Rapid Access to 10-(Cyclohexylimino)-7,9-diazaspiro[4.5]decane-6,8-dione Derivatives for HIV-1 Reverse Transcriptase Inhibition via Ruthenium-Catalyzed Ring-Closing Metathesis

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Abstract: HIV-1 reverse transcriptase, a multifunctional enzyme critical in the viral replication process, is an important target for suppression of virus spread. To date, there has been considerable effort to develop drugs against this enzyme with high activity and specificity, notably TNK-651 and its derivatives. In order to further improve the efficacy and to explore the structure–activity relationship, we have introduced the diazaspiro[4.5]decane-6,8-dione scaffold, with both a pyrimidine and an alicyclic ring, and have synthesized several new compounds in this class. Appreciable overall yield was achieved with minimized purification of the intermediates. Several compounds were tested against HIV-1 reverse transcriptase *in vitro* using nevirapine as a reference. One compound showed potent inhibitory activity, with an IC_{50} value (ca. 1.65 μM) comparable to that of nevirapine. Our synthetic method provides a rapid access to compounds in this class. Thus, many other similar compounds can be further studied in a timely and cost-effective manner.

Key words: heterocycles, olefination, antiviral agents, HIV, ring closure, NNRTIs

Reverse transcriptase (RT) of human immunodeficiency virus type 1 (HIV-1) is a multifunctional enzyme that is crucial for HIV replication. Since identified, this enzyme has been one of the most attractive targets in anti-HIV-1 drug development. Nowadays, non-nucleoside RT inhibitors (NNRTIs) with unique antiviral potency and low toxicity are widely used in the clinic and have proven effective in stopping HIV-1 replication. However, patients treated with NNRTIs are often found to develop drug resistance very rapidly. Therefore, new NNRTIs with novel scaffolds need to be developed in order to combat this severe drug resistance. Among more than 50 different series of NNRTIs that have been reported so far, TNK-651 and its derivative TNK-6132[1] (Figure 1) have attracted our attention because of their unique scaffold, in particular the isopropyl group at the C-5 position. Previous work has indicated that a bulky hydrophobic group like isopropyl is needed in this class of compounds for the activity against RT. We wondered if an alicyclic structure such as spirocyclopentyl could be used to replace the isopropyl group at the C-5 position, since it may possess the same perpendicular configuration in space.

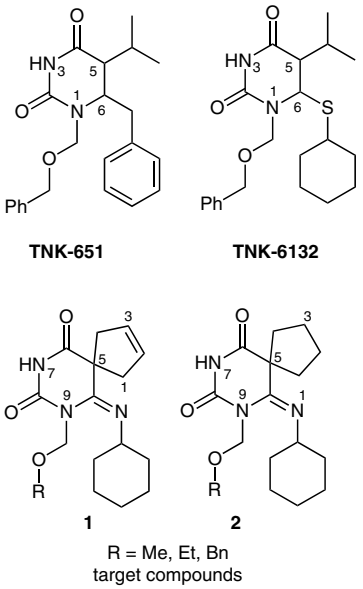

Figure 1 Structures of the target compounds

Compounds based on an azaspiro scaffold, as an important class of new structures, have shown inhibitory effects on many important biological targets including glycogen phosphorylase,[2] the NK_1 receptor,[3] glycine transporter 1 (GlyT1),[4] aldose reductase[5] and neuronal nicotinic acetylcholine receptors.[6] However, the synthesis of such systems is not an easy task due to the lack of effective and general methods to set up the center quaternary carbon (Figure 1). In order to synthesize the 10-(cyclohexylimino)-7,9-diazaspiro[4.5]dec-2-ene-6,8-diones **1** and 10-(cyclohexylimino)-7,9-diazaspiro[4.5]decane-6,8-diones **2**, a conventional route is described (Scheme 1) with ruthenium-catalyzed ring-closing metathesis (RCM) as the key synthetic step.

Based on the structure–activity relationship studies of NNRTIs, the conformational flexibility of compounds is an important parameter for potency toward viral mutant strains. For example, replacement of the C-6 aromatic moiety of TNK-651 by a cyclohexylthio group resulted in

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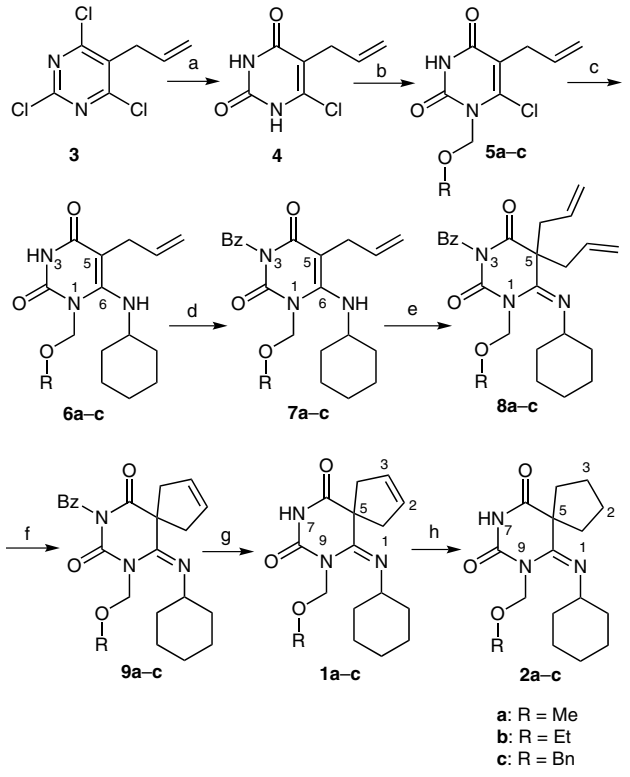
TNK-6132 (Figure 1), which has an improved activity against drug-resistant HIV-1 mutants. The rationalization has been that the cyclohexyl moiety, which possesses more conformational flexibility than the aromatic ring, could fit into the binding pocket of HIV-1 RT more tightly.[1] In accordance with the literature, we thought that a spiro five-membered ring as the 5-substituent in the uracil ring could influence the conformation of an adjacent cyclohexylimino group (Figure 1) and affect the binding affinity with HIV-1 RT.[7] In addition, the introduction of the cyclohexyl group at the imine position, with a better conformational flexibility than an aromatic ring, would result in an efficient binding to mutant RT to improve the activity against HIV mutant strains.[1,8]

Accordingly, several compounds based on the azaspiro scaffold with two basic structures, **1** and **2**, were designed (Figure 1), and a synthetic route planned in such a way that rapid medicinal chemistry optimization can be easily made after the initial lead identification (Scheme 1).

