# Synthesis of Fluorine-containing Analogues of *N*-Aminoglutethimide

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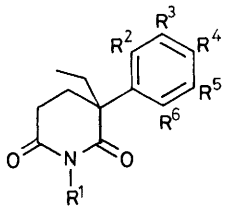
Three fluorine-containing analogues of *N*-aminoglutethimide, a selective inhibitor of the enzyme complex desmolase, have been synthesized. *N*-Amino-4-fluoro-(**3**), *N*-aminopentafluoro- (**6**), and *N*-amino-3-trifluoromethyl-glutethimide (**8**) were all prepared from the corresponding glutethimides [(**5**), (**7**), and (**9**) respectively] *via* amide hydrazide intermediates, which were thermally cyclised to the target *N*-aminoglutethimides. That compound (**3**) was indeed an *N*-aminoglutethimide was confirmed by an alternative approach, which avoided glutarimide ring cleavage and recyclisation, and instead involved the direct *N*-amination of the anion derived from 4-fluoroglutethimide (**5**). Compounds (**3**), (**6**), and (**8**) were all found to be powerful and selective desmolase inhibitors.

Aminoglutethimide [3-(4-aminophenyl)-3-ethylpiperidine-2,6-dione, (**1**)], first introduced in 1958 as an anticonvulsant drug,[1] has become widely used in recent years for the treatment of hormone-dependent metastatic breast carcinoma.[2,3] The inhibition of tumour growth is achieved by interfering with estrogen biosynthesis. In particular, aminoglutethimide inhibits the enzyme complex desmolase, which is responsible for the conversion of cholesterol into pregnenolone,[4] and the enzyme complex aromatase, which converts the androgens androstene-3,17-dione and testosterone into the estrogens estrone and estradiol.[5]

Previous work by others[6,7] and by this group[8–10] has suggested that the presence of an amino or other basic function within the glutethimide framework is necessary for significant desmolase and/or aromatase inhibition. Relocation of the basic group about the glutethimide structure has been shown[6–8] to affect the enzyme-inhibitory properties of the molecule. A particularly interesting example is the relocation of the amino moiety to the N-position of the glutarimide ring [*N*-aminoglutethimide (**2**)].[6,7] This compound proved a powerful and selective desmolase inhibitor, while exhibiting no observable inhibition of aromatase.[7] The availability of such highly selective desmolase inhibitors should allow a better understanding of the relative importance of desmolase and aromatase inhibition in the role of aminoglutethimide as an anti-breast cancer agent.

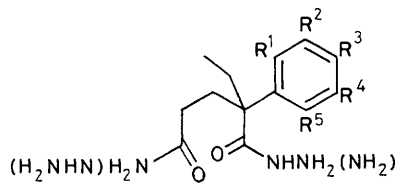
The work described here involves the synthesis of three fluorinated analogues of *N*-aminoglutethimide (**2**). These compounds were made in order to investigate how the introduction of fluorine and trifluoromethyl groups onto the aromatic ring would affect the desmolase-inhibitory properties of the molecules.



| | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^5$ | $R^6$ |
|---|---|---|---|---|---|---|
| (**1**) | H | H | H | $NH_2$ | H | H |
| (**2**) | $NH_2$ | H | H | H | H | H |
| (**3**) | $NH_2$ | H | H | F | H | H |
| (**4**) | $NH_2$ | H | H | OH | H | H |
| (**5**) | H | H | H | F | H | H |
| (**6**) | $NH_2$ | F | F | F | F | F |
| (**7**) | H | F | F | F | F | F |
| (**8**) | $NH_2$ | H | $CF_3$ | H | H | H |
| (**9**) | H | H | $CF_3$ | H | H | H |

