Reductive Condensation between β-Keto Esters and Aldehydes: Preparation of Novel Carbon-Linked Dihydropyrone Inhibitors of Hepatitis C Virus Polymerase

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Abstract: The route for the preparation of carbon-linked pyrone libraries involving an optimized one-step reductive condensation between active methylene compounds and aldehydes is described. The initial synthesis of these analogues utilizing conventional alkylation methods proved to be unsuitable for singleton or library application. The chemistry was not only low-yielding but presented serious purification challenges. The optimized route reported herein utilizes a Lewis base-borane complex that acts in situ first as a catalyst for the condensation, then as a mild reducing agent to cleanly yield the desired product in a one-pot reaction.

Key words: Knoevenagel condensation, C–C bond formation, HCV polymerase inhibitor, dihydropyrone, amine-borane reagents

Hepatitis C virus (HCV) continues to be a major public health problem worldwide.[1] Although this area of research has been the subject of intensive investigation for the past 20 years, these efforts have yielded relatively few marketed drugs, each with their own liabilities. There is an ongoing need for new therapies utilizing alternate mechanistic approaches.[2]

Development of HCV NS5B polymerase inhibitors, particularly those which bind to allosteric sites, has gained increasing interest.[3] We have reported previously the identification of a novel class of non-nucleoside HCV NS5B polymerase inhibitors from high-throughput screening (Figure 1, compound **1,** IC_{50} = 0.93 μM, genotype 1b).[4] Moreover, we described how our team was able to achieve low nanomolar activity in an enzymatic assay against the truncated genotype 1b HCV NS5B Δ21 polymerase with sulfur-linked dihydropyrone analogues (S-linked dihydropyrones, Figure 1, e.g., compound **2**, IC_{50} = 0.04 μM and EC_{50} = 3.25 μM).[4,5] This class of compounds, although potent in the enzymatic assay (IC_{50}) only demonstrated moderate antiviral activity in the cell-based replicon assay (EC_{50}) at micromolar concentrations. Additionally the S-linked analogue demonstrated poor absorption after oral dosing (2.5% absorbed) in rat pharmacokinetic evaluation.[6]

It was reasoned that the acidity of the dihydropyrone was responsible for the large EC_{50}/IC_{50} ratio due to poor cell permeability. Experimental pK_a measurements of the sulfur-linked compounds were shown to have a pK_a ~3–5 (**2**, Figure 1, exp. pK_a = 3.41), indicating that the compound is isosterically similar to most carboxylic acids. In order to ensure cellular permeation, further modifications were necessary to achieve desired potency in the cell-based replicon assay. Knowing that the enol moiety within the dihydropyrone central core was critical for enzyme potency, we envisioned a way to modulate the pK_a by replacing the sulfur with a methylene linker. The strategy towards lowering the ionization state of target molecules by reducing the acidity of the pyrone in order to improve the permeability of this series of compounds led to the discovery of carbon-linked dihydropyrones (C-linked dihydropyrones, Figure 1, e.g., compound **3**, IC_{50} = 0.02 μM, EC_{50} = 0.33 μM). The experimental pK_a of these carbon-linked compounds was ~5–6 (e.g., compound **3**, Figure 1, pK_a = 6).

