Prostate cancer has become the most common cancer among men, and the second leading cause of male cancer deaths in the United States.\(^{3,4}\) Testosterone and 5α-dihydrotestosterone are androgens that are required for the development of both the normal prostate and prostate cancer.\(^{5,6}\) Androgens act through the androgen receptor (AR), which belongs to the steroid-receptor superfamily of ligand-dependent transcription factors.\(^{7,8}\) Both steroidal and nonsteroidal antiandrogens are available, and these molecules are of clinical utility as chemotherapeutic agents for prostate cancer (Fig. 1).\(^{5,6}\) Cyproterone acetate (CPA: 1) is a typical steroidal AR antagonist.\(^{9}\) It was one of the earliest of these drugs to be administered orally, but CPA shows agonistic activity and overlapping effects with other hormonal systems, leading to a range of unpleasant side effects. A number of nonsteroidal AR antagonists have been reported in the literature\(^{8—17}\) and three of these, flutamide (2),\(^{18—20}\) nilutamide (3)\(^{21}\) and bicalutamide (4)\(^{22—25}\) (Fig. 1), are pure antiandrogens used in the treatment of prostate cancer.\(^{26,27}\) However, these nonsteroidal AR antagonists exhibit adverse effects such as mastodynia, gynaecomastia and hepatotoxicity\(^{28—35}\) ; and therefore potent AR antagonists with fewer adverse effects are highly desirable. Moreover, flutamide therapy requires administration three times each day, and bicalutamide is taken once a day. Therefore, from a quality of life perspective, it would be desirable for new generation AR antagonists to have a longer duration of action, at least equal to that of bicalutamide.

In a previous paper,\(^{27}\) we reported a new series of N-arylpiperazine-1-carboxamide derivatives as pot AT nonsteroidal AR antagonists. Among these derivatives, YM-92088 (5) was shown to be a more potent than bicalutamide as an in vitro AR antagonist (4). However, the in vivo antiandrogenic activity of 5 was lower than that of bicalutamide. Hence, to find AR antagonists with greater oral potency, we have conducted further modification of 5, and in this paper we describe the results of our studies on the synthesis and pharmacological evaluation of a series of N-arylpiperazine-1-carboxamide derivatives as AR antagonists.

**Chemistry**

Compounds selected for biological evaluation were prepared as described in Charts 1—4. All synthesized compounds were characterized by 1H-NMR, mass spectrometry and elemental analysis.

As shown in Chart 1, compounds 7—12 and 19 were prepared in good yields by ipso substitution of 4-fluoro-2-(trifluoromethyl)benzonitrile (6) with the corresponding cyclic amines and, in the case of compound 9, by subsequent deprotection of the Boc group. Treatment of 7—12 with 4-fluorophenyl isocyanate afforded the urea derivatives 13—18a. The amide derivative (20) was obtained from compound 19 by hydrolysis followed by conventional amidation. Compound 22 was obtained by coupling N-Boc piperidinone with 4-bromo-2-(trifluoromethyl)benzonitrile, which was prepared by a Sandmeyer reaction with 21, followed by dehydration using POCI\(_3\). Hydrogenation of the dihydropyridine moiety of 22 gave the piperidine (23) in good yields. After deprotection of the Boc groups of 22 and 23, the piperidines were treated with 4-fluorophenyl isocyanate to give compounds 24 and 25, respectively (Chart 2). A Pd-C catalyzed Suzuki coupling\(^{28,29}\) between 4-bromo-2-(trifluoromethyl)benzonitrile and 4-carboxyphenylboronic acid provided the biphenyl 26, which was then converted to compound 27 in a similar manner to that described for compound 20 (Chart 3). Compound 28 was obtained by ipso substitution of 6 with excess ethylenediamine, followed by reductive amination with benzaldehyde using NaBH(\(\text{OAc})_3\). The piperazine framework was constructed in moderate yield by treatment of 28 with glyoxal in aqueous conditions,\(^{30}\) and subsequent removal of the benzyl group by hydrogenolysis gave compound 29. Com-

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*N-Arylpiperazine-1-carboxamide Derivatives: a Novel Series of Orally Active Nonsteroidal Androgen Receptor Antagonists*

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A novel series of N-arylpiperazine-1-carboxamide derivatives was synthesized and their androgen receptor (AR) antagonist activities and in vivo antiandrogenic properties were evaluated. Reporter assays indicated that trans-2,5-dimethylpiperazine derivatives are potent AR antagonists, and in this series trans-4-[4-cyano-3-(trifluoromethyl)phenyl]-N-(2,4-difluorophenyl)-2,5-dimethylpiperazine-1-carboxamide (18g, YM-175735) exhibited the most potent antiandrogenic activity. Compared to bicalutamide, YM-175735 is an approximately 4-fold stronger AR antagonist and has slightly increased antiandrogenic activity, suggesting that YM-175735 may be useful in the treatment of prostate cancer.

