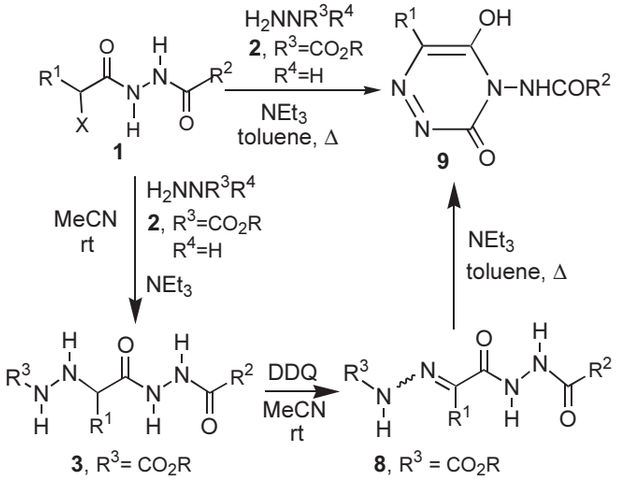
3d *(R^1 = pMeC_6H_4, R^2 = $OtBu$, R^3 = CO_2Me, R^4 = H)*: Yield 60%, mp 100°C ($CHCl_3$–Et_2O). IR (CCl_4), ν: 3405, 3310, 1720, 1700 cm^{-1}. ^{1}H NMR (80 MHz, $CDCl_3$), δ: 1.45 (s, 9 H), 2.32 (s, 3 H), 3.67 (s, 3 H), 4.67 (s, 1 H), 6.80 (br, 1 H), 7.07–7.40 (m, 6 H), 8.30 (br, 1 H). Anal. calcd. for $C_{16}H_{24}N_4O_5$: C 54.56, H 6.82, N 15.91%; found: C 54.86, H 6.83, N 16.12%.

3e *(R^1 = pClC_6H_4, R^2 = $OtBu$, R^3 = $CO2Me$, R^4 = H)*: Yield 82%, mp 113°C ($CHCl_3$–Et_2O). IR (CCl_4), ν: 3410, 3280, 1735, 1715 cm^{-1}. ^{1}H NMR (80 MHz, $CDCl_3$), δ: 1.40 (s, 9 H), 3.65 (s, 3 H), 4.67 (s, 1 H), 6.85 (br, 1 H), 7.15–7.47 (m, 6 H), 8.95 (br, 1 H). Anal. calcd. for $C_{15}H_{21}N_4O_5Cl$: C 48.32, H 5.64, N 15.03, Cl 9.53%; found: C 48.42, H 5.83, N 15.12, Cl 9.64%.

Preparation of hydrazinoazapeptides 3f–3h

The α-halohydrazide **1** (6 mmol) was added to a solution of benzoylhydrazine **2** (R^3 = COPh, R^4 = H) (18 mmol) and NEt_3 (18 mmol) in toluene (30 mL). The mixture was then heated for 24 h. Cooling afforded a precipitate of α-hydrazinohydrazide **3**, which was filtered and dried.

Scheme 4.



3f *(R^1 = pClC_6H_4, R^2 = Ph, R^3 = COPh, R^4 = H)*: Yield 65%, mp 247°C. IR (CCl_4), ν: 3280, 3262, 3240, 1678, 1630, 1605 cm^{-1}. ^1H NMR (80 MHz, DMSO-d_6), δ: 4.85 (s, 1 H), 5.25–4.62 (br, 1 H), 7.25–8.00 (m, 14 H), 10.00 (s, 1 H), 10.25 (s, 1 H), 10.40 (s, 1 H). Anal. calcd. for $C_{23}H_{22}N_4O_3$: C 62.48, H 4.50, N 13.25, Cl 8.40%; found: C 62.52, H 4.33, N 13.43, Cl 8.54%.

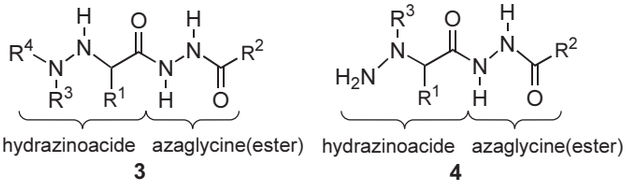
3g *(R^1 = pMeC_6H_4, R^2 = OMe, R^3 = COPh, R^4 = H)*: Yield 70%, mp 154°C. IR (Nujol), ν: 3310, 3260, 3190, 1678, 1630, 1605 cm^{-1}. ^1H NMR (80 MHz, DMSO-d_6), δ: 2.30 (s, 3 H), 3.55 (s, 3 H), 4.70 (s, 1 H),5.60 (br, 1 H), 7.07–7.85 (m, 9 H), 9.02 (s, 1 H), 9.95 (s, 2 H). ^{13}C NMR (75 MHz, DMSO-d_6), δ: 170 (d, ^2J = 9 Hz), 165, 156, 137 (q, ^2J = 6 Hz), 134, 133 (t, ^2J = 8 Hz), 131 (dt, ^1J = 205 Hz, ^2J = 8 Hz), 128 (dd, ^1J = 161 Hz, ^2J = 7 Hz), 65 (d, ^1J = 142 Hz), 52 (q, ^1J = 157 Hz), 20 (q, ^1J = 117 Hz). HRMS, $M^{+\bullet}$ calcd. for $C_{18}H_{20}N_4O_4$: 356.1484; found: 356.1489. Anal. calcd.: C 60.67, H 5.62, N 15.73%; found: C 60.29, H 5.62, N 14.95%.