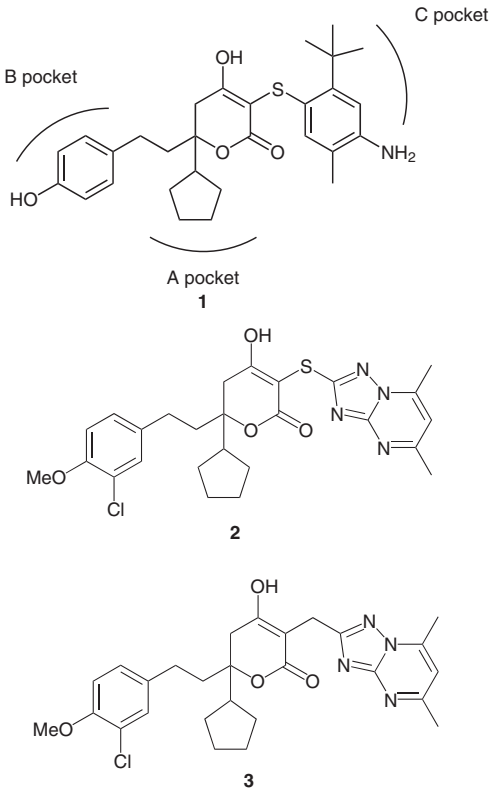

Figure 1 Progression of dihydropyrones as HCV polymerase inhibitors

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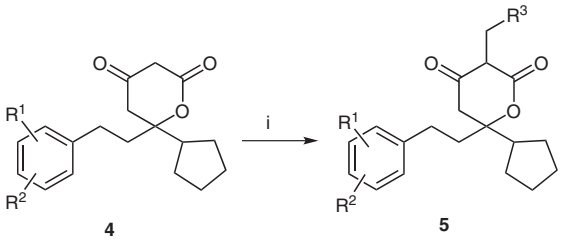
Although the chemistry to obtain the S-linked analogues proved to be straightforward and was suitable for library production,[5] the preparation of the C-linked analogues demonstrated to be quite challenging (Scheme 1). The carbon-linked C fragment analogues were originally prepared from **4**, employing an enolate formation under basic conditions followed by nucleophilic displacement of heterobenzylic and other alkyl halides under Finkelstein conditions. However, these reactions were very low yielding (0–20%), and separation of the desired product from the undesired O-alkylated and bis-alkylated side products was inefficient.



Scheme 1 Preparation of carbon-linked pyrones via alkylation under basic conditions. *Reagents and conditions*: (i) XCH_2R^3, NaI, Na_2CO_3, H_2O–DME (1:1), 80 °C, 5 h, yield: 0–20%.

The main objective as described in this paper was to develop a simple, safe, environmentally friendly, and inexpensive procedure for the synthesis of the C-linked dihydropyrones.

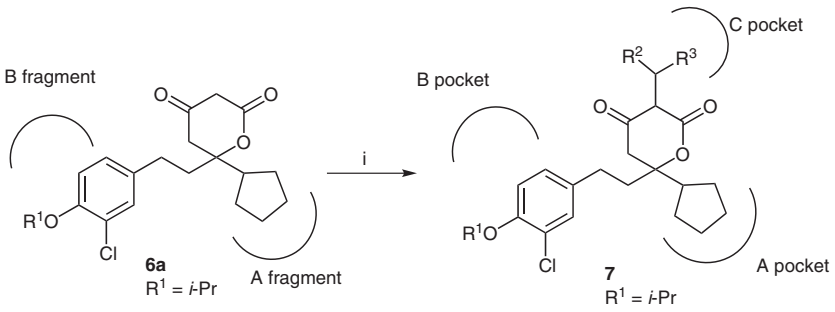
The reaction of active methylene compounds with aldehydes in the presence of chlorotrimethylsilane/sodium iodide/acetonitrile reagent has been previously reported.[7] Although the reaction worked well with aryl aldehydes, use of aliphatic primary aldehydes or isobutyraldehyde afforded alkylidenation products or dihydrofurans. Jursic and Stevens reported a very efficient two-step preparative procedure for the synthesis of 5-alkyl and 5-benzylbarbituric acids derivatives via the reduction of alkylidine intermediates with zinc in acetic acid.[8] It has also been reported that the condensation of barbituric acid derivatives with aromatic aldehydes is a simple and straightforward procedure.[9] The reaction of aryl aldehydes with Meldrum's acid in the presence of formic acid and triethylammonium formate (TEAF) followed by the spontaneous reduction of the resultant benzylidene Meldrum's acid has been reported.[10]

Hrubowchak and Smith were able to induce a reductive alkylation of Meldrum's acid using a dimethylamine-borane complex.[11] Additionally, Feeney and co-workers utilized amine-borane complexes for the reductive methylation of amino groups in several proteins, concluding that dimethylaminoborane is a slightly weaker reducing agent compared to sodium cyanoborohydride although less toxic.[12] In a comparison that included the various borane complexes, pyridine-borane was found to be slightly stronger than sodium cyanoborohydride.

A safe, easy to handle and mild reducing agent to perform under neutral conditions, selective towards functionalities that could be present in our complex scaffold such as esters, nitriles, olefins, etc., as well as applicable to library production and large-scale manufacturing was desired. After careful examination of the physical and chemical properties of the commercially available amine-borane reagents we decided to investigate the reaction with dimethylaminoborane.[13] The reagent has a reasonable thermal stability, is soluble in water and a variety of other solvents[14] and can be hydrolyzed via acidic aqueous extraction all of which make it suitable for synthetic procedures. Dimethylaminoborane can also be stored at ambient temperature for long periods of time without significant deterioration.[15] To our satisfaction, the novel method involving the reductive alkylation of intermediate **4** with commercially available aldehydes in the presence of dimethylaminoborane ($BH_3{\cdot}NHMe_2$) complex, resulted in exclusive carbon alkylation in 30–70% yields. Hence, the scope of the reaction was explored further.