**Key words** androgen receptor; antagonist; antiandrogen; prostate cancer
compound 30 was synthesized by treatment of 29 with 4-fluorophenyl isocyanate (Chart 4). Chart 5 shows the synthesis of compounds with bulky groups at the α position on the piperazine framework, such as compound 33. Introduction of the alkyl groups on the piperazine framework was achieved by alkylation of the arylpiperazinone with the corresponding
alkyl halides, using lithium diisopropylamide (LDA). Reduction of the amide with a borane-tetrahydrofuran (THF) complex gave the corresponding amine derivatives (31–33).Syntheses of compounds 34–36 were similar to that for compound 30.

Results and Discussion

All the analogues were evaluated for their AR antagonistic activity using a reporter assay; the resulting IC_{50} values are listed in Tables 1—3. As described in the introduction, YM-92088 (5) shows less potent in vivo antiandrogenic activity than bicalutamide (4); the reason is unclear, but we speculate that the piperazine framework of 5 is easily metabolized. In fact, compound 5 has been found to be metabolically unstable in human liver microsomes (54% remaining after 1 h), and therefore to find more potent and orally active AR antagonists, we concentrated our efforts on further modification of 5, focusing mainly on the piperazine framework.

Firstly, we converted the piperazine ring of 5 into alternative cyclic amines, such as homo-piperazine and piperidine (Table 1). Ring expansion of the piperazine (compound 13) resulted in an approximately 3-fold decrease in the inhibitory activity. Replacement of the sp^3-like urea nitrogen atom on the piperazine ring with an sp^2 carbon atom in compound 20 led to a substantial reduction in potency, relative to 5. The piperidine derivative (25) also exhibited a weaker inhibitory activity, probably due to the change from the sp^3-like aniline nitrogen to an sp^2 carbon. However, introduction of the sp^2 carbon atom into the piperidin ring in compound 24 provided a 4-fold improvement in potency, compared to 25. Moreover, biphenyl derivative (27) was approximately equipotent with 5. These results suggest that both sp^3-like nitrogen atoms in the piperazine ring were important for potency, and that the piperazine framework of 5 plays a spatial role as a linker with planar geometry at the N atoms. Consequently, we selected the 4-arylpiperazine-1-carboxamide as an optimal scaffold, and introduced further substituents onto the piperazine framework of 5.

Next, we introduced an alkyl group onto the piperazine ring. As shown in Table 2, methyl substitution at the 2-position caused an approximately 3-fold increase in the potency (IC_{50}=0.18 and 0.47 μM for 14 and 5, respectively). Since addition of a methyl group at the 3-position (15) was preferred over the 2-position, we further introduced another alkyl group at the 3-position. Although the ethyl derivative (34) exhibited comparable inhibitory activity, introduction of an isopropyl group (35) resulted in 8-fold reduction in potency, compared to 15, indicating that increased bulkiness at this position may be unfavorable for AR antagonism. Introduction of an oxo group onto the piperazine ring at the 3-position resulted in particularly deleterious effects on the inhibitory activity (compound 30). Subsequently, we synthesized di-substituted derivatives for further investigation of the substituent effects on the piperazine framework. The 3,3-dimethyl derivative (36) showed a slight decrease in inhibitory activity, but the 2,2-dimethyl derivative (16) was significantly less active relative to the corresponding monomethyl derivative (14). As shown by compound 17, introduction of 2,6-cis-dimethyl substituents was also detrimental to AR antagonism, probably due to an unfavorable conformation by the interference of free rotation around the urea bond. Interestingly, the 2,5-trans-dimethyl derivative (18a) exhibited comparable activity to the monomethyl derivatives (14, 15) (IC_{50}=0.13, 0.18 and 0.10 μM, respectively). These results suggest that introduction of specific methyl group(s) may lead to a preferred conformation of the piperazine ring that increases the AR antagonist activity.

Lastly, we conducted further modification of the 4-fluorophenyl group of the 2,5-trans-dimethyl derivative (18a). Replacement of the fluorine atom with another halogen, such as a chlorine or bromine, at the para position resulted in only a small reduction in potency, and other derivatives (18d —g) exhibited comparable inhibitory activity to 18a (Table 3).

Table 1. AR Antagonistic Activities of Arylpiperazine, Arylpiperidine and Biphenyl Derivatives

<table>
<thead>
<tr>
<th>Compound</th>
<th>A</th>
<th>IC_{50} (μM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>+</td>
<td>0.47</td>
</tr>
<tr>
<td>13</td>
<td>+</td>
<td>1.6</td>
</tr>
<tr>
<td>20</td>
<td>+</td>
<td>7.2</td>
</tr>
<tr>
<td>25</td>
<td>+</td>
<td>4.9</td>
</tr>
<tr>
<td>24</td>
<td>+</td>
<td>1.2</td>
</tr>
<tr>
<td>27</td>
<td>+</td>
<td>0.61</td>
</tr>
<tr>
<td>4</td>
<td>+</td>
<td>0.89</td>
</tr>
</tbody>
</table>