## Results and Discussion

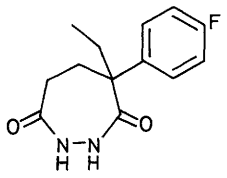
The first analogue to be investigated was *N*-amino-4-fluoroglutethimide (**3**). A likely metabolic pathway for *N*-aminoglutethimide (**2**) is hydroxylation to its 4-hydroxy derivative (**4**).[11] The presence of the 4-fluorine substituent in (**3**) should prevent this process, increasing the metabolic stability of the molecule. Our initial approach to the *N*-amino derivative (**3**) was based on the strategy of Foster *et al.*[7] Treatment of 4-fluoroglutethimide (**5**)[10] with hydrazine hydrate at room temperature afforded an excellent yield of a single amide hydrazide (**10**). Two structures are possible but an unambiguous assignment cannot be made from the available spectroscopic data. Subsequent thermal cyclisation of this compound (refluxing *p*-xylene for 6 h) resulted in the formation of a cyclised product in reasonable yield. However, two products are possible, the desired *N*-aminoglutethimide (**3**) or the isomeric diazepine (**14**). The desired and thermodynamically favoured *N*-aminoglutethimide would be formed by attack of the less nucleophilic hydrazide nitrogen on the amide carbonyl carbon, whereas attack by the more nucleophilic hydrazide nitrogen would afford the diazepine product. A study of the i.r. spectrum of the product formed suggested that the former is produced. The spectrum of (**3**), and indeed those of (**2**), (**6**), and (**8**), contain a characteristic twin peak centred around 3 300 $cm^{-1}$ ($NH_2$, symmetrical and asymmetrical stretching) as shown in other *N*-amino compounds.[12] Data for diazepines are not readily available but diacylhydrazines have i.r. spectra in which the twin peak is replaced by a single peak in the region 3 200—3 100 $cm^{-1}$.[13] That the *N*-aminoglutethimide (**3**) had indeed been produced was confirmed by an alternative approach, which avoided glutarimide ring cleavage and recyclisation. This strategy, which had not previously been applied to the synthesis of 1-aminopiperidine-2,6-diones, involved the attack of an imide nitrogen anion on an electrophilic aminating agent.[14] Generation of the anion of compound (**5**) [sodium hydride, dimethylformamide (DMF)] followed by treatment with hydroxylamine-*O*-



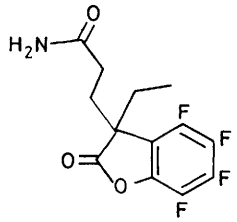
| | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^5$ |
|---|---|---|---|---|---|
| (**10**) | H | H | F | H | H |
| (**11**) | F | F | F | F | F |
| (**12**) | F | F | $NHNH_2$ | F | F |
| (**13**) | H | $CF_3$ | H | H | H |

sulphonic acid[15] at 110 °C for 8 h afforded, after column chromatography, a 49% yield of the *N*-aminoglutethimide (**3**), which was identical in all respects with the product obtained from the cyclisation of the amide hydrazide. Therefore, ring closure of the amide hydrazide (**10**) does indeed occur under thermodynamic control, producing the desired *N*-aminoglutethimide product.

The success of this direct *N*-amination strategy initiated an investigation of its applicability to the synthesis of *N*-aminopentafluoroglutethimide (**6**). However, under similar conditions to those employed above, but using pentafluoroglutethimide (**7**) as the starting material,[9] a mixture of several compounds was obtained. The major component, isolated in 29% yield, was identified as the benzofuranone (**15**). Under milder reaction conditions, only unchanged starting material could be isolated.



