Organic & Biomolecular Chemistry

Electronic Supplementary Information

Tuning and predicting biological affinity: aryl-nitriles as cysteine protease inhibitors†

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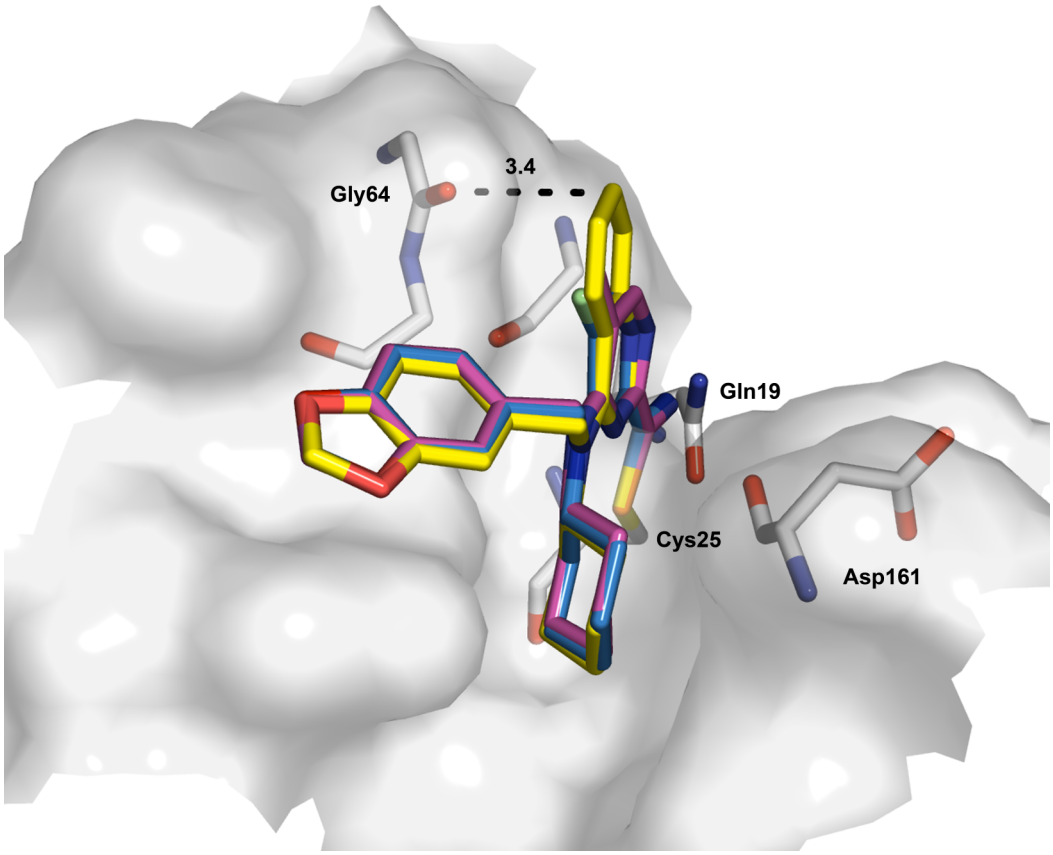


Fig. 1ESI Superimposition of 5-fluoro-substituted pyrimidine **4** (blue), quinazoline **6** (yellow) and methylpyrimidine **8** (magenta) in the active site of rhodesain (PDB code: 2P86, resolution 1.16 Å). The substituents on the aryl nitrile core are selected in a way that they do not undergo additional interactions with the enzyme possibly influencing the biological affinities. Bromo-derivative **5** is not shown in this overlay for clarity. Its binding mode, however, corresponds to the one depicted here. Colour code: C_{enyzme} grey, O red, N blue, S yellow. Distance is given in Å.

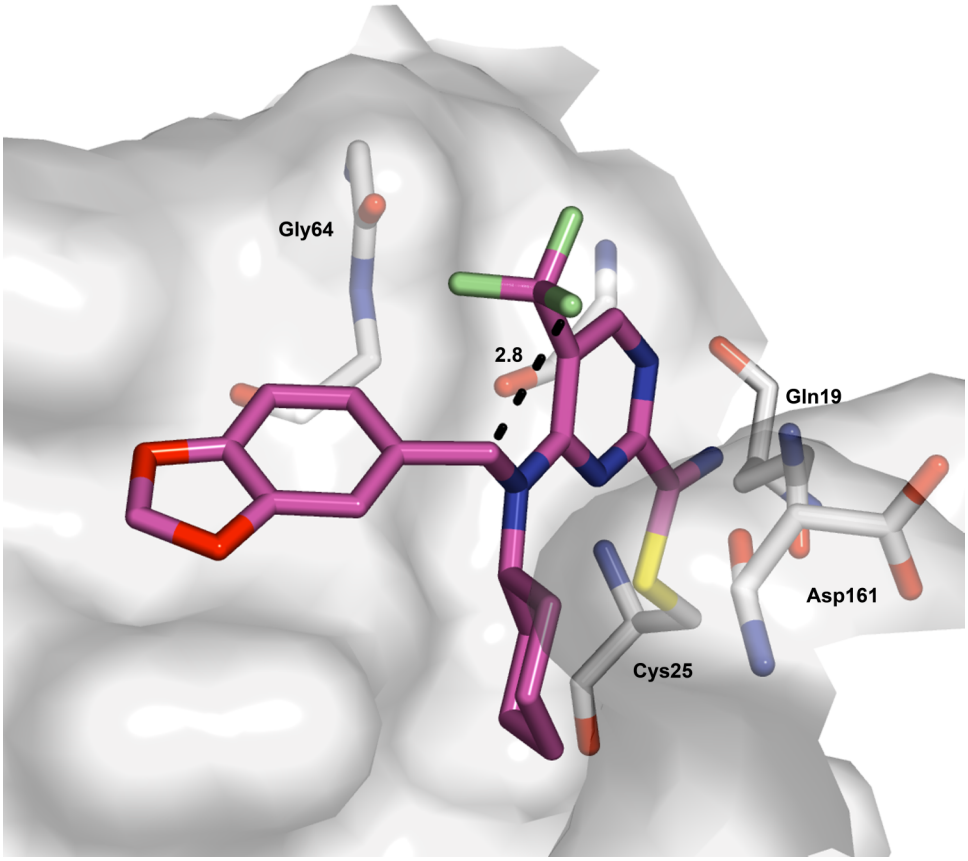
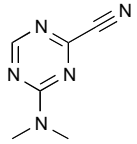
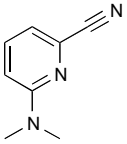
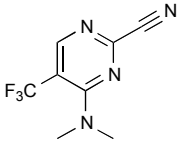
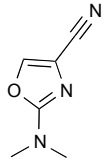
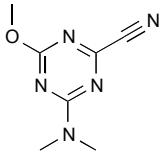
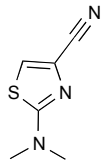
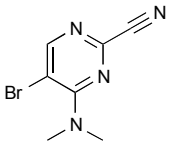
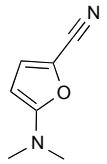
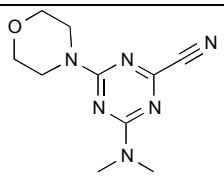
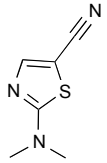
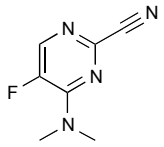
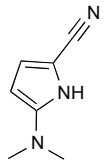
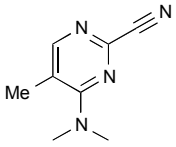
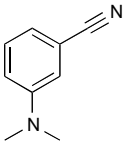
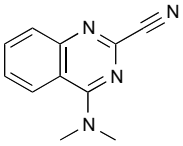
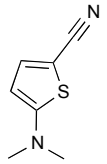
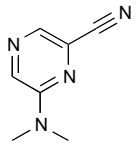


Fig. 2ESI Binding mode of trifluoromethylpyrimidine **7** in the active site of rhodesain (PDB code: 2P86, resolution 1.16 Å). The CF_3 group undergoes steric repulsion with the benzylic CH_2 group, which could influence the binding mode of **7** compared to the binding of the other ligands. This variation might explain the unexpectedly low affinity of **7** against both rhodesain and hCatL despite the calculated high electrophilicity of the nitrile head group. In this figure, the positioning of the S2 and S3 vectors based on lead compound **1** was constrained in the modeling to visualize the intramolecular repulsion. Colour code: C_{enyzme} grey, C_{ligand} magenta, O red, N blue, S yellow. Distance is given in Å.

DFT-calculations

All calculations were carried out using Gaussian 09 (for the full reference see page ESI-51). Optimisations were performed without geometric constraints at the B3LYP/6-311G(d,p) level of theory. To simulate the effect of solvent, in this case H_2O, the polarizable continuum method (PCM) was used. The electrophilicity index is defined as the difference between the formation enthalpy of the thioimidate adduct and the respective nitrile and methanethiol: $\Delta H_{\text{thioimidate}}-(\Delta H_{\text{nitrile}} + \Delta H_{\text{methanethiol}})$. The electrophilicity is given in kJ mol^{-1}. The values obtained give only thermodynamic information within the model reaction and therefore should only be used to qualitatively arrange or rank the aryl nitriles.

Table 1ESI Extended electrophilicity scale of all aromatic nitriles with theoretical electrophilicities as obtained by DFT calculations given in kJ mol^{-1}. Very negative values indicate high electrophilicity and small negative values poor electrophilicity.

structure	electrophilicity	structure	electrophilicity
	–42.3		–22.6
	–39.8		–22.2
	–39.4		–20.9
	–37.3		–16.5
	–36.8		–4.6
	–35.2		–4.2
	–34.3		–2.5
	–33.1		–1.2
	–27.2		

Biological assays

Enzyme assays: Assays with rhodesain and human cathepsin L (hCatL) were performed as described previously.[1,2] An initial screen was performed to identify compounds with an inhibition higher than 35% at an inhibitor concentration of 20 μM. For active compounds, continuous assays with progress curve methods[3] were carried out to determine the corresponding inhibition constants K_i. For the determination of the dissociation constants, inhibitors were used at seven different inhibitor concentrations spanning from weak to nearly total inhibition of the enzyme. Fluorescence increase resulting from hydrolysis of the substrate Z-Phe-Arg-AMC (AMC = 7-amino-4-methylcoumarin) was measured over a period of 10 min. The residual enzyme activities v_i for various inhibitor concentrations were fitted against the inhibitor concentrations using a 2-parameter IC_{50} equation. The true K_i values were calculated by correction to zero substrate concentration using the Cheng-Prusoff equation $K_i = IC_{50}/(1 + [S]/K_m])$ with K_m(rhodesain) = 830 nM and K_m(hCatL) = 6.5 μM.[4] Inhibitory constants are average values of at least two independent assays, each performed in duplicate. *GraFit*® software version 5.0.13 (*Erithacus Software Ltd*., UK, 2006) was used to calculate the inhibitory constants.

Cytotoxicity: Rat skeletal myoblasts (L-6 cells) in RPMI 1640 medium with 10% FCS and 2 mM L-glutamine were added to each well of a 96-well microtiter plate and incubated at 37 °C under a 5% CO_2 atmosphere for 24 h. Compounds were added directly into the wells and subsequently serial drug dilutions were prepared covering a range from 100–0.002 μM. The plates were incubated for another 72 h. 10 mm^3 of Alamar Blue (12.5 mg resazurin dissolved in 100 cm^3 H_2O) were then added to each

well and incubation continued for a further 1–4 h. The plates were read with a *Spectramax Gemini XS* microplate fluorometer (*Molecular Devices Cooperation*, Sunnyvale, CA, USA) using an excitation wavelength of 536 nm and an emission wavelength of 588 nm. Data were analysed using the software *Softmax Pro* (*Molecular Devices Cooperation*, Sunnyvale, CA, USA). Decrease of fluorescence (= inhibition) was expressed as percentage of the fluorescence of control cultures and plotted against the drug concentrations. From the sigmoidal inhibition curves, the IC_{50} values were calculated. Podophyllotoxin was used as positive control in the assay (IC_{50} = 0.0082 μM).

Synthesis

Materials and methods

Solvents and reagents were purchased from *Acros*, *Aldrich* and *Fluka* at reagent-grade and used without further purification. All reactions were carried out in oven-dried glassware and under argon atmosphere unless otherwise stated. Solvents for extraction or flash column chromatography (FC) were of technical quality and distilled before use. Dry solvents for reactions were purified by a solvent drying system from *LC Technology Solutions Inc. SP-105* under nitrogen atmosphere (H_2O content < 10 ppm as determined by *Karl-Fischer* titration). Other solvents were purchased in *p.a.* quality. All products were dried under high vacuum (10^{-2} Torr) before analytical characterisation. Thin-layer chromatography was carried out on glass plates coated with SiO_2-60 UV_{254} from *Merck*. Visualisation was achieved by UV light at 245 nm. Flash column chromatography (FC) was perfomed using SiO_2-60 (230–400 mesh, particle size 0.040-0.063 mm) from *Fluka* with a head pressure of 0.1–0.4 bar. The used eluent compositions are reported in parentheses for each compound. Liquid chromatography/mass spectrometry (LC/MS) for reaction control was performed on an *Ultimate 3000* series LC instrument combined with a *MSQ Plus* mass spectrometer from *Dionex*, using *Zorbax Eclipse Plus C18* columns (30 x 3 mm; 3.5 µm pore size) from *Agilent*. Melting points (mp) were determined on a *Büchi B-540* capillary melting point apparatus and are uncorrected. IR Spectra were recorded on a *Perkin-Elmer FT-IR 1600* spectrometer (*ATR-unit, Attenuated Total Reflection*). The spectra were measured between 4000–600 cm^{-1}, and absorption bands are reported in wavenumbers (cm^{-1}). NMR spectra (^{1}H, ^{13}C and ^{19}F) were measured on a *Varian Gemini-300*, *Mercury-300*, *Bruker ARX-300, AV-400* or *DRX-400* spectrometer at

298 K using the solvent peak as an internal reference. Coupling constants (*J*) are given in Hz. The resonance multiplicity is described as s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). Broad signals are abbreviated with br. All assignments of proton and carbon signals are based on HSQC spectra. High-resolution mass spectroscopy spectra were measured on a *Bruker maXis ESI-Q-TOF* (HR-ESI-MS) spectrometer. The relevant signals are reported in *m/z* units and relative intensities given in parenthesis. Elemental analyses were performed by the Mikrolabor at the Laboratorium für Organische Chemie, ETH Zürich. Nomenclature follows the suggestions of the computer program *ACD/Name 9* (*Advanced Chemistry Development Inc.*).

For some triazine derivatives, rotamers could be observed in the ^{1}H and ^{13}C NMR spectra as their interconversion was sufficiently slow on the NMR time scale. These cases are mentioned with the individual compounds. The rotational barrier of triazine **1** was determined exemparily by variable temperature NMR studies (see page ESI-11).[5]

Synthetic protocols for ligands 1–12

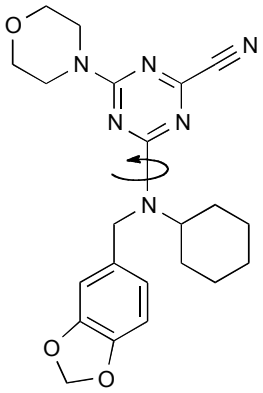
General Procedure A (GP-A) for the S_NAr-reaction of pyrimidines with a secondary amine:

Substituted 2-chloropyrimidines (1.0 equiv.) were dissolved in ^{i}PrOH and treated with **13** (1.0 equiv.) and $^{i}Pr_2NEt$ (1.0 to 1.3 equiv.). The mixture was stirred at 80 °C overnight. After cooling to 25 °C, the solvent was removed and the residue purified by FC according to experimental details mentioned individually for each compound.

General Procedure B (GP-B) for the cyanation reaction of aryl-chlorides using KCN:

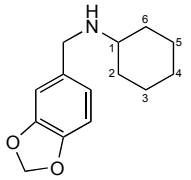
Chloro-substituted triazines, pyrimidines or quinazolines (1 equiv.) were suspended in Me_2SO or in Me_2SO/H_2O (9:1) and treated with KCN (1.1 to 2.0 equiv.). In the case of pyrimidines, 1,4-diazabicyclo[2.2.2]octane (DABCO, 1.0 equiv.) was added. The mixture was heated to 120 °C in a sealed tube and stirred at this temperature overnight. After cooling to 25 °C, the mixture was diluted with EtOAc and washed thoroughly with brine (3–5 times). The organic layer was separated, dried over Na_2SO_4 or $MgSO_4$, filtered and evaporated. The residue was purified by FC according to experimental details mentioned individually for each compound.

Rotational isomerism of triazine 1



Variable temperature ^{1}H NMR studies were conducted for triazine **1**. The rate constants were determined between 80–120 °C. Coalescence was observed at 120 °C. Data for $\Delta S^{\ddagger}$ and $\Delta H^{\ddagger}$ were calculated using the statistical mechanics model proposed by Eyring.[7] The activation parameters for the rotation around the indicated C–N bond were determined as $\Delta H^{\ddagger} = 74.9$ kJ mol^{-1} and $\Delta S^{\ddagger} = 1.7$ J mol^{-1} K^{-1}. These values are in agreement to literature data for various triazine rotamers.[5] The hindered internal rotation of the alkylamino groups bonded to the electron-deficient triazine is due to an increased bond order of the C–N bond. The triazine π-system interacts significantly with the lone pair of the nitrogen to give a barrier comparable to that of formamide.[5]

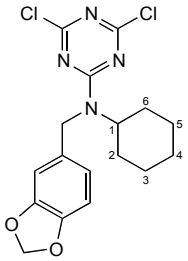
_N_-(1,3-Benzodioxol-5-ylmethyl)cyclohexanamine (13)[6]



A solution of cyclohexanone (3.42 cm^3, 33.08 mmol) in CH_2Cl_2 (80 cm^3) over molecular sieves (4 Å) was treated with piperonylamine (4.13 cm^3, 33.08 mmol) at 25 °C. The mixture was stirred at this temperature for 1.5 h. $NaBH(OAc)_3$ (17.53 g, 66.16 mmol) was added in one portion and the mixture stirred for 17 h at 25 °C. The suspension was diluted with EtOAc (120 cm^3) and filtered. After washing with a saturated aqueous solution of $NaHCO_3$ (3 x 150 cm^3), the organic layer was separated, dried over Na_2SO_4, filtered and evaporated. Purification by FC (SiO_2; EtOAc) gave **13** as a pale yellow oil (6.35 g, 82%).