Our initial study focused first on the reactivity of dihydropyrones towards various aldehydes with the A and B fragments fixed as a cyclopentane and as a 4-isopropoxy-3-chlorophenyl, respectively (Compound **6a**, Scheme 2).[16]

The first screening tested the initial reaction conditions between the dihydropyrone **6a** (R^1 = *i*-Pr) and four aliphatic aldehydes and one ketone (Table 1). The best yields were obtained by mixing stoichiometric amounts of the two reactants and the borane complex in a 3:1 CH_2Cl_2–MeOH solution (0.5 M final concentration) and stirring together at room temperature overnight. Use of



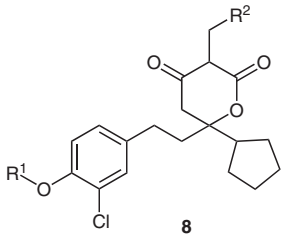
Scheme 2 Reductive condensation of 6-{2-[3-chloro-4-(propan-2-yloxy)phenyl]ethyl}-6-cyclopentyldihydro-2*H*-pyran-2,4(3*H*)-dione (**6a**, R^1 = *i*-Pr) with alkyl aldehydes and a ketone. *Reagents and conditions*: (i) R^2R^3CO, $BH_3{\cdot}NHMe_2$, CH_2Cl_2–MeOH (3:1).

Table 1 Reductive Condensation of Active Methylene Dihydropyrone **6a** (R^1 = *i*-Pr) with Alkyl Aldehydes and a Ketone

Entry	R^2	R^3	Product	Yield (%)[a]
1	H	H	**7a**	50
2	Me	H	**7b**	40
3	Et	H	**7c**	49
4	*i*-Pr	H	**7d**	50
5	Me	Me	**7e**	30

[a] The compounds were purified by preparative HPLC.

Table 2 Reductive Condensation of Active Methylene Dihydropyrones **6a** (R^1 = *i*-Pr) and **6b** (R^1 = Me) with Alkyl Aldehydes and Ketones



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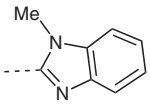
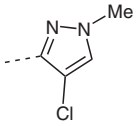
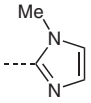
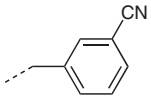
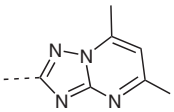
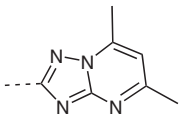
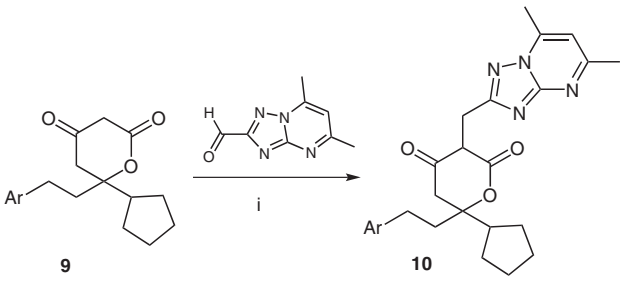
Entry	R^1	R^2	Product	Yield (%)
1	*i*-Pr		**8a**	60
2	Me		**8b**	55
3	Me		**8c**	63
4	Me		**8d**	57
5	Me		**8e**	50
6	*i*-Pr		**8f**	40

CH_2Cl_2 as a co-solvent was necessary owing to the poor solubility of the pyrone in pure methanol. Experiments were performed to determine the optimal order of addition. Results indicated that the best yields were obtained from stirring the reactants together overnight at room temperature, then adding the borane complex and stirring for an additional 16 hours at room temperature, followed by an acidic quench to pH 3 to destroy any residual borane.

In another experiment, pyrones **6a** (R = *i*-Pr) and **6b** (R = Me) were combined with several aryl aldehydes (Table 2). Results indicated that the best yields were obtained when the temperature was raised to 40 °C after addition of the borane reagent. Heating above 40 °C was found to be detrimental to the reaction. Maintaining a slightly elevated, but still mild temperature helped to optimize the reaction with aryl aldehydes.

Next, the stability of various functional groups on the B pocket substituent under this reaction conditions was explored (Scheme 3). We selected the most potent C fragment: 5,7-dimethyl[1,2,4]triazolo[1,5-*a*]pyrimidine-2-carbaldehyde, based on the replicon based assay (EC_{50})[6] and combined it with dihydropyrones incorporating a large variety of functional groups at the B pockets substituent. An array containing ethers, ketones, esters, acetals, nitriles, alcohols, and amines is shown in Table 3 indicating that the reaction conditions are quite mild and are compatible with various functionalities.



9 **10**

Scheme 3 Reductive condensation of aryl-6-cyclopentyldihydropyran-2,4-diones **9** with 5,7-dimethyl[1,2,4]triazolo[1,5-*a*]pyrimidine-2-carbaldehyde. *Reagents and conditions*: (i) $BH_3{\cdot}NH\,Me_2$, CH_2Cl_2–MeOH (3:1), 35–40 °C.