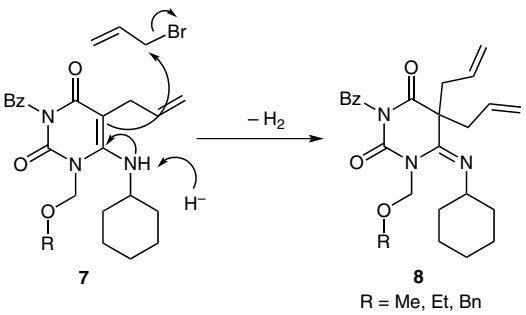
The key precursor to compounds **1** are the 1-(alkoxymethyl)-5-allyl-6-(cyclohexylamino)pyrimidine-2,4(1*H*,3*H*)-diones **6** (Scheme 1), which were synthesized in three steps starting from 5-allyl-2,4,6-trichloropyrimidine (**3**) according to a previous report.[9] Compound **3** was refluxed with 2 M aqueous sodium hydroxide (4 equiv) overnight to afford 5-allyl-6-chlorouracil (**4**) in good yield (80%). For the subsequent alkylation step, we first tried to use chloromethyl ethers to install the N-substitution at position 1. Compound **4** was stirred with alkyl chloromethyl ethers in *N*,*N*-dimethylformamide at room temperature for 12 hours, using K_2CO_3 (or Cs_2CO_3) as base; however, instead of the expected products, the corresponding N^1,N^3-dialkyl derivatives were obtained. In order to improve the selectivity of the N-1 position, uracil **4** was silylated using *N*,*O*-bis(trimethylsilyl)acetamide (BSA) in *N*,*N*-dimethylformamide at room temperature and subsequently alkylated with the corresponding alkyl chloromethyl ethers to give the desired 1-alkylated 5-allyl-6-chlorouracils **5** in 41–85% yield.[10] Cyclohexylamine was then used both as nucleophile and base to substitute the chloro group, furnishing the key intermediate 5-allyl-6-(cyclohexylamino)pyrimidine derivatives **6** in good yield (80–85%).



Scheme 1 Synthetic route to target compounds **1** and **2**. *Reagents and conditions*: (a) 2 M aq NaOH (4 equiv), reflux, 12 h, 80%; (b) (1) BSA (2.5 equiv), DMF, r.t., 30 min; (2) $ROCH_2Cl$ (1.0 equiv), DMF, r.t., 6–9 h, 41–85%; (c) $CyNH_2$ (2.5 equiv), dioxane, reflux, 24 h, 80–85%; (d) BzCl (1.2 equiv), Et_3N (1.2 equiv), CH_2Cl_2, r.t., overnight, 88–95%; (e) allyl bromide (1.2 equiv), NaH (1.2 equiv), anhyd DMF, r.t., 1 h, 71–74%; (f) 1st generation Grubbs' catalyst (5 mol%), CH_2Cl_2, r.t., overnight, 75–85%; (g) 9 M NH_3 in MeOH (10 equiv), CH_2Cl_2, r.t., 1 h, 73–78%; (h) H_2, 10% Pd/C, EtOAc, r.t., 36 psi, 1 h, 73–80%.

In a subsequent alkylation reaction, the 4-O-alkylated byproduct was obtained when N-3 was not protected. We concluded that it was necessary to introduce a protecting group at N-3 before substitution at the C-5 position of compounds **6** to avoid isomerization of the pyrimidine ring. Of all the protecting groups that we have tried, only the benzoyl group provided a satisfactory deprotection yield without affecting other functional groups in this experimental setting. Protection was accomplished by stirring the intermediates **6** with benzoyl chloride (1.2 equiv) and triethylamine (1.2 equiv) in anhydrous dichloromethane at room temperature overnight, which afforded compounds **7** in 88–95% yield (Scheme 1).

To effectively transform compounds **7** into **8**, we used a base to remove the proton from the secondary amine group at C-6, which resulted in a carbanion at the C-5 position. The proposed mechanism is outlined in Scheme 2.[11,12] In particular, sodium hydride was used as the appropriate base for the reaction, in which hydrogen gas would be produced and removed from the system. Thus, the equilibrium is driven to form the carbanion at C-5, with simultaneous formation of the C=N double bond.



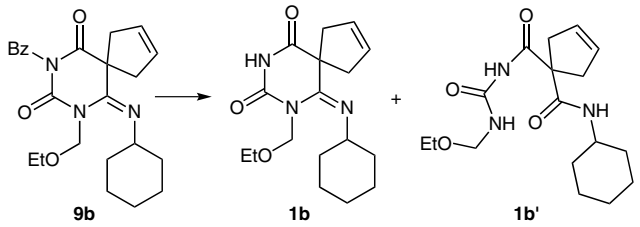
Scheme 2 Proposed mechanism for the formation of **8**

The reaction was performed by stirring compounds **7** with allyl bromide (1.2 equiv) in anhydrous *N*,*N*-dimethylformamide while sodium hydride (60% dispersion in min-

eral oil) was added in portions.[12] A color change of the solution from red to pale yellow is a good indication of the completeness of the reaction. Compounds **8** were obtained in 71–74% yield; the structures were confirmed by ^{1}H NMR spectroscopy.

Ring-closing metathesis (RCM) is a very powerful synthetic tool for carbon–carbon bond formation.[13] A ruthenium catalyst, namely 1st generation Grubbs' catalyst, was used in the RCM reaction. Thus, in order to form the azaspiro ring system containing the quaternary carbon center, compounds **8** were treated with Grubbs' catalyst (5 mol%) in dichloromethane at room temperature overnight to give azaspiro compounds **9** in 75–85% yield.[13c,14] The formation of the ring-closed compounds **9** was confirmed by their ^{1}H NMR spectra that exhibited, in each case, signals located at δ ~5.60–5.85 ppm (representing C*H*=C*H*), and by their high-resolution mass spectra which showed that the molecular weight of compounds **9** is 28 less than that of the corresponding compounds **8** (see experimental section).