$\tilde{\nu}_{max}$(neat)/cm^{-1} 2924, 2851, 1673, 1608, 1501, 1488, 1439, 1365, 1244, 1183, 1110, 1037, 927, 888, 860, 805, 770, 728, 713, 651; δ_H(300 MHz; $CDCl_3$) 1.02–1.31 (6 H, m, H–C(3,4,5)), 1.57–1.74 (2 H, m, H_{ax}–C(2,6)), 1.86–1.90 (2 H, m, H_{eq}–C(2,6)), 2,44 (1 H, tt, *J* 10.0, 3.7, H–C(1)), 3.69 (2 H, s, CH_2NH), 5.90 (2 H, s, CH_2O), 6.70–6.73 (2 H, m), 6.81 (1 H, s); δ_C(100 MHz; $CDCl_3$) 24.99 (2 C, C(3,5)), 26.20 (C(4)), 33.57 (2 C, C(2,6)), 50.79 (CH_2NH), 55.97 (C(1)), 100.80 (CH_2O), 108.02 (arom. CH), 108.64 (arom. CH), 121.02 (arom. CH), 135.07 (arom. C), 146.32 (arom. C), 147.64 (arom. C); HR-ESI-MS *m/z* calc. for $C_{14}H_{19}NNaO_2^+$ (100, $[M + Na]^+$): 256.1308; found: 256.1297.

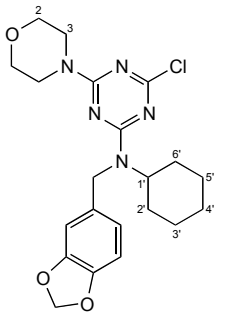
_N_-(1,3-Benzodioxol-5-ylmethyl)-4,6-dichloro-_N_-cyclohexyl-1,3,5-triazin-2-amine (19)



A solution of cyanuric chloride (715 mg, 3.88 mmol) and **13** (905 mg, 3.88 mmol) in CH_2Cl_2 (15 cm^3) was treated with $^iPr_2NEt$ (668 mm^3, 3.88 mmol) at 0 °C. The mixture was stirred at this temperature for 4 h. The solvent was removed and the residue purified by FC (cyclohexane/EtOAc 10:1) to give **19** (1.18 g, 80%) as a white solid.

mp 110–111 °C; elemental analysis found: C, 53.39; H, 4.84; N, 14.80; calc. for $C_{17}H_{18}Cl_2N_4O_2$: C, 53.56; H, 4.76; N, 14.70%; $\tilde{\nu}_{max}$(neat)/cm^{-1} 2934, 2860, 1711, 1608, 1557, 1503, 1488, 1470, 1462, 1448, 1373, 1350, 1319, 1288, 1257, 1244, 1228, 1179, 1156, 1132, 1117, 1096, 1071, 1056, 1037, 1005, 970, 939, 925, 919, 895, 839, 817, 803, 793, 769, 715, 660, 637; δ_H(300 MHz; $CDCl_3$) 1.01–1.21 (6 H, m, H–C(3,4,5)), 1.54–1.81 (4 H, m, H–C(2,6)), 4.44 (1 H, tt, *J* 11.7, 3.5, H–C(1)), 4.72 (2 H, s, CH_2N), 5.94 (2 H, s, CH_2O), 6.65–6.75 (3 H, m); δ_C(100 MHz; $CDCl_3$) 25.30 (C(4)), 25.68 (2 C, C(3,5)), 30.45 (2 C, C(2,6)), 46.89 (CH_2N), 57.17 (C(1)), 101.10 (CH_2O), 107.34 (arom. CH), 108.22 (arom. CH), 120.38 (arom. CH), 131.24 (arom. C), 146.85 (arom. C), 147.81 (arom. C), 165.00 (NCN), 169.98 (CCl), 170.04 (CCl); HR-ESI-MS *m/z* calc. for $C_{17}H_{19}{}^{37}Cl_2N_4O_2^+$ (56, $[M+H]^+$): 383.0851, found: 383.0846; calc. for $C_{17}H_{19}{}^{35}Cl^{37}ClN_4O_2^+$ (18, $[M+H]^+$): 382.0914, found: 382.0911; calc. for $C_{17}H_{19}{}^{35}Cl_2N_4O_2^+$ (100, $[M+H]^+$): 381.0880, found: 381.0874.

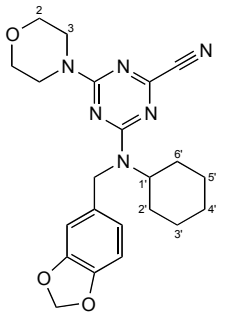
_N_-(1,3-Benzodioxol-5-ylmethyl)-4-chloro-_N_-cyclohexyl-6-(morpholin-4-yl)-1,3,5-triazin-2-amine (20)



A solution of **19** (150 mg, 0.393 mmol) and morpholine (34 mm^3, 0.393 mmol) in CH_2Cl_2 (4 cm^3) was treated with $^iPr_2NEt$ (68 mm^3, 0.393 mmol) at 0 °C. The mixture was stirred at 0 °C for 4 h and at 25 °C for 17 h. The solvent was removed and the residue purified by FC (SiO_2; cyclohexane/EtOAc 10:1) to give **20** (143 mg, 84%) as a colourless oil.

$\tilde{\nu}_{max}$(neat)/cm^{-1} 2928, 2854, 1736, 1556, 1478, 1439, 1367, 1302, 1213, 1163, 1146, 1114, 1037, 1004, 989, 967, 925, 894, 870, 855, 799, 769, 733, 667, 613; δ_H(300 MHz; $CDCl_3$; mixture of rotamers) 1.00–1.48 (6 H, m, H–C(3',4',5')), 1.53–1.78 (4 H, m, H–C(2',6')), 3.56–3.79 (8 H, m, H–C(2,3)), 4.26–4.35 and 4.36–4.40 (1 H, br m, H–C(1')), 4.54 and 4.71 (2 H, s, CH_2N), 5.93 (2 H, s, CH_2O), 6.64–6.74 (3 H, m); δ_C(100 MHz; $CDCl_3$; mixture of rotamers) 25.51 (CH_2), 25.61 (CH_2), 25.74 (CH_2), 26.14 (CH_2), 30.54 (CH_2), 30.93 (CH_2), 43.82 (2 C, C(3)), 46.16 (CH_2N), 55.20 and 56.54 (C(1')), 66.68 (2 C, C(2)), 101.92 (CH_2O), 107.24 (arom. CH), 107.94 (arom. CH), 119.60 and 120.31 (arom. CH), 133.48 and 133.61 (arom. C), 147.18 (arom. C), 147.60 (arom. C), 164.43 (NCN), 165.13 (NCN), 170.00 (CCl); HR-ESI-MS _m/z_ calc. for $C_{21}H_{27}{}^{37}ClN_5O_3{}^+$ (35, $[M + H]^+$): 434.1773, found: 434.1788; calc. for $C_{21}H_{27}{}^{35}ClN_5O_3{}^+$ (100, $[M + H]^+$): 432.1797, found: 432.1803.

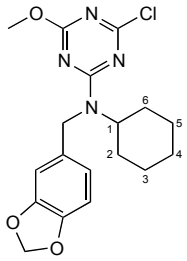
4-[(1,3-Benzodioxol-5-ylmethyl)(cyclohexyl)amino]-6-(morpholin-4-yl)-1,3,5-triazine-2-carbonitrile (1)



GP-B starting from **20** (123 mg, 0.323 mmol) and KCN (25 mg, 0.387 mmol) in Me_2SO (4 cm^3). Purification by FC (SiO_2; cyclohexane/EtOAc 10:1) gave **1** (108 mg, 79%) as a white foam.

$\tilde{\nu}_{max}$(neat)/cm^{-1} 2928, 2857, 1611, 1561, 1486, 1461, 1442, 1428, 1372, 1303, 1290, 1246, 1233, 1188, 1143, 1111, 1093, 1069, 1036, 1008, 969, 938, 925, 905, 894, 864, 820, 805, 791, 769, 736, 705, 674; δ_H(400 MHz; $CDCl_3$; mixture of rotamers) 1.04–1.50 (6 H, m, H–C(3',4',5')), 1.68–1.81 (4 H, m, H–C(2',6')), 3.58–3.83 (8 H, m, H–C(2,3)), 4.30 (0.4 H, tt, *J* 11.8, 3.2, H–C(1')), 4.54–4.60 (0.6 H, m, H–C(1')), 4.63 and 4.72 (2 H, s, CH_2N), 5.95 (2 H, 2 s, CH_2O), 6.60–6.75 (3 H, m); δ_C(100 MHz; $CDCl_3$; mixture of rotamers) 25.46 (CH_2), 25.55 (CH_2), 25.77 (CH_2), 25.08 (CH_2), 30.38 (CH_2), 30.90 (CH_2), 43.43 (C(3)), 43.91 (C(3)), 46.07 (CH_2N), 55.59 and 56.36 (C(1')), 66.36 and 66.65 (C(2)), 100.97 (CH_2O), 107.17 (arom. CH), 108.01 (arom. CH), 115.72 (CN), 119.63 (arom. CH), 120.20 (arom. CH), 133.00 and 133.09 (arom. C), 146.30 and 146.51 (arom. C), 147.66 (arom. C), 151.84 and 152.01 (*C*CN), 163.49 and 163.56 (NCN), 164.15 (NCN); HR-ESI-MS *m/z* calc. for $C_{22}H_{27}N_6O_3^+$ (100, $[M + H]^+$): 423.2139, found: 423.2138.

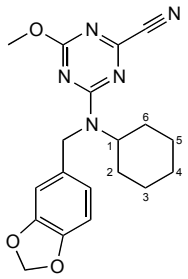
_N_-(1,3-Benzodioxol-5-ylmethyl)-4-chloro-_N_-cyclohexyl-6-methoxy-1,3,5-triazin-2-amine (21)



A solution of 2,6-dichloro-3-methoxy-1,3,5-triazine (200 mg, 1.118 mmol) in CH_2Cl_2 (6 cm^3) was treated with **13** (210 mg, 1.118 mmol) and $^iPr_2NEt$ (260 mm^3, 1.118 mmol) at 0 °C. The mixture was stirred at 25 °C for 2.5 h. The solvent was evaporated and the residue purified by FC (SiO_2; pentane/Et_2O 7:1 → 5:1) to give **21** (285 mg, 68%) as a colourless oil.

$\tilde{\nu}_{max}$(neat)/cm^{-1} 2931, 2857, 2778, 2243, 1865, 1712, 1565, 1542, 1498, 1488, 1466, 1442, 1365, 1326, 1303, 1284, 1232, 1162, 1144, 1095, 1038, 1004, 973, 912, 895, 867, 806, 770, 730, 685, 666, 647; δ_H(400 MHz; $CDCl_3$; mixture of rotamers) 0.95–1.57 (6 H, m, H–C(3,4,5)), 1.57–1.93 (4 H, m, H–C(2,6)), 3.84 and 4.00 (3 H, s, OMe), 4.43 and 4.57 (1 H, tt, _J_ 11.7, 3.6, H–C(1)), 4.71 and 4.75 (2 H, s, CH_2N), 5.93 and 5.94 (2 H, s, CH_2O), 6.61–6.79 (3 H, m); δ_C(100 MHz; $CDCl_3$; mixture of rotamers) 25.41 and 25.45 (C(4)), 25.70 and 25.89 (2 C, C(3,5)), 30.51 and 30.67 (2 C, C(2,6)), 46.45 and 46.62 (CH_2N), 54.98 and 55.01 (OMe), 56.80 (C(1)), 100.99 (CH_2O), 107.24 and 107.74 (arom. CH), 108.07 (arom. CH), 119.79 and 120.33 (arom. CH), 132.42 and 132.45 (arom. C), 146.47 and 146.61 (arom. C), 146.69 and 147.71 (arom. C), 165.25 (CCl), 170.68 and 170.72 (_C_OMe), 170.81 (NCN); HR-ESI-MS _m/z_ calc. for $C_{18}H_{22}{}^{37}ClN_4O_3^+$ (34, $[M + H]^+$): 379.1346, found: 379.1357; calc. for $C_{18}H_{22}{}^{35}ClN_4O_3^+$ (100, $[M + H]^+$): 377.1375, found: 377.1386.

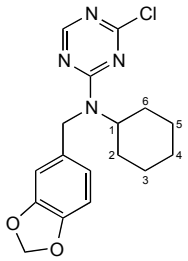
4-[(1,3-Benzodioxol-5-ylmethyl)(cyclohexyl)amino]-6-methoxy-1,3,5-triazine-2-carbonitrile (2)



GP-B starting from **21** (119 mg, 0.316 mmol) and KCN (25 mg, 0.380 mmol) in Me_2SO (3 cm^3). Purification by FC (SiO_2; cyclohexane/EtOAc 20:1 → 8:1) gave **2** (120 mg, 44%) as a colourless oil.

$\tilde{\nu}_{max}$(neat)/cm^{-1} 2934, 2815, 2251, 1858, 1720, 1565, 1503, 1490, 1469, 1445, 1380, 1358, 1326, 1242 , 1071, 1040, 977, 909, 811, 732; δ_H(400 MHz; $CDCl_3$; mixture of rotamers) 0.96–1.17 (1 H, m, H_{ax}–C(4)), 1.21–1.59 (4 H, m, H–C(3,5)), 1.59–1.96 (5 H, m, H–C(2,6), H_{eq}–C(4)), 3.87 and 4.03 (3 H, s, OMe), 4.43 and 4.57 (1 H, tt, *J* 11.7, 3.6, H–C(1)), 4.73 and 4.77 (2 H, s, CH_2N), 5.96 and 5.97 (2 H, s, CH_2O), 6.62–6.71 (2 H, m), 6.71–6.79 (1 H, m); δ_C(100 MHz; $CDCl_3$; mixture of rotamers) 25.34 and 25.40 (C(4)), 25.70 and 25.84 (2 C, C(3,5)), 30.35 and 30.65 (2 C, C(2,6)), 46.49 and 46.87 (CH_2N), 55.12 and 55.15 (OMe), 56.66 and 56.85 (C(1)), 101.07 (CH_2O), 107.17 and 107.54 (arom. CH), 108.18 (arom. CH), 114.85 and 114.97 (CN), 119.83 and 120.24 (arom. CH), 131.78 and 131.81 (arom. C), 146.63 and 146.77 (arom. C), 147.80 (arom. C), 153.19 and 153.30 (*C*CN), 165.61 and 165.66 (*C*OMe), 170.46 and 170.48 (NCN); HR-ESI-MS *m/z* calc. for $C_{19}H_{22}N_5O_3^+$ (100, $[M+H]^+$): 368.1717, found: 368.1722.

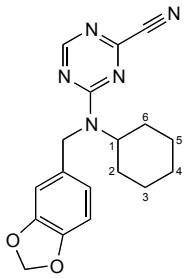
_N_-(1,3-Benzodioxol-5-ylmethyl)-4-chloro-_N_-cyclohexyl-1,3,5-triazin-2-amine (22)



A solution of 2,4-dichlorotriazine (200 mg, 1.334 mmol) and **13** (311 mg, 1.334 mmol) in CH_2Cl_2 (5 cm^3) was treated with $^iPr_2NEt$ (230 mm^3, 1.334 mmol) at 0 °C. The mixture was stirred at this temperature for 2.5 h. The solvent was removed and the residue purified by FC (cyclohexane/EtOAc 15:1 → 10:1) to give **22** (270 mg, 58%) as a colourless oil.

$\tilde{\nu}_{max}$(neat)/cm^{-1} 2931, 2856, 1561, 1526, 1485, 1441, 1392, 1368, 1349, 1287, 1237, 1194, 1151, 1136, 1117, 1094, 1063, 1038, 1004, 974, 924, 861, 804, 769, 751, 730, 647; δ_H(400 MHz; $CDCl_3$; mixture of rotamers) 1.04–1.15 (1 H, m, H_{ax}–C(4)), 1.31–1.53 (4 H, m, H–C(3,5)), 1.65–1.81 (5 H, m, H–C(2,6), H_{eq}–C(4)), 4.52 (1 H, tt, J 11.7, 3.6, H–C(1)), 4.73 and 4.76 (2 H, s, CH_2N), 5.94 (2 H, s, CH_2O), 6.64–6.76 (3 H, m), 8.35 and 8.41 (1 H, s); δ_C(100 MHz; $CDCl_3$; mixture of rotamers) 25.04 (CH_2), 25.38 (CH_2), 25.69 and 25.81 (CH_2), 30.40 and 30.55 (CH_2), 46.24 and 46.42 (CH_2N), 56.07 and 56.71 (C(1)), 101.02 and 101.04 (CH_2O), 107.27 (arom. CH), 107.70 (arom. CH), 108.13 (arom. CH), 108.18 (arom. CH), 119.77 (arom. CH), 120.34 (arom. CH), 131.77 and 131.93 (arom. C), 146.65 and 146.67 (arom. C), 147.72 and 147.79 (arom. C), 164.77 (arom. CCl), 164.81 (arom. CCl), 166.37 and 166.62 (arom. CH), 170.04 and 170.14 (NCN); HR-ESI-MS _m/z_ calc. for $C_{17}H_{20}{}^{37}ClN_4O_2^+$ (34, $[M+H]^+$): 349.1245, found: 349.1247; calc. for $C_{17}H_{20}{}^{35}ClN_4O_2^+$ (100, $[M+H]^+$): 347.1269, found: 347.1266.

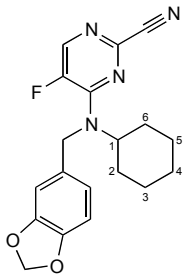
4-[(1,3-Benzodioxol-5-ylmethyl)(cyclohexyl)amino]-1,3,5-triazine-2-carbonitrile (3)



GP-B starting from **22** (80 mg, 0.231 mmol) and KCN (20 mg, 0.300 mmol) in Me_2SO (2 cm^3). Purification by FC (SiO_2; pentane/EtOAc 10:1) gave **3** (25 mg, 32%) as a pale yellow oil.