(**14**)



(**15**)

Failure to produce the desired *N*-aminoglutethimide (**6**) by this direct *N*-amination strategy prompted us to revert to the original glutarimide ring cleavage/recyclisation methodology. Addition of hydrazine hydrate to compound (**7**) at room temperature gave a mixture of amide hydrazide (**11**) (77%) and the corresponding 4-hydrazinophenyl derivative (**12**) (15%). However, slow addition of the hydrazine hydrate at 0 °C afforded compound (**11**) in high purity and excellent yield. Cyclisation to the *N*-aminoglutethimide required more forcing conditions than those employed in the synthesis of (**3**). After vigorous refluxing in *p*-xylene for 7 days, a 51% yield of a product was obtained. While the preparation of compound (**6**) could not be achieved by the direct *N*-amination strategy, it was presumed, by analogy with the preparation of compound (**3**), that the product derived from the glutarimide ring cleavage/recyclisation protocol was indeed the desired *N*-aminoglutethimide (**6**) (see earlier comment on i.r. spectrum).

The previously discussed *N*-amination strategies were also applied to the synthesis of *N*-amino-3-trifluoromethylglutethimide (**8**). Attempts to *N*-aminate directly the anion derived from 3-trifluoromethylglutethimide (**9**)[10] using hydroxylamine-*O*-sulphonic acid were unsuccessful. In addition to a 40% recovery of starting material, a small amount of a mixture of unidentified compounds (three by g.l.c.) was formed. However, satisfactory results were obtained *via* the amide hydrazine route. Treatment of compound (**9**) with hydrazine hydrate at room temperature afforded 68% of the expected amide hydrazide (**13**), which was successfully cyclised to the *N*-aminoglutethimide (**8**) (in 52% isolated yield) by refluxing in *p*-xylene for 6 h.

Compounds (**3**), (**6**), and (**8**) have been assayed* for inhibitory activity against desmolase and aromatase, and the results obtained are presented in the Table. As expected, none of the compounds showed any aromatase-inhibitory properties, in line with current theories regarding the necessity of a basic function on the aromatic ring for such inhibition to be observed.[7-10] Compound (**3**) was approximately equal to *N*-aminoglutethimide in its desmolase-inhibitory power. Since it is likely to prove more metabolically stable than *N*-aminoglutethimide itself, this compound is a highly attractive selective desmolase inhibitor. Compounds (**6**) and (**8**) were also active and highly selective desmolase inhibitors.

In conclusion, three fluorine-containing analogues of *N*-aminoglutethimide have been prepared, and have all proved to be selective desmolase inhibitors.

**Table.**

| Compound | I.C.$_{50}$* for desmolase inhibition (μM) | I.C.$_{50}$* for aromatase inhibition (μM) |
|---|---|---|
| (**1**) | 30 | 8 |
| (**3**) | 35 | *a* |
| (**6**) | 60 | *a* |
| (**8**) | 42 | *a* |

[a] No inhibition was observed at any substrate concentration.

* The I.C.$_{50}$ value is the substrate concentration at which 50% inhibition of the enzyme complex was observed.

## Experimental

M.p.s were determined using an Electrothermal or Gallenkamp apparatus and are uncorrected. I.r. spectra (liquids as films and solids as Nujol mulls between sodium chloride discs) were obtained with a Perkin-Elmer 257 or Unicam SP 1050 spectrometer. N.m.r. spectra were recorded on a Perkin-Elmer R12B spectrometer: $^1$H N.m.r. spectra at 60 MHz using tetramethylsilane as an internal standard, and $^{19}$F n.m.r. spectra at 56.4 MHz using chlorotrifluoromethane as an internal standard. Mass spectra were recorded with a Kratos M.S. 80 spectrometer, using the direct insertion method and an ionizing voltage of 70 eV. Polygram SIL N-HR/UV$_{254}$ silica gel plates were used for t.l.c., with visualization of spots by u.v. light or iodine vapour. Silica gel (Merck, Kieselgel 60, 70—230 mesh ASTM type 7734) was used for all column chromatographic separations. G.l.c. analyses were carried out using a 3% dimethylsilicone gum (OV1) on Gas Chrom Q (80—120 mesh) packing and utilising flame ionization detection.

Unless otherwise stated, organic extracts were combined, dried (magnesium sulphate), and concentrated on a rotary evaporator. Solvents were dried by standard procedures. All non-aqueous reactions were protected against atmospheric moisture by the use of silica gel or calcium chloride guard tubes.