Deprotection of the benzoyl group of derivatives **9** proceeded successfully with ammonia (9 M) dissolved in methanol to give target compounds **1** in 73–78% yield (Scheme 1).



Scheme 3 Deprotection of **9b**. *Reagents and conditions*: 9 M NH_3 in MeOH (10 equiv), CH_2Cl_2, r.t., 1 h.

To avoid formation of the ring-opened byproduct **1b′** (Scheme 3), the methanolic ammonia must be added dropwise over a prolonged period of time. Crude product was carefully separated by silica gel column chromatography with ethyl acetate–petroleum ether (1:3 v/v) as eluent. The structure of compound **1b′** was characterized by ^{1}H NMR, ^{13}C NMR, HSQC, HMBC and HRMS analysis. The main supporting evidence for the location of the cleavage site was provided by the HMBC data in which the methylene signal (δ_H 4.79–4.81, 2 H, d, OCH_2N) correlated with the carbonyl carbon (δ_C 153.4, C=O) and the methylene carbon (δ_C 63.7, OCH_2CH_3) (Figure 2).

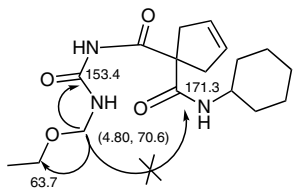


Figure 2 HMBC correlations of **1b′**

Alkenes **1** were subjected to hydrogenation (H_2, Pd/C, EtOAc, r.t., 36 psi, 1 h) to yield the target saturated derivatives **2** (73–80%),[15] in which the reaction time must be controlled to avoid hydrogenation of the C=N double bond.

Compounds **1a**–**c** and **2a**–**c** were tested for their activity against HIV-1 RT in an assay using a poly(rA)/oligo(dT)$_{15}$ homopolymer template with the HIV-1 antigen detection ELISA method[16] and nevirapine as a reference compound. The results indicated that compound **2c** has potent inhibitory activity against HIV-1 RT with an IC_{50} value of 1.65 μM, comparable to that of nevirapine (IC_{50} = 4.37 μM).

Here, we have reported an efficient strategy for the synthesis of the 10-(cyclohexylimino)-7,9-diazaspiro[4.5]dec-2-ene-6,8-dione **1** and 10-(cyclohexylimino)-7,9-diazaspiro[4.5]decane-6,8-dione **2** heterocyclic scaffold via ring-closing metathesis. The overall yield is acceptable and the purification of intermediates is trouble-free. Our ongoing efforts will presumably show that this strategy is also suitable for other azaspiro heterocyclic scaffolds.

The biological results showed that target compound **2c** has potent inhibitory activity against HIV-1 RT, with an IC_{50} value of 1.65 μM, which could be explained by favorable formation of π–π interactions between the phenyl moiety at the terminus of the N-9 side chain and some aromatic amino acid residues. Moreover, the double bond at C-2,C-3 of target compounds **1** would be unfavorable for improving the inhibitory activity. In light of the biological activity of azaspiro derivatives, the 10-(cyclohexylimino)-7,9-diazaspiro[4.5]dec-2-ene-6,8-dione **1** and 10-(cyclohexylimino)-7,9-diazaspiro[4.5]decane-6,8-dione **2** derivatives are currently under further investigation and the results will be reported in due course.

All reagents were purchased from commercial suppliers and used without further purification. All solvents were dried and redistilled before use. Flash chromatography was carried out with silica gel (400 mesh). Analytical TLC was performed with silica gel GF254 plates, and the products were visualized by UV detection. Melting points were determined on an X4-type melting-point apparatus and are uncorrected. FTIR spectra were recorded in the solid state as KBr dispersions using a Nicolet NEXUS 470 FTIR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 on a Bruker AV-400 spectrometer. Chemical shifts (δ) are reported in ppm referenced to internal TMS. Coupling constants (*J*) are reported in hertz (Hz). The signals are expressed as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) or br (broad). ESI-MS spectra were obtained with a Linear Scientific LDI-1700 mass spectrometer. HRMS data were measured using ESI on a Bruker Daltonics APEX IV spectrometer. Elemental analysis was performed by the State Key Laboratory of Natural and Biomimetic Drugs, Peking University with a Vario EL III CHN Analyzer (Elementar Analysensysteme GmbH, Germany). All values for C, H and N were found to be within +0.3% of theoretical values. Purity of all tested compounds was >97%, as estimated by HPLC analysis (the major peak accounted for >97% of the combined total peak area, as monitored by a UV detector at 240 nm).

5-Allyl-6-chloropyrimidine-2,4(1*H*,3*H*)-dione (5-Allyl-6-chlorouracil, 4)
A mixture of 5-allyl-2,4,6-trichloropyrimidine (**3**; 45 g, 0.2 mol), NaOH (32 g, 0.8 mol) and H_2O (400 mL) was refluxed with stirring for 10–12 h, until a clear solution was obtained. After cooling, the solution was washed with Et_2O (60 mL), and the water phase was acidified with concd aq HCl to pH 3–4. The white crystals formed after standing for 2 h at r.t. were collected by filtration and recrystallized (EtOH) to give **4**.[9]

Yield: 30 g (80%); white crystals; mp 212–214 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.05–3.06 (d, J = 6.0 Hz, 2 H), 5.00–5.04 (m, J_1 = 10.0 Hz, J_2 = 17.2 Hz, 2 H), 5.73–5.80 (m, 1 H), 11.39 (s, 1 H), 11.95 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 29.3, 108.3, 116.0, 134.5, 142.3, 150.1, 163.1.

Compounds 5a–c; General Procedure
To a suspension of **4** (1.86 g, 0.01 mol) in DMF (30 mL) was added *N*,*O*-bis(trimethylsilyl)acetamide (5.1 g, 0.025 mol, 2.5 equiv), and the resulting mixture was stirred for 30 min at r.t. to obtain a clear solution. Then, the chloromethyl ether (0.01 mol, 1 equiv) was added, and the mixture was stirred at r.t. for 6–9 h. When the reaction was complete (TLC), the solvent was completely evaporated under reduced pressure. EtOAc (100 mL) was added to the residue, and the mixture was washed with brine (70 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was chromatographed on silica gel (EtOAc–petroleum ether, 1:5 v/v) to afford the pure N^1-alkylated product and part of the starting material.