$\tilde{\nu}_{max}$(neat)/cm^{-1} 2930, 2856, 2332, 1565, 1530, 1489, 1442, 1403, 1383, 1347, 1239, 1187, 1137, 1095, 1038, 976, 926, 895, 812, 770, 732, 646; δ_H(300 MHz; $CDCl_3$; mixture of rotamers) 0.83–1.83 (10 H, m, H–C(2–6)), 4.43–4.54 (1 H, m, H–C(1)), 4.72 and 4.75 (2 H, s, CH_2N), 5.94 (2 H, s, CH_2O), 6.61–6.75 (3 H, m), 8.54 and 8.60 (1 H, s); δ_C(100 MHz; $CDCl_3$; mixture of rotamers) 25.32 (CH_2), 25.68 (CH_2), 25.76 (CH_2), 30.36 (2 C), 46.40 and 46.46 (CH_2N), 56.50 and 56.71 (C(1)), 101.11 (CH_2O), 107.24 (arom. CH), 107.46 (arom. CH), 108.25 (arom. CH), 108.27 (arom. CH), 114.81 and 114.94 (CN), 119.84 (arom. CH), 120.23 (arom. CH), 131.24 (arom. C), 131.27 (arom. C), 146.80 (arom. C), 146.83 (arom. C), 147.83 (arom. C), 147.87 (arom. C), 152.21 and 152.41 (*C*CN), 163.44 (NCN), 166.20 and 166.48 (arom. CH); HR-ESI-MS *m/z* calc. for $C_{18}H_{20}N_5O_2^+$ (100, $[M + H]^+$): 338.1612, found: 338.1624.

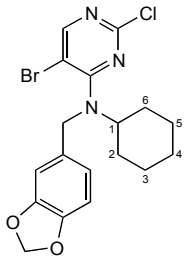
4-[(1,3-Benzodioxol-5-ylmethyl)(cyclohexyl)amino]-5-fluoro-pyrimidine-2-carbonitrile (4)



A solution of 2,4-dichloro-5-fluoropyrimidine (500 mg, 2.994 mmol) and **13** (699 mg, 2.994 mmol) in ^{i}PrOH (5 cm^3) was treated with $^{i}Pr_2NEt$ (516 mm^3, 2.994 mmol) at 25 °C. The mixture was stirred at 80 °C for 13 h. The solvent was evaporated and the residue filtered through a silica plug and evaporated. The obtained oily residue (280 mg, 0.770 mmol) was used directly in the cyanation step (GP-B) with KCN (55 mg, 0.847 mmol) and DABCO (86 mg, 0.770 mmol) in Me_2SO/H_2O (9:1, 3 cm^3). Purification by FC (SiO_2; pentane/EtOAc 10:1 → 5:1) gave **4** (120 mg, 44%) as a pale yellow oil.

$\tilde{\nu}_{max}$(neat)/cm^{-1} 2932, 2857, 1586, 1545, 1503, 1489, 1443, 1407, 1371, 1321, 1239, 1183, 1118, 1093, 1037, 1002, 953, 925, 895, 852, 807, 769, 732, 656; δ_H(400 MHz; $CDCl_3$) 0.85–1.83 (10 H, m, H–C(2–6)), 4.41–4.49 (1 H, m, H–C(1)), 4.70 (2 H, s, CH_2N), 5.96 (2 H, s, CH_2O), 6.63–6.75 (3 H, m), 8.01 (1 H, d, $^3J_{HF}$ 6.6); δ_C(100 MHz; $CDCl_3$) 25.31 (C(4)), 25.74 (2 C, C(3,5), 30.95 (2 C, C(2,6)), 47.63 (d, $^4J_{CF}$ 6.8, CH_2N), 55.12 (d, $^4J_{CF}$ 6.2 Hz, C(1)), 101.11 (CH_2O), 106.88 (arom. CH), 108.25 (arom. CH), 116.73 (CN), 119.50 (arom. CH), 132.21 (arom. C), 139.31 (d, $^4J_{CF}$ 5.9, *C*CN), 142.74 (d, $^3J_{CF}$ 27.5, arom. CH_{pyr}), 146.66 (arom. C), 146.81 (d, $^1J_{CF}$ 265.6, arom. CF), 147.88 (arom. C), 152.18 ($^2J_{CF}$ 5.2, NCN); δ_F(367 MHz; $CDCl_3$) –138.84 (s, arom. CF); HR-ESI-MS *m/z* calc. for $C_{19}H_{20}FN_4O_2^+$ (100, $[M + H]^+$): 355.1565, found: 355.1569.

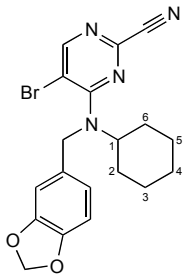
4-[(1,3-Benzodioxol-5-ylmethyl)(cyclohexyl)amino]-6-(morpholin-4-yl)-1,3,5-triazine-2-carbonitrile (14)



GP-A starting from 5-bromo-2,4-dichloropyrimidine (168 mm^3, 1.317 mmol), **13** (307 mg, 1.317 mmol) and $^{i}Pr_2NEt$ (294 mm^3, 1.712 mmol) in $^{i}PrOH$ (8 cm^3). Purification by FC (SiO_2; cyclohexane/EtOAc 20:1) gave **14** (471 mg, 84%) as a pale yellow oil.

$\tilde{\nu}_{max}$(neat)/cm^{-1} 2929, 2855, 1547, 1500, 1488, 1468, 1441, 1362, 1323, 1236, 1186, 1152, 1131, 1112, 1093, 1037, 1008, 995, 926, 894, 870, 855, 805, 778, 757, 725, 684, 646, 621; δ_H(400 MHz; $CDCl_3$) 1.05–1.69 (6 H, m, H–C(3,4,5)), 1.82–1.94 (4 H, m, H–C(2,6)), 4.27 (1 H; tt, *J* 11.7, 3.5, H–C(1)), 4.59 (2 H, s, CH_2N), 5.90 (2H, s, CH_2O), 6.67–6.74 (3 H, m), 8.18 (1 H, s); δ_C(100 MHz; $CDCl_3$) 25.39 (CH_2), 25.93 (CH_2), 26.92 (CH_2), 31.40 (2 C, C(2,6)), 47.14 (CH_2N), 59.93 (C(1)), 100.93 (CH_2O), 104.20 (CBr), 107.96 (arom. CH), 108.15 (arom. CH), 121.06 (arom. CH), 132.46 (arom. C), 146.45 (arom. C), 147.56 (arom. C), 157.83 (CCl), 161.24 (arom. CH_{pyr}), 161.74 (NCN); HR-ESI-MS *m/z* calc. for $C_{18}H_{20}{}^{81}Br^{37}ClN_3O_2^+$ (32, $[M+H]^+$): 428.0379, found: 428.0375; calc. for $C_{18}H_{20}{}^{79}Br^{37}ClN_3O_2^+$ and $C_{18}H_{20}{}^{81}Br^{35}ClN_3O_2^+$ (100, $[M+H]^+$): 426.0398, found: 426.0404; calc. for $C_{18}H_{20}{}^{79}Br^{35}ClN_3O_2^+$ (86, $[M+H]^+$): 424.0422, found: 424.0420.

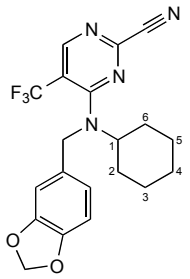
4-[(1,3-Benzodioxol-5-ylmethyl)(cyclohexyl)amino]-5-bromo-pyrimidine-2-carbonitrile (5)



GP-B starting from **14** (330 mg, 0.777 mmol), KCN (61 mg, 0.932 mmol) and DABCO (87 mg, 0.777 mmol) in Me_2SO/H_2O (9:1, 5 cm^3). Purification by FC (SiO_2; cyclohexane/EtOAc 20:1 → 10:1) gave **5** (287 mg, 89%) as a white foam.

$\tilde{\nu}_{max}$(neat)/cm^{-1} 2931, 2856, 1549, 1501, 1489, 1469, 1441, 1398, 1380, 1326, 1302, 1235, 1187, 1152, 1136, 1115, 1094, 1037, 1010, 996, 924, 894, 855, 804, 770, 729, 648, 627; δ_H(300 MHz; $CDCl_3$) 1.04–1.38 (3 H, m, H_{ax}–C(3,4,5)), 1.55–1.70 (3 H, m, H_{eq}–C(3,4,5)), 1.83–1.93 (4 H, m, H–C(2,6)), 4.29 (1 H, tt, *J* 11.8, 3.4, H–C(1)), 4.62 (2 H, s, CH_2N), 5.88 (2 H, s, CH_2O), 6.66–6.72 (3 H, m), 8.33 (1 H, s); δ_C(100 MHz; $CDCl_3$) 25.32 (CH_2), 25.90 (CH_2), 26.92 (CH_2), 31.32 (2 C, C(2,6)), 47.28 (CH_2N), 60.10 (C(1)), 101.01 (CH_2O), 107.82 (arom. CH), 108.04 (arom. CH), 108.74 (CBr), 115.58 (CN), 120.92 (arom. CH), 131.96 (arom. C), 141.46 (*C*CN), 146.58 (arom. C), 147.69 (arom. C), 160.21 (arom. CH_{pyr}), 160.68 (NCN); HR-ESI-MS *m/z* calc. for $C_{19}H_{20}{}^{81}BrN_4O_2^+$ (90, $[M + H]^+$): 417.0749, found: 417.0750; calc. for $C_{19}H_{20}{}^{79}BrN_4O_2^+$ (100, $[M + H]^+$): 415.0764, found: 415.0767.

4-[(1,3-Benzodioxol-5-ylmethyl)(cyclohexyl)amino]-5-(trifluoromethyl)-pyrimidine-2-carbonitrile (7)

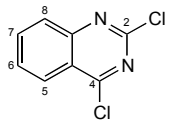


A solution of **5** (106 mg, 0.255 mmol) in *N*,*N*-dimethylformamide (4 cm^3) was treated with CuI (63 mg, 0.332 mmol) and heated to 80 °C in a sealed tube. Methyl fluorosulphonyldifluoroacetate (161 mm^3, 1.276 mmol) and hexamethylphosphoramide (224 mm^3, 1.276 mmol) were added and the mixture stirred at 80 °C for 2.5 h. The mixture was allowed to cool to 25 °C, diluted with EtOAc (20 cm^3), washed with brine (2 x 20 cm^3) and NH_4Cl (2 x 20 cm^3), dried over Na_2SO_4, filtered and evaporated. Purification by FC (SiO_2; cyclohexane/EtOAc 20:1) gave **7** (75 mg, 73%) as a white solid.

mp 89–91 °C; elemental analysis found: C, 59.19; H, 4.82; N, 13.66; calc. for $C_{20}H_{19}F_3N_4O_2$: C, 59.40; H, 4.74; N, 13.85%; $\tilde{\nu}_{max}$(neat)/cm^{-1} 2932, 2859, 1576, 1525, 1504, 1493, 1478, 1444, 1412, 1370, 1342, 1308, 1251, 1209, 1186, 1129, 1098, 1053, 1019, 995, 943, 925, 895, 851, 803, 786, 753, 713, 665, 623; δ_H(300 MHz; $CDCl_3$) 1.06–1.43 (3 H, m, H_{ax}–C(3,4,5)), 1.55–1.73 (3 H, m, H_{eq}–C(3,4,5)), 1.87–1.91 (4 H, m, H–C(2,6)), 3.85 (1 H, tt, *J* 11.4, 3.1, H–C(1)), 4.62 (2 H, s, CH_2N), 5.92 (2 H, s, CH_2O), 6.69–6.75 (3 H, m), 8.54 (1 H, s); δ_C(100 MHz; $CDCl_3$) 25.24 (C(4)), 25.82 (2 C, C(3,5)), 31.36 (2 C, C(2,6)), 47.55 (CH_2N), 62.04 (q, $^5J_{CF}$ 3.7, C(1)), 101.03 (CH_2O), 107.88 (arom. CH), 108.15 (arom. CH), 111.29 (q, $^2J_{CF}$ 32.2, CCF_3), 115.16 (CN), 121.09 (arom. CH), 126.08 (q, $^1J_{CF}$ 270.8, CF_3), 131.16 (arom. C), 144.90 (*C*CN), 146.67 (arom. C), 147.76 (arom. C), 157.59 (q, $^3J_{CF}$ 6.4, arom. CH_{pyr}),

159.61 (NCN); δ_F(282 MHz; $CDCl_3$) –57.85 (s, CF_3); HR-ESI-MS *m/z* calc. for $C_{20}H_{20}F_3N_4O_2^+$ (100, $[M + H]^+$): 405.1533, found: 405.1540.

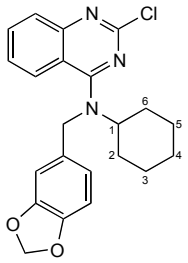
2,4-Dichloroquinazoline (23)[8]



2,4-Quinazolinedione (1.50 g, 9.25 mmol) was dissolved in dry toluene (20 cm^3) and subsequently degassed by bubbling argon through the solution for 15 min. The solution was heated to 50 °C and treated with $POCl_3$ (8.47 cm^3, 92.50 mmol) over a period of 10 min. 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU, 2.77 cm^3, 18.50 mmol) was added at 105 °C and the mixture stirred at 120 °C for 23 h. After cooling to 25 °C, the mixture was poured on ice-water (300 cm^3), extracted with EtOAc (3 x 300 cm^3), dried over Na_2SO_4, filtered and evaporated. Purification by FC (SiO_2; CH_2Cl_2) gave **23** (1.38 g, 75%) as a white crystalline solid.

mp 119–120 °C (lit.,[8] 118–120 °C); δ_H(300 MHz; $CDCl_3$) 7.71–7.80 (1 H, m, H–C(6)), 7.98–8.04 (2 H, m, H–C(5,7)), 8.26–8.30 (1 H, m, H–C(8)); δ_C(100 MHz; $CDCl_3$) 122.38 (arom. C), 126.09 (C(8)), 128.04 (C(5) or C(7)), 129.26 (C(6)), 136.17 (C(5) or C(7)), 152.40 (arom. C), 155.16 (CCl), 164.03 (CCl).

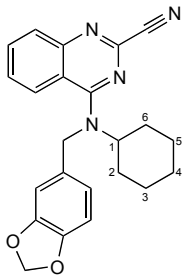
_N_-(1,3-Benzodioxol-5-ylmethyl)-2-chloro-_N_-cyclohexylquinazolin-4-amine (24)



GP-A starting from **23** (200 mg, 1.005 mmol), **13** (234 mg, 1.005 mmol) and $^{i}Pr_2NEt$ (208 mm^3, 1.206 mmol) in $^{i}PrOH$ (5 cm^3). Purification by FC (SiO_2; cyclohexane/EtOAc 10:1) gave **24** (300 mg, 75%) as a white foam.

$\tilde{\nu}_{max}$(neat)/cm^{-1} 2929, 2855, 1612, 1562, 1524, 1488, 1438, 1362, 1319, 1280, 1232, 1194, 1156, 1137, 1090, 1036, 1004, 924, 905, 894, 881, 853, 804, 764, 734, 688, 627; δ_H(300 MHz; $CDCl_3$) 1.07–1.38 (3 H, m, H_{ax}–C(3,4,5)), 1.59–2.02 (7 H, m, H_{eq}–C(3,4,5), H–C(2,6)), 4.31 (1 H, tt, *J* 11.6, 3.6, H–C(1)), 4.73 (2 H, s, CH_2N), 5.92 (2 H, s, CH_2O), 6.72–6.75 (1 H, m), 6.86–6.89 (2 H, m), 7.30–7.36 (1 H, m), 7.64–7.70 (1 H, m), 7.75–7.86 (2 H, m); δ_C(100 MHz; $CDCl_3$) 25.47 (CH_2), 25.97 (2 C, C(3,5)), 31.07 (2 C, C(2,6)), 48.70 (CH_2N), 62.53 (C(1)), 101.00 (CH_2O), 108.15 (arom. CH), 115.70 (arom. C), 121.06 (arom. CH), 124.78 (arom. CH), 125.19 (arom. CH), 128.04 (arom. CH), 132.54 (arom. CH), 132.95 (arom. CH), 146.60 (arom. C), 147.71 (arom. C), 153.55 (arom. C), 156.18 (CCl), 165.11 (NCN), one signal not visible; HR-ESI-MS *m/z* calc. for $C_{22}H_{23}{}^{37}ClN_3O_2{}^{+}$ (34, $[M + H]^+$): 398.1449, found: 398.1453; calc. for $C_{22}H_{23}{}^{35}ClN_3O_2{}^{+}$ (100, $[M + H]^+$): 396.1473, found: 396.1469.

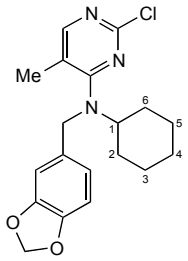
4-[(1,3-Benzodioxol-5-ylmethyl)(cyclohexyl)amino]quinazoline-2-carbonitrile (6)



GP-B starting from **24** (100 mg, 0.253 mmol) and KCN (20 mg, 0.303 mmol) in Me_2SO (2 cm^3). Purification by FC (SiO_2; cyclohexane/EtOAc 20:1 → 10:1) gave **6** (69 mg, 70%) as a white solid.

mp 126–127 °C; elemental analysis found: C, 71.31; H, 5.82; N, 14.37; calc. for $C_{23}H_{22}N_4O_2$: C, 71.48; H, 5.74; N, 14.50%; $\tilde{\nu}_{max}$(neat)/cm^{-1} 2931, 2857, 1610, 1562, 1523, 1489, 1440, 1367, 1320, 1286, 1234, 1187, 1111, 1093, 1037, 1007, 958, 925, 895, 865, 805, 768, 729, 713, 685, 647, 624; δ_H(300 MHz; $CDCl_3$) 1.10–1.42 (3 H, m, H_{ax}–C(3,4,5)), 1.68–2.00 (7 H, m, H_{eq}–C(3,4,5), H–C(2,6)), 4.33 (1 H, tt, *J* 11.5, 3.5, H–C(1)), 4.75 (2 H, s, CH_2N), 5.91 (2 H, s, CH_2O), 6.72–6.75 (1 H, m), 6.83–6.88 (2 H, m), 7.44–7.49 (1 H, m), 7.72–7.77 (1 H, m), 7.85–7.91 (2 H, m); δ_C(100 MHz; $CDCl_3$) 25.41 (C(4)), 25.95 (2 C, C(3,5)), 30.99 (2 C, C(2,6)), 48.86 (CH_2N), 62.51 (C(1)), 101.06 (CH_2O), 107.84 (arom. CH), 108.23 (arom. CH), 116.83 (CN), 117.39 (arom. C), 120.92 (arom. CH), 124.73 (arom. CH), 127.42 (arom. CH), 129.13 (arom. CH), 132.19 (arom. C), 133.20 (arom. CH), 139.72 (*C*CN), 146.71 (arom. C), 147.83 (arom. C), 151.68 (arom. C), 163.78 (NCN); HR-ESI-MS *m/z* calc. for $C_{23}H_{23}N_4O_2^+$ (100, $[M + H]^+$): 387.1816, found: 387.1817.