Table 2. AR Antagonistic Activities of the N-Arylpiperazine-1-carboxamide Derivatives

<table>
<thead>
<tr>
<th>Compound</th>
<th>R</th>
<th>IC_{50} (μM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>H</td>
<td>0.47</td>
</tr>
<tr>
<td>14</td>
<td>2-Methyl</td>
<td>0.18</td>
</tr>
<tr>
<td>15</td>
<td>3-Methyl</td>
<td>0.10</td>
</tr>
<tr>
<td>34</td>
<td>3-Ethyl</td>
<td>0.14</td>
</tr>
<tr>
<td>35</td>
<td>3-Isopropyl</td>
<td>0.77</td>
</tr>
<tr>
<td>30</td>
<td>3-Oxo</td>
<td>17%</td>
</tr>
<tr>
<td>36</td>
<td>3,3-Dimethyl</td>
<td>0.25</td>
</tr>
<tr>
<td>16</td>
<td>2,2-Dimethyl</td>
<td>8.5</td>
</tr>
<tr>
<td>17</td>
<td>cis-2,6-Dimethyl</td>
<td>5.0</td>
</tr>
<tr>
<td>18a</td>
<td>trans-2,5-Dimethyl</td>
<td>0.13</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>0.89</td>
</tr>
</tbody>
</table>

a) Compounds were tested for their ability to inhibit AR mediated transcriptional activation using a reporter assay. IC_{50} values were determined by a single experimental run in triplicate.

b) Percent inhibition at 10 μM.
and in this series, methylpiperazine derivatives were potent AR antagonists, potent than bicalutamide (ED 50 value of 0.11 µM). Although there may be some species difference in metabolic stability in human liver microsomes, compared to compound 5 (72% and 54% remaining, respectively, after 1 h). Although there may be some species difference in metabolic stability, the relative antiandrogenic activities suggest that the metabolic stability of 18a in rat is also better than that of 5. Interestingly, different substituents on the phenyl ring produced various in vivo results. Hence, the activity of the bromine derivative (18c) was comparable to 18a, but the chlorine (18b) and methyl (18d) derivatives were less active than 18a. Although the methoxy derivative (18e) was a potent in vitro AR antagonist, with an IC 50 value of 0.11 µM, its in vivo potency was very weak. Surprisingly, the 2,4-difluoro derivative (18g) strongly inhibited the growth of rat prostate by 85% at a dose of 10 µg/kg, whereas the 3,4-difluoro derivative (18f) had an effect comparable to that of the 4-fluoro derivative (18a). These results indicate that introduction of an additional fluorine atom at the 2-position on the phenyl ring may be important for in vivo activity. Compound 18g showed dose-dependent inhibition of the growth of rat prostate, and its ED 50 value was 1.1 µg/kg, making it more potent than bicalutamide (ED 50 = 1.6 µg/kg) and suggesting that 18g (YM-175735) has potential as a novel nonsteroidal AR antagonist.

Conclusion

A novel series of N-arylpiperazine-1-carboxamide derivatives were synthesized and their androgen receptor (AR) antagonist activities and in vivo antiandrogenic effects were evaluated. Reporter assays indicated that trans-2,5-dimethylpiperazine derivatives were potent AR antagonists, and in this series, trans-N-4-[4-cyano-3(trifluoromethyl)phenyl]-N-(2,4-difluorophenyl)-2,5-dimethylpiperazine-1-carboxamide (18g, YM-175735) exhibited the most potent antiandrogenic activity. Compared to bicalutamide, YM-175735 showed an approximately 4-fold stronger activity as an AR antagonist, and showed a slightly increase in in vivo antiandrogenic activity, suggesting that YM-17535 may be useful for the treatment of prostate cancer.

Experimental

In general, all reagents and solvents were commercial quality and were used without further purification unless otherwise noted. Melting points were determined on a Yanaco MP-5000 micro melting point apparatus with our correction. 1H-NMR spectra were measured with a JMN-LA300 or JMN-EX400 spectrometer; chemical shifts are expressed in δ units using tetramethylsilane as the standard (in NMR description, s=singlet, d=doublet, t=triplet, m=multiplet, and br=broade peak). MS spectra were determined with a JEOIL JMS-LX2000 spectrometer. Elemental analysis was performed with a Yanaco MT-5 microanalyzer (C, H, N) and Yokogawa IC-7000S ion chromatographic analyzer (halogens) and were within ±0.4% of theoretical values.