5-Allyl-6-chloro-1-(methoxymethyl)pyrimidine-2,4(1*H*,3*H*)-dione (5a)
Yield: 1.96 g (85%); white solid; mp 105–107 °C.

IR (KBr): 3435, 3163, 3124, 3019, 2825, 1732, 1677, 1639, 1603 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.23–3.25 (d, J = 6.0 Hz, 2 H), 3.43 (s, 3 H), 5.01–5.04 (d, J = 10.0 Hz, 1 H). 5.07–5.12 (d, J = 17.2 Hz, 1 H), 5.45 (s, 2 H), 5.72–5.82 (m, 1 H), 10.39 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.5, 57.4, 76.2, 112.7, 116.5, 132.7, 144.1, 150.6, 161.7.

ESI-HRMS: m/z [M + Na]$^+$ calcd for $C_9H_{11}ClN_2O_3Na$: 253.0356; found: 253.0367.

5-Allyl-6-chloro-1-(ethoxymethyl)pyrimidine-2,4(1*H*,3*H*)-dione (5b)
Yield: 1.83 g (75%); white solid; mp 117–119 °C.

IR (KBr): 3434, 3154, 3119, 3013, 2981, 2923, 2868, 2819, 1725, 1671, 1640, 1456, 1425, 1343, 960, 923 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.21–1.25 (t, J = 6.8 Hz, 3 H), 3.27–3.29 (d, J = 6.0 Hz, 2 H), 3.65–3.70 (q, J = 7.2 Hz, 2 H), 5.05–5.08 (d, J = 10.0 Hz, 1 H) , 5.11–5.16 (d, J = 17.2 Hz, 1 H), 5.51 (s, 2 H), 5.76–5.86 (m, 1 H), 9.75 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.0, 30.6, 65.5, 74.8, 112.6, 116.6, 132.7, 144.3, 150.3, 161.3.

ESI-HRMS: m/z [M + Na]$^+$ calcd for $C_{10}H_{13}ClN_2O_3Na$: 267.0512; found: 267.0510.

5-Allyl-1-(benzyloxymethyl)-6-chloropyrimidine-2,4(1*H*,3*H*)-dione (5c)
Yield: 1.26 g (41%); white solid; mp 104–106 °C.

IR (KBr): 3474, 3168, 3040, 2930, 2876, 2831, 1699, 1683, 1607, 1494, 1447, 980, 926, 747 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.23–3.25 (d, J = 6.0 Hz, 2 H), 4.69 (s, 2 H), 5.05–5.08 (d, J = 10.0 Hz, 1 H), 5.10–5.14 (d, J = 17.2 Hz, 1 H), 5.58 (s, 2 H), 5.74–5.83 (m, 1 H), 7.27–7.33 (m, 5 H), 10.07 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.6, 72.1, 74.8, 112.7, 116.6, 127.7, 128.0, 128.5, 132.8, 137.1, 144.1, 150.5, 161.5.

ESI-HRMS: m/z [M + Na]$^+$ calcd for $C_{15}H_{15}ClN_2O_3Na$: 329.0669; found: 329.0656.

Compounds 6a–c; General Procedure
$CyNH_2$ (2.48 g, 0.025 mol, 2.5 equiv) was added to compound **5a–c** (0.01 mol) in dioxane (30 mL), and the resulting mixture was refluxed for 24 h. When the reaction was complete (TLC), the volatiles were evaporated under reduced pressure. CH_2Cl_2 (100 mL) was added to the residue, and the mixture was washed with 1 M aq HCl (80 mL) and sat. aq $NaHCO_3$ (100 mL) successively. The organic layer was dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc–petroleum ether, 1:1 v/v).

5-Allyl-6-(cyclohexylamino)-1-(methoxymethyl)pyrimidine-2,4(1*H*,3*H*)-dione (6a)
Yield: 2.34 g (80%); white solid; mp 135–138 °C.

IR (KBr): 3325, 3024, 2930, 2855, 1704, 1646, 1624, 1603, 1451, 1350 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.15–1.35 (m, 5 H), 1.61–1.64 (m, 1 H), 1.72–1.76 (m, 2 H), 1.95–1.97 (m, 2 H), 3.17–3.18 (d, J = 5.6 Hz, 2 H), 3.46 (s, 3 H), 3.48–3.50 (m, 1 H), 4.75–4.77 (d, J = 5.6 Hz, 1 H), 5.02–5.04 (m, 1 H), 5.06–5.07 (m, 1 H), 5.35 (s, 2 H), 5.88–5.95 (m, 1 H), 10.00 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.8, 25.3, 28.8, 34.7, 54.6, 56.6, 75.6, 92.2, 114.7, 136.2, 151.7, 153.5, 164.2.

ESI-MS: m/z = 294.4 [M + H]$^+$, 316.4 [M + Na]$^+$.

ESI-HRMS: m/z [M + H]$^+$ calcd for $C_{15}H_{24}N_3O_3$: 294.1818; found: 294.1817.

5-Allyl-6-(cyclohexylamino)-1-(ethoxymethyl)pyrimidine-2,4(1*H*,3*H*)-dione (6b)
Yield: 2.61 g (85%); white solid; mp 176–179 °C.

IR (KBr): 3313, 3181, 3044, 2974, 2928, 2854, 2819, 1709, 1656, 1453, 1326, 996, 940, 910 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.17–1.33 (m, 8 H), 1.63–1.66 (m, 1 H), 1.74–1.78 (m, 2 H), 1.97–1.99 (m, 2 H), 3.18–3.19 (d, J = 5.2 Hz, 2 H), 3.50–3.58 (m, 1 H), 3.68–3.73 (q, J = 7.2 Hz, 2 H), 4.90–4.92 (d, J = 9.2 Hz, 1 H), 5.04–5.09 (m, 2 H), 5.38 (s, 2 H), 5.88–5.97 (m, 1 H), 8.67 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.0, 24.8, 25.3, 28.8, 34.8, 54.5, 64.7, 74.2, 91.8, 114.8, 136.2, 151.3, 153.6, 163.5.

ESI-MS: m/z = 308.5 [M + H]$^+$, 330.5 [M + Na]$^+$.

ESI-HRMS: m/z [M + H]$^+$ calcd for $C_{16}H_{26}N_3O_3$: 308.1974; found: 308.1972.