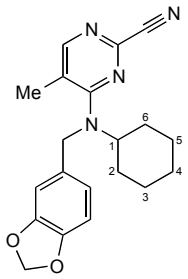
_N_-(1,3-Benzodioxol-5-ylmethyl)-2-chloro-_N_-cyclohexyl-5-methyl-pyrimidin-4-amine (25)



GP-A starting from 2,4-dichloro-5-methylpyrimidine (200 mg, 1.227 mmol), **13** (286 mg, 1.227 mmol) and $^{i}Pr_2NEt$ (211 mm^3, 1.227 mmol) in $^{i}PrOH$ (3 cm^3). Purification by FC (SiO_2; pentane/EtOAc 7:1 → 5:1) gave **25** (130 mg, 29%) as a pale yellow oil.

$\tilde{\nu}_{max}$(neat)/cm^{-1} 2929, 2856, 1572, 1519, 1489, 1441, 1366, 1307, 1227, 1186, 1168, 1145, 1111, 1036, 999, 904, 880, 804, 769, 729, 675, 645, 618; δ_H(400 MHz; $CDCl_3$) 0.86–1.70 (10 H, m, H–C(2–6)), 2.20 (3 H, s, Me), 3.84–3.90 (1 H, m, H–C(1)), 4.56 (2 H, s, CH_2N), 5.92 (2 H, s, CH_2O), 6.70–6.76 (3 H, m), 7.88 (1 H, s); δ_C(100 MHz; $CDCl_3$) 17.30 (Me), 25.49 (C(4)), 26.07 (2 C, C(3,5)), 31.37 (2 C, C(2,6)), 46.85 (CH_2N), 59.39 (C(1)), 100.90 (CH_2O), 107.92 (arom. CH), 107.98 (arom. CH), 115.57 (*C*Me), 120.75 (arom. CH), 133.44 (arom. C), 146.32 (arom. C), 147.55 (arom. C), 157.50 (CCl), 159.64 (arom. CH_{pyr}), 165.31 (NCN); HR-ESI-MS *m/z* calc. for $C_{19}H_{23}{}^{37}ClN_3O_2^+$ (30, $[M + H]^+$): 362.1444, found: 362.1456; calc. for $C_{19}H_{23}{}^{35}ClN_3O_2^+$ (100, $[M + H]^+$): 360.1473, found: 360.1477.

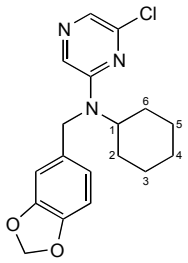
_N_-(1,3-Benzodioxol-5-ylmethyl)-2-chloro-_N_-cyclohexyl-5-methyl-pyrimidin-4-amine (8)



GP-B starting from **25** (50 mg, 0.139 mmol), KCN (18 mg, 0.278 mmol) and DABCO (16 mg, 0.139 mmol) in Me_2SO/H_2O (9:1, 1 cm^3). Purification by FC (SiO_2; pentane/EtOAc 3:1) gave **8** (18 mg, 37%) as a pale yellow oil.

$\tilde{\nu}_{max}$(neat)/cm^{-1} 2929, 2856, 1569, 1522, 1502, 1489, 1443, 1378, 1338, 1310, 1237, 1185, 1133, 1093, 1038, 999, 927, 894, 806, 779, 744; δ_H(400 MHz; $CDCl_3$) 0.84–1.86 (10 H, m, H–C(2–6)), 2.26 (3 H, s, Me), 3.88 (1 H, tt, *J* 11.7, 3.3, H–C(1)), 4.56 (2 H, s, CH_2N), 5.91 (2 H, s, CH_2O), 6.69–6.70 (3 H, m), 8.03 (1 H, s); δ_C(100 MHz; $CDCl_3$) 18.24 (Me), 25.44 (C(4)), 26.03 (2 C, C(3,5)), 31.28 (2 C, C(2,6)), 46.99 (CH_2N), 59.55 (C(1)), 100.98 (CH_2O), 107.58 (arom. CH), 108.11 (arom. CH), 116.33 (CN), 120.40 (*C*Me), 120.61 (arom. CH), 132.98 (arom. C), 141.65 (*C*CN), 146.46 (arom. C), 147.69 (arom. C), 158.20 (arom. CH_{pyr}), 163.90 (NCN); HR-ESI-MS *m/z* calc. for $C_{20}H_{23}N_4O_2^+$ (100, $[M + H]^+$): 351.1816, found: 351.1819.

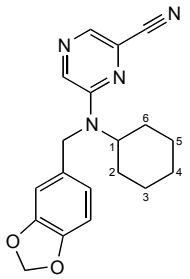
_N_-(1,3-Benzodioxol-5-ylmethyl)-6-chloro-_N_-cyclohexylpyrazin-2-amine (26)



A solution of 2,6-dichloropyrazine (500 mg, 3.356 mmol) in toluene (4 cm^3) was treated with **13** (1.017 g, 4.363 mmol), [$Pd(OAc)_2$] (38 mg, 0.168 mmol), 1,1'-bis(diphenylphosphino)ferrocene (190 mg, 0.336 mmol) and NaO^{t}Bu (419 mg, 4.363 mmol) at 25 °C. The mixture was stirred at 80 °C for 48 h. The mixture was filtered through celite and the solvent removed. The residue was purified by FC (SiO_2; pentane/EtOAc 10:1) to give **26** (41 mg, 4%) as a pale yellow oil.

$\tilde{\nu}_{max}$(neat)/cm^{-1} 2927, 2855, 1557, 1502, 1488, 1443, 1411, 1371, 1314, 1237, 1199, 1179, 1150, 1135, 1116, 1092, 1037, 1004, 988, 938, 924, 893, 831, 802, 768, 738, 693, 627; δ_H(300 MHz; $CDCl_3$) 0.86–1.84 (10 H, m, H–C(2–6)), 4.39–4.47 (1 H, m, H–C(1)), 4.54 (2 H, s, CH_2N), 5.93 (2 H, s, CH_2O), 6.64–6.75 (3 H, m), 7.67 (1 H, s), 7.74 (1 H, s); δ_C(100 MHz; $CDCl_3$) 25.55 (C(4)), 25.81 (2 C, C(3,5)), 30.45 (2 C, C(2,6)), 46.76 (CH_2N), 55.17 (C(1)), 101.05 (CH_2O), 106.83 (arom. CH), 108.41 (arom. CH), 119.33 (arom. CH), 128.18 (arom. C), 129.85 (arom. C), 132.07 (arom. C), 146.44 (CCl), 146.63 (arom. CH_{pyr}), 148.01 (arom. CH_{pyr}), 153.67 (NCN); HR-ESI-MS *m/z* calc. for $C_{18}H_{21}{}^{37}ClN_3O_2{}^+$ (30, $[M + H]^+$): 348.1293, found: 348.1295; calc. for $C_{18}H_{21}{}^{35}ClN_3O_2{}^+$ (100, $[M + H]^+$): 346.1317, found: 346.1319.

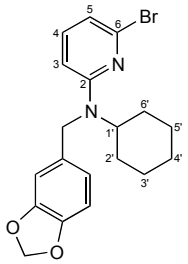
6-[(1,3-Benzodioxol-5-ylmethyl)(cyclohexyl)amino]pyrazine-2-carbonitrile (9)



A solution of **26** (38 mg, 0.110 mmol) in *N*,*N*-dimethylacetamide (1 cm^3) was treated with [$Pd(OAc)_2$] (1 mg, 0.006 mmol), 1,1'-bis(diphenylphosphino)ferrocene (6 mg, 0.011 mmol), $Zn(CN)_2$ (8 mg, 0.066 mmol) and zinc dust (1 mg, 0.013 mmol) at 25 °C. The mixture was stirred at 120 °C for 6 h. The mixture was diluted with EtOAc (20 cm^3), washed with brine (3 x 30 cm^3), dried over Na_2SO_4, filtered and evaporated. Purification by FC (pentane/EtOAc 5:1) gave **9** (25 mg, 68%) as a yellow oil.

$\tilde{\nu}_{max}$(neat)/cm^{-1} 2930, 2856, 2346, 2117, 1571, 1513, 1489, 1444, 1418, 1367, 1316, 1237, 1143, 1092, 1039, 990, 925, 853, 808, 736, 656; δ_H(300 MHz; $CDCl_3$) 0.83–1.83 (10 H, m, H–C(2–6)), 4.45–4.53 (1 H, m, H–C(1)), 4.56 (2 H, s, CH_2N), 5.94 (2 H, s, CH_2O), 6.64–6.76 (3 H, m), 7.94 (1 H, s), 8.06 (1 H, s); δ_C(100 MHz; $CDCl_3$) 25.49 (C(4)), 25.77 (2 C, C(3,5)), 30.36 (2 C, C(2,6)), 46.70 (CH_2N), 55.12 (C(1)), 101.15 (CH_2O), 106.60 (arom. CH), 108.55 (arom. CH), 116.51 (CN), 119.19 (arom. CH), 126.99 (arom. C), 127.24 (arom. C), 134.57 (arom. CH_{pyr}), 135.05 (arom. CH_{pyr}), 146.84 (*C*CN), 148.16 (arom. C), 153.31 (NCN); HR-ESI-MS *m/z* calc. for $C_{19}H_{21}N_4O_2^+$ (100, $[M + H]^+$): 337.1659, found: 337.1661.

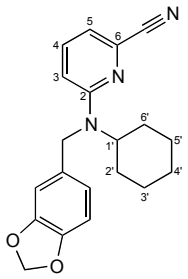
_N_-(1,3-Benzodioxol-5-ylmethyl)-6-bromo-_N_-cyclohexyl-pyridin-2-amine (27)



A solution of 2,6-dibromopyridine (621 mg, 2.621 mmol) in toluene (15 cm^3) was treated with **13** (795 mg, 3.407 mmol), [$Pd(OAc)_2$] (29 mg, 0.131 mmol), 1,1'-bis(di-phenylphosphino)-ferrocene (148 mg, 0.262 mmol) and NaO^{t}Bu (504 mg, 5.242 mmol) at 25 °C. The mixture was stirred at 80 °C for 22 h in a sealed tube. The mixture was filtered through celite and the solvent removed. The residue was purified by FC (SiO_2; pentane/EtOAc 20:1) to give **27** (102 mg, 10%) as a white crystalline solid.

mp 97–98 °C; $\tilde{\nu}_{max}$(neat)/cm^{-1} 2935, 2853, 1591, 1537, 1499, 1488, 1472, 1459, 1443, 1407, 1372, 1313, 1243, 1195, 1170, 1120, 1109, 1090, 1032, 1005, 969, 938, 925, 889, 848, 823, 795, 770, 726, 677, 607; δ_H(300 MHz; $CDCl_3$) 1.03–1.83 (10 H, m, H–C(2'–6')), 4.43–4.51 (3 H, m, CH_2N, H–C(1')), 5.92 (2 H, s, CH_2O), 6.20 (1 H, d, *J* 8.4, H–C(5)), 6.65–6.75 (4 H, m, 3 arom. CH, H–C(3)), 7.14 (1 H, dd, *J* 8.3, 7.5, H–C(4)); δ_C(100 MHz; $CDCl_3$) 25.74 (C(4')), 25.97 (2 C, C(3',5')), 30.62 (2 C, C(2',6')), 46.98 (CH_2N), 55.05 (C(1')), 100.93 (CH_2O), 105.10 (C(3)), 107.01 (arom. CH), 108.20 (arom. CH), 114.76 (C(5)), 119.30 (arom. CH), 133.38 (arom. C), 139.12 (C(4)), 139.91 (C(6)), 146.29 (arom. C), 147.81 (arom. C), 158.39 (C(2)); HR-ESI-MS *m/z* calc. for $C_{19}H_{22}{}^{81}BrN_2O_2^+$ (100, $[M + H]^+$): 391.0844, found: 391.0846; calc. for $C_{19}H_{22}{}^{79}BrN_2O_2^+$ (92, $[M + H]^+$): 389.0859, found: 389.0864.

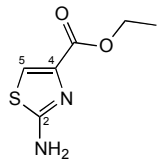
6-[(1,3-Benzodioxol-5-ylmethyl)(cyclohexyl)amino]pyridine-2-carbonitrile (10)



A solution of **27** (50 mg, 0.128 mmol) in *N*,*N*-dimethylacetamide (1 cm^3) was treated with [$Pd(OAc)_2$] (1 mg, 0.006 mmol), 1,1'-bis(diphenylphosphino)ferrocene (7 mg, 0.013 mmol), $Zn(CN)_2$ (9 mg, 0.077 mmol) and zinc dust (1 mg, 0.015 mmol). The mixture was stirred at 120 °C for 2.5 h. The mixture was diluted with EtOAc (20 cm^3), washed with brine (3 x 30 cm^3), dried over Na_2SO_4, filtered and evaporated. Purification by FC (pentane/EtOAc 10:1) gave **10** (36 mg, 84%) as a white solid.

mp 131–132 °C; $\tilde{\nu}_{max}$(neat)/cm^{-1} 2929, 2855, 2232, 1590, 1552, 1502, 1476, 1443, 1397, 1364, 1313, 1235, 1208, 1172, 1117, 1091, 1038, 1005, 974, 938, 924, 788, 727, 663; δ_H(300 MHz; $CDCl_3$) 0.83–1.83 (10 H, m, H–C(2'–6')), 4.50 (2 H, s, CH_2N), 4.54–4.61 (1 H, m, H–C(1')), 5.93 (2 H, s, CH_2O), 6.48 (1 H, d, *J* 8.8, H–C(5)), 6.65–6.75 (3 H, m), 6.90 (1 H, d, *J* 7.1, H–C(3)), 7.36 (1 H, dd, *J* 8.8, 7.2, H–C(4)); δ_C(100 MHz; $CDCl_3$) 25.68 (C(4')), 25.92 (2 C, C(3',5')), 30.55 (2 C, C(2',6')), 46.96 (CH_2N), 54.79 (C(1')), 101.01 (CH_2O), 106.76 (arom. CH), 108.32 (arom. CH), 111.08 (C(5)), 116.86 (C(3)), 118.31 (CN), 119.13 (arom. CH), 131.47 (C(6)), 132.75 (arom. C), 137.39 (C(4)), 146.45 (arom. C), 147.93 (arom. C), 158.37 (C(2)); HR-ESI-MS *m/z* calc. for $C_{20}H_{22}N_3O_2^+$ (100, $[M + H]^+$): 336.1707, found: 336.1709.

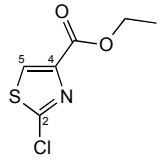
Ethyl 2-Amino-1,3-thiazole-4-carboxylate (15)[9]



A solution of thiourea (7.0 g, 98.0 mmol) and ethyl bromopyruvate (12.3 cm^3, 98.0 mmol) in EtOH (100 cm^3) was stirred at 105 °C for 1.5 h. Upon cooling to 0 °C, a white precipitate was formed which was filtered and washed with cold EtOH. Thiazole **15** (16.6 g, 98%) was obtained as a white solid.

mp 193–194 °C (lit.,[9] 175 °C); δ_H(400 MHz; MeOD) 1.40 (3 H, t, *J* 7.1, Me), 4.42 (2 H, q, *J* 7.1, CH_2), 4.99 (2 H, br s, NH_2), 7.76 (1 H, s, H–C(5)); δ_C(100 MHz; MeOD) 13.08 (Me), 62.34 (CH_2), 116.98 (C(5)), 130.75 (C(4)), 156.87 (CO_2Et), 170.52 (C(2)); HR-ESI-MS *m/z* calc. for $C_6H_8N_2NaO_2S^+$ (100, $[M + H]^+$): 195.0199, found: 195.0195.

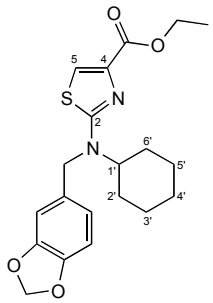
Ethyl 2-Chloro-1,3-thiazole-4-carboxylate (16)[10]



A solution of *tert*-butylnitrite (9.4 cm^3, 78.4 mmol) and $CuCl_2$ (8.43 g, 62.7 mmol) in MeCN (30 cm^3) was treated with **15** (9.0 g, 52.3 mmol). The mixture was stirred at 65 °C for 1 h. The solution was allowed to cool to 25 °C and poured into an ice-cold 1 M aqueous HCl solution (300 cm^3). The solution was extracted with EtOAc (3 x 200 cm^3). The combined organic layers were washed with brine (100 cm^3), dried over $MgSO_4$, filtered and concentrated. Purification by FC (SiO_2; cyclohexane/EtOAc 10:1) gave **16** (2.66 g, 27%) as a yellow solid**.**

mp 79–80 °C (lit.,[10] 79 °C); δ_H(400 MHz; $CDCl_3$) 1.42 (3 H, t, *J* 7.1, Me), 4.44 (2 H, q, *J* 7.1, CH_2), 8.09 (1 H, s, H–C(5)); δ_C(100 MHz; $CDCl_3$) 14.31 (Me), 61.87 (CH_2), 129.08 (C(5)), 145.76 (C(4)), 152.63 (C(2)), 160.31 (CO_2Et); HR-ESI-MS *m/z* calc. for $C_6H_7{}^{37}ClNO_2S^+$ (40, $[M + H]^+$): 193.9852, found: 193.9845; calc. for $C_6H_7{}^{35}ClNO_2S^+$ (100, $[M + H]^+$): 191.9874, found: 191.9881.