3h *(R^1 = pClC_6H_4, R^2 = OMe, R^3 = COPh, R^4 = H)*: Yield 78%, mp 199°C. IR (Nujol), ν: 3310, 3240, 3180, 1725, 1680, 1645 cm^{-1}. ^1H NMR (80 MHz, DMSO-d_6), δ: 3.55 (s, 3 H), 4.75 (d, 1 H, ^3J = 6 Hz), 5.72 (t, 1 H, ^3J = 6 Hz,), 7.32–7.85 (m, 9 H), 9.05 (br s, 1 H), 10.02 (br s, 2 H). Anal. calcd. for $C_{17}H_{17}N_4O_4Cl$: C 54.18, H 4.51, N 14.87, Cl 9.43%; found: C 54.25, H 4.62, N 15.11, Cl 9.60%.

Preparation of hydrazinoazapeptides 3i–3j

To a mixture of ethylhydrazinocarboxylate **2** (R^3 = CO_2Et, R^4 = H) (30 mmol) and NEt_3 (30 mmol) in CH_3CN (30 mL) was added the α-halohydrazide **1** (10 mmol). After 24 h stirring at room temperature the solvent was removed under reduced pressure. The residue was diluted in CH_2Cl_2 (50 mL). The organic layer was washed with an aqueous solution of HCl (50 mL) and with water (50 mL) and then dried (Na_2SO_4). Evaporation of the solvent afforded the α-hydrazinohydrazide **3.**

Scheme 5.



3i *(R^1 = pClC_6H_4, R^2 = Ph, R^3 = CO_2Et, R^4 = H)*: Yield 69%, mp 152°C (EtOH). IR (Nujol), ν: 3280, 3240, 3210, 1700, 1675, 1655 cm^{-1}. ^1H NMR (80 MHz, DMSO-d_6), ν: 1.22 (t, 3 H, ^3J = 8 Hz), 4.07 (q, 2 H, ^3J = 8 Hz), 4.72 (s, 1 H), 5.12 (br s, 1 H), 7.30–7.97 (m, 9 H), 8.35 (br s, 1 H), 10.10 (br s, 1 H), 10.40 (br s, 1 H). Anal. calcd. for $C_{18}H_{19}N_4O_4Cl$: C 55.31, H 4.86, N 14.34, Cl 9.10%; found: C 55.00, H 4.97, N 14.01, Cl 8.99%.

3j *(R^1 = pMeC_6H_4, R^2 = Ph, R^3 = CO_2Et, R^4 = H)*: Yield 71%, mp 136°C (CH_2Cl_2). IR (Nujol), ν: 3310, 3280, 3210, 1660, 1655 cm^{-1}. ^1H NMR (80 MHz, DMSO-d_6), δ: 1.20 (t, 3 H, ^3J = 8 Hz), 2.30 (s, 3 H), 4.05 (q, 2 H, ^3J = 8 Hz), 4.65 (s, 1 H), 5.10 (br s, 1 H), 7.07–7.95 (m, 9 H), 8.37 (br s, 1 H), 10.00 (br s, 1 H), 10.35 (br s, 1 H). Anal. calcd. for $C_{19}H_{22}N_4O_4$: C 61.62, H 5.95, N 15.14%; found: C 61.50, H 5.89, N 15.25%.

Preparation of hydrazinoazapeptides 3k–3l

To a mixture of tertiobutylhydrazino carboxylate **2** (R^3 = CO_2tBu, R^4 = H) (30 mmol) and NEt_3 (30 mmol) in CH_3CN (10 mL) was added the α-halohydrazide **1** (10 mmol). After 24 h stirring at room temperature the solvent was removed under reduced pressure, and the residue was diluted in CH_2Cl_2 (50 mL). The organic layer was washed with an aqueous solution of HCl (50 mL) and with water (50 mL) and finally dried (Na_2SO_4). Evaporation afforded the α-hydrazinohydrazide **3**, pure enough for analysis.

3k *(R^1 = pMeC_6H_4, R^2 = OMe, R^3 = CO_2tBu, R^4 = H)*: Yield 60%, mp 112°C. IR (CCl_4), ν: 3410, 3300, 1745, 1720 cm^{-1}. ^1H NMR (80 MHz, $CDCl_3$), δ: 1.42 (s, 9 H), 2.27 (s, 3 H), 3.40 (br s, 1 H), 3.67 (s, 3 H), 4.62 (s, 1 H), 6.82 (s, 1 H), 7.00–7.45 (m, 5 H), 9.07 (br s, 1 H). Anal. calcd. for $C_{16}H_{24}N_4O_5$: C 54.54, H 6.82, N 15.91%; found: C 54.35, H 6.79, N 15.97%.

3l *(R^1 = pClC_6H_4, R^2 = CO_2Me, R^3 = CO_2tBu, R^4 = H)*: Yield 88%, mp 128°C. IR (CCl_4), ν: 3410, 3300, 1750, 1715 cm^{-1}. ^1H NMR (80 MHz, $CDCl_3$), δ: 1.42 (s, 9 H), 3.60 (s, 3 H), 4.60 (s, 1 H), 4.90 (br s, 1 H), 7.40 (m, 4 H), 7.97 (br s, 1 H), 8.97 (br s, 2 H), 9.82 (br s, 1 H). Anal. calcd. for $C_{15}H_{21}N_4O_5Cl$: C 48.32, H 5.64, N 15.03, Cl 9.53%; found: C 48.35, H 5.78, N 15.12, Cl 9.78%.

Preparation of hydrazinoazapeptides 3m and 3n

To a solution of *N*,*N*-dimethylhydrazine **2** (R^3 = R^4 = Me) (30 mmol) in CH_3CN (10 mL) was added the α-halohydrazide **1** (5 mmol). The α-hydrazinohydrazide **3** precipitated after 16 h (R^1 = *p*ClC_6H_4) or 60 h (R^1 = *p*MeC_6H_4) of stirring at room temperature and was then filtered and dried (pure enough for analysis).