5-Allyl-1-(benzyloxymethyl)-6-(cyclohexylamino)pyrimidine-2,4(1*H*,3*H*)-dione (6c)
Yield: 3.10 g (84%); white solid; mp 157–160 °C.

IR (KBr): 3355, 3150, 3064, 2975, 2935, 2855, 2819, 1715, 1648, 1599, 1484, 1463, 987, 935, 907, 745 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.11–1.29 (m, 5 H), 1.60–1.74 (m, 3 H), 1.93–1.96 (m, 2 H), 3.18–3.19 (d, J = 5.6 Hz, 2 H), 3.51–3.54 (m, 1 H), 4.71 (s, 2 H), 4.77–4.80 (d, J = 9.6 Hz, 1 H), 5.03–5.08 (m, 2 H), 5.48 (s, 2 H), 5.87–5.95 (m, 1 H), 7.32–7.37 (m, 5 H), 9.52–9.56 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.8, 30.3, 33.8, 39.8, 59.6, 76.3, 79.1, 97.3, 119.8, 133.1, 133.2, 133.5, 141.2, 141.8, 156.6, 158.5, 169.0.

ESI-MS: m/z = 370.5 [M + H]$^+$, 392.4 [M + Na]$^+$.

ESI-HRMS: m/z [M + H]$^+$ calcd for $C_{21}H_{28}N_3O_3$: 370.2131; found: 370.2135.

Compounds 7a–c; General Procedure
To a soln of compound **6a–c** (0.01 mol) in anhyd CH_2Cl_2 (30 mL) was added BzCl (1.69 g, 0.012 mol, 1.2 equiv) and anhyd Et_3N (1.21 g, 0.012 mol, 1.2 equiv). The mixture was stirred at r.t. overnight. When the reaction was complete (TLC), the solution was washed with 1 M aq HCl (20 mL) and sat. aq $NaHCO_3$ (30 mL) successively. The organic layer was dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc–petroleum ether, 1:5 v/v).

5-Allyl-3-benzoyl-6-(cyclohexylamino)-1-(methoxymethyl)pyrimidine-2,4(1*H*,3*H*)-dione (7a)
Yield: 3.49 g (88%); pale yellow oil.

IR (KBr): 3365, 3193, 3073, 2930, 2853, 1747, 1713, 1694, 1643, 1602, 1535, 1449, 1423, 1088, 912, 790, 714 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.19–1.34 (m, 5 H), 1.61–1.65 (m, 1 H), 1.75–1.79 (m, 2 H), 1.99–2.02 (m, 2 H), 3.19–3.20 (d, *J* = 5.6 Hz, 2 H), 3.46 (s, 3 H), 3.54–3.58 (m, 1 H), 4.92–4.95 (d, *J* = 5.6 Hz, 1 H), 5.08–5.13 (t, *J* = 10.0 Hz, 2 H), 5.34 (s, 2 H), 5.87–5.96 (m, 1 H), 7.45–7.49 (t, *J* = 7.6 Hz, 2 H), 7.59–7.63 (t, *J* = 7.6 Hz, 1 H), 7.91–7.94 (d, *J* = 7.2 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.8, 25.3, 28.9, 34.8, 54.7, 56.9, 76.2, 91.6, 115.1, 129.1, 130.3, 132.1, 134.7, 136.0, 150.4, 151.7, 153.2, 162.7, 169.3.

ESI-MS: *m*/*z* = 398.5 $[M + H]^+$, 420.4 $[M + Na]^+$.

ESI-HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{28}N_3O_4$: 398.2080; found: 398.2078.

5-Allyl-3-benzoyl-6-(cyclohexylamino)-1-(ethoxymethyl)pyrimidine-2,4(1*H*,3*H*)-dione (7b)
Yield: 3.70 g (90%); pale yellow oil.

IR (KBr): 3363, 3170, 3073, 2974, 2931, 2855, 1747, 1713, 1646, 1601, 1533, 1450, 1215, 1087, 911, 892, 712 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.20–1.37 (m, 8 H), 1.62–1.65 (m, 1 H), 1.75–1.78 (m, 2 H), 1.99–2.03 (m, 2 H), 3.19–3.20 (d, *J* = 5.6 Hz, 2 H), 3.56–3.63 (m, 1 H), 3.67–3.72 (q, *J* = 6.8 Hz, 2 H), 5.07–5.12 (br, 3 H), 5.38 (s, 2 H), 5.87–5.96 (m, 1 H), 7.44–7.48 (t, *J* = 7.6 Hz, 2 H), 7.59–7.62 (t, *J* = 7.6 Hz, 1 H), 7.91–7.93 (d, *J* = 7.2 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.9, 24.8, 25.3, 28.9, 34.8, 54.6, 65.0, 74.6, 91.3, 115.0, 129.0, 130.3, 132.1, 134.7, 136.1, 150.4, 153.3, 162.7, 169.4.

ESI-MS: *m*/*z* = 412.5 $[M + H]^+$, 434.5 $[M + Na]^+$.

ESI-HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{23}H_{30}N_3O_4$: 412.2236; found: 412.2227.

5-Allyl-3-benzoyl-1-(benzyloxymethyl)-6-(cyclohexylamino)pyrimidine-2,4(1*H*,3*H*)-dione (7c)
Yield: 4.50 g (95%); pale yellow oil.

IR (KBr): 3356, 3152, 3065, 2922, 2853, 2815, 1713, 1640, 1600, 1547, 1484, 1452, 1422, 1367, 1326, 1069, 908, 890, 707 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.18–1.34 (m, 5 H), 1.63–1.75 (m, 1 H), 1.75–1.78 (m, 2 H), 2.00–2.02 (m, 2 H), 3.21–3.22 (d, *J* = 5.2 Hz, 2 H), 3.59–3.62 (m, 1 H), 4.74 (s, 2 H), 4.98–5.00 (d, *J* = 9.6 Hz, 1 H), 5.08–5.13 (dq, *J* = 13.2 Hz, *J* = 1.6 Hz, 2 H), 5.49 (s, 2 H), 5.87–5.97 (m, 1 H), 7.34–7.39 (m, 5 H), 7.48–7.51 (t, *J* = 7.6 Hz, 2 H), 7.62–7.66 (t, *J* = 7.6 Hz, 1 H), 7.93–7.96 (d, *J* = 7.2 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.8, 25.3, 28.8, 34.8, 54.7, 71.7, 74.7, 91.7, 115.1, 128.0, 128.2, 128.6, 129.0, 130.4, 132.1, 134.7, 136.0, 136.7, 150.4, 153.2, 162.7, 169.3.