*Preparation of* 4-(4-*Fluorophenyl*)-4-*hydrazinocarbonylhexanamide* (**10**).—To 3-ethyl-3-(4-fluorophenyl)piperidine-2,6-dione (**5**) (1.0 g, 4.26 mmol) was added hydrazine hydrate (5.0 g, 100 mmol), and the suspension was stirred. Compound (**5**) slowly dissolved and another white powdery solid precipitated from solution. After being stirred at room temperature for 18 h, the white powdery precipitate was filtered at the pump and dried *in vacuo* to afford 4-(4-*fluorophenyl*)-4-*hydrazinocarbonylhexanamide* (**10**) as a white solid (1.0 g, 88%), m.p. 149—151 °C (Found: C, 58.1; H, 6.7; F, 7.0; N, 16.0. $C_{13}H_{18}FN_3O_2$ requires C, 58.4; H, 6.7; F, 7.1; N, 15.7%); $\nu_{max.}$(Nujol) 3 360 (NH), 3 320 (NH), 3 200 (NH), 1 600 (amide C=O), and 1 620 cm$^{-1}$ (hydrazide C=O); $\delta_H$($C_5D_5N$) 0.84 (3 H, t, *J* 7 Hz, Me), 1.98—2.90 (6 H, m, $CH_2$), 4.77 (2 H, s, hydrazide $NH_2$), 6.86—7.65 (4 H, $A_2B_2X$, ArH), 7.68 (2 H, br s, amide $NH_2$), and 9.95 (1 H, br s, NH); $\varphi_F$ 116.4 (1 F, tt); *m/z* 250 (7), 235 (5), 220 (5), 207 (74), 193 (50), 178 (45), 162 (54), 150 (71), 135 (100), and 109 (52%).

*Preparation of* 1-*Amino*-3-*ethyl*-3-(4-*fluorophenyl*)*piperidine*-2,6-*dione* (**3**).—(i) Via 4-(4-*fluorophenyl*)-4-*hydrazinocarbonyl*-

* The reagents and conditions for the assays for inhibitory activity against desmolase and aromatase were those described in ref. 7.

*hexanamide* (**10**). A suspension of compound (**10**) (1.0 g, 3.75 mmol) in *p*-xylene (30 ml) was stirred and refluxed at 160 °C. A copious evolution of ammonia was observed, which ceased after 6 h. The cooled, colourless solution was decanted from a brown residual solid, the solid was washed with chloroform (3 × 20 ml), and the washings were combined with the *p*-xylene solution and concentrated under reduced pressure. The residue was extracted into chloroform (50 ml), and the extract was washed with water (3 × 20 ml), dried ($CaCl_2$), concentrated, and eluted with chloroform down a short silica column to afford an oil (0.60 g). After drying *in vacuo* for several days, crystallisation occurred to afford 1-*amino*-3-*ethyl*-3-(4-*fluorophenyl*)*piperidine*-2,6-*dione* (**3**) as a solid (0.60 g, 64%), m.p. 67—68 °C (Found: C, 62.7; H, 6.3; F, 7.6; N, 10.9. $C_{13}H_{15}FN_2O_2$ requires C, 62.4; H, 6.0; F, 7.6; N, 11.2%); $\nu_{max.}$($CHCl_3$) 3 340 (NH), 3 250 (NH), 1 720 (C=O), and 1 660 $cm^{-1}$ (C=O); $\delta_H$($CDCl_3$) 0.85 (3 H, t, *J* 7 Hz, Me), 1.99 (2 H, br q, $CH_2$Me), 2.21—2.73 (4 H, m, $CH_2CH_2$), 5.20 (2 H, br s, $NH_2$), and 6.89—7.39 (4 H, $A_2B_2X$, ArH); $\varphi_F$ 115.1 (1 F, tt, *J* 5, 8 Hz); *m*/*z* 250 (13, $M^+$), 235 (1), 222 (2), 207 (15), 194 (12), 193 (100), 150 (14), 135 (25), and 109 (16%).