3m *(R^1 = pMeC_6H_4, R^2 = OMe, R^3 = R^4 = Me)*: Yield 48%, mp 171°C. IR (Nujol), ν: 3260, 3180, 1740, 1696 cm^{-1}. ^1H NMR (80 MHz, $CDCl_3$ + CF_3CO_2H), δ: 2.40 (s, 3 H), 3.27 (s, 3 H), 3.47 (s, 3 H), 3.72 (s, 3 H), 5.62 (s, 1 H), 7.40–7.60 (m, 4 H). Anal. calcd. for $C_{13}H_{20}N_4O_3$: C 55.71, H 7.14, N 17.14%; found: C 55.72, H 7.32, N 17.29%.

3n *(R^1 = pClC_6H_4, R^2 = OMe):* Yield 44%, mp 180°C. IR (Nujol), ν: 3280, 3240, 3180, 3140, 1700 cm^{-1}. ^1H NMR ($CDCl_3$ + DMSO-d_6), δ: 2.97 (s, 3 H), 3.37 (s, 3 H), 3.52 (s, 3 H), 4.98 (s, 1 H), 6.61 (br s, 2 H), 7.61 (A_2B_2, 4 H, ^3J = 4 Hz), 8.45 (br s, 1 H). Anal. calcd. for $C_{12}H_{17}N_4O_3Cl$: C 47.92, H 5.69, N 18.63, Cl 11.78%; found: C 47.72, H 5.70, N 18.46, Cl 11.87%.

Preparation of α-hydrazinohydrazide 3o

To a solution of *N*-aminomorpholine **2** (R^3, R^4 = -$(CH_2)_2O(CH_2)_2$-) (25 mmol) in CH_3CN (10 mL) was added the α-halohydrazide **1** (5 mmol). After 16 h stirring at room temperature the solvent was removed under reduced pressure, the residue was partially dissolved in CH_2Cl_2 (10 mL), the halohydrate of *N*-aminomorpholine was filtered, and the filtrate saturated by addition of petroleum ether. Cooling afforded a precipitate of α-hydrazinohydrazide **3o.**

3o *(R^1 = 2,4-$Cl_2C_6H_3$, R^2 = OMe, R^3, R^4 = -$(CH_2)_2O(CH_2)_2$-)*: Yield 40%, mp 149°C (CH_2Cl_2 – petroleum ether). IR (Nujol), ν: 3362, 3270, 3227, 1728, 1700 cm^{-1}. ^1H NMR (80 MHz, $CDCl_3$ + CF_3CO_2H), δ: 2.72 (m, 4 H), 3.57 (m, 4 H), 3.60 (s, 3 H), 4.87 (s, 1 H), 7.28–7.77 (m, 3 H), 9.00 (br s, 1 H), 9.85 (br s, 1 H). HRMS, $M^{+\bullet}$ calcd for $C_{14}H_{18}N_4O_4Cl_2$: 376.0705; found: 376.0721. Anal. calcd.: C 44.57, H 4.80, N 14.85, Cl 18.80%; found: C 44.32, H 4.84, N 14.62, Cl 19.26%.

Preparation of α-hydrazinohydrazide 3p

To a solution of *N*-aminopiperidine **2** (R^3, R^4 = -$(CH_2)_5$) (25 mmol) in CH_3CN (10 mL) was added the α-halohydrazide **1** (5 mmol). After 16 h stirring at room temperature a first precipitate of α-hydrazinohydrazide **3p** was filtered, the solvent was then evaporated, the residue dissolved in CH_2Cl_2 (50 mL) and thenwashed by water (50 mL). The organic layer was dried (Na_2SO_4) and concentrated by evaporation of the solvent. Addition of acetone and cooling afforded a new fraction of **3p**.

3p *(R^1 = pMeC_6H_4, R^2 = Ph, R^3, R^4 = -$(CH_2)_5$)*: Yield 74%, mp 201°C (acetone). IR (Nujol), ν: 3321, 3255, 3200, 3155, 1695, 1670 cm^{-1}. ^1H NMR (80 MHz, $CDCl_3$ + CF_3CO_2H), δ: 2.00 (m, 6H), 2.42 (s, 3H), 3.47–4.00 (m, 4H), 5.96 (s, 1H), 7.27–7.90 (m, 9H). HRMS, $M^{+\bullet}$ calcd. for $C_{21}H_{26}N_4O_2$: 366.2055; found: 366.2065. Anal. calcd. for $C_{21}H_{26}N_4O_2 \cdot HBr$: C 56.37, H 6.08, N 12.52, Br 17.86%; found: C 56.09, H 6.06, N 12.59, Br 17.41%.

Preparation of hydrazinoazapeptides 4a–4k

To a solution of methylhydrazine **2** (R^3 = Me, R^4 = H) (30 mmol) in CH_3CN (10 mL) was added the α-halohydrazide **1** (5 mmol). When R^2 = OMe, Me, Ph, or CH_2Ph, after 2 h stirring at room temperature, the α-hydrazinohydrazide **4** precipitated and was filtered. When R^2 = O*t*Bu or R^1 = H the solution was evaporated and the residue was dissolved in CH_2Cl_2 (50 mL) and washed with water (50 mL). The organic layer was dried (Na_2SO_4) and concentrated by evaporation of the solvent. Addition of ether afforded **4**.

4a *(R^1 = pClC_6H_4, R^2 = OMe, R^3 = Me)*: Yield 73%, mp 178°C (EtOH). IR (Nujol), ν: 3310, 3250, 3150, 1730, 1670 cm^{-1}. ^1H NMR (80 MHz, $CDCl_3$ + DMSO-d_6), δ: 2.31 (s, 3 H), 3.25 (br, 1 H),3.60 (s, 3 H), 3.96 (s, 1 H), 4.15–5.47 (br, 1 H), 8.50–9.50 (br, 1 H), 7.41 (m, 4 H). ^{13}C NMR (75 MHz, DMSO-d_6–D_2O), δ: 45 (q, ^1J = 135 Hz), 52 (q, ^1J = 148 Hz), 75 (d, ^1J = 136 Hz), 128 (d, ^1J = 168 Hz), 130 (d, ^1J = 138 Hz), 133, 134, 157, 171. HRMS, $M^{+\bullet}$ calcd. for $C_{11}H_{15}N_4O_3Cl$: 286.0832; found: 286.0823. Anal. calcd.: C 46.07, H 5.24, N 19.55, Cl 12.39%; found: C 46.16, H 5.30, N 19.44, Cl 12.56%.