4-(1,4-Diazepan-1-yl)-2-(trifluoromethyl)benzonitrile (7)

To a solution of 4-fluoro-2-(trifluoromethyl)benzonitrile (6, 5.0 g, 26.4 mmol) in N,N-dimethylformamide (DMF, 50 ml) was added 1,4-diazepane (1.1 g, 105.8 mmol) at ambient temperature and stirred at 80 °C for 21 h. The reaction mixture was diluted with H 2O and extracted with AcOEt. The organic layer was washed with H 2O, dried over MgSO 4 and concentrated in vacuo. The residue was purified by silica gel column chromatography (CHCl 3 /MeOH=10:1) to give the title compound (4.55 g, 64%) as a colorless solid. 1H-NMR (400 MHz, DMSO-d 6 ) δ 1.68—1.80 (2H, m), 2.60—2.66 (2H, m), 2.82—2.90 (2H, m), 3.54—3.70 (4H, m), 7.00—7.06 (2H, m), 7.74 (1H, d, J=8.4 Hz). FAB-MS m/z: 270 (M + H)+.

4-(3-Methylpiperazin-1-yl)-2-(trifluoromethyl)benzonitrile (8)
The title compound was prepared from 2-methylpiperazine in a manner similar to that described for compound 7 as a colorless solid (quant.). 1H-NMR (300 MHz, DMSO-d 6 ) δ 1.03 (3H, d, J=6.3 Hz), 2.36—2.48 (1H, m), 2.62—2.85 (3H, m), 2.90—2.99 (1H, m), 3.79—3.93 (2H, m), 7.16—7.31 (2H, m), 7.79 (1H, d, J=9.3 Hz). FAB-MS m/z: 270 (M + H)+.

4-(3,3-Dimethylpiperazin-1-yl)-2-(trifluoromethyl)benzonitrile (9)

To a solution of 4-fluoro-2-(trifluoromethyl)benzonitrile (7) (155 mg, 0.5 mmol) in THF (2 ml) was added 4-fluorophenyl isocyanate (0.23 ml, 2.04 mmol) at ambient temperature. After stirring for 1 h, the reaction mixture was diluted with H 2O and treated with AcOH. The organic layer was washed with H 2O, dried over MgSO 4 and concentrated in vacuo. The residue was purified by column chromatography (SiO 2 , CHCl 3 / MeOH=20:1) to give the title compound (71 mg, 40%) as a colorless solid. 1H-NMR (400 MHz, DMSO-d 6 ) δ 1.03 (3H, d, J=6.6 Hz), 2.36—2.48 (1H, m), 2.62—2.85 (3H, m), 2.90—2.99 (1H, m), 3.79—3.93 (2H, m), 7.16—7.31 (2H, m), 7.79 (1H, d, J=9.3 Hz). FAB-MS m/z: 270 (M + H)+.

4-(2-Methylpiperazin-1-yl)-2-(trifluoromethyl)benzonitrile (10)

The title compound was prepared from tert-butylicarboxylic acid prepared from tert-butyl 3-methylpiperazine-1-carboxylate (31) in a manner similar to that described for compound 7 (65%) as a colorless powder. A mixture of the intermediate (1.2 g, 3.25 mmol) and TFA (6 ml) was stirred at 0°C for 30 min and the solution was concentrated in vacuo. The residue was diluted with saturated aqueous NaHCO 3 , and extracted with AcOEt. The organic layer was dried and concentrated under reduced pressure to give 9 (920 mg, quant.) as a pale yellow oil. 1H-NMR (300 MHz, DMSO-d 6 ) δ 1.11 (3H, d, J=6.6 Hz), 2.56—2.70 (1H, m), 2.74—2.89 (2H, m), 2.90—3.05 (2H, m), 3.54—3.67 (2H, m), 4.05—4.23 (1H, m), 7.11—7.24 (2H, m), 7.80 (1H, d, J=9.0 Hz). FAB-MS m/z: 270 (M + H)+.

4-(3,3-Dimethylpiperazin-1-yl)-2-(trifluoromethyl)benzonitrile (11)
The title compound was prepared from cis-2,6-dimethylpiperazine in a manner similar to that described for 7 as a colorless solid (55%). 1H-NMR (300 MHz, DMSO-d 6 ) δ 1.05 (6H, s), 2.77—2.90 (2H, m), 3.21 (2H, s), 3.29—3.39 (2H, m), 7.14—7.29 (2H, m), 7.76 (1H, d, J=8.7 Hz). FAB-MS m/z: 284 (M + H)+.

4-(3,5-Dimethylpiperazin-1-yl)-2-(trifluoromethyl)benzonitrile (12)
The title compound was prepared from trans-2,5-dimethylpiperazine in a manner similar to that described for compound 7 as a yellow oil (quant.). 1H-NMR (300 MHz, CDCl 3 ) δ 1.16—1.24 (6H, m), 2.67—2.77 (1H, m), 3.06—3.18 (1H, m), 3.25—3.41 (3H, m), 3.70—3.83 (1H, m), 6.96 (1H, d, J=8.7, 2.4 Hz), 7.12 (1H, d, J=2.4 Hz), 7.62 (1H, d, J=8.7 Hz). EI-MS m/z: 283 (M)+.