(ii) *Direct from* 3-*ethyl*-3-(4-*fluorophenyl*)*piperidine*-2,6-*dione* (**5**). To a stirred suspension of sodium hydride pellets (0.13 g, 5.42 mmol) in anhydrous DMF (10 ml) at room temperature was added dropwise a solution of 3-ethyl-3-(4-fluorophenyl)-piperidine-2,6-dione (**5**) (1.20 g, 5.11 mmol) in anhydrous DMF (15 ml) during 10 min, when hydrogen was evolved. The mixture was stirred at room temperature for 1 h and then at 110 °C for 2 h. To the resulting orange solution at 100 °C was added dropwise, during 10 min, a solution of hydroxylamine-*O*-sulphonic acid (1.08 g, 9.56 mmol) in anhydrous DMF (40 ml). Further heating at 110 °C for 8 h caused the slow precipitation of a white solid. The cooled pale green suspension was poured into water (400 ml), extracted with chloroform (3 × 100 ml), and the combined extracts were washed with water (3 × 100 ml), dried ($CaCl_2$), and concentrated to a pale yellow oil (1.08 g) which crystallised after a time. Column chromatography [silica gel; dichloromethane–methanol (99:1)] gave (i) 3-ethyl-3-(4-fluorophenyl)piperidine-2,6-dione (**5**) (0.38 g, 32% recovery); and (ii) 1-amino-3-ethyl-3-(4-fluorophenyl)piperidine-2,6-dione (**3**) (0.52 g, 49%).

*Preparation of* 3-(2-*Carbamoylethyl*)-3-*ethyl*-4,5,6,7-*tetrafluorobenzofuran*-2(3H)-*one* (**15**).—To a stirred suspension of sodium hydride pellets (0.07 g, 2.92 mmol) in anhydrous DMF (10 ml) at room temperature was added a solution of 3-ethyl-3-pentafluorophenylpiperidine-2,6-dione (**7**) (0.80 g, 2.61 mmol) in anhydrous DMF (10 ml). After a short induction period, effervescence was observed and continued for 1 h as a yellow colour developed. The solution was heated at 120 °C for 1 h, and then, at this temperature, a solution of hydroxylamine-*O*-sulphonic acid (0.59 g, 5.22 mmol) in anhydrous DMF (25 ml) was added. During several minutes, the red-coloured solution was slowly replaced by a pale yellow opaque solution. After being stirred at 120 °C for a further 3 h, the cooled pale orange solution and white solid were poured into water (250 ml) and, after some time a pale yellow solid precipitated from solution. This was extracted into dichloromethane (3 × 70 ml), the combined extracts washed with water (3 × 70 ml), dried ($CaCl_2$), and concentrated under reduced pressure to afford a red oil (0.75 g). Column chromatography [silica gel; dichloromethane–methanol (98:2)] gave, in addition to several unidentified components, (i) unchanged 3-ethyl-3-pentafluorophenylpiperidine-2,6-dione (**7**) (0.08 g, 10% recovery), and (ii) 3-(2-*carbamoylethyl*)-3-*ethyl*-4,5,6,7-*tetrafluorobenzofuran*-2(3H)-*one* (**15**) (0.23 g, 29%), which was recrystallised from dichloromethane–light petroleum (b.p. 40—60 °C) to afford crystals, m.p. 125.0—125.5 °C (Found: C, 51.1; H, 3.6; F, 25.4; N, 4.7. $C_{13}H_{11}F_4NO_3$ requires C, 51.1; H, 3.6; F, 24.9; N, 4.65%); $\nu_{max.}$(Nujol) 3 460 (NH), 3 190 (NH), 1 820 (lactone C=O), and 1 670 $cm^{-1}$ (amide C=O); $\delta_H$($CDCl_3$) 0.77 (3 H, t, *J* 7 Hz, Me), 1.75—2.72 (6 H, m, $CH_2$), and 6.16 (2 H, br s, $NH_2$); $\varphi_F$ 143.9 (1 F, ddd, *J* 3, 14, 20 Hz, 7-F), 152.7 (1 F, dt, *J* 3, 20 Hz, 5-F), 157.7 (1 F, dd, *J* 14, 20 Hz, 4-F), and 161.3 (1 F, t, *J* 20 Hz, 6-F); *m*/*z* 305 (16, $M^+$), 290 (12), 233 (21), and 203 (100%).