4b *(R^1 = pMeC_6H_4, R^2 = OMe)*: Yield 70%, mp 158°C (EtOH). IR (Nujol), ν: 3318, 3180, 3150, 1732, 1670 cm^{-1}. ^1H NMR (80 MHz, $CDCl_3$ + DMSO-d_6), δ: 2.30 (s, 3 H), 2.32 (s, 3 H), 3.57 (s, 3 H), 3.95 (s, 1 H), 4.25–5.25 (br, 1 H), 9.00 (br, 1 H), 7.25 (A_2B_2, 4 H, ^3J = 8 Hz). Anal. calcd. for $C_{12}H_{18}N_4O_3$: C 54.13, H 6.76, N 21.05%; found: C 53.73, H 6.55, N 20.81%.

4c *(R^1 = pClC_6H_6, R^2 = Ph)*: Yield 68%, mp 132°C (EtOH). IR (Nujol), ν: 3275, 3210, 1695, 1645 cm^{-1}. ^1H NMR (80 MHz, $CDCl_3$ + DMSO-d_6), δ: 2.32 (s, 3H), 3.30 (br, 2H), 4.07 (s, 1H), 7.32–8.10 (m, 9H), 10.50 (br, 1H). Anal. calcd. for $C_{16}H_{17}N_4O_2Cl + H_2O$: C 54.77, H 5.46, N 15.97, Cl 10.10%; found: C 54.68, H 5.36, N 15.99, Cl 10.09%.

4d *(R^1 = Et, R^2 = Ph)*: Yield 68%, mp 132°C (EtOH). IR (Nujol), ν: 3290, 3160, 1685, 1645 cm^{-1}. ^1H NMR (80 MHz, $CDCl_3$ + DMSO-d_6), δ: 0.92 (t, 3 H, ^3J = 6 Hz), 1.65 (m, 2 H), 2.50 (s, 3 H), 3.00 (t, 1 H, ^3J = 7 Hz), 5.55–7.05 (br, 3 H), 7.70 (m, 5 H). Anal. calcd. for $C_{12}H_{18}N_4O_2$: C 57.60, H 7.20, N 22.40%; found: C 57.34, H 7.46, N 22.32%.

4e *(R^1 = pClC_6H_4, R^2 = Me)*: Yield 47%, mp 188°C (EtOH). IR (Nujol): ν: 3280, 3210, 3180, 1690, 1650 cm^{-1}. ^1H NMR (80 MHz, $CDCl_3$ + CF_3CO_2H), δ: 2.17 (s, 3 H), 2.87 (s, 3 H), 5.00 (s, 1 H), 7.45 (m, 4 H). Anal. calcd. for $C_{11}H_{15}N_4O_2Cl$: C 48.80, H 5.54, N 20.70, Cl 13.12%; found: C 48.70, H 5.83, N 20.54, Cl 13.41%.

4f *(R^1 = pClC_6H_4, R^2 = O*t*Bu)*: Yield 93%, mp 166°C (toluene). IR (Nujol), ν: 3300, 3170, 1720, 1675 cm^{-1}. ^1H NMR (80 MHz, $CDCl_3$ + CD_3COCD_3), δ: 1.42(s, 9 H), 2.22 (s, 3 H), 4.05 (s, 1 H), 7.35 (m, 4 H), 7.67 (s, 1 H). ^{13}C NMR (75 MHz, CD_3COCD_3), δ: 28 (q, ^1J = 125 Hz), 44(q, ^1J = 140 Hz), 75 (d, ^1J = 130 Hz), 80 (q, ^3J = 4 Hz), 129 (d, ^1J = 159 Hz), 129.5 (d, ^1J = 166 Hz), 132, 134, 156, 167. HRMS, $M^{+\bullet}$ calcd. for $C_{14}H_{21}N_4O_3Cl$: 328.1302; found: 328.1301. Anal. calcd.: C 51.14, H 6.44, N 17.04, Cl 10.78%; found: C 51.24, H 6.52, N 16.70, Cl 10.97%.

4g *(R^1 = pMeC_6H_4, R^2 = O*t*Bu)*: Yield 70%, mp 135°C (toluene). IR (Nujol), ν: 3370, 3300, 1720, 1705, 1685 cm^{-1}. ^1H NMR (80 MHz, $CDCl_3$), δ: 1.40 (s, 9 H), 2.29 (s, 3 H), 2.35 (s, 3 H), 3.76 (s, 1 H), 7.17 (m, 4 H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 21 (q, 1*J* = 126 Hz), 28 (q, ^1J = 127 Hz), 46 (q, ^1J = 136 Hz), 76 (d, ^1J = 136 Hz), 81 (q, ^3J = 4 Hz), 128 (d, ^1J = 156 Hz), 129 (d, ^1J = 153 Hz), 131,

138 (q, ^3J = 7 Hz), 155, 171. HRMS, $M^{+\bullet}$ calcd. for $C_{15}H_{24}N_4O_3$: 308.1848; found: 308.1835. Anal. calcd.: C 58.42, H 7.84, N 18.17%; found: C 58.54, H 7.88, N 18.02%.