4-(3-Cyano-3(trifluoromethyl)phenyl)-N-(4-fluorophenyl)-1,4-di-azepane-1-carboxamide (13) To a solution of 4-(1,4-diazepan-1-yl)-2-(trifluoromethyl)benzonitrile (7, 500 mg, 1.86 mmol) in CH 2 Cl 2 (10 ml) was added 4-fluorophenyl isocyanate (0.23 ml, 2.04 mmol) at ambient temperature and stirred for 2h. The reaction mixture was concentrated in vacuo and the residue was purified by silica gel column chromatography
methylpiperazine-1-carboxamide (15) in a manner similar to that described for compound 13 as a colorless solid (84%). mp 211—216 °C (AcOEt/PrOr). 1H-NMR (400 MHz, DMSO-d6, δ 1.16 (3H, d, J = 6.9 Hz), 3.39—3.41 (2H, m), 3.84—4.01 (1H, m), 4.35—4.48 (1H, m, 7.03—7.12 (2H, m), 7.25 (1H, dd, J = 8.8, 2.5 Hz), 7.31 (1H, d, J = 2.5 Hz), 7.42—7.52 (2H, m), 7.64 (1H, d, J = 8.8 Hz), 8.74 (1H, s). FAB-MS m/z: 407 (M + H+). Anal. Calcld for C14H13N4O2F: C, 59.38; H, 4.45; N, 13.82; F , 18.60.

(2Z)-4-[4-(3-Chlorophenyl)-6-fluoropiperidin-1-yl]-2-( trifluoromethyl)benzonitrile (16) The title compound was prepared from (2Z)-4-(3-methylpiperazin-1-yl)-2-(trifluoromethyl)benzamide (8) in a manner similar to that described for compound 13 as a colorless solid (6%). mp 195 °C (MeOH). 1H-NMR (400 MHz, DMSO-d6, δ 1.10 (3H, d, J = 6.6 Hz), 1.31—1.33 (2H, m), 3.76—3.86 (1H, m, 3.95—4.10 (1H, m), 4.29—4.40 (1H, m), 7.04—7.12 (2H, m), 7.19—7.30 (2H, m), 7.44—7.51 (2H, m), 7.86 (1H, d, J = 8.7 Hz), 8.61 (1H, s). FAB-MS m/z: 421 (M+H+). Anal. Calcld for C14H13N4O2F: C, 59.11; H, 4.46; N, 13.79; F, 18.70. Found: C, 59.38; H, 4.45; N, 13.83; F, 18.59.

(2Z)-4-[4-(3-Chlorophenyl)-6-fluoropiperidin-1-yl]-2-( trifluoromethyl)benzonitrile (17) The title compound was prepared from (2Z)-4-(3,3-dimethylpiperazin-1-yl)-2-(trifluoromethyl)benzamide (10) in a manner similar to that described for compound 13 as a colorless solid (60%). mp 197—201 °C (AcOEt). 1H-NMR (400 MHz, DMSO-d6, δ 1.43 (6H, s), 3.54—3.61 (2H, m), 3.67 (2H, s), 3.75—3.86 (2H, m), 7.02—7.09 (2H, m), 7.11 (1H, dd, J = 8.8, 2.5 Hz), 7.17 (1H, d, J = 2.5 Hz), 7.35—7.45 (2H, m), 7.83 (1H, d, J = 8.8 Hz), 8.45 (1H, s). FAB-MS m/z: 421 (M+H+). Anal. Calcld for C15H15N4O2F: C, 60.00; H, 4.80; N, 13.33; F, 18.08. Found: C, 59.98; H, 4.45; N, 13.71; F, 18.19.

(2Z)-4-[4-(3-Chlorophenyl)-6-fluoropiperidin-1-yl]-2-( trifluoromethyl)benzonitrile (18) The title compound was prepared from (2Z)-4-(2,5-dimethylpiperazin-1-yl)-2-(trifluoromethyl)benzonitrile (12) and 4-bromophenyl isocyanate in a manner similar to that described for compound 13 as a colorless solid (50%). mp 185 °C (MeOH). 1H-NMR (300 MHz, DMSO-d6, δ 1.10 (3H, d, J = 6.6 Hz), 1.53 (3H, d, J = 6.6 Hz), 3.28—3.47 (2H, m), 3.67—3.78 (1H, m), 3.82—3.92 (1H, m), 4.28—4.41 (1H, m), 4.43—4.56 (1H, m), 7.05 (2H, d, J = 8.8 Hz), 7.22—7.39 (4H, m), 7.84 (1H, d, J = 9.0 Hz), 8.46 (1H, s). FAB-MS m/z: 439 (M+H+). Anal. Calcld for C18H19N4O2F: C, 57.53; H, 4.37; N, 12.78; F, 21.67. Found: C, 57.51; H, 4.52; N, 12.74; F, 21.40.