*Attempted Preparation of* 4-*Hydrazinocarbonyl*-4-*pentafluorophenylhexanamide* (**11**).—Hydrazine hydrate (5.15 g, 103 mmol) was added, at room temperature, to 3-ethyl-3-pentafluorophenylpiperidine-2,6-dione (**7**), when a slightly exothermic reaction occurred. The mixture was stirred at room temperature for 19 h, and the fine white precipitate was then filtered off at the pump, washed only with the mother liquor, and dried *in vacuo* for 2 days to afford a white powder (1.02 g), m.p. 180—200 °C, identified as a mixture of 4-hydrazinocarbonyl-4-pentafluorophenylhexanamide (**11**) (0.85 g, 77%) and 4-hydrazinocarbonyl-4-(2,3,5,6-tetrafluoro-4-hydrazinophenyl)hexanamide (**12**) (0.17 g, 15%).

*Preparation of* 4-*Hydrazinocarbonyl*-4-*pentafluorophenylhexanamide* (**11**).—Hydrazine hydrate (15.5 g, 310 mmol) was added dropwise during 5 min to stirred 3-ethyl-3-pentafluorophenylpiperidine-2,6-dione (**7**) (3.0 g, 9.77 mmol) at 2 °C. The temperature was allowed to rise slowly to room temperature and was then maintained there for 5 h. The fine white solid was filtered off at the pump, washed only with the mother liquor, and dried *in vacuo* for 3 days to afford the *title compound* (**11**) as a white powder (3.04 g, 92%), m.p. 202—203 °C (Found: C, 46.1; H, 4.1; F, 28.3; N, 12.6. $C_{13}H_{14}F_5N_3O_2$ requires C, 46.0; H, 4.1; F, 28.0; N, 12.4%); $\nu_{max.}$(Nujol) 3 380 (NH), 3 300 (NH), 3 200 (NH), 1 670 (amide C=O), and 1 640 $cm^{-1}$ (hydrazide C=O); $\delta_H$[$(CD_3)_2SO$] 0.78 (3 H, t, *J* 7 Hz, Me), 1.60—2.60 (6 H, m, $CH_2$), 4.05 (2 H, br s, hydrazide $NH_2$), 7.05 (2 H, br s, amide $NH_2$), and 8.88 (1 H, br s, NH); $\varphi_F$ 135.6 (2 F, m, *ortho* Fs), 157.1 (1 F, t, *J* 22 Hz, *para* F), and 163.1 (2 F, m, *meta* Fs).