ESI-MS: *m*/*z* = 474.6 $[M + H]^+$, 496.6 $[M + Na]^+$.

ESI-HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{28}H_{32}N_3O_4$: 474.2393; found: 474.2395.

Compounds 8a–c; General Procedure
To a soln of compound **7a–c** (0.001 mol) and allyl bromide (0.15 g, 0.0012 mol, 1.2 equiv) in anhyd DMF (20 mL) was added 60% NaH (0.048 g, 0.0012 mol, 1.2 equiv) in portions, and the mixture was stirred at r.t. for 1 h. After completion of the reaction as indicated by TLC, the solution was concentrated under reduced pressure. The residue was dissolved in EtOAc (50 mL) and washed with brine (2 × 50 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc–petroleum ether, 1:10 v/v).

5,5-Diallyl-3-benzoyl-6-(cyclohexylimino)-1-(methoxymethyl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (8a)
Yield: 0.31 g (71%); white solid; mp 106–108 °C.

IR (KBr): 3081, 2931, 2853, 1756, 1713, 1678, 1655, 1599, 1547, 1450, 1417, 1345, 972, 942, 922, 785 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.33–1.44 (m, 3 H), 1.51–1.59 (m, 2 H), 1.73–1.76 (m, 3 H), 1.84–1.87 (m, 2 H), 2.91 (br, 4 H), 3.45 (s, 3 H), 4.03–4.05 (br, 1 H), 5.21–5.52 (m, 6 H), 5.76–5.86 (m, 2 H), 7.46–7.50 (t, *J* = 7.6 Hz, 2 H), 7.63–7.67 (t, *J* = 7.6 Hz, 1 H), 7.91–7.93 (d, *J* = 7.6 Hz, 2 H).

ESI-MS: *m*/*z* = 438.7 $[M + H]^+$, 460.7 $[M + Na]^+$.

ESI-HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{25}H_{32}N_3O_4$: 438.23873; found: 438.23921.

5,5-Diallyl-3-benzoyl-6-(cyclohexylimino)-1-(ethoxymethyl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (8b)
Yield: 0.33 g (73%); white solid; mp 102–104 °C.

IR (KBr): 3079, 2927, 2852, 1756, 1714, 1677, 1656, 1600, 1552, 1438, 1417, 1345, 1313, 1092, 971, 942, 785 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.19–1.23 (t, *J* = 6.8 Hz, 3 H), 1.32–1.43 (m, 3 H), 1.50–1.58 (m, 2 H), 1.67–1.75 (m, 3 H), 1.84–1.86 (m, 2 H), 2.78–2.91 (br, 4 H), 3.63–3.68 (q, *J* = 6.4 Hz, 2 H), 4.04 (br, 1 H), 5.20–5.24 (m, 5 H), 5.55 (m, 1 H), 5.76–5.86 (m, 2 H), 7.46–7.50 (t, *J* = 7.6 Hz, 2 H), 7.63–7.66 (t, *J* = 7.6 Hz, 1 H), 7.91–7.93 (d, *J* = 7.6 Hz, 2 H).

ESI-MS: *m*/*z* = 474.7 $[M + Na]^+$.

ESI-HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{26}H_{33}N_3O_4Na$: 474.23633; found: 474.23627.

5,5-Diallyl-3-benzoyl-1-(benzyloxymethyl)-6-(cyclohexylimino)dihydropyrimidine-2,4(1*H*,3*H*)-dione (8c)
Yield: 0.38 g (74%); white solid; mp 88–90 °C.

IR (KBr): 3248, 3089, 3034, 2931, 2855, 1750, 1713, 1679, 1656, 1598, 1548, 1498, 1450, 1422, 1347, 926, 788, 743 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.28–1.38 (m, 3 H), 1.55–1.62 (m, 2 H), 1.71–1.86 (m, 5 H), 2.67–3.01 (m, 4 H), 3.99–4.13 (m, 1 H), 4.73 (s, 2 H), 5.19–5.22 (br, 5 H), 5.63–5.67 (m, 1 H), 5.75–5.79 (m, 2 H), 7.30–7.36 (m, 5 H), 7.46–7.50 (t, *J* = 7.6 Hz, 2 H), 7.64–7.68 (t, *J* = 7.6 Hz, 1 H), 7.90–7.93 (d, *J* = 7.6 Hz, 2 H).

ESI-MS: *m*/*z* = 536.7 $[M + Na]^+$.

ESI-HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{31}H_{36}N_3O_4$: 514.27003; found: 514.27108.

Compounds 9a–c; General Procedure
A soln of 1st generation Grubbs' catalyst (82 mg, 5 mol%) in anhyd CH_2Cl_2 (20 mL) was added via cannula to a soln of compound **8a–c** (0.002 mol) in CH_2Cl_2 (0.02 M). The resulting dark brown solution was stirred at r.t. until TLC indicated that the starting material was no longer present. The volatiles were removed under reduced pressure, and the residue was purified by flash chromatography (EtOAc–petroleum ether, 1:10 v/v).

7-Benzoyl-10-(cyclohexylimino)-9-(methoxymethyl)-7,9-diazaspiro[4.5]dec-2-ene-6,8-dione (9a)
Yield: 0.61 g (75%); white solid; mp 129–131 °C.

IR (KBr): 3066, 2935, 2856, 1753, 1716, 1684, 1654, 1597, 1535, 1450, 1334, 1085, 969, 890, 757, 711 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.30–1.31 (m, 3 H), 1.49–1.51 (m, 2 H), 1.65–1.67 (m, 3 H), 1.74–1.92 (m, 2 H), 2.93–3.14 (m, 2 H), 3.16–3.28 (br, 2 H), 3.48–3.72 (br, 4 H), 5.02–5.84 (m, 4 H), 7.49–7.50 (t, *J* = 7.6 Hz, 2 H), 7.65–7.68 (t, *J* = 7.6 Hz, 1 H), 7.91–7.93 (br, 2 H).

ESI-HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{23}H_{28}N_3O_4$: 410.20743; found: 410.20610.