4h *(R^1 = Et, R^2 = OtBu)*: Yield 70%, mp 121°C (toluene). IR (Nujol), ν: 3310, 3160, 1720, 1715, 1680 cm^{-1}. ^{1}H NMR (80 MHz, $CDCl_3$), δ: 1.00 (t, 3 H, ^3J = 3 Hz),1.51 (s, 9 H), 2.65 (s, 3 H), 2.78 (m, 2 H), 3.00 (t, 1 H, ^3J = 7 Hz), 6.9 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 10 (q, ^1J = 126 Hz), 22 (t, ^1J = 128 Hz), 28 (q, ^1J = 125 Hz), 45 (q, ^1J = 135 Hz), 72 (d, ^1J = 137 Hz), 81, 155, 172. Anal. calcd. for $C_{10}H_{22}N_4O_3$: C 48.78, H 8.94, N 22.76%; found: C 48.29, H 9.00, N 22.65%.

4i *(R^1 = H, R^2 = OtBu)*: Yield 76%, mp 103°C (toluene). IR (Nujol), ν: 3340, 3310, 1730, 1705, 1680, 1650 cm^{-1}. ^{1}H NMR (80 MHz, $CDCl_3$), δ: 1.45 (s, 9 H), 2.57 (s, 3 H), 3.25 (s, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 10 (q, ^1J = 126 Hz), 22 (t, ^1J = 128 Hz), 28 (q, ^1J = 125 Hz), 45 (q, ^1J = 135 Hz), 72 (d, ^1J = 137 Hz), 81, 155, 172. Anal. calcd. for $C_8H_{18}N_4O_3$: C 44.03, H 8.26, N 25.69%; found: C 43.92, H 8.03, N 25.53%.

4j *(R^1 = pClC_6H_4, R^2 = OCH_2Ph)*: Yield 78%, mp 169°C (EtOH). IR (Nujol), ν: 3295, 3115, 1715, 1660 cm^{-1}. ^{1}H NMR (80 MHz, $CDCl_3$ + CF_3CO_2H), δ: 2.66 (s, 3 H), 4.98 (s, 1 H), 5.03 (s, 2 H) 7.29 (m, 9 H). ^{13}C NMR (75 MHz, $CDCl_3$ + CF_3CO_2H), δ: 42 (q, ^1J = 138 Hz), 68 (t, ^1J = 151 Hz), 70 (d, ^1J = 139 Hz), 127 (d, ^1J = 164 Hz), 128 (d, ^1J = 165 Hz), 129.2 (d, ^1J = 160 Hz), 129.6 (d, ^1J = 159 Hz), 130 (d, ^1J = 160 Hz), 134.2, 134.8, 136, 156, 169. Anal. calcd. for $C_{17}H_{19}N_4O_3Cl$: C 56.27, H 5.28, N 15.44, Cl 9.77%; found: C 56.05, H 5.07, N 15.45, Cl 9.72%.

4k *(R^1 = pMeC_6H_4, R^2 = OCH_2Ph)*: Yield 60%, mp 148°C (EtOH). IR (Nujol), ν: 3290, 3140, 1725, 1660, 1685 cm^{-1}. ^{1}H NMR (80 MHz, $CDCl_3$ + CF_3CO_2H), δ: 2.36 (s, 3 H), 2.81 (s, 3 H), 5.04 (s, 1 H), 5.14 (s, 2 H), 7.26 (m, 9 H). Anal. calcd. for $C_{18}H_{22}N_4O3$: C 58.42, H 7.84, N 18.17%; found: C 58.54, H 7.88, N 18.02%.

Preparation of hydrazinoazapeptides 4l–4m

To a suspension of benzylhydrazine dihydrochloride **2**·2HCl (R^3 = $PhCH_2$, R^4 = H) (9 mmol) in CH_3CN (15 mL) was added NEt_3 (27 mmol) and water (1 mL) to afford a homogeneous solution, after which the α-halohydrazide **1** (3 mmol) was added in small portions. After 6 h stirring at room temperature the solution was evaporated and the residue dissolved in CH_2Cl_2 (30 mL) and then washed with water (2 × 30 mL). The organic layer was dried (Na_2SO_4) and concentrated by evaporation of the solvent. Addition of ether afforded **4**.

4l *(R^1 = pClC_6H_4, R^2 = OMe)*: Yield 55%, mp 179°C (EtOH). IR (Nujol), ν: 3335, 3310, 3280, 3200, 1735, 1705, 1665 cm^{-1}. ^{1}H NMR (80 MHz, $CDCl_3$ + CF_3CO_2H), δ: 3.69 (s, 3 H), 4.03 (br, 2 H), 5.00 (s, 1 H), 7.29–7.42 (m, 9 H). HRMS, $M^{+\bullet}$ calcd. for $C_{17}H_{19}N_4O_3Cl$: 362.1145; found: 362.1135. Anal. calcd.: C 56.27, H 5.24, N 15.48, Cl 9.80%; found: C 56.29, H 5.17, N 15.42, Cl 9.51%.

4m *(R^1 = pMeC_6H_4, R^2 = OMe)*: Yield 41%, mp 158°C (EtOH). IR (Nujol), ν: 3340, 3300, 3200, 1730, 1700, 1665 cm^{-1}. ^{1}H NMR (80 MHz, $CDCl_3$ + CF_3CO_2H), δ: 2.37 (s, 3H), 3.80 (s, 3H), 4.15 (s, 2H), 7.05–7.47 (m, 9H). Anal. calcd. for $C_{18}H_{22}N_4O_3$: C 63.14, H 6.47, N 16.36%; found: C 62.89, H 6.42, N 16.18%.

Preparation of hydrazinoazapeptides 3q and 4n

To a solution of **2** (R^3 = CF_3CH_2, R^4 = H) (36 mmol, in solution in water 60%) in CH_3CN (10 mL) was added the α-halohydrazide **1** (6 mmol). After 12 h stirring at room temperature the solvent was evaporated and the residue dissolved in CH_2Cl_2 (100 mL) and washed with water (2 × 50 mL). The organic layer was dried (Na_2SO_4) and then concentrated by evaporation of the solvent. The oil was separated by silica gel chromatography, and eluted by 80:20 Et_2O:petroleum ether to afford **4n** (R_f 0.18) and **3q** (R_f 0.12).

