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Discovery and SAR of orally efficacious tetrahydropyridopyridazinone PARP inhibitors for the treatment of cancer

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ABSTRACT

PARP-1, the most abundant member of the PARP superfamily of nuclear enzymes, has emerged as a promising molecular target in the past decade particularly for the treatment of cancer. A number of PARP-1 inhibitors, including veliparab discovered at Abbott, have advanced into different stages of clinical trials. Herein we describe the development of a new tetrahydropyridopyridazinone series of PARP-1 inhibitors. Many compounds in this class, such as 20w, displayed excellent potency against the PARP-1 enzyme with a K_i value of <1 nM and an EC_{50} value of 1 nM in a C41 whole cell assay. The presence of the NH in the tetrahydropyridyl ring of the tetrahydropyridopyridazinone scaffold improved the pharmacokinetic properties over similar carbon based analogs. Compounds **8c** and **20u** are orally available, and have demonstrated significant efficacy in a B16 murine xenograft model, potentiating the efficacy of temozolomide (TMZ).

1. Introduction

DNA damage occurs constantly due to environmental factors and normal metabolic processes inside the cell. A DNA repair process is rapidly initiated in response to the damage, and is a critical cellular event to maintain genome integrity. DNA repair is a very complex process, with up to 150 genes involved. More than 5 principle pathways have been identified, including base excision repair (BER), homology directed repair (HDR), nucleotide excision repair (NER), mismatch repair (MMR), and non-homologous endjoining (NHEJ).[1] Repair of DNA damage, the double-strand DNA breaks (DSBs) in particular, have become an increasingly attractive anticancer target since DSBs are the death-provoking effectors of therapeutic radiation and some cytotoxic chemotherapy. Homologous recombination (HR), a BRCA-dependent and high-fidelity process, is considered to be the primary repair mechanism for the repair of DSBs. Therefore, tumors with inherited BRCA1 or BRCA2 mutations are typically defective in DNA repair of double-strand breaks.[2]

Poly(ADP-ribose)polymerases (PARPs) are a family of nuclear enzymes that polymerize poly(adenosine diphosphate–ribose) on substrate proteins critical for cellular regulations including DNA repair, gene transcription, and chromatin architecture. Members in the PARP super family share a common and highly homologous catalytic domain that catalyzes the transfer of ADP-ribose units from intracellular nicotinamide adenine dinucleotide (NAD^+) to the acceptor proteins, leading to the formation of mostly branched ADP-ribose polymers (PARs). This cellular event is a key process during base excision repair (BER) of single-strand DNA breaks caused by ionizing radiation or DNA-damaging chemotherapeutic treatments, and contributes to the resistance mechanism that often develops after these cancer therapies. PARP1 is the most abundant member of the PARP family and responsible for >90% of the poly(ADP-ribosyl)ation activity in cells of all higher eukaryotes. Evidences have also been reported that PARP1 contributes to DSB, NHEJ and HR repair pathways.[3] PARP2, which is the closest relative but less active than PARP1, also participates in BER, contributing only 5 to 10% of the total PARP activity in response to DNA damage.[4] Both PARP1, and to a lesser extent PARP2, function as DNA damage sensor by binding with high affinity to the site of single- and double-stranded DNA breaks. The binding to the damaged DNA triggers poly(ADP-ribosyl)ation of various proteins that is believed to be essential in recruiting other repair proteins to the site of molecular lesions.[5]

Abrogation of the PARP-mediated DNA repair would enhance the anticancer activity of traditional cancer therapies. In addition, since tumor cells are frequently defective in DNA repair pathways like homologous recombination, inhibition of PARP-1 leads to the persistence of single-strand DNA lesions that degenerates

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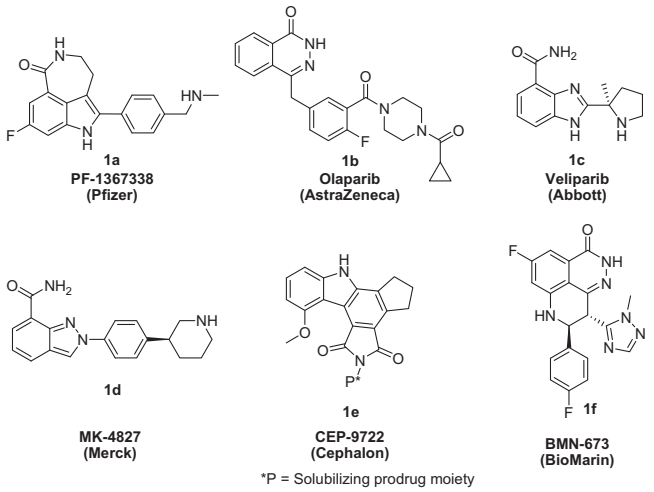


Fig. 1. Current PARP inhibitors in clinical trials.

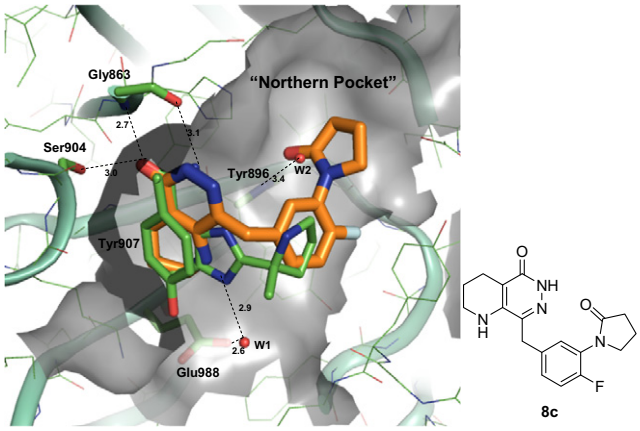


Fig. 2. X-Ray Co-crystal structure of veliparib overlaid with the proposed binding mode of compound **8c**.

double-strand breaks during DNA replication. Inhibition of homologous recombination or PARP may be well tolerated in isolation, but combined inactivation of these distinct DNA-repair pathways results in cell death — a process called "synthetic lethality". Therefore PARP inhibition can be toxic to cells deficient in tumor-suppressor genes BRCA1 or BRCA2 that underlie high-penetrance, hereditary breast and ovarian carcinomas. Normally, homologous recombination repairs these breaks, but should this mechanism be unavailable, as is the case when BRCA1 or BRCA2 