Anal. Calcd for $C_{23}H_{27}N_3O_4$: C, 67.46; H, 6.65; N, 10.26. Found: C, 67.25; H, 6.78; N, 10.25.

7-Benzoyl-10-(cyclohexylimino)-9-(ethoxymethyl)-7,9-diazaspiro[4.5]dec-2-ene-6,8-dione (9b)
Yield: 0.68 g (80%); white solid; mp 117–119 °C.

IR (KBr): 2930, 2855, 1751, 1715, 1683, 1654, 1597, 1449, 1366, 969, 797, 757, 715 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.21–1.31 (m, 6 H), 1.49–1.51 (m, 2 H), 1.65–1.67 (m, 3 H), 1.74–1.90 (m, 2 H), 2.94–3.10 (m, 2 H), 3.18–3.42 (m, 2 H), 3.52–3.71 (m, 3 H), 5.07–5.83 (m, 4 H), 7.49–7.52 (t, *J* = 7.2 Hz, 2 H), 7.64–7.67 (t, *J* = 7.2 Hz, 1 H), 7.91 (br, 2 H).

ESI-HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{24}H_{30}N_3O_4$: 424.22308; found: 424.22362.

Anal. Calcd for $C_{24}H_{29}N_3O_4$: C, 68.06; H, 6.90; N, 9.92. Found: C, 68.04; H, 6.92; N, 9.96.

7-Benzoyl-9-(benzyloxymethyl)-10-(cyclohexylimino)-7,9-diazaspiro[4.5]dec-2-ene-6,8-dione (9c)
Yield: 0.82 g (85%); white solid; mp 137–138 °C.

IR (KBr): 3066, 2935, 2856, 1754, 1715, 1682, 1652, 1598, 1497, 1450, 1428, 1367, 1334, 1074, 695 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.27–1.32 (m, 3 H), 1.51–1.53 (m, 2 H), 1.58–1.73 (m, 3 H), 1.74–1.90 (m, 2 H), 2.78–3.35 (m, 4 H), 3.52–3.77 (m, 1 H), 4.76 (s, 2 H), 5.11–5.81 (m, 4 H), 7.31–7.37 (m, 5 H), 7.49–7.53 (t, *J* = 7.6 Hz, 2 H), 7.65–7.68 (t, *J* = 7.6 Hz, 1 H), 7.87–7.89 (d, *J* = 7.6 Hz, 2 H).

ESI-MS: *m*/*z* = 486.3 $[M + H]^+$, 508.3 $[M + Na]^+$.

ESI-HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{29}H_{32}N_3O_4$: 486.23873; found: 486.23966.

Anal. Calcd for $C_{29}H_{31}N_3O_4$: C, 71.73; H, 6.43; N, 8.65. Found: C, 71.74; H, 6.55; N, 8.58.

Compounds 1a–c; General Procedure
A 9 M soln of NH_3 in MeOH (0.11 mL, 10 equiv) was added dropwise to a soln of compound **9a–c** (0.1 mmol) in anhyd CH_2Cl_2 (5 mL) at r.t., and the resulting solution was stirred at r.t. until TLC indicated that the starting material was no longer present. Silica gel (0.5 g) was added to the solution, and the resulting suspension was concentrated to dryness under reduced pressure. A white solid was obtained from preloaded silica gel column chromatography (EtOAc–petroleum ether, 1:3 v/v).

10-(Cyclohexylimino)-9-(methoxymethyl)-7,9-diazaspiro[4.5]dec-2-ene-6,8-dione (1a)
Yield: 23 mg (75%); white solid; HPLC purity >98%; mp 118–122 °C.

IR (KBr): 3201, 3124, 2931, 2852, 1712, 1652, 1447, 1344, 1085 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.26–1.27 (m, 3 H), 1.41–1.48 (q, *J* = 10.8 Hz, 2 H), 1.59–1.62 (d, *J* = 14.0 Hz, 3 H), 1.78 (br, 2 H), 2.82–2.86 (d, *J* = 16.6 Hz, 2 H), 3.09–3.16 (m, 2 H), 3.45 (s, 4 H), 4.97–5.46 (m, 2 H), 5.59–5.85 (m, 2 H), 8.23 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.3, 25.8, 34.3, 47.9, 49.4, 55.6, 57.8, 73.0, 77.2, 128.8, 150.0, 150.4, 174.4.

ESI-HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{24}N_3O_3$: 306.1807; found: 306.1818.

Anal. Calcd for $C_{16}H_{23}N_3O_3$: C, 62.93; H, 7.59; N, 13.76. Found: C, 62.78; H, 7.66; N, 13.62.

10-(Cyclohexylimino)-9-(ethoxymethyl)-7,9-diazaspiro[4.5]dec-2-ene-6,8-dione (1b)
Yield: 25 mg (78%); white solid; HPLC purity >98%; mp 98–101 °C.

IR (KBr): 3195, 3072, 2927, 2854, 1738, 1697, 1638, 1447, 1372 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.20–1.30 (m, 6 H), 1.40–1.48 (m, 2 H), 1.59–1.62 (m, 3 H), 1.76–1.79 (m, 2 H), 2.82–2.86 (d, *J* = 16.8 Hz, 2 H), 3.12–3.16 (d, *J* = 15.6 Hz, 2 H), 3.48 (br, 1 H), 3.64–3.70 (q, *J* = 6.8 Hz, 2 H), 5.03–5.49 (m, 2 H), 5.60–5.85 (m, 2 H), 8.13 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.3, 24.3, 25.8, 34.2, 47.8, 55.6, 65.3, 71.4, 77.3, 127.2, 128.8, 150.0, 150.6, 174.6.

ESI-HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{26}N_3O_3$: 320.19687; found: 320.19756.

Anal. Calcd for $C_{17}H_{25}N_3O_3$: C, 63.93; H, 7.89; N, 13.16. Found: C, 63.65; H, 7.88; N, 13.19.