4n *(R^1 = pMeC_6H_4, R^2 = OMe)*: Yield 63%, mp 122°C. IR (Nujol), ν: 3410, 3330, 3250, 1745, 1697 cm^{-1}. ^{1}H NMR (80 MHz, $CDCl_3$), δ: 2.33 (s, 3 H), 3.21 (q, 2 H, $^3J_{HF}$ = 18), 3.70 (br, 2 H), 3.71 (s, 3 H), 4.50 (s, 1 H), 7.15–7.29 (m, 5 H), 8.60 (br, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ: 21 (q, ^1J = 128 Hz), 53.1 (q, ^1J = 148 Hz), 57 (tq, ^1J = 138 Hz, $^2J_{CF}$ = 30 Hz), 74 (d, ^1J = 139 Hz), 125 (q, $^1J_{CF}$ = 279 Hz), 129 (d), 129.6 (d), 130, 138.9, 157.1, 171. HRMS $M^{+\bullet}$ calcd. for $C_{13}H_{17}N_4O_3F_3$: 334.1252; found: 334.1249. Anal. calcd.: C 46.70, H 5.13, N 16.76, F 17.05%; found: C 46.78, H 5.04, N 16.70, F 16.99%.

3q *(R^1 = pMeC_6H_4, R^2 = OMe)*: Yield 27%, oil. IR (Nujol), ν: 3410, 3220, 1745, 1697 cm^{-1}. ^{1}H NMR (80 MHz, $CDCl_3$), δ: 2.30 (s, 3 H), 3.30 (q, 2 H, $^3J_{HF}$ = 18 Hz), 3.69 (s, 3 H), 4.47 (s, 1 H), 7.10–7.47 (m, 7 H), 8.75 (br, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 21 (q, ^1J = 126 Hz), 53 (q, ^1J = 147 Hz), 52 (tq, ^1J = 122 Hz, $^2J_{CF}$ = 26 Hz), 67 (d, ^1J = 141 Hz), 125.2 (q, $^1J_{CF}$ = 278 Hz), 129 (d), 129.6 (d), 132, 138.6, 157, 172. HRMS, $M^{+\bullet}$ calcd. for $C_{13}H_{17}N_4O_3F_3$: 334.1252; found: 334.1249. Anal. calcd.: C 46.70, H 5.13, N 16.76; F 17.05%; found: C 46.27, H 5.45, N 16.32, F 16.44%.

Preparation of hydrazone 5a

A mixture of α-hydrazinohydrazide **4a** (2 mmol) and *p*-tolualdehyde (2.5 mmol) in MeCN was stirred for 15 h at room temperature. After evaporation of the solvent, the crude product afforded the hydrazone **5a**, by trituration with ether.

5a *(R^1 = pClC_6H_4, R^2 = OMe, R^3 = Me, R^5 = pMeC_6H_4, R^6 = H)*: Yield 64%, mp 100°C (CH_2Cl_2). IR (Nujol), ν: 3400, 3260, 1750, 1670 cm^{-1}. ^{1}H NMR (80 MHz, DMSO-d_6 – $CDCl_3$), δ: 2.25 (s, 3 H), 2.75 (s, 3 H), 3.62 (s, 3 H), 5.22 (s, 1 H), 7.02–7.47 (m, 9 H), 8.84 (br, 1 H), 9.65 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 21 (q, ^1J = 126 Hz), 36 (q, ^1J = 136 Hz), 73 (d, ^1J = 136 Hz), 126 (d), 128 (d), 129 (d), 130, 132 (d), 133, 134, 137 (d, ^1J = 160 Hz), 138, 156, 170. HRMS, $M^{+\bullet}$ calcd. for $C_{19}H_{21}N_4O_3Cl$: 388.1302; found: 388.1283.

Preparation of hydrazones 5l, 5n

α-Hydrazinohydrazide **4** (2 mmol) was refluxed in acetone (25 mL) for 30 min. After evaporation of the solvent the crude product, by trituration with ether, afforded the hydrazone **5** (R^5 = R^6 = Me).

5l *(R^1 = pClC_6H_4, R^2 = OMe, R^3 = $PhCH_2$, R^5 = Me, R^6 = Me)*: Yield 100%, mp 108°C. IR (Nujol), ν: 3410, 3360, 3230, 1770, 1670 cm^{-1}. ^1H NMR ($CDCl_3$), δ: 1.35 (s, 3 H), 1.52 (s, 3 H), 3.27–3.77 (m, 2 H), 3.67 (s, 3 H), 4.22 (s, 1 H), 6.97–7.40 (m, 11 H). ^{13}C NMR ($CDCl_3$), δ: 24 (q, ^1J = 125 Hz), 53 (q, ^1J = 147 Hz), 58 (t, ^1J = 135 Hz), 77 (d, ^1J = 136 Hz), 127, 128.2, 128.6, 128.9, 129, 129.2, 130, 134, 136, 157, 168. HRMS, $M^{+\bullet}$ calcd. for $C_{20}H_{23}N_4O_3Cl$: 402.1458; found: 402.1442.

5n *(R^1 = pMeC_6H_4, R^2 = OMe, R^3 = CF_3CH_2, R^4 = H, R^5 = Me, R^6 = Me)*: Yield 100%, mp 195°C. IR (Nujol), ν: 3480, 3220, 3170, 1715, 1650 cm^{-1}. ^1H NMR (80 MHz, $CDCl_3$), δ: 1.42 (s, 3 H), 1.57 (s, 3 H), 2.32 (s, 3 H), 3.02 (q, 2 H, ^3J = 10 Hz), 3.72 (s, 3 H), 4.45 (s, 1 H), 6.77 (s, 1 H), 7.25 (m, 5 H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 20 (q, ^1J = 126 Hz), 24.1 (q, ^1J = 129 Hz), 24.3 (q, ^1J = 129 Hz), 53 (q, ^1J = 147 Hz), 58 (t, ^1J = 132 Hz), 71 (d, ^1J = 135 Hz), 124 (q, $^1J_{CF}$ = 281 Hz), 128.2 (d, ^1J = 157 Hz), 128.7 (d, ^1J = 158 Hz), 137, 138, 156, 167. HRMS, calcd. for $C_{13}H_{16}N_2F_3$: 257.1265; found, M^+ – $CONHNHCO_2Me$: 257.1263.