*Preparation of* 1-*Amino*-3-*ethyl*-3-*pentafluorophenylpiperidine*-2,6-*dione* (**6**).—A stirred suspension of finely divided 4-hydrazinocarbonyl-4-pentafluorophenylhexanamide (**11**) (1.0 g, 2.95 mmol) in *p*-xylene (110 ml) was refluxed at 190 °C for 7 days. The resulting pale yellow solution was filtered, the filtered solid was washed with chloroform (100 ml), and the filtrate was distilled under reduced pressure to leave a yellow paste. This was taken up in chloroform (100 ml), and the solution was washed with water (2 × 50 ml), dried ($MgSO_4$), and concentrated to give a pale yellow oil, which was dried *in vacuo* at 110 °C to remove any traces of *p*-xylene. Column chromatography (silica gel; chloroform) gave an oil, identified as 1-*amino*-3-*ethyl*-3-*pentafluorophenylpiperidine*-2,6-*dione* (**6**) (0.48 g, 51%) (Found: C, 48.4; H, 3.6; N, 8.7. $C_{13}H_{11}F_5N_2O_2$ requires C, 48.4; H, 3.4; N, 8.7%); $\nu_{max.}$($CHCl_3$) 3 340 (NH), 3 260 (NH), 1 720 (C=O), and 1 670 (C=O); $\delta_H$($CDCl_3$) 1.03 (3 H, t, *J* 7 Hz, Me), 2.01—3.10 (6 H, m, $CH_2$), and 5.08 (2 H, br s, $NH_2$); $\varphi_F$ 137.8 (2 F, m, *ortho* Fs), 153.9 (1 F, tt, *J* 3, 21 Hz, *para* F), and 160.4 (2 F, m, *meta* Fs); *m*/*z* 322 (49, $M^+$), 279 (37), 265 (95), 222 (43), 207 (77), and 181 (100%).

*Preparation of* 4-*Hydrazinocarbonyl*-4-(3-*trifluoromethylphenyl*)*hexanamide* (**13**).—Hydrazine hydrate (13 ml) was added to 3-ethyl-3-(3-trifluoromethylphenyl)piperidine-2,6-dione (**9**) (0.645 g, 2.26 mmol), and the suspension was stirred at room temperature. Compound (**9**) slowly dissolved and another white powdery solid precipitated from solution. After the mixture had been stirred for 18 h, the white precipitate was filtered under suction and dried (60 °C/0.3 mmHg) for 3 h. 4-*Hydrazinocarbonyl*-4-(3-*trifluoromethylphenyl*)*hexanamide* (**13**) was obtained as white powder (0.49 g, 68%), m.p. 150—

152 °C (Found: C, 52.8; H, 5.7; N, 13.2. $C_{14}H_{18}F_3N_3O_2$ requires C, 53.0; H, 5.7; N, 13.2%); *m/z* 300 (6, $M^+$), 257 (86), 243 (67), 200 (97), 185 (100), and 159 (73%).

*Preparation of* 1-*Amino*-3-*ethyl*-3-(3-*trifluoromethylphenyl*)-*piperidine*-2,6-*dione* (**8**).—A suspension of 4-hydrazinocarbonyl-4-(3-trifluoromethylphenyl)hexanamide (**13**) (0.49 g, 1.55 mmol) in *p*-xylene (50 ml) was heated at reflux for 6 h. After cooling to room temperature, the solvent was removed under reduced pressure, yielding a pale yellow oil, which was purified by column chromatography [silica gel; dichloromethane–ethanol (9:1)] to afford a pale yellow viscous oil, identified as 1-*amino*-3-*ethyl*-3-(3-*trifluoromethylphenyl*)*piperidine*-2,6-*dione* (**8**) (0.243 g, 52.4%) (Found: C, 56.3; H, 4.7; F, 18.8; N, 9.6. $C_{14}H_{15}F_3N_2O_2$ requires C, 56.0; H, 5.0; F, 19.0; N, 9.3%); $\nu_{max.}$ 3 340 and 3 260 ($NNH_2$), 1 725 and 1 670 $cm^{-1}$ (imide C=O); $\delta_H(CHCl_3)$ 0.88 (3 H, t, *J* 7 Hz, Me), 1.8—2.9 (6 H, m, $CH_2$), 7.53 (4 H, s, ArH), and 8.83 (2 H, br s, $NH_2$); $\varphi_F$ 63.0 (3 F, s, $CF_3$); *m/z* 300 (10, $M^+$), 257 (50), 243 (100), 200 (56), 185 (47), and 159 (23%).

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