Table 3 Reductive Condensation of Aryl-6-cyclopentyldihydropyran-2,4-diones **9**

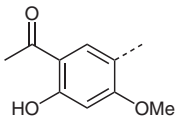
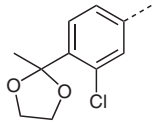
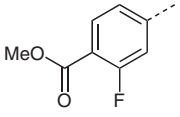
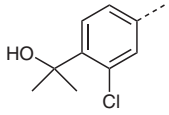
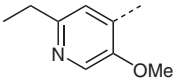
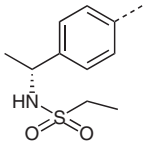
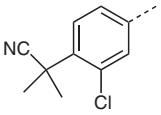
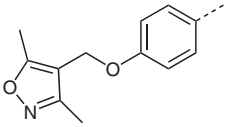
Entry	Ar	Product	Yield (%)
1		**10a**	35
2		**10b**	37
3		**10c**	57
4		**10d**	42

Table 3 Reductive Condensation of Aryl-6-cyclopentyldihydropyran-2,4-diones **9** (continued)

Entry	Ar	Product	Yield (%)
5		**10e**	20
6		**10f**	66
7		**10g**	60
8		**10h**	35

It is worth noting that the preformed alkylidine intermediates studied in this investigation were not reduced by the addition of dimethylaminoborane.

In conclusion, we have demonstrated that the preparation of carbon-linked pyrone analogues can be achieved utilizing a one-step reductive condensation between active methylene compounds and alkyl and aryl aldehydes employing dimethylaminoborane reagent, which acts first as a catalyst of the Knovenagel condensation then as a mild reducing agent to produce a clean desired product in one pot. This chemistry was used for the preparation of single compounds or the parallel synthesis of compound libraries, as well as enabling the preparation of kilogram-scale batches for animal studies.[17]

All reactions were performed in septum-sealed flasks under a slight positive pressure of argon unless otherwise noted. All starting materials and chemical reagents were purchased from commercial suppliers and used without further purification, unless otherwise indicated. ^{1}H NMR spectra were recorded on a Bruker instrument operating at 300 MHz or 400 MHz and are obtained as DMSO-d_6 or $CDCl_3$ solutions (reported in ppm), using $CDCl_3$ as the reference standard (7.26 ppm) or DMSO-d_6 (2.49 ppm). Other NMR solvents were used as needed. The mass spectra were obtained using LC/MS or APCI. The inhibitors were prepared as racemates.

Reductive Condensation Reaction between Active Methylene Compounds with Aldehydes; Compound 8f; Typical Procedure

5,7-Dimethyl[1,2,4]triazolo[1,5-*a*]pyrimidine-2-carbaldehyde[17] (0.39 g, 2.20 mmol) was added to a solution of 6-{2-[3-chloro-4-(propan-2-yloxy)phenyl]ethyl}-6-cyclopentyldihydro-2*H*-pyran-2,4(3*H*)-dione (**6a**;[16] 0.71 g, 1.87 mmol) in MeOH–CH_2Cl_2 (3:1, 4 mL). The reaction mixture was stirred for 15 hours at r.t. and then treated with BH_3·$NHMe_2$ (0.13 g, 2.20 mmol) and the temperature was increased to 40 °C. After 15 h, the reaction mixture was quenched with 1 N aq HCl (4 mL) and extracted with CH_2Cl_2 containing 10% MeOH (2 × 50 mL). The combined organic layers were concentrated and purified by preparative HPLC to give the title compound as a white solid; yield: 0.40 g (40%).

^{1}H NMR (DMSO-d_6): δ = 1.14 (d, *J* = 6.30 Hz, 6 H), 1.40–1.53 (m, 8 H), 1.70–1.75 (m, 2 H), 1.95–1.98 (m, 1 H), 2.35–2.44 (m, 8 H), 3.19 (s, 2 H), 3.57 (d, *J* = 16 Hz, 1 H), 3.69 (d, *J* = 16 Hz, 1 H), 4.41–4.47 (m, 1 H), 6.91–6.93 (s, 1 H), 7.00–7.07 (m, 2 H), 7.10 (d, *J* = 2.00 Hz, 1 H), 10.70 (br s, 1 H).

MS (ESI): *m*/*z* = 540.2 $[M + H]^+$.

Anal. Calcd for $C_{29}H_{35}N_4O_4$: C, 64.61; H, 6.54; N, 10.39. Found: C, 64.30; H, 6.81; N, 10.35.