Preparation of triazolium salt 7

To a solution of 4-amino-4*H*-1,2,4-triazole **6** (28 mmol) in CH_3CN (20 mL) was added α-halohydrazide **1** (9 mmol) under stirring, and the solution was then heated (water bath) for 30 min. After 16 h stirring at room temperature the precipitate of salt **7** was filtered, and washed with hot CH_3CN.

7 *(R^1 = pClC_6H_4, R^2 = OMe)*: Yield 56%, mp 234°C (EtOH). IR (Nujol), ν: 3260, 3110, 3020, 1690, 1612 cm^{-1}. ^1H NMR (DMSO–$CDCl_3$), δ: 3.57 (s, 3 H), 6.75 (s, 1 H), 7.10 (br, 2 H), 7.57 (A_2B_2, 4 H, ^3J = 8 Hz), 9.20 (br, 2 H), 10.25 (s, 1 H), 10.52 (s, 1 H). ^{13}C NMR (DMSO-d_6), δ: 52 (q, ^1J = 147 Hz), 65 (d, ^1J = 146 Hz), 129 (d, ^1J = 169 Hz), 131 (d, ^1J = 160 Hz), 130, 134, 143 (d, ^1J = 229 Hz), 145 (d, ^1J = 228 Hz), 156, 164. Anal. calcd. for $C_{12}H_{14}N_6O_3BrCl$: C 35.5, H 3.45, N 20.70, Cl 18.75, Br 19.73%; found: C 35.68, H 3.59, N 20.38, Cl 8.81, Br 19.25%.

Preparation of hydrazone 8

NEt_3 (20 mmol) was added to a solution of α-halohydrazide **1** (7 mmol) and phenylhydrazine **2** (R^3 = Ph, R^4 = H) (20 mmol) in toluene (20 mL) and refluxed for 65 h. The solvent was then removed and the residue was dissolved in Et_2O (60 mL) and washed with water (2 × 50 mL). The organic layer was dried (Na_2SO_4), and concentrated by evaporation of the solvent. The oil was resolved by silica gel chromatography, eluted by 50:50 Et_2O:petroleum ether to afford *syn* and *anti* **8**. It was not possible to determine which was the *syn* or the *anti* isomer.

8 *(R^1 = pMeC_6H_4, R^2 = OMe, R^3 = Ph)*: R_f 0.38, yield 38%. IR (Nujol), ν: 3420, 3270, 1740, 1710, 1640 cm^{-1}. ^1H NMR (80 MHz, $CDCl_3$), δ: 2.37 (s, 3 H), 3.77 (s, 3 H), 6.80–7.62 (m, 11 H), 12.30 (s, 1 H). ^{13}C NMR (75 MHz, DMSO), δ: 20 (q, ^1J = 126 Hz), 51 (q, ^1J = 146 Hz), 112 (d, ^1J = 161 Hz), 120 (d, ^1J = 159 Hz), 125 (d, ^1J = 159 Hz), 129(d), 131, 137, 138, 144, 156, 164. HRMS, $M^{+\bullet}$ calcd. for $C_{17}H_{18}N_4O_3$: 326.1378; found: 326.1375.

8 *(R^1 = pMeC_6H_4, R^2 = OMe, R^3 = Ph)*: R_f 0.10, yield 25%. IR (Nujol), ν: 3420, 3260, 1735, 1665, 1610 cm^{-1}. ^1H NMR (80 MHz, $CDCl_3$), δ: 2.37 (s, 3 H), 3.72 (s, 3 H), 6.87–7.35 (m, 10 H), 8.15 (s, 1 H), 8.62 (s, 1 H). ^{13}C NMR (75 MHz, DMSO), δ: 20 (q, ^1J = 126 Hz), 51 (q, ^1J = 146 Hz), 114 (d, ^1J = 162 Hz), 120 (d, ^1J = 161 Hz), 127 (d, ^1J = 156 Hz), 127, 129(d), 135, 138, 144, 157, 164. HRMS,$M^{+\bullet}$ calcd. for $C_{17}H_{18}N_4O_3$: 326.1378; found: 326.1375.

Preparation of hydrazones 8 by oxydation of 3

To a solution of DDQ (dichloro-2,3-dicyano-5,6-parabenzoquinone) (12 mmol) in CH_3CN (150 mL) was added the α-halohydrazide **1** (12 mmol). After 1 h stirring the solvent was removed under reduced pressure and the residue dissolved in CH_2Cl_2 (60 mL), and washed by $NaHCO_3$ (2 × 50 mL). The organic layer was dried (Na_2SO_4), and concentrated by evaporation of the solvent to afford **8** as a mixture of two isomers, *syn* and *anti*, in the ratio 6:4. NMR data of only the major isomer are reported.

8a *(R^1 = pMeC_6H_4, R^2 = Ph, R^3 = OMe)*: Yield 60%, mp 130°C. IR (Nujol), ν: 3420, 3260, 1735, 1665, 1610 cm^{-1}. ^1H NMR (80 MHz, DMSO-d_6), δ: 2.37 (s, 3 H), 3.72 (s, 3 H), 7.32–7.47 (m, 9 H), 10.22 (s, 1 H), 10.54 (s, 1 H) ; 10.75 (s, 1 H). ^{13}C NMR (75 MHz, DMSO-d_6), δ: 21 (q, ^1J = 129 Hz), 52 (q, ^1J = 146 Hz), 127.5, 127.6, 128.7, 131, 131.5, 132.5, 135, 143, 154, 163, 167, 169. Anal. calcd. for $C_{18}H_{18}N_4O_4$: C 61.02, H 5.08, N 15.82%; found: C 60.86, H 4.95, N 15.96%.