Ethyl 2-[(1,3-Benzodioxol-5-ylmethyl)(cyclohexyl)amino]-1,3-thiazole-4-carboxylate (17)

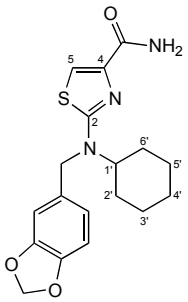


A solution of **13** (1.0 g, 5.24 mmol) and **16** (3.0 g, 15.71 mmol) in dioxane (0.5 cm^3) was stirred at 130 °C for 7 d. After cooling to 25 °C, a saturated aqueous $NaHCO_3$ solution (50 cm^3) was added. The aqueous phase was extracted with CH_2Cl_2 (3 x 50 cm^3). The combined organic layers were washed with brine (50 cm^3), dried over Na_2SO_4, filtered and concentrated. The residue was purified by FC (SiO_2; pentane/Et_2O 10:1 → 3:1) to give **17** (175 mg, 9%) as a yellow oil.

$\tilde{\nu}_{max}$(neat)/cm^{-1} 2931, 2855, 1726, 1609, 1530, 1502, 1443, 1371, 1339, 1231, 1203, 1090, 1036, 926, 894, 809, 729, 630; δ_H(400 MHz; $CDCl_3$) 1.00–1.50 (5 H, m, H–C(3'–5')), 1.39 (3 H, t, *J* 7.1, Me), 1.64–1.74 (1 H, m, H_{eq}–C(4')), 1.81–1.83 (2 H, m, H_{ax}–C(2',6')), 1.90–1.93 (2 H, m, H_{eq}–C(2',6')), 4.00–4.25 (1 H, m, H–C(1')), 4.36 (2 H, q, *J* 7.1, CH_2Me), 4.57 (2 H, s, CH_2N), 5.95 (2 H, s, CH_2O), 6.74–6.80 (2 H, m), 6.84 (1 H, s), 7.37 (1 H, s, H–C(5)); δ_C(100 MHz; $CDCl_3$) 14.35 (Me), 25.49 (C(4')), 25.82 (2 C, C(3',5')), 30.66 (2 C, C(2',6')), 49.94 (CH_2N), 60.54 (C(1')), 60.91

(*C*H$_2$Me), 100.99 (CH$_2$O), 107.62 (arom. CH), 108.13 (arom. CH), 115.53 (C(5)), 120.19 (arom. CH), 132.03 (arom. C), 143.56 (C(4)), 146.68 (arom. C), 147.81 (arom. C), 161.97 (*C*O$_2$Et), 170.39 (C(2)); HR-ESI-MS *m/z* calc. for $C_{20}H_{25}N_2O_4S^+$ (100, $[M + H]^+$): 389.1530, found: 389.1528.

2-[(1,3-Benzodioxol-5-ylmethyl)(cyclohexyl)amino]-1,3-thiazole-4-carboxamide (18)



A solution of **17** (85 mg, 0.219 mmol) in THF/MeOH/H$_2$O (2:2:1, 4 cm^3) was treated with LiOH·H$_2$O (28 mg, 0.657 mmol) and stirred at 40 °C for 5 h. The solution was allowed to cool to 25 °C and diluted with EtOAc (15 cm^3). H$_2$O (15 cm^3) was added and the layers separated. The pH of the aqueous layer was adjusted to pH = 2 using 1 M aqueous HCl, and extracted with EtOAc (30 cm^3). The combined organic layers were dried over Na$_2$SO$_4$ and the solvent evaporated to give the crude carboxylic acid (71 mg) as a yellow solid.

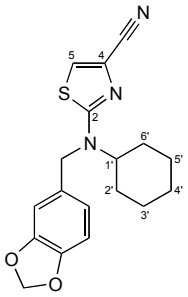
The residue (71 mg, 0.197 mmol) was dissolved in toluene (12 cm^3) and treated with SOCl$_2$ (57 mm^3, 0.789 mmol) and *N*,*N*-dimethylformamide (6 mm^3, 0.079 mmol) at 25 °C. The mixture was stirred at 80 °C for 1.5 h. After cooling to 25 °C, the solvent was evaporated to give the crude acid chloride (80 mg) as a yellow oil.

The residue was taken up in toluene (10 cm^3) and treated with a 7 N NH$_3$ solution in MeOH (1.04 cm^3, 7.39 mmol) at 0 °C. The mixture was stirred at 25 °C for 1 h. The

solvent was evaporated and the residue purified by FC (SiO_2; CH_2Cl_2/MeOH 20:1) to give **18** (55 mg, 73%) as a yellow oily solid.

$\tilde{\nu}_{max}$(neat)/cm^{-1} 3464, 2931, 2251, 1673, 1538, 1507, 1443, 1395, 1312, 1292, 1238, 1169, 1035, 903, 810, 724, 649; δ_H(600 MHz; $CDCl_3$) 1.00–1.62 (5 H, m, H–C(3'–5')), 1.67–1.79 (1 H, m, H_{eq}–C(4')), 1.80–1.85 (2 H, m, H_{ax}–C(2',6')), 1.90–1.95 (2 H, m, H_{eq}–C(2',6')), 3.70□3.92 (1 H, m, H–C(1')), 4.55 (2 H, s, CH_2N), 5.45 (1 H, br s, NH), 5.94 (2 H, s, CH_2O), 6.75 (2 H, br s), 6.80 (1 H, s), 7.00 (1 H, br s, NH), 7.34 (1 H, s, H–C(5)); δ_C(150 MHz; $CDCl_3$) 25.45 (C(4')), 25.95 (2 C, C(3',5')), 30.06 (2 C, C(2',6')), 49.89 (CH_2N), 61.39 (C(1')), 101.05 (CH_2O), 107.40 (arom. CH), 108.18 (arom. CH), 112.00 (C(5)), 120.00 (arom CH), 132.36 (arom. C), 145.44 (C(4)), 146.68 (arom. C), 147.86 (arom. C), 163.60 ($CONH_2$), 170.08 (C(2)); HR-ESI-MS *m/z* calc. for $C_{18}H_{22}N_3O_3S^+$ (100, $[M + H]^+$): 360.1376, found: 360.1381.

2-[(1,3-Benzodioxol-5-ylmethyl)(cyclohexyl)amino]-1,3-thiazole-4-carbonitrile (11)

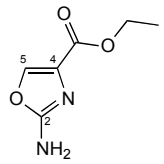


A solution of **18** (43 mg, 0.120 mmol) in CH_2Cl_2 (3 cm^3) was treated with Burgess reagent (96 mg, 0.402 mmol) and stirred at 25 °C for 2 h. The solvent was evaporated and the residue purified by FC (SiO_2; cyclohexane/Et_2O 6:1) to give **11** (42 mg, 82%) as a yellow solid.

mp 84–85 °C; elemental analysis found: C, 63.11; H, 5.85; N, 12.57; calc. for $C_{18}H_{19}N_3O_2S$: C, 63.32; H, 5.61; N, 12.31%; $\tilde{\nu}_{max}$(neat)/cm^{-1} 3116, 2931, 2856, 2227,

1862, 1607, 1532, 1502, 1489, 1443, 1373, 1316, 1241, 1170, 1121, 1094, 1038, 997, 956, 926, 894, 851, 808, 768, 732, 649; δ_H(400 MHz; $CDCl_3$) 1.00□1.57 (5 H, m, H–C(3'–5')), 1.68–1.72 (1 H, m, H_{eq}–C(4')), 1.82–1.86 (2 H, m, H_{ax}–C(2',6')), 1.90–1.93 (2 H, m, H_{eq}–C(2',6')), 3.80□4.15 (1 H, m, H–C(1')), 4.55 (2 H, s, CH_2N), 5.96 (2 H, s, CH_2O), 6.76 (2 H, br s), 6.79 (1 H, s), 7.16 (1 H, s, H–C(5)); δ_C(100 MHz; $CDCl_3$) 25.38 (C(4'), 25.82 (2 C, C(3',5')), 30.52 (2 C, C(2',6')), 50.24 (CH_2N), 61.27, (C(1')), 101.10 (CH_2O), 107.42 (arom. CH), 108.27 (arom. CH), 115.17 (CN), 118.36 (C(5)), 120.18 (arom CH), 123.13 (C(4)), 131.19 (arom. C), 146.91 (arom. C), 147.95 (arom. C), 170.45 (C(2)); HR-ESI-MS *m/z* calc. for $C_{18}H_{20}N_3O_2S^+$ (100, $[M+H]^+$): 342.1271, found: 342.1279.

Ethyl 2-Amino-1,3-oxazole-4-carboxylate (28)[11]

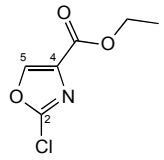


A solution of urea (5.0 g, 83.3 mmol) and ethyl bromopyruvate (10.5 cm^3, 83.3 mmol) in EtOH (60 cm^3) was heated to reflux for 3 h. The solution was allowed to cool to 25 °C and concentrated. The residue was taken up in EtOAc (150 cm^3). H_2O (100 cm^3) was added and the layers separated. The aqueous layer was extracted with EtOAc (150 cm^3). The combined organic layers were washed with brine (100 cm^3), dried over $MgSO_4$, filtered and concentrated. The residue was purified by FC (SiO_2; cyclohexane/EtOAc/Et_3N 2:3:0.01 → EtOAc/Et_3N 100:1) to give **28** (2.16 g, 17%) as a yellow solid.

mp 138–141 °C (lit.,[11] 133–135°C); δ_H(400 MHz; $CDCl_3$) 1.36 (3 H, t, *J* 7.1, Me), 4.34 (2 H, q, *J* 7.1, CH_2), 5.65 (2 H, br s, NH_2), 7.73 (1 H, s, H–C(5)); δ_C(100 MHz;

$CDCl_3$) 14.27 (Me), 60.86 (CH_2), 132.71 (C(4)), 137.58 (C(5)), 160.84 (C(2)), 161.73 (CO_2Et); HR-ESI-MS *m/z* calc. for $C_6H_9N_2O_3^+$ (100, $[M+H]^+$): 157.0600, found: 157.0600.

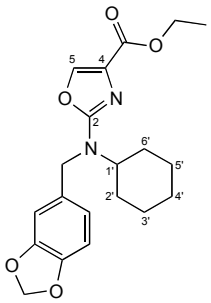
Ethyl 2-Chloro-1,3-oxazole-4-carboxylate (29)[11]



A solution of **28** (2.0 g, 12.8 mmol), $CuCl_2$ (2.58 g, 19.2 mmol) and *tert*-butylnitrite (2.3 cm^3, 19.2 mmol) in MeCN (60 cm^3) was heated to reflux for 3 h. The solution was diluted with CH_2Cl_2 (70 cm^3), H_2O (35 cm^3) and concentrated HCl (3.5 cm^3). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (50 cm^3). The combined organic layers were washed with brine (35 cm^3), dried over $MgSO_4$ and evaporated. The residue was purified by FC (cyclohexane/Et_2O 3:1) to give **29** (1.25 g, 56%) as a white foam.

δ_H(400 MHz; $CDCl_3$) 1.40 (3 H, t, *J* 7.1, Me), 4.41 (2 H, q, *J* 7.1, CH_2), 8.20 (1 H, s, H–C(5)); δ_C(100 MHz; $CDCl_3$) 14.22 (Me), 61.66 (CH_2), 135.15 (C(4)), 145.34 (C(5)), 148.26 (C(2)), 159.98 (CO_2Et); HR-ESI-MS *m/z* calc. for $C_6H_7{}^{37}ClNO_3^+$ (34, $[M+H]^+$): 178.0080, found: 178.0074; calc. for $C_6H_7{}^{35}ClNO_3^+$ (100, $[M+H]^+$): 176.0109, found: 176.0100.

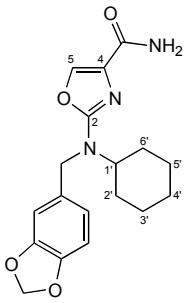
Ethyl 2-[(1,3-Benzodioxol-5-ylmethyl)(cyclohexyl)amino]-1,3-oxazole-4-carboxylate (30)



A solution of **29** (500 mg, 2.86 mmol) and **13** (1.33 g, 5.71 mmol) in dioxane (1.5 cm^3) was stirred at 80 °C for 3 d. The solution was allowed to cool to 25 °C, treated with a saturated aqueous $NaHCO_3$ solution (30 cm^3) and extracted with CH_2Cl_2 (3 x 40 cm^3). The combined organic layers were washed with brine (30 cm^3), dried over Na_2SO_4 and concentrated. The residue was purified by FC (SiO_2; pentane/Et_2O 8:1 → 6:1) to give **30** (284 mg, 27%) as a yellow oil.

$\tilde{\nu}_{max}$(neat)/cm^{-1} 2931, 2855, 1726, 1609, 1530, 1502, 1443, 1371, 1339, 1231, 1203, 1090, 1036, 926, 894, 809, 729, 630; δ_H(400 MHz; $CDCl_3$) 1.00–1.55 (5 H, m, H–C(3'–5')), 1.37 (3 H, t, *J* 7.1, Me), 1.62–1.66 (1 H, m, H_{eq}–C(4')), 1.70–1.90 (4 H, m, H–C(2',6')), 3.90–4.02 (1 H, m, H–C(1')), 4.36 (2 H, q, *J* 7.1, CH_2Me), 4.54 (2 H, s, CH_2N), 5.95 (2 H, s, CH_2O), 6.74 (2 H, br s), 6.78 (1 H, s), 7.74 (1 H, s, H–C(5)); δ_C(100 MHz; $CDCl_3$) 14.35 (Me), 25.43 (C(4')), 25.77 (2 C, C(3',5')), 30.84 (2 C, C(2',6')), 47.71 (CH_2N), 57.97 (C(1')), 60.81 (CH_2Me), 100.97 (CH_2O), 107.53 (arom. CH), 108.08 (arom. CH), 119.99 (arom. CH), 133.08 (arom. C), 133.20 (arom. C), 137.38 (C(5)), 146.58 (arom. C), 147.74 (arom. C), 162.06 (C(2)), 162.20 (CO_2Et); HR-ESI-MS *m/z* calc. for $C_{20}H_{25}N_2O_5^+$ (100, $[M + H]^+$): 373.1758, found: 373.1752.

2-[(1,3-Benzodioxol-5-ylmethyl)(cyclohexyl)amino]-1,3-oxazole-4-carboxamide (31)



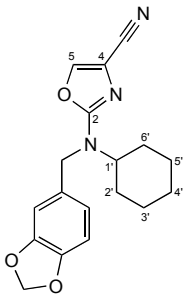
A solution of **30** (115 mg, 0.309 mmol) in THF/MeOH/H_2O (2:2:1, 5 cm^3) was treated with $LiOH{\cdot}H_2O$ (39 mg, 0.927 mmol) and stirred at 40 °C for 2 h. The solution was allowed to cool to 25 °C and diluted with EtOAc (50 cm^3). H_2O (30 cm^3) was added and the layers separated. The pH of the aqueous layer was adjusted to pH = 2 using 1 M aqueous HCl and extracted with EtOAc (2 x 50 cm^3). The combined organic layers were dried over Na_2SO_4 and the solvent evaporated to give the crude carboxylic acid (100 mg) as a yellow solid.

The residue (100 mg, 0.291 mmol) was taken up in *N*,*N*-dimethyl-formamide (5 cm^3). 1-Hydroxybenzotriazole (78 mg, 0.581 mmol), (1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoro-borate (187 mg, 0.581 mmol), a 7 N NH_3 solution in MeOH (125 mm^3, 0.872 mmol) and $^{i}Pr_2NEt$ (100 mm^3, 0.581 mmol) were added at 25 °C. The mixture was stirred for 15 h. The solvent was evaporated and the residue purified by FC (CH_2Cl_2/MeOH 25:1) to give **31** (58 mg, 58%) as a yellowish oily solid.

$\tilde{\nu}_{max}$(neat)/cm^{-1} 3448, 3157, 2933, 2856, 2245, 1676, 1618, 1574, 1489, 1443, 1404, 1368, 1323, 1237, 1171, 1091, 1038, 907, 808, 728, 647; δ_H(400 MHz; $CDCl_3$) 1.05–1.49 (5 H, m, H–C(3'–5')), 1.51–1.66 (3 H, m, H_{ax}–C(2',4',6')), 1.80–1.82 (2 H, m, H_{eq}–C(2',6')), 3.80–3.88 (1 H, m, H–C(1')), 4.51 (2 H, s, CH_2N), 5.66 (1 H, s, NH), 5.96 (2 H, s, CH_2O), 6.76–6.79 (2 H, m), 6.78 (1 H, s, NH), 7.74 (1 H, s, H–C(5));

δ_C(100 MHz; $CDCl_3$) 25.43 (C(4')), 25.94 (2 C, C(3',5')), 30.80 (2 C, C(2',6')), 48.24 (CH_2N), 58.29 (C(1')), 101.02 (CH_2O), 107.58 (arom. CH), 108.12 (arom. CH), 120.10 (arom. CH), 133.02 (arom. C), 134.76 (arom. C), 135.21 (C(5)), 146.66 (arom. C), 147.79 (arom. C), 161.24 (C(2)), 162.20 (CO_2NH_2); HR-ESI-MS *m/z* calc. for $C_{18}H_{22}N_3O_4^+$ (100, $[M + H]^+$): 344.1605, found: 344.1595.

2-[(1,3-Benzodioxol-5-ylmethyl)(cyclohexyl)amino]-1,3-oxazole-4-carbonitrile (12)



A solution of **31** (50 mg, 0.146 mmol) in CH_2Cl_2 (8 cm^3) was treated with Burgess reagent (104 mg, 0.437 mmol) and stirred at 25 °C for 5 h. The solvent was evaporated and the residue was purified by FC (SiO_2; pentane/EtOAc 5:1) to give **12** (37 mg, 79%) as a colourless oil.

$\tilde{\nu}_{max}$(neat)/cm^{-1} 3152, 2931, 2856, 2238, 1619, 1558, 1503, 1489, 1444, 1403, 1367, 1324, 1291, 1241, 1170, 1094, 1039, 1004, 988, 926, 908, 809, 768, 732, 627; δ_H(400 MHz; $CDCl_3$) 1.05–1.56 (6 H, m, H–C(3'–5')), 1.51–1.83 (4 H, m, H–C(2',6')), 3.83–3.91 (1 H, m, H–C(1')), 4.51 (2 H, s, CH_2N), 5.97 (2 H, s, CH_2O), 6.73–6.79 (3 H, m), 7.68 (1 H, s, H–C(5)); δ_C(100 MHz; $CDCl_3$) 5.34 (C(4')), 25.83 (2 C, C(3',5')), 30.71 (2 C, C(2',6')), 48.28 (CH_2N), 58.66 (C(1')), 101.10 (CH_2O), 107.53 (arom. CH), 108.22 (arom. CH), 113.02 (CN), 114.62 (*C*CN), 120.17 (arom. CH), 133.25 (arom. C), 139.68 (C(5)), 146.84 (arom. C), 147.88 (arom. C), 162.00 (C(2)); HR-ESI-MS *m/z* calc. for $C_{18}H_{20}N_3O_3^+$ (100, $[M + H]^+$): 326.1499, found: 326.1490.