Targeted Library Protocol for the Reductive Condensation Reaction between Active Methylene Compounds with Aldehydes; General Procedure

The reactions were carried out in 10 × 75 mm test tubes, each equipped with a 3 × 6 mm stir bar. Solutions of pyrone **9**[17] were prepared in CH_2Cl_2 (0.2 M, reactant **A**). Solutions of the aldehydes were prepared in MeOH (0.1 M, reactant **B**, which should be freshly prepared before use). A solution of Me_2NH·BH_3 (dimethylaminoborane reagent) in MeOH (1.0 M) and a 1 M solution of aq HCl were also prepared. Using an Eppendorf pipette reactant **A** (400 μL, 0.08 mmol) was placed into the appropriate test tubes. The tubes were placed in a SpeedVac™ and the CH_2Cl_2 was evaporated in vacuo for 2 h. The reactant **A** in the tubes was the reconstituted with MeOH (400 μL). Using a Rainin pipette, reactant **B** (840 μL, 0.08 mmol, 1.05 equiv) was delivered in the appropriate tubes. The tubes were then placed in an Alasyn™ block and the reaction mixtures were heated at 40 °C and stirred for 16 h. Using a Rainin pipette, the borane reagent solution (84 μL, 0.08 mmol, 1.05 equiv) was delivered to the tubes and once again the tubes were placed in the Alasyn™ block and the reaction mixtures were heated at 40 °C and stirred for an additional 16 h. 1 M aq HCl (125 μL) was delivered to each of the tubes and they were stirred/shaken for 20 min at r.t. The volatiles were removed in vacuo using the Speed-Vac.™ The residual of the tubes was dissolved in DMSO (1.340 mL) and purified by preparative HPLC.

6-{2-[3-Chloro-4-(propan-2-yloxy)phenyl]ethyl}-6-cyclopentyl-4-hydroxy-3-methyl-5,6-dihydro-2*H*-pyran-2-one (7a)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.10–7.20 (m, 1 H), 6.90–7.02 (m, 1 H), 6.74–6.90 (m, 1 H), 4.28–4.61 (m, 1 H), 2.96–3.44 (m, 1 H), 2.39–2.81 (m, 4 H), 1.43–2.36 (m, 12 H), 1.32–1.39 (m, 6 H), 1.02–1.15 (m, 2 H).

MS (APCI): *m*/*z* = 393.30 $[M + H]^+$.

6-{2-[3-Chloro-4-(propan-2-yloxy)phenyl]ethyl}-6-cyclopentyl-3-ethyl-4-hydroxy-5,6-dihydro-2*H*-pyran-2-one (7b)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.87–1.03 (m, 3 H), 1.35 (s, 3 H), 1.37 (s, 3 H), 1.39–2.43 (m, 13 H), 2.49–2.86 (m, 4 H), 3.12–3.30 (m, 1 H), 4.40–4.62 (m, 1 H), 6.86 (d, *J* = 8.59 Hz, 1 H), 6.92–6.99 (m, 1 H), 7.14 (s, 1 H).

MS (APCI): *m*/*z* = 407.20 $[M + H]^+$.

6-{2-[3-Chloro-4-(propan-2-yloxy)phenyl]ethyl}-6-cyclopentyl-4-hydroxy-3-propyl-5,6-dihydro-2*H*-pyran-2-one (7c)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.91–0.99 (m, 22 H), 1.33–1.39 (m, 6 H), 3.12–3.29 (m, 1 H) 4.45–4.56 (m, 1 H), 6.81–6.92 (m, 1 H), 6.93–7.06 (m, 1 H), 7.08–7.23 (m, 1 H).

MS (APCI): *m*/*z* = 421.20 $[M + H]^+$.

6-{2-[3-Chloro-4-(propan-2-yloxy)phenyl]ethyl}-6-cyclopentyl-4-hydroxy-3-(2-methylpropyl)-5,6-dihydro-2*H*-pyran-2-one (7d)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.86–1.03 (m, 6 H), 1.34–1.41 (m, 6 H), 1.42–3.29 (m, 19 H) 4.46–4.56 (m, 1 H), 6.82–6.92 (m, 1 H), 6.93–6.99 (m, 1 H), 7.08–7.24 (m, 1 H).

MS (APCI): *m*/*z* = 435.30 $[M + H]^+$.

6-{2-[3-Chloro-4-(propan-2-yloxy)phenyl]ethyl}-6-cyclopentyl-4-hydroxy-3-(propan-2-yl)-5,6-dihydro-2*H*-pyran-2-one (7e)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.64–7.26 (m, 3 H), 4.41–4.60 (m, 1 H), 3.00–3.25 (m, 1 H), 1.48–2.87 (m, 15 H), 1.29–1.40 (m, 6 H), 1.02–1.19 (m, 6 H).

MS (APCI): *m*/*z* = 421.40 $[M + H]^+$.