(2Z)-4-[4-(3-Chlorophenyl)-6-fluoropiperidin-1-yl]-2-( trifluoromethyl)benzonitrile (19) The title compound was prepared from (2Z)-4-(2,5-dimethylpiperazin-1-yl)-2-(trifluoromethyl)benzonitrile (12) and 2,4-difluorophenyl isocyanate in a manner similar to that described for compound 13 as a colorless solid (82%). mp 185 °C (AcOEt/PrOr). 1H-NMR (400 MHz, DMSO-d6, δ 1.10 (3H, d, J = 6.6 Hz), 1.38 (3H, d, J = 6.6 Hz), 3.28—3.47 (2H, m), 3.67—3.78 (1H, m), 4.28—4.51 (2H, m), 6.96—7.07 (1H, m), 7.18—7.43 (4H, m), 7.84 (1H, d, J = 8.7 Hz), 8.39 (1H, s). FAB-MS m/z: 439 (M+H+). Anal. Calcld for C18H19N4O2F: C, 57.53; H, 4.37; N, 12.78; F, 21.67. Found: C, 57.51; H, 4.52; N, 12.74; F, 21.38.

Ethyl 1-[4-(3-Chlorophenyl)-6-(trifluoromethyl)piperidin-4-yl]carboxylate (1) A mixture of 4-fluoro-2-(trifluoromethyl)benzonitrile (6, 1.0 g, 5.29 mmol), ethyl piperidine-4-carboxylate (0.92 ml, 5.82 mmol) and K 2CO3 (1.1 g, 7.94 mmol) in DMF (50 ml) was stirred at ambient temperature for 17 h. The mixture was poured into water and the precipitate was filtered and washed with water to give the title compound (1, 51.8 g) as a colorless solid. 1H-NMR (400 MHz, DMSO-d6, δ 1.19 (3H, t, J = 7.1 Hz), 1.52—1.66 (2H, m), 1.85—1.97 (2H, m), 2.59—2.71 (1H, m), 3.01—3.17 (2H, m), 3.92—4.02 (2H, m), 4.08 (2H, d, J = 7.1 Hz), 7.24 (1H, dd, J = 8.8, 2.5 Hz), 7.30 (1H, d, J = 2.5 Hz), 7.81 (1H, d, J = 8.8 Hz). EI-MS m/z: 326 (M+).
Pd-C (36 mg) in MeOH (20 ml) was stirred under H2 at ambient temperature for 4 h. The residue was dissolved in CH2Cl2 (10 ml) and added to a cooled solution of 4-fluoroaniline (0.48 ml, 5.04 mmol) in CH2Cl2 (10 ml). After stirring at ambient temperature for 1 h, the precipitate was filtered off and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (n-hexane/AcOEt=1/1). The resulting solid was further purified by recrystallization from AcOEt to give the title compound (371 mg, 56%) as a colorless crystalline solid. mp 185—187 °C. H-NMR (400 MHz, DMSO-d6) δ 1.60—1.76 (2H, m), 1.83—1.96 (2H, m), 2.59—2.70 (1H, m), 2.96—3.13 (2H, m), 4.05—4.19 (2H, m), 7.09—7.18 (2H, m), 7.23—7.29 (1H, m), 7.30—7.35 (1H, m), 7.58—7.67 (2H, m), 7.82 (1H, d, J=8.8 Hz, 1H, m), 8.01 (1H, s). FAB-MS m/z: 392 (M+H+) . Anal. Calcld for C20H17N3OF4: C, 61.38; H, 4.38; N, 10.74; F, 19.42. Found: C, 61.42; H, 4.30; N, 10.72; F, 19.60.

tert-Butyl 4-[4-Cyano-3-( trifluoromethyl)phenyl]-3,6-dihydropridine-1(2H)-carboxylate (21, 10.0 g, 53.72 mmol) in 48% HBr (50 ml) was cooled in an ice- bath at 0 °C. A solution of sodium nitrite (3.71 g, 53.72 mmol) in water (10 ml) was added dropwise at such a rate that the temperature of the reaction mixture was below 10°C. After stirring for 1 h, the reaction mixture was poured into a solution of copper(I) bromide (7.71 g, 53.72 mmol) in 48% HBr (50 ml). The mixture was stirred at ambient temperature for 2 h. The reaction mixture was poured into ice-water and extracted with AcOEt. The organic layer was washed with saturated NaHCO3, H2O and concentrated in vacuo. The residue was purified by silica gel column chromatography (n-hexane/AcOEt=10/1) to give 4-bromo-2-( trifluoromethyl)benzonitrile (11.37 g, 85%) as a pale brown oil. A solution of n-BuLi in n-hexane (2.2 ml, 1.59 m, 3.48 mmol) was added dropwise to a solution of 4-bromo-2-( trifluoromethyl)benzonitrile (790 mg, 3.16 mmol) in dry THF (30 ml) at 78°C (N2 atmosphere). The reaction mixture was stirred for 15 min, and a solution of tert-butyl 4-oxo-piperidine-1-carboxylate (693 mg, 3.48 mmol) in dry THF (30 ml) was added to the reaction mixture at 78°C. After stirring at ambient temperature for 1 h, the reaction mixture was poured into ice-water and extracted with AcOEt. The organic layer was dried over Na2SO4, H2O and concentrated under reduced pressure. The precipitate was purified by silica gel column chromatography (CHCl3/MeOH=20/1) to give tert-butyl 4-[4-cyano-( trifluoromethyl)phenyl]-4-hydroxypiperidine-1-carboxylate (380 mg, 32%) as a pale brown solid. To a solution of tert-butyl 4-[4-(4-fluorophenyl)piperidine-1-carboxylate (1.27 g, 3.43 mmol) in pyridine (25 ml) was added phosphorus chloride (3.2 ml, 34.3 mmol) at 0°C. After stirring at ambient temperature for 1 d, the reaction mixture was quenched with saturated NaHCO3, and the resultant precipitate was filtered off and washed with H2O to give the title compound (973 mg, 81%) as a pale brown solid. H-NMR (300 MHz, DMSO-d6) δ 1.43 (9H, s), 2.47—2.58 (2H, m), 4.02—4.19 (2H, m), 6.52—6.60 (1H, m), 6.54—6.79 (1H, m), 7.90—8.00 (2H, m), 8.15 (1H, d, J=8.7 Hz). FAB-MS m/z: 353 (M+H+) .