8b *(R^1 = pClC_6H_4, R^2 = Ph, R^3 = OMe)*: Yield 60%, mp 100°C. IR (Nujol), ν: 3420, 3260, 1735, 1665, 1610 cm^{-1}. ^1H NMR (80 MHz, DMSO-d_6), δ: 3.80 (s, 3 H), 7.18–7.79 (m, 9 H), 8.31 (s, 1 H), 9.09 (s, 1 H), 9.85 (s, 1 H). ^{13}C NMR (75 MHz, DMSO), δ: 54 (q, ^1J = 146 Hz), 125.5, 127.5, 128.7, 129.8, 130, 131.5, 132.5, 137, 141.7, 153, 161, 166. Anal. calcd. for $C_{17}H_{15}N_4O_4Cl$: C 54.47, H 4.01, N 14.95, Cl 9.48%; found: C 54.68, H 3.94, N 15.03, Cl 9.03%.

Preparation of azaaminouracils 9

General procedure

NEt_3 (12 mmol) was added to a mixture of α-halohydrazide **1** (4 mmol) and hydrazine **2** (R^3 = OMe, R^4 = H) (12 mmol) in toluene (25 mL) and refluxed for 20 h. After cooling, the solvent was removed and the residue dissolved in CH_2Cl_2 (60 mL). Addition of acidified water (4 N HCl) afforded a precipitate of **9**.

Via the hydrazone 8

NEt_3 (14 mmol) was added to hydrazone **8** (7 mmol) in toluene (80 mL) and refluxed for 24 h. After cooling, the azaaminouracil **9** was filtered.

9a *(R^1 = pClC_6H_4, R^2 = Ph)*: Yield 61%, mp > 260°C (ethyl acetate). IR (Nujol) ν: 3378, 3300, 3120, 1752, 1730, 1675 cm^{-1}. ^1H NMR (80 MHz, DMSO–$CDCl_3$), δ: 7.40–8.00 (m, 9 H), 11.28 (s, 1 H), 13.06 (s, 1 H). ^{13}C NMR (75 MHz, DMSO-d_6), δ: 127.8, 128.3, 128.6, 129, 130.8 (t, J = 7 Hz), 131 (t, J = 8 Hz), 132, 134 (t, J = 11 Hz), 140 (d, J = 7 Hz), 148 (d, J = 7 Hz), 154.2, 165 (d, J = 7 Hz), 156, 164.

HRMS, $M^{+\bullet}$ calcd. for $C_{16}H_{11}N_4O_3Cl$: 342.0519; found: 342.0509. Anal. calcd.: C 56.06, H 3.23, N 16.35, Cl 10.34%; found: C 56.11, H 3.22, N 16.47, Cl 10.23%.

9b *(R^1 = pMeC_6H_4, R^2 = Ph)*: Yield 40%, mp 240°C (ethyl acetate). IR (Nujol), ν: 3185, 3120, 1720, 1670, 1650 cm^{-1}. ^1H NMR (80 MHz, DMSO-d_6 – $CDCl_3$), δ: 2.35 (s, 3 H), 7.28–7.58 (m, 4 H), 7.81–8.02 (m, 4 H), 11.47 (s, 1 H), 13.13 (s, 1 H). ^{13}C NMR (75 MHz, DMSO), δ: 20.8 (q, ^1J = 127 Hz), 127.7 (d, ^1J = 161 Hz), 127.8 (d, ^1J = 162 Hz), 128.6 (d, ^1J = 162 Hz), 128.8 (d, ^1J = 160 Hz), 129.2, 131, 132.6 (d, ^1J = 162 Hz), 139.6, 141, 148.2, 154.3, 164.9. HRMS, $M^{+\bullet}$ calcd. for $C_{17}H_{14}N_4O_3$: 322.1066; found: 322.1052. Anal. calcd.: C 63.35, H 4.35, N 17.39%; found: C 63.52, H 4.36, N 17.28%.

9c *(R^1 = mClC_6H_4, R^2 = Me)*: Yield 42%, mp 209°C (ethyl acetate). IR (Nujol): ν = 3290, 3200, 3110, 1732, 1660, 1675 cm^{-1}. ^1H NMR (80 MHz, DMSO – $CDCl_3$), δ: 2.05 (s, 3 H), 7.30–7.97 (m, 4 H), 12.77 (s, 1 H), 13.05 (br,1 H). HRMS, $M^{+\bullet}$ calcd. for $C_{11}H_9N_4O_3Cl$: 280.0363; found: 280.0411. Anal. calcd.: C 47.14, H 3.21, N 20.00, Cl 12.70%; found: 280.0411. C 47.23, H 3.43, N 19.58, Cl 12.68%.

9d *(R^1 = pClC_6H_4, R^2 = Me)*: Yield 40%, mp > 209°C (ethyl acetate). IR (Nujol), ν: 3230, 3130, 1730, 1680 cm^{-1}. ^1H NMR (80 MHz, DMSO-d_6 – $CDCl_3$), δ: 2.02 (s, 3 H), 7.67 (m, 4 H), 10.67 (s, 1 H), 12.97 (s, 1 H). HRMS, $M^{+\bullet}$ calcd. for $C_{11}H_9N_4O_3Cl$: 280.0363; found: 280.0379. Anal. calcd.: C 47.14, H 3.21, N 20.00, Cl 12.70%; found: C 47.07, H 3.23, N 19.96, Cl 12.63%.

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