6-{2-[3-Chloro-4-(propan-2-yloxy)phenyl]ethyl}-6-cyclopentyl-4-hydroxy-3-[(1-methyl-1*H*-benzimidazol-2-yl)methyl]-5,6-dihydro-2*H*-pyran-2-one (8a)

^{1}H NMR (DMSO-d_6): δ = 0.90–1.36 (m, 14 H), 1.54–1.61 (m, 2 H), 2.20–2.39 (m, 3 H), 2.57–2.73 (m, 4 H), 4.10 (s, 3 H), 4.44–4.49 (m, 1 H), 6.49–6.48 (m, 7 H), 13.50 (br s, 1 H).

MS (ESI): *m*/*z* = 524.20 $[M + H]^+$.

Anal. Calcd for $C_{30}H_{35}ClN_4O_4$: C, 68.89; H, 6.74; N, 5.36. Found: C, 69.11; H, 6.73; N, 5.36.

6-[2-(3-Chloro-4-methoxyphenyl)ethyl]-3-[(4-chloro-1-methyl-1*H*-pyrazol-3-yl)methyl]-6-cyclopentyl-4-hydroxy-5,6-dihydro-2*H*-pyran-2-one (8b)

^{1}H NMR (DMSO-d_6): δ = 1.50–1.71 (m, 8 H), 2.01–2.05 (m, 2 H), 2.39–2.41 (m, 1 H), 2.49–2.57 (m, 2 H), 2.74 (d, *J* = 16 Hz, 1 H), 3.18 (d, *J* = 5.30 Hz, 1 H), 3.39 (d, *J* = 16.00 Hz, 1 H), 3.47 (d, *J* = 16 Hz, 1 H), 3.60 (s, 3 H), 3.83 (s, 3 H), 7.05 (d, *J* = 8.30 Hz, 1 H), 7.11 (dd, *J* = 8.30, 2.00 Hz, 1 H), 7.23 (d, *J* = 2.00 Hz, 1 H), 7.76 (s, 1 H), 10.64 (s, 1 H).

MS (ESI): *m*/*z* = 479.20 $[M + H]^+$.

Anal. Calcd for $C_{24}H_{28}Cl_2N_2O_4$: C, 60.13; H, 5.89; N, 5.84. Found: C, 59.94; H, 5.95; N, 5.69.

6-[2-(3-Chloro-4-methoxyphenyl)ethyl]-6-cyclopentyl-3-[(1-methyl-1*H*-imidazol-2-yl)methyl]dihydro-2*H*-pyran-2,4(3*H*)-dione (8c)

^{1}H NMR ($CDCl_3$): δ = 1.44– 1.70 (br m, 8 H), 2.00 (m, 2 H), 2.20 (m, 3 H), 2.30 (m, 2 H), 2.99 (m, 2 H), 3.01 (m, 2 H), 3.46 (s, 3 H), 3.78 (m, 1 H), 3.89 (s, 3 H), 6.72 (d, *J* = 2.15 Hz, 1 H), 6.83, (d, *J* = 2.15 Hz, 1 H), 6.90 (s, 1 H), 7.14 (d, *J* = 3.07 Hz, 1 H), 7.24 (d, *J* = 3.06 Hz, 1 H).

MS (ESI): *m*/*z* = 445.20 $[M + H]^+$.

Anal. Calcd for $C_{25}H_{31}ClN_2O_3$: C, 67.78; H, 7.05; N, 6.32. Found: C, 67.48; H, 7.25; N, 6.37.

3-({6-[2-(3-Chloro-4-methoxyphenyl)ethyl]-6-cyclopentyl-4-hydroxy-2-oxo-5,6-dihydro-2*H*-pyran-3-yl}methyl)benzonitrile (8d)

^{1}H NMR ($CDCl_3$): δ = 1.43–1.86 (br m, 8 H), 2.02 (m, 2 H), 2.29 (m, 1 H), 2.44–3.02 (m, 7 H), 3.95 (s, 3 H), 6.88–7.91 (m, 7 H).

MS (ESI): *m*/*z* = 511.20 $[M + H]^+$.

Anal. Calcd for $C_{27}H_{28}ClNO_4$: C, 69.59; H, 6.06; N, 3.01. Found: C, 69.67; H, 6.14; N, 3.13.

6-[2-(3-Chloro-4-methoxyphenyl)ethyl]-6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-*a*]pyrimidin-2-yl)methyl]-4-hydroxy-5,6-dihydro-2*H*-pyran-2-one (8e)

^{1}H NMR ($CDCl_3$): δ = 1.37–1.85 (br m, 8 H), 1.98 (m, 2 H), 2.37 (m, 1 H), 2.49–2.80 (m, 11 H), 3.86 (s, 3 H), 4.05 (d, *J* = 15.60 Hz, 1 H), 4.12 (d, *J* = 15.60 Hz, 1 H), 6.81 (d, *J* = 8.60 Hz, 1 H), 6.85 (s, 1 H), 7.00 (d, *J* = 8.60 Hz, 1 H), 7.12 (s, 1 H).