tert-Butyl 4-[4-Cyano-3-( trifluoromethyl)phenyl] piperidine-1-carboxylate (22) A suspension of 4-amino-2-( trifluoromethyl)benzonitrile (21, 10.0 g, 53.72 mmol) in 48% HBr (50 ml) was cooled in an ice- bath at 0 °C. A solution of sodium nitrite (3.71 g, 53.72 mmol) in water (10 ml) was added dropwise at such a rate that the temperature of the reaction mixture was below 10°C. After stirring for 1 h, the reaction mixture was poured into ice-water and extracted with AcOEt. The organic layer was washed with saturated NaHCO3, H2O and concentrated in vacuo. The residue was purified by silica gel column chromatography (n-hexane/AcOEt=1/1) to give the title compound (550 mg, 76%) as a yellow oil. H-NMR (300 MHz, DMSO-d6) δ 1.42 (9H, s), 1.50—1.65 (2H, m), 1.72—1.85 (2H, m), 2.71—3.01 (3H, m), 3.99—4.17 (2H, m), 7.77—7.85 (1H, m), 7.88—7.93 (1H, m), 8.10 (1H, d, J=8.1 Hz). FAB-MS m/z: 355 (M+H+) .

4-[4-Cyano-( trifluoromethyl)phenyl]-N-(4-fluorophenyl)-3,6-dihydropyridine-1(2H)-carboxamide (24) To a cooling solution of tert-butyl 4-[4-cyano-3-( trifluoromethyl)phenyl]-3,6-dihydropridine-1(2H)-carboxylate (22, 274 mg, 2.05 mmol) and 10% Pd-C (36 mg) in MeOH (20 ml) was stirred under H2 at ambient temperature for 4 h. The precipitate was filtered off and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (n-hexane/AcOEt=1/1) to give the title compound (550 mg, 76%) as a yellow oil. H-NMR (300 MHz, DMSO-d6) δ 1.42 (9H, s), 1.50—1.65 (2H, m), 1.72—1.85 (2H, m), 2.71—3.01 (3H, m), 3.99—4.17 (2H, m), 7.77—7.85 (1H, m), 7.88—7.93 (1H, m), 8.10 (1H, d, J=8.1 Hz). FAB-MS m/z: 355 (M+H+) .
(±)-4-(4-Benzyl-2-ethylpiperazin-1-yl)-2-(trifluoromethyl)benzonitrile (31) 4-(4-Benzyl-3-oxopiperazin-1-yl)-2-(trifluoromethyl)benzonitrile was prepared from 1-benzylpiperazin-2-one in a manner similar to that described for compound 7 as a colorless solid (73%). A solution of 4-(4-benzyl-3-oxopiperazin-1-yl)-2-(trifluoromethyl)benzonitrile (2.0 g, 5.57 mmol) in dry THF (20 ml) was added dropwise to a solution of LDA (300 MHz, DMSO-d$_6$) at 0 °C for 5 h, the reaction mixture was quenched with MeOH dropwise to a solution of 4-(4-benzyl-2-ethyl-3-oxopiperazin-1-yl)-2-(trifluoromethyl)benzonitrile (1.50 g, 72%) as a yellow pale yellow. A solution of borane THF complex in THF (6.10 ml, 1.0 M, 6.10 mmol) was added dropwise to a solution of 4-(4-benzyl-2-ethyl-3-oxopiperazin-1-yl)-2-(trifluoromethyl)benzonitrile (1.47 g, 3.80 mmol) in dry THF (30 ml) at 0 °C. After stirring at 0 °C for 5 h, the reaction mixture was quenched with MeOH (10 ml) and 1% HCl (38 ml, 38 mmol) and concentrated in vacuo. The residue was neutralized by saturated NaHCO$_3$ and extracted with AcOEt. The organic layer was washed with H$_2$O and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane/AcOEt=2/1) to give 4-(2-ethylpiperazin-1-yl)-2-(trifluoromethyl)benzonitrile (31, 560 mg, 1.74 mmol) and 10% Pd-C (65 mg) in MeOH (20 ml) was stirred under 1 atm H$_2$ gas at ambient temperature for 7 h. The precipitate was filtered off and the filtrate was concentrated in vacuo. A solution of 4-(2-ethylpiperazin-1-yl)-2-(trifluoromethyl)benzonitrile (460 mg, 93%) as a pale yellow oil. $^1$H-NMR (300 MHz, DMSO-d$_6$) $\delta$ 6.07—7.77 (3H, m), 7.14—7.23 (1H, d, $J=7.3$ Hz), 7.26 (1H, d, $J=8.6$ Hz), 7.32—7.42 (2H, m), 7.44—7.53 (2H, m), 7.89 (1H, m). $^1$H-NMR (300 MHz, DMSO-d$_6$) $\delta$ 1.17 (6H, s), 2.30 (2H, s), 2.47—2.57 (2H, m), 3.23—3.33 (2H, m), 3.51 (2H, s), 7.14—7.39 (5H, m), 7.46—7.52 (2H, m), 7.95 (1H, d, $J=9.0$ Hz). FAB-MS $m/z$: 374 (M$^+$+H$^+$).