NMR spectra of ligands 1–5, 8–10 and 12

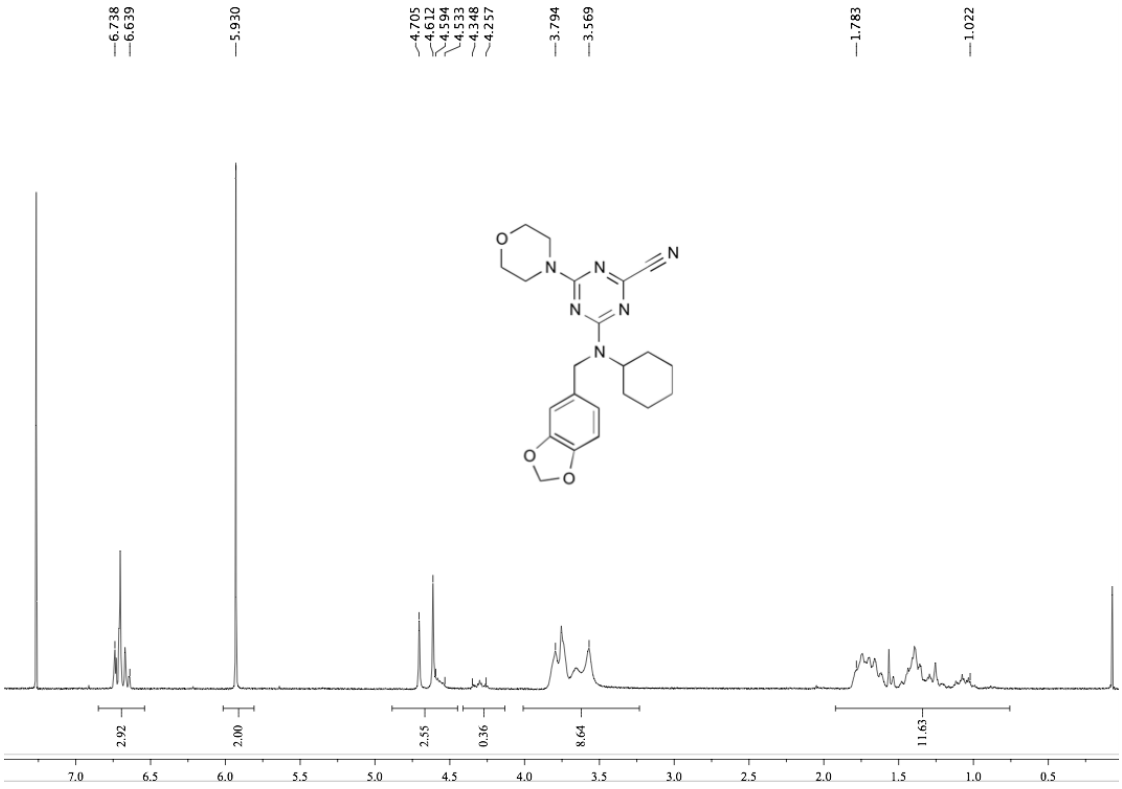


Fig. 3ESI ^{1}H NMR spectrum (300 MHz, 298 K, $CDCl_3$) of **1**.

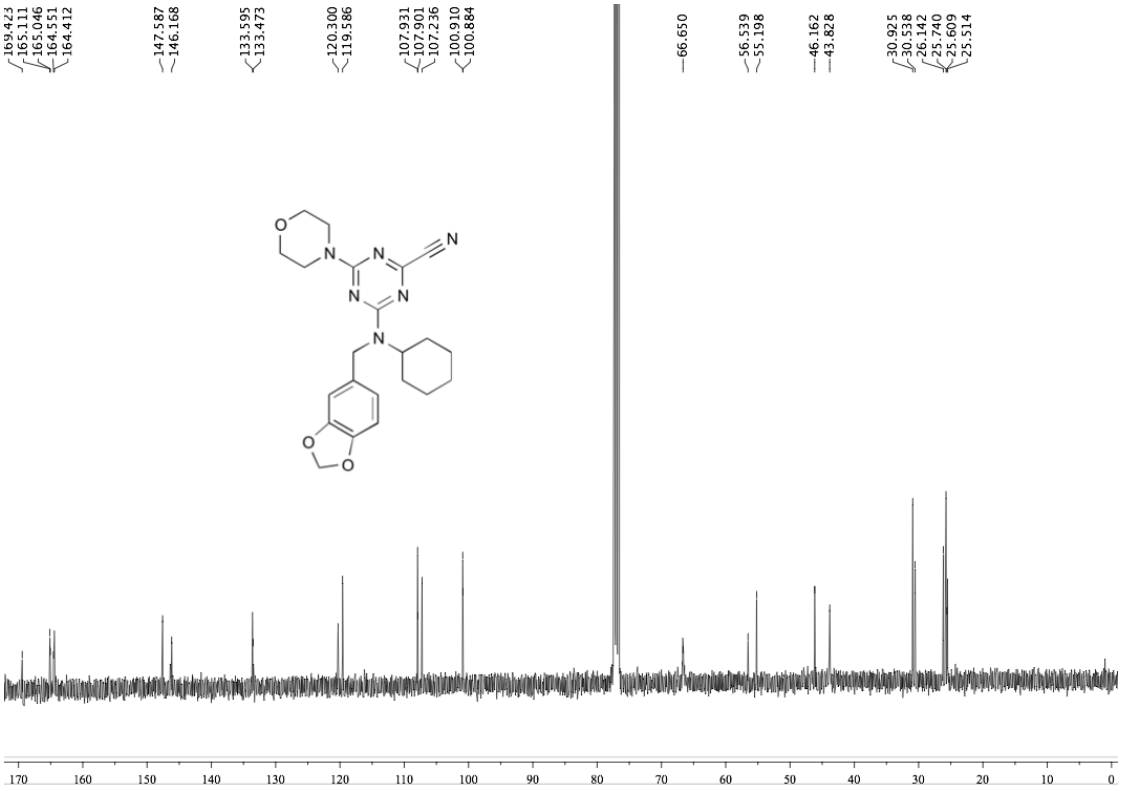


Fig. 4ESI ^{13}C NMR spectrum (100 MHz, 298 K, $CDCl_3$) of **1**.

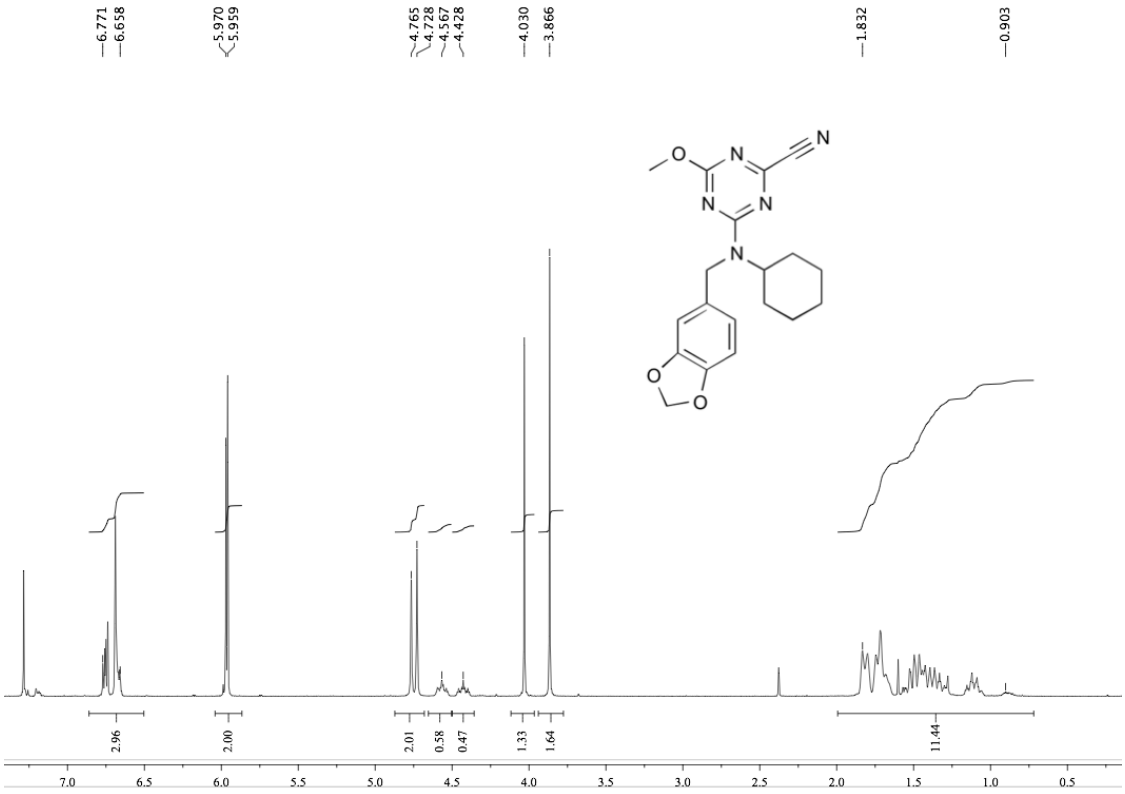


Fig. 5ESI ^{1}H NMR spectrum (400 MHz, 298 K, $CDCl_3$) of **2**.

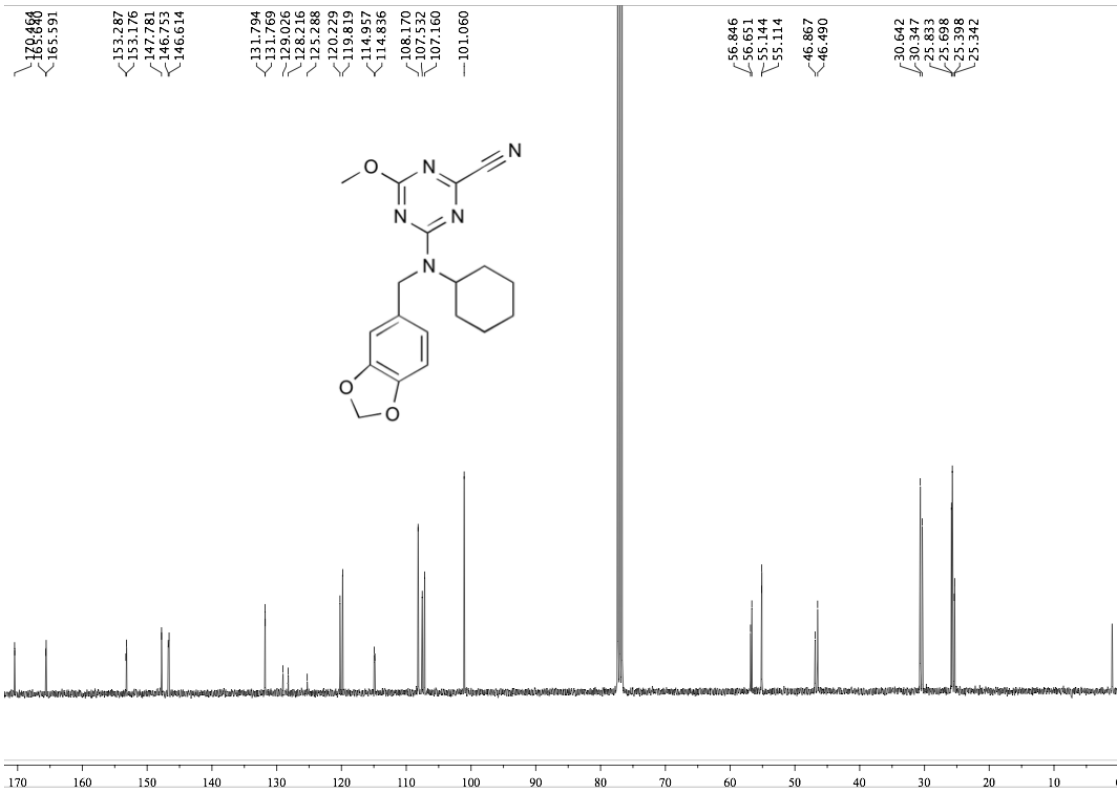


Fig. 6ESI ^{13}C NMR spectrum (100 MHz, 298 K, $CDCl_3$) of **2**.

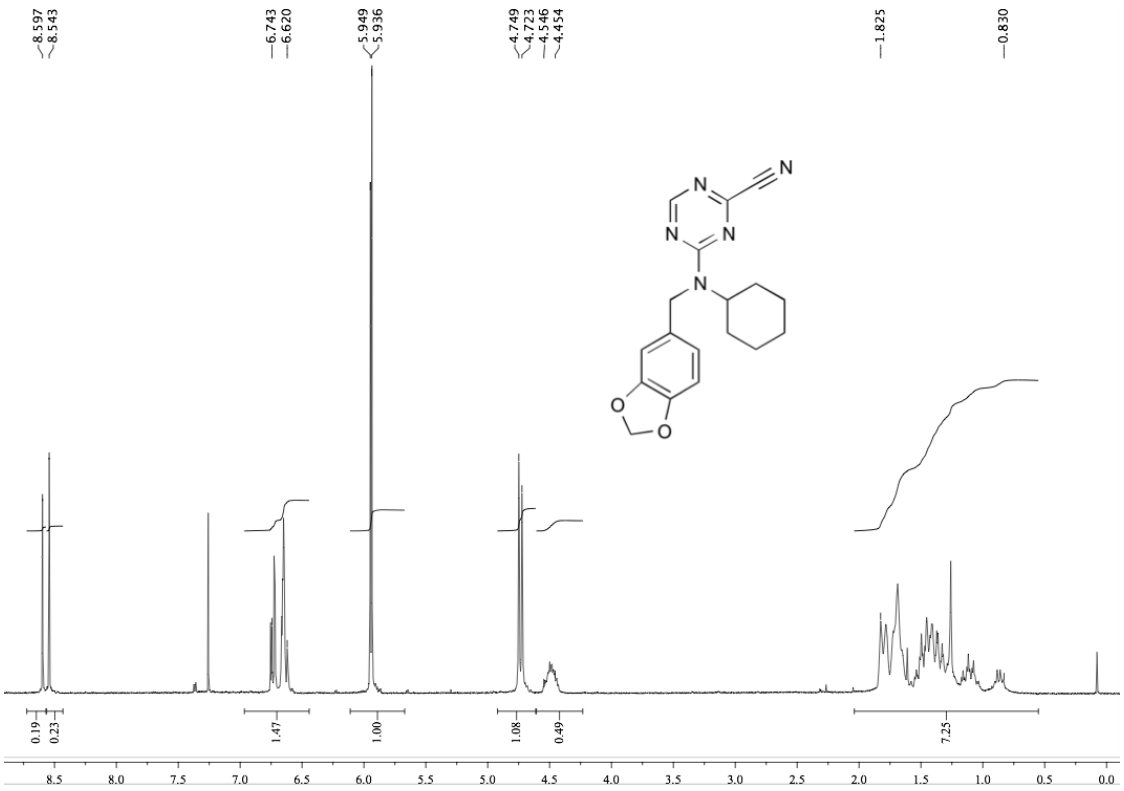


Fig. 7ESI ^{1}H NMR spectrum (400 MHz, 298 K, $CDCl_3$) of **3**.

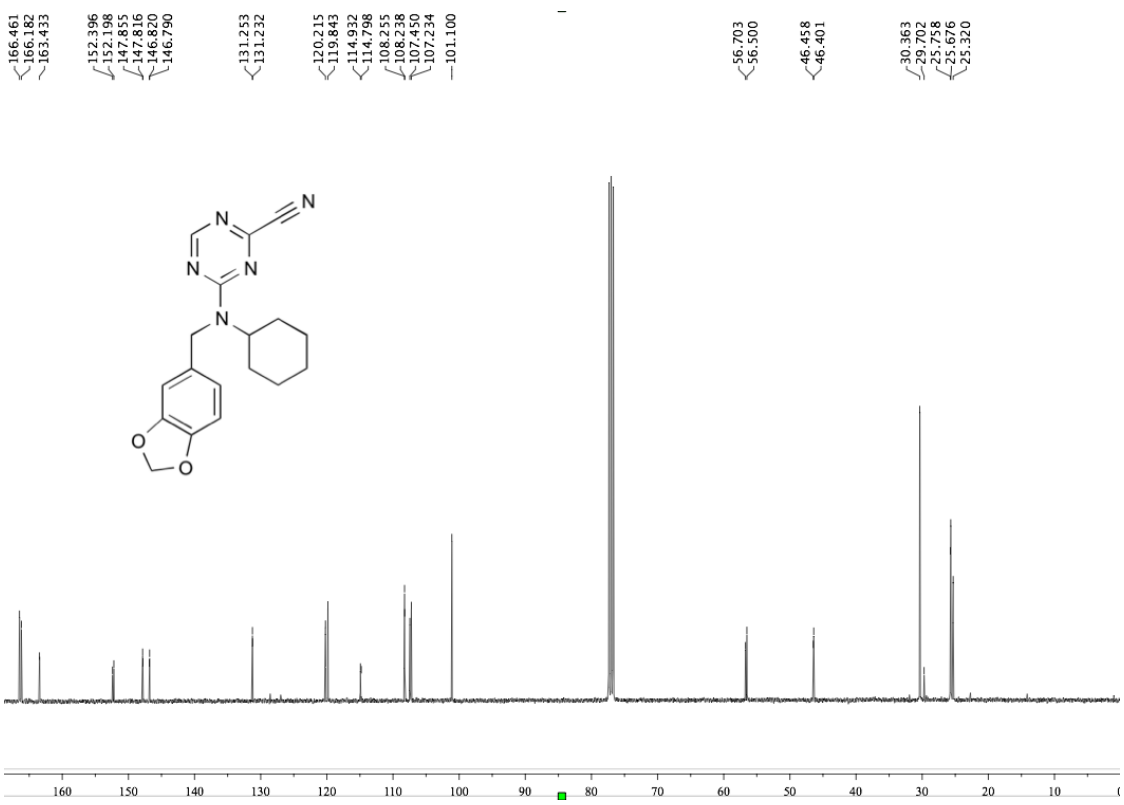


Fig. 8ESI ^{13}C NMR spectrum (100 MHz, 298 K, $CDCl_3$) of **3**.