MS (ESI): *m*/*z* = 466.20 $[M + H]^+$.

Anal. Calcd for $C_{27}H_{31}ClN_4O_4$: C, 63.46; H, 6.11; N, 10.96. Found: C, 63.23; H, 6.27; N, 10.74.

6-[2-(5-Acetyl-4-hydroxy-2-methoxyphenyl)ethyl]-6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-*a*]pyrimidin-2-yl)methyl]-4-hydroxy-5,6-dihydro-2*H*-pyran-2-one (10a)

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.34–1.66 (m, 8 H), 1.80–2.06 (m, 3 H), 2.32–2.49 (m, 12 H), 2.65 (d, *J* = 17 Hz, 1 H), 3.57–3.72 (m, 6 H), 6.31 (s, 1 H), 6.90 (s, 1 H), 7.46 (s, 1 H), 12.52 (s, 1 H).

MS (ESI): *m*/*z* = 535.20 $[M + H]^+$.

Anal. Calcd For $C_{29}H_{34}N_4O_6 \cdot 0.25H_2O$: C, 64.61; H, 6.45; N, 10.39. Found: C, 64.57; H, 6.39; N, 10.22.

6-{2-[3-Chloro-4-(2-methyl-1,3-dioxolan-2-yl)phenyl]ethyl}-6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-*a*]pyrimidin-2-yl)methyl]-4-hydroxy-5,6-dihydro-2*H*-pyran-2-one (10b)

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.50–1.70 (m, 9 H), 2.20–2.22 (m, 2 H), 2.49–2.90 (m, 10 H), 3.39 (s, 3 H), 3.70–3.74 (m, 2 H), 3.78 (d, *J* = 16 Hz, 1 H), 3.90 (d, *J* = 16 Hz, 1 H), 4.04–4.07 (m, 2 H), 7.13 (s, 1 H), 7.32 (s, 1 H), 7.36 (d, *J* = 8 Hz, 1 H), 7.61 (d, *J* = 8 Hz, 1 H), 10.90 (s, 1 H).

MS (ESI): *m*/*z* = 567.20 $[M + H]^+$.

Anal. Calcd for $C_{30}H_{35}ClN_4O_5$: C, 63.54; H, 6.22; N, 9.88. Found: C, 63.27; H, 6.27; N, 9.56.

Methyl 4-(2-{2-Cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-*a*]pyrimidin-2-yl)methyl]-4,6-dioxotetrahydro-2*H*-pyran-2-yl}ethyl)-2-fluorobenzoate (10c)

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.25–1.85 (m, 8 H), 2.01–1.10 (m, 3 H), 2.58–2.80 (m, 10 H), 3.10 (t, *J* = 12.57 Hz, 1 H), 3.88 (s, 3 H), 6.91 (d, *J* = 2.57 Hz, 1 H), 6.99 (s, 1 H), 7.15 (d, *J* = 1.58 Hz, 1 H), 7.92 (m, H).

MS (ESI): *m*/*z* = 523.20 $[M + H]^+$.

Anal. Calcd for $C_{28}H_{31}FN_4O_5$: C, 64.36; H, 5.98; N, 10.72. Found: C, 64.50; H, 5.40; N, 10.70.

6-{2-[3-Chloro-4-(2-hydroxypropan-2-yl)phenyl]ethyl}-6-cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-*a*]pyrimidin-2-yl)methyl]-4-hydroxytetrahydro-2*H*-pyran-2-one (10d)

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.55 (s, 1 H), 1.64–1.71 (m, 12 H), 1.94–2.03 (m, 2 H), 2.30–2.43 (m, 2 H), 2.50 (d, *J* = 17.90 Hz, 2 H), 2.58–2.64 (m, 2 H), 2.64–2.72 (m, 5 H), 2.78 (s, 3 H), 4.07 (s, 2 H), 6.83 (s, 1 H), 6.98–7.04 (m, 1 H), 7.11 (d, *J* = 1.13 Hz, 1 H), 7.50 (d, *J* = 8.10 Hz, 1 H).

MS (ESI): *m*/*z* = 561.00 $[M + Na]^+$.

Anal. Calcd for $C_{29}H_{35}ClN_4O_4 \cdot 1.5AcOH$: C, 61.09; H, 6.57; N, 8.91. Found: C, 61.22; H, 6.50; N, 8.65.