(±)-4-(4-Benzyl-2-isopropylpiperazin-1-yl)-2-(trifluoromethyl)benzonitrile (32) The title compound was prepared from 2-sodopropene in a manner similar to that described for compound 31 as a colorless oil (3 steps 56%). $^1$H-NMR (300 MHz, DMSO-d$_6$) $\delta$ 0.66 (3H, d, $J=6.6$ Hz), 0.81 (3H, d, $J=6.6$ Hz), 1.91—2.13 (2H, m), 2.47—2.63 (1H, m), 2.81—2.95 (2H, m), 3.16—3.40 (2H, m), 3.57 (1H, d, $J=13.2$ Hz), 3.75—3.93 (2H, m), 7.14—7.39 (7H, m), 7.73 (1H, d, $J=9.0$ Hz). FAB-MS $m/z$: 388 (M$^+$+H$^+$).

4-(Benzyl-2,2-dimethylpiperazin-1-yl)-2-(trifluoromethyl)benzonitrile (33) The title compound was prepared using 2 equivalents of LDA in dry THF (10 ml) at 78 °C. The reaction mixture was stirred for 20 min, and NaOH (0.76 g, 19.3 mmol) was added to the reaction mixture at −78 °C. The cold bath was removed and the reaction mixture was poured into saturated NH$_4$Cl at −10 °C and extracted with AcOEt. The organic layer was washed with H$_2$O and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane/AcOEt=10/1) to give the title compound (670 mg, 47%) as a pale yellow oil. $^1$H-NMR (300 MHz, DMSO-d$_6$) $\delta$ 0.67—7.37 (3H, m), 1.40—1.57 (1H, m), 1.76—1.92 (1H, m), 2.02—2.17 (2H, m), 2.77—2.97 (2H, m), 3.08—3.20 (1H, m), 3.40 (1H, d, $J=13.2$ Hz), 3.60 (1H, d, $J=13.2$ Hz), 3.73—3.86 (1H, m), 3.94—4.08 (1H, m), 7.12—7.42 (7H, m), 7.79 (1H, d, $J=8.7$ Hz). FAB-MS $m/z$: 374 (M$^+$+H$^+$).

(±)-4-(4-Benzyl-2-isopropylpiperazin-1-yl)-2-(trifluoromethyl)benzonitrile (34) A mixture of (±)-4-(4-benzyl-2-ethylpiperazin-1-yl)-2-(trifluoromethyl)benzonitrile (31, 650 mg, 1.74 mmol) and 10% Pd-C (65 mg) in MeOH (20 ml) was stirred under 1 atm H$_2$ gas at ambient temperature for 7 h. The precipitate was filtered off and the filtrate was concentrated in vacuo. A solution of 4-(2-ethylpiperazin-1-yl)-2-(trifluoromethyl)benzonitrile (460 mg, 93%) as a pale yellow oil. The title compound was prepared from (±)-4-(2-ethylpiperazin-1-yl)-2-(trifluoromethyl)benzonitrile in a manner similar to that described for compound 31 as a colorless powder (2 steps 21%). mp 179—180 °C (AcOEt/PtO$_2$). $^1$H-NMR (400 MHz, DMSO-d$_6$) $\delta$ 1.31 (6H, s), 3.52—3.61 (4H, m), 3.62—3.70 (2H, m), 7.03—7.12 (2H, m), 7.32—7.42 (2H, m), 7.44—7.53 (2H, m), 7.89 (1H, d, $J=8.3$ Hz), 8.46 (1H, s), FAB-MS $m/z$: 421 (M$^+$+H$^+$).

References