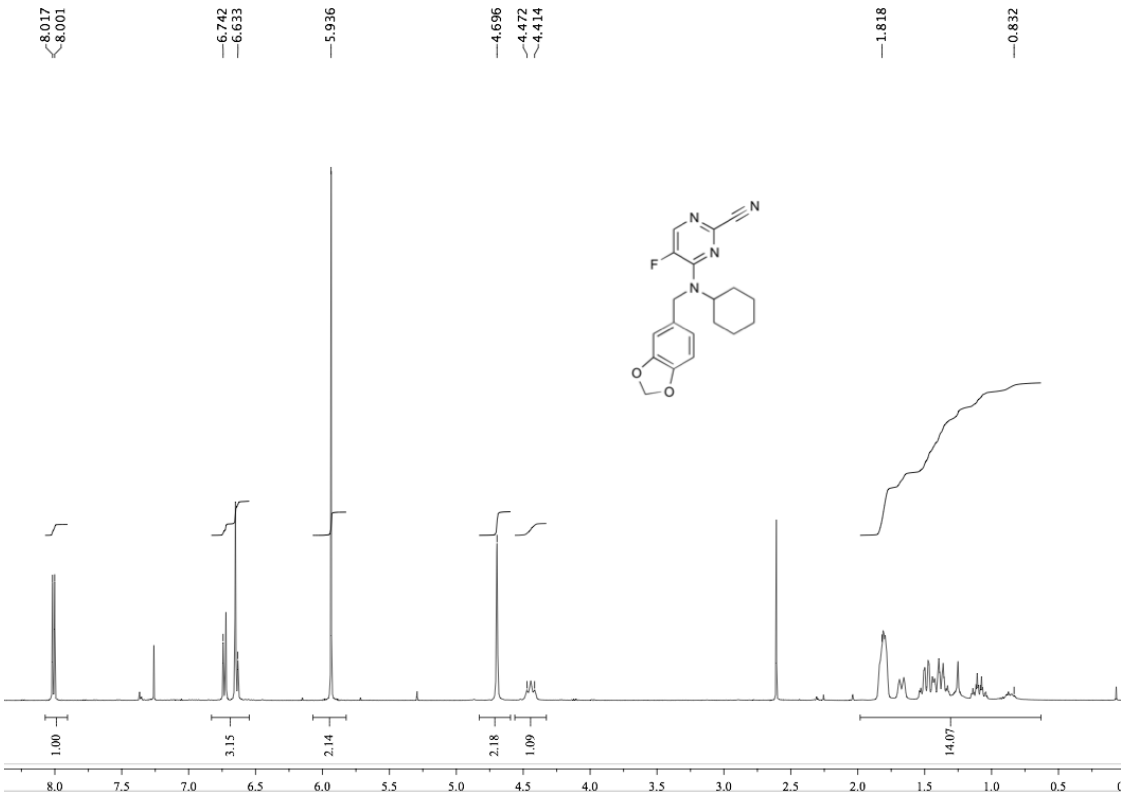


Fig. 9ESI ^{1}H NMR spectrum (400 MHz, 298 K, $CDCl_3$) of **4**.

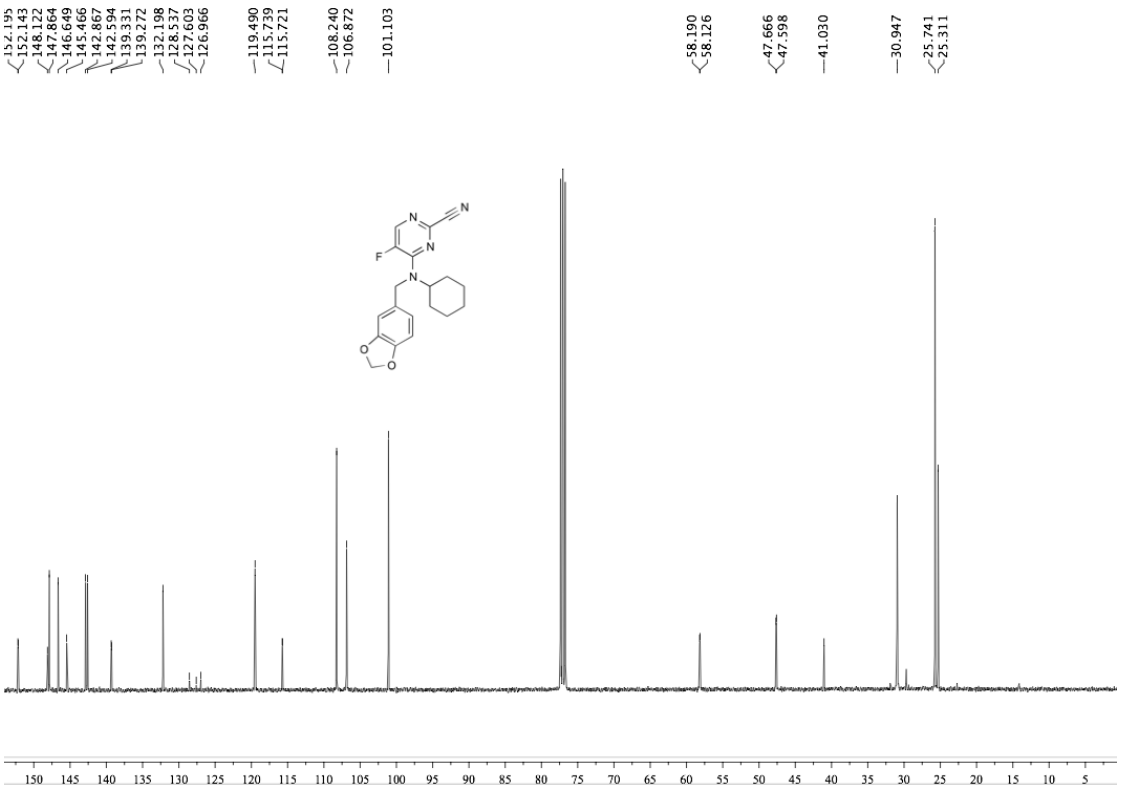


Fig. 10ESI ^{13}C NMR spectrum (100 MHz, 298 K, $CDCl_3$) of **4**.

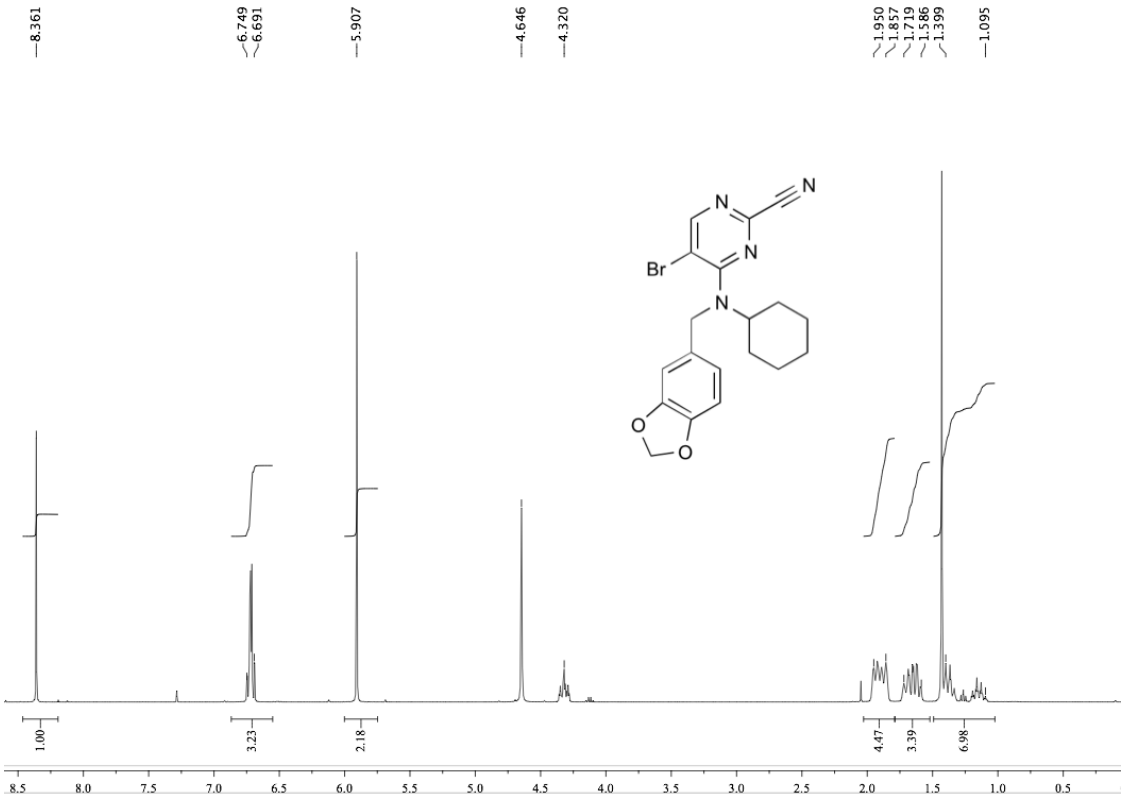


Fig. 11ESI ^{1}H NMR spectrum (400 MHz, 298 K, $CDCl_3$) of **5**.

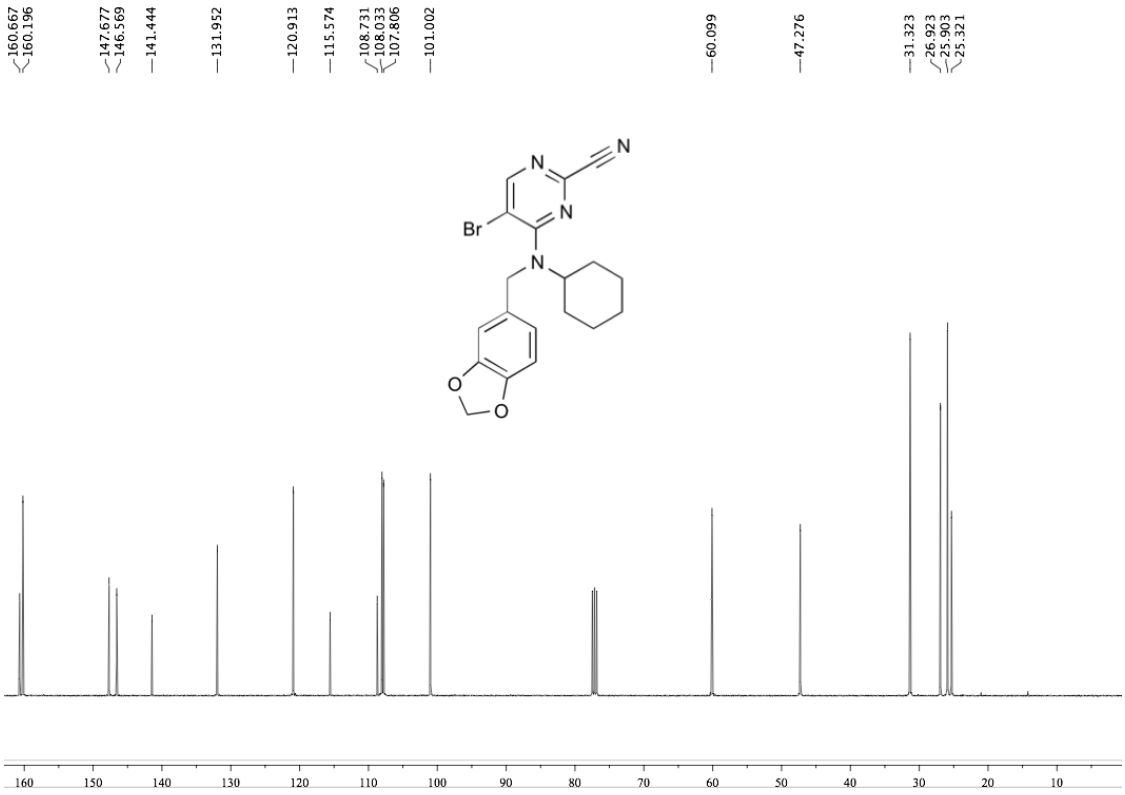


Fig. 12ESI ^{13}C NMR spectrum (100 MHz, 298 K, $CDCl_3$) of **5**.

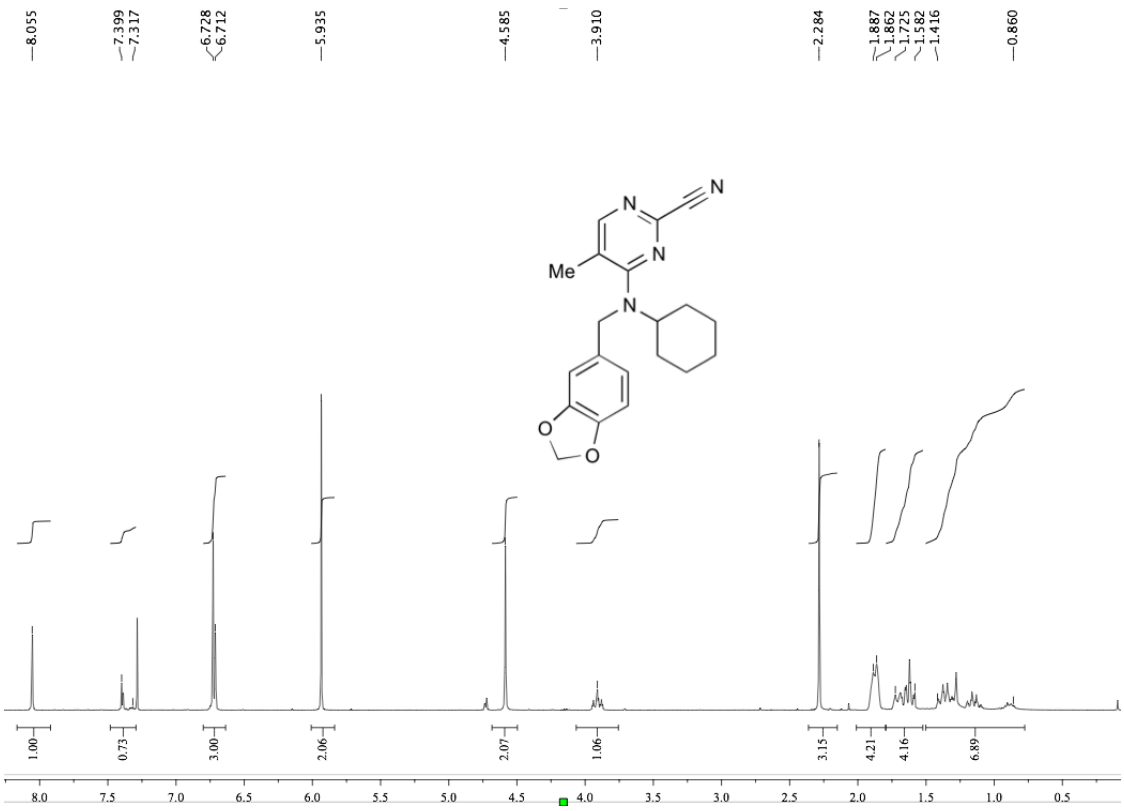


Fig. 13ESI ^{1}H NMR spectrum (400 MHz, 298 K, $CDCl_3$) of **8**.

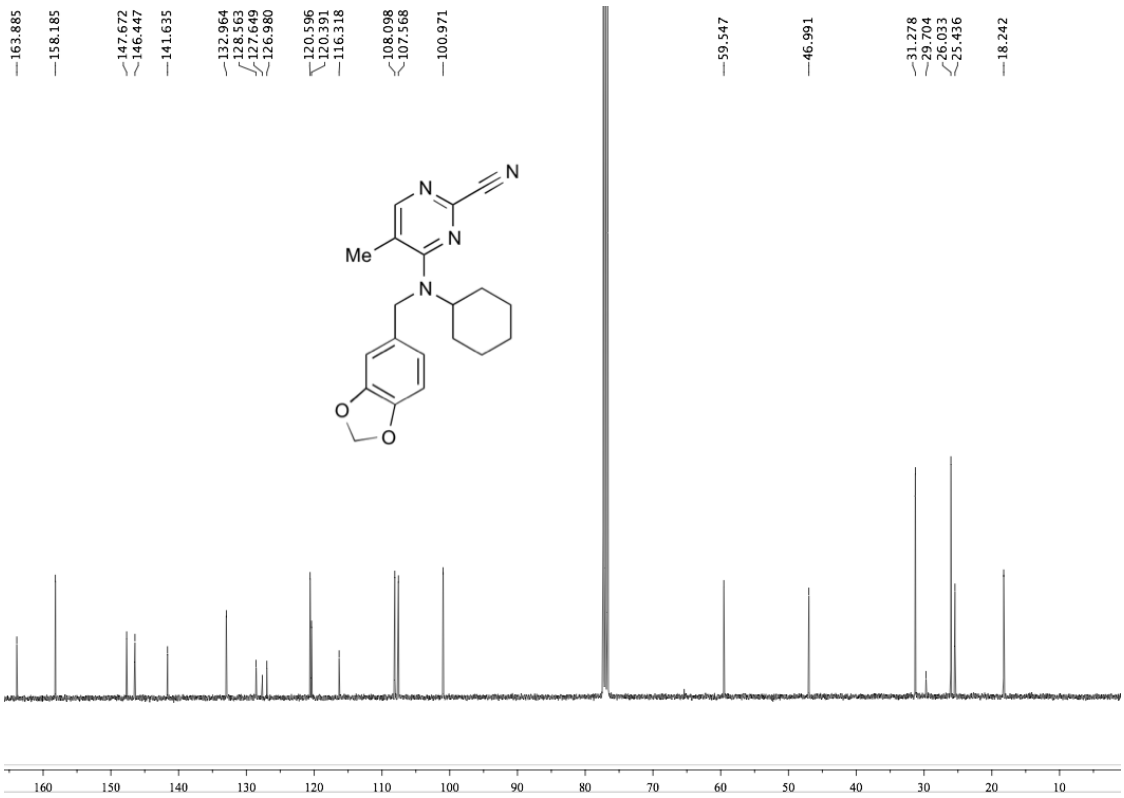


Fig. 14ESI ^{13}C NMR spectrum (100 MHz, 298 K, $CDCl_3$) of **8**.