6-Cyclopentyl-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-*a*]pyrimidin-2-yl)methyl]-6-[2-(2-ethyl-5-methoxypyridin-4-yl)ethyl]-4-hydroxy-5,6-dihydro-2*H*-pyran-2-one (10e)

^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.94 (t, *J* = 7.58 Hz, 3 H), 1.19–1.53 (m, 8 H), 1.83 (m, 1 H), 1.91 (m, 1 H), 2.20 (m, 4 H), 2.29–2.37 (m, 6 H), 2.43 (q, *J* = 7.58 Hz, 2 H), 2.59 (d, *J* = 17.2 Hz, 1 H), 3.50 (d, *J* = 16.2 Hz, 1 H), 3.56 (s, 3 H), 3.61 (d, *J* = 16.2 Hz, 1 H), 6.83 (s, 1 H), 6.85 (s, 1 H), 7.88 (s, 1 H), 10.82 (s, 1 H).

MS (ESI): *m*/*z* = 506.20 $[M + H]^+$.

Anal. Calcd for $C_{28}H_{35}N_5O_4 \times 0.5AcOH$: C, 65.03; H, 6.96; N, 13.08. Found: C, 65.15; H,7.05; N, 12.79.

***N*-{(1*R*)-1-[4-(2-{2-Cyclopentyl-5-[(5,7 dimethyl[1,2,4]triazolo[1,5-*a*]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2*H*-pyran-2-yl}ethyl)phenyl]ethyl}ethanesulfonamide (10f)**

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.07 (t, *J* = 7.30 Hz, 3 H), 1.40 (d, *J* = 6.90 Hz, 3 H), 1.50–1.80 (m, 9 H), 2.11–2.16 (m, 2 H), 2.48–2.59 (m, 7 H), 2.78–2.83 (m, 3 H), 3.71 (d, *J* = 16 Hz, 1 H), 3.85 (d,

J = 16 Hz, 1 H), 4.03 (t, *J* = 14, 7.30 Hz, 2 H), 4.39–4.45 (m, 1 H), 7.06 (s, 1 H), 7.21–7.31 (m, 4 H), 7.66 (d, *J* = 8.30 Hz, 1 H), 10.90 (s, 1 H).

MS (ESI): *m*/*z* = 582.20 $[M + H]^+$.

Anal. Calcd for $C_{30}H_{39}N_5O_5S$: C, 61.94; H, 6.76; N, 12.04. Found: C, 61.80; H, 6.87; N, 12.20.

2-[2-Chloro-4-(2-{2-cyclopentyl-5-[(5,7-dimethyl[1,2,4]triazolo[1,5-*a*]pyrimidin-2-yl)methyl]-4-hydroxy-6-oxo-3,6-dihydro-2*H*-pyran-2-yl}ethyl)phenyl]-2-methylpropanenitrile (10g)
IR (neat): 2243, 2355, 1666, 1625, 1543, 1390 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 1.39–1.64 (m, 8 H), 1.67 (s, 6 H), 2.01–2.05 (m, 2 H), 2.36–2.46 (m, 7 H), 2.51–2.57 (m, 2 H), 2.69 (d, *J* = 17 Hz, 2 H), 3.61 (d, *J* = 16 Hz, 1 H), 3.72 (d, *J* = 16 Hz, 1 H), 6.94 (s, 1 H), 7.25 (s, 1 H), 7.28 (s, 1 H), 7.35 (d, *J* = 8 Hz, 1 H), 10.75 (s, 1 H).

MS (ESI): *m*/*z* = 548.20 $[M + H]^+$.

Anal. Calcd for $C_{30}H_{34}ClN_5O_3{\times}1H_2O$: C, 63.65; H, 6.41; N, 12.37. Found: C, 63.60; H, 6.30; N, 12.21.

6-Cyclopentyl-6-(2-{4-[(3,5-dimethylisoxazol-4 yl)methoxy]phenyl}ethyl)-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-*a*]pyrimidin-2-yl)methyl]-4-hydroxy-5,6-dihydro-2*H*-pyran-2-one (10h)
^1H NMR (DMSO-d_6): δ = 1.39–1.72 (br m, 8 H), 2.19 (m, 2 H), 2.21 (s, 3 H), 2.39 (s, 3 H), 2.47–2.70 (m, 10 H), 2.81 (d, *J* = 17.50 Hz, 1 H), 3.71 (d, *J* = 16.10 Hz, 1 H), 3.85 (d, *J* = 16.20 Hz, 1 H), 7.04 (s, 1 H), 7.27 (d, *J* = 8.10 Hz, 2 H), 7.36 (d, *J* = 8.10 Hz, 2 H), 10.98 (s, 1 H).

MS (ESI): *m*/*z* = 570.20 $[M + H]^+$.

Anal. Calcd for $C_{31}H_{35}N_5O_4{\cdot}0.6H_2O$: C, 67.39; H, 6.61; N, 12.68. Found: C, 67.39; H, 6.52, N, 12.45.

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