***N*^{1}-Cyclohexyl-*N*^{1}-[(ethoxymethyl)aminocarbonyl]cyclopent-3-ene-1,1-dicarboxamide (1b′)**
Yield: 4 mg (12%); white solid; mp 175–178 °C.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.13–1.24 (m, 6 H), 1.34–1.43 (m, 2 H), 1.61–1.72 (m, 3 H), 1.88–1.91 (m, 2 H), 2.93–2.97 (d, *J* = 15.2 Hz, 2 H), 3.09–3.13 (d, *J* = 15.6 Hz, 2 H), 3.56–3.61 (q, *J* = 7.2 Hz, 2 H), 3.75–3.79 (m, 1 H), 4.79–4.81 (d, *J* = 6.8 Hz, 2 H), 5.74 (s, 2 H), 5.83–5.85 (d, *J* = 7.2 Hz, 1 H), 8.83–8.84 (t, *J* = 5.6 Hz, 1 H), 9.18 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.0, 24.6, 25.3, 32.6, 41.7, 48.8, 59.7, 63.6, 70.6, 128.6, 153.2, 171.3, 174.1.

ESI-HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{17}H_{27}N_3O_4Na$: 360.1893; found: 360.1899.

9-(Benzyloxymethyl)-10-(cyclohexylimino)-7,9-diazaspiro[4.5]dec-2-ene-6,8-dione (1c)
Yield: 28 mg (73%); white solid; HPLC purity >98%; mp 114–117 °C.

IR (KBr): 3223, 3127, 3064, 2927, 2853, 1718, 1654, 1494, 1449, 1340 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.27–1.28 (m, 3 H), 1.46–1.63 (m, 5 H), 1.79 (br, 2 H), 2.74–2.78 (m, 2 H), 3.03–3.07 (m, 2 H), 3.47 (m, 1 H), 4.74 (s, 2 H), 5.60 (s, 2 H), 5.81 (s, 2 H), 7.28–7.35 (m, 5 H), 8.55 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.4, 25.9, 29.7, 34.3, 47.9, 49.3, 55.6, 72.0, 77.4, 127.3, 127.5, 128.3, 128.8, 138.8, 149.9, 150.6, 174.4.

ESI-HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{28}N_3O_3$: 382.21252; found: 382.21298.

Anal. Calcd for $C_{22}H_{27}N_3O_3$: C, 69.27; H, 7.13; N, 11.02. Found: C, 69.09; H, 7.18; N, 10.83.

Compounds 2a–c; General Procedure
To a soln of compound **1a–c** (0.2 mmol) in EtOAc (10 mL) was added 10% Pd on activated carbon (5 mg), and the resulting suspension was stirred under H_2 atmosphere (36 psi) at r.t. for 1 h. The catalyst was removed by filtration through Celite®, and the filtrate was concentrated under reduced pressure to give **2** in good yield.

10-(Cyclohexylimino)-9-(methoxymethyl)-7,9-diazaspiro[4.5]decane-6,8-dione (2a)
Yield: 47 mg (76%); white solid; HPLC purity >98%; mp 103–105 °C.

IR (KBr): 3278, 3114, 2936, 2852, 1743, 1712, 1666, 1469, 1449, 1423, 1386, 963, 767 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.31–1.34 (m, 3 H), 1.45–1.47 (m, 2 H), 1.59–1.63 (m, 3 H), 1.68–1.91 (m, 6 H), 2.08 (br, 2 H), 2.30 (br, 2 H), 3.47 (s, 3 H), 3.64 (s, 1 H), 4.97 (s, 2 H), 8.15 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.0, 25.6, 25.7, 33.8, 34.1, 57.2, 57.6, 58.4, 77.2, 77.6, 145.2, 152.4, 173.9.

ESI-HRMS: *m/z* $[M + H]^+$ calcd for $C_{16}H_{26}N_3O_3$: 308.1970; found: 308.1974.

Anal. Calcd for $C_{16}H_{25}N_3O_3$: C, 62.52; H, 8.20; N, 13.67. Found: C, 62.29; H, 8.26; N, 13.65.

10-(Cyclohexylimino)-9-(ethoxymethyl)-7,9-diazaspiro[4.5]decane-6,8-dione (2b)
Yield: 51 mg (80%); white solid; HPLC purity >97%; mp 111–114 °C.

IR (KBr): 3203, 3087, 2930, 2856, 1739, 1700, 1656, 1537, 1450, 1425, 1089, 982 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.21–1.25 (t, *J* = 10.8 Hz, 3 H), 1.31–1.35 (m, 3 H), 1.45–1.47 (m, 2 H), 1.55–1.67 (br, 4 H), 1.69–1.86 (m, 5 H), 2.07 (br, 2 H), 2.32 (br, 2 H), 3.65–3.70 (m, 3 H), 5.02 (s, 2 H), 7.86 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.1, 24.1, 25.5, 25.7, 33.8, 34.1, 38.6, 57.2, 65.4, 70.7, 76.1, 145.3, 152.2, 173.7.

ESI-MS: *m/z* = 322.3 $[M + H]^+$, 344.2 $[M + Na]^+$.

ESI-HRMS: *m/z* $[M + H]^+$ calcd for $C_{17}H_{28}N_3O_3$: 322.21252; found: 322.21280.

Anal. Calcd for $C_{17}H_{27}N_3O_3$: C, 63.53; H, 8.47; N, 13.07. Found: C, 63.33; H, 8.47; N, 13.06.

9-(Benzyloxymethyl)-10-(cyclohexylimino)-7,9-diazaspiro[4.5]decane-6,8-dione (2c)
Yield: 56 mg (73%); white solid; HPLC purity >98%; mp 130–133 °C.

IR (KBr): 3208, 3089, 3032, 2932, 2854, 1734, 1698, 1671, 1498, 1450, 1417, 1372, 743 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.29–1.45 (m, 5 H), 1.53–1.62 (m, 3 H), 1.70–1.77 (m, 6 H), 2.08 (br, 2 H), 2.33 (br, 2 H), 3.68 (m, 1 H), 4.73 (s, 2 H), 5.08 (s, 2 H), 7.28–7.36 (m, 5 H), 8.15 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.0, 25.5, 25.7, 33.8, 34.1, 57.2, 58.5, 72.0, 75.9, 77.2, 127.6, 127.9, 128.4, 137.4, 145.2, 152.1, 173.6.

ESI-HRMS: *m/z* $[M + H]^+$ calcd for $C_{22}H_{30}N_3O_3$: 384.22817; found: 384.22841.

Anal. Calcd for $C_{22}H_{29}N_3O_3$: C, 68.90; H, 7.62; N, 10.96. Found: C, 68.62; H, 7.65; N, 10.85.

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