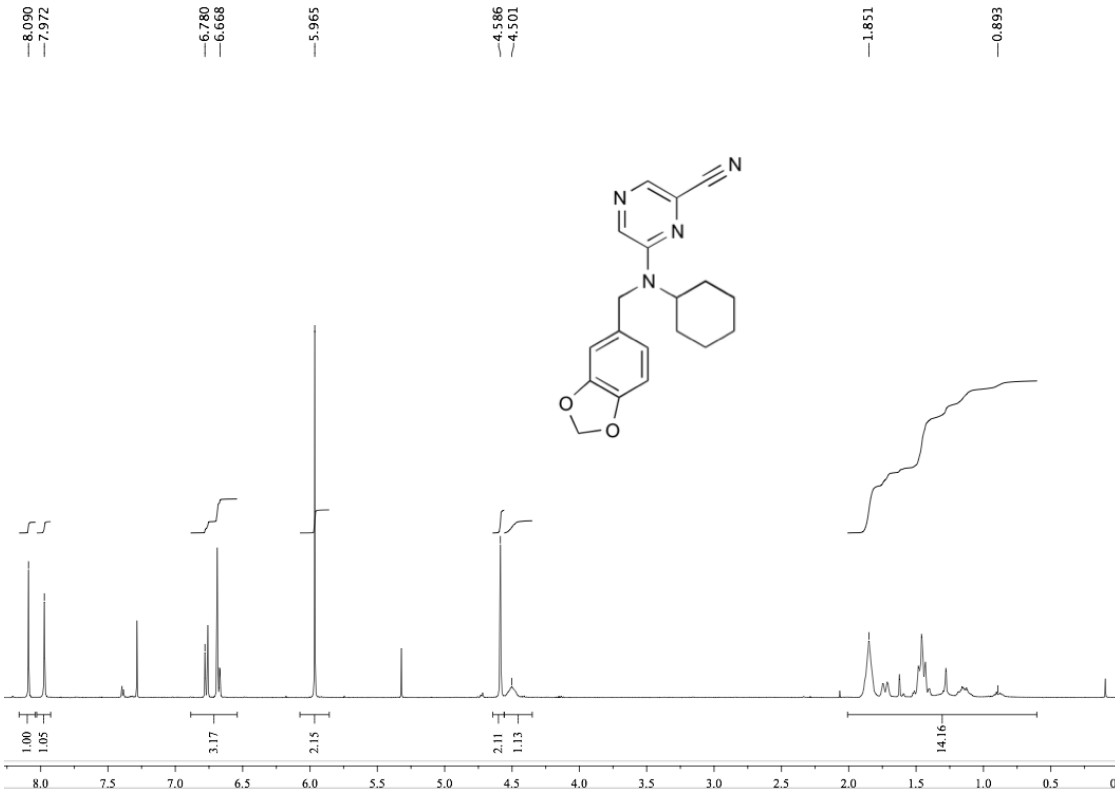


Fig. 15ESI ^{1}H NMR spectrum (400 MHz, 298 K, $CDCl_3$) of **9**.

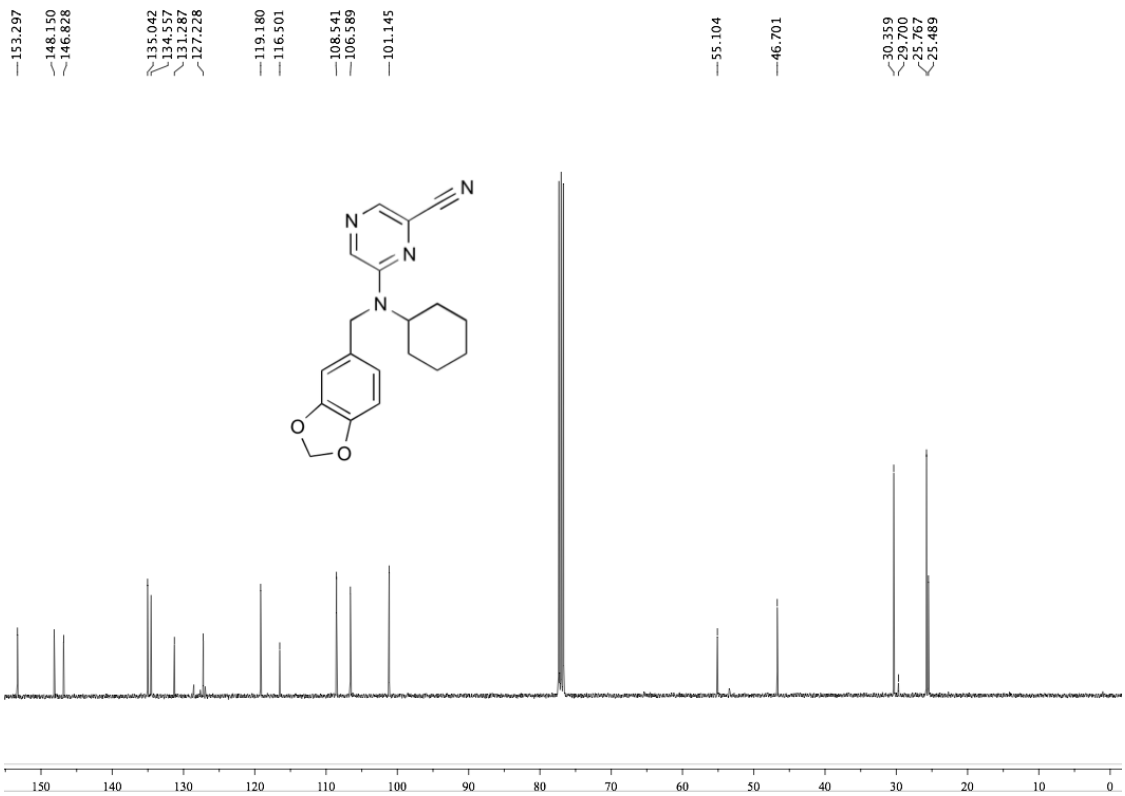


Fig. 16ESI ^{13}C NMR spectrum (100 MHz, 298 K, $CDCl_3$) of **9**.

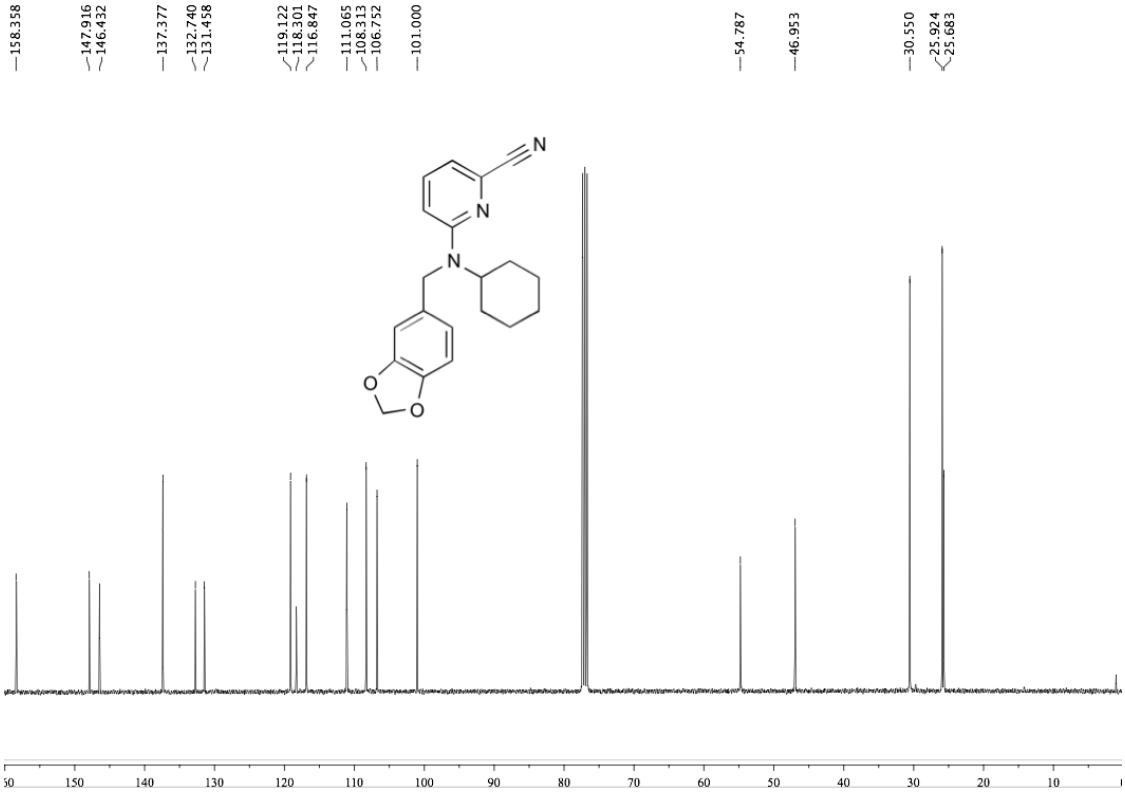


Fig. 17ESI ^{1}H NMR spectrum (400 MHz, 298 K, $CDCl_3$) of **10**.

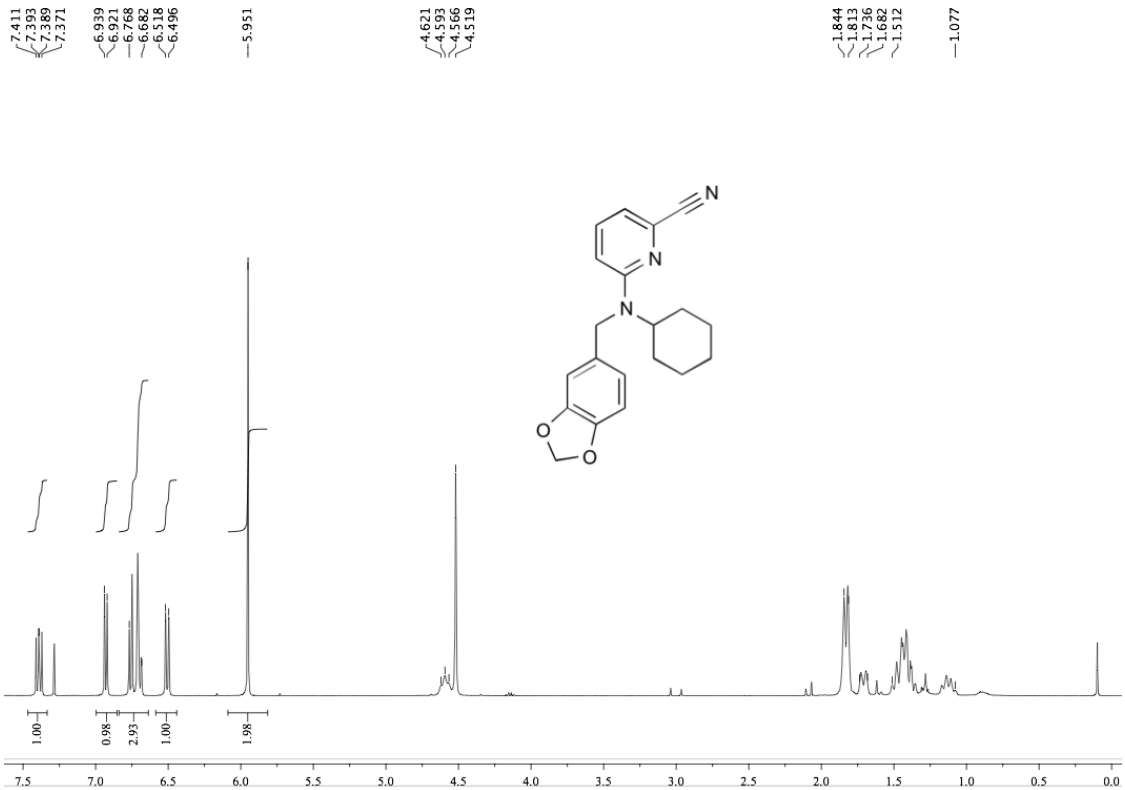


Fig. 18ESI ^{13}C NMR spectrum (100 MHz, 298 K, $CDCl_3$) of **10**.

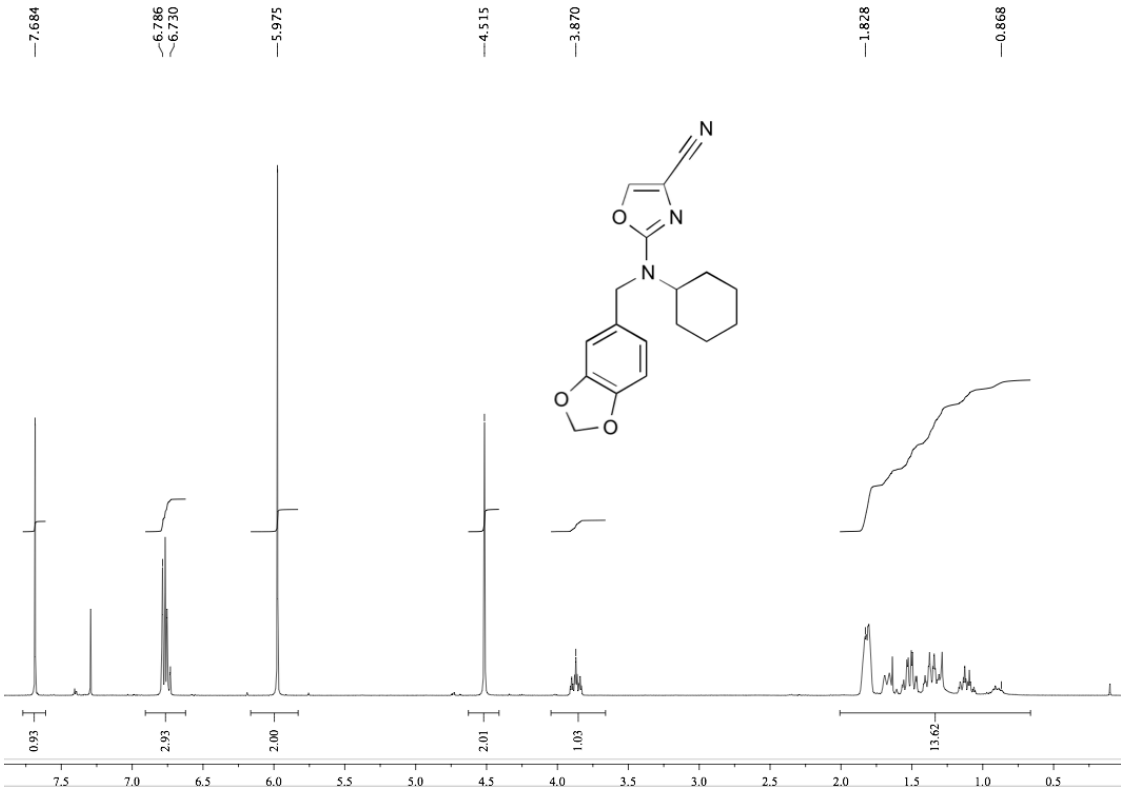


Fig. 19ESI ^{1}H NMR spectrum (400 MHz, 298 K, $CDCl_3$) of **12**.

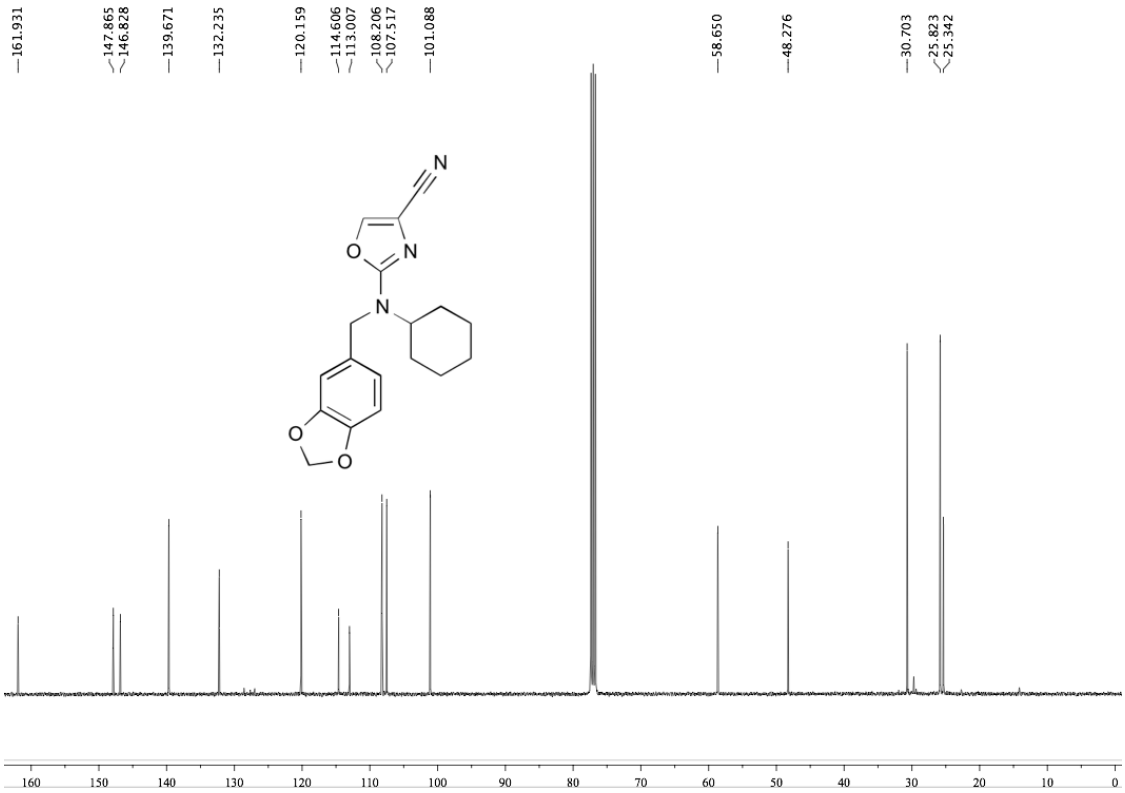


Fig. 20ESI ^{13}C NMR spectrum (100 MHz, 298 K, $CDCl_3$) of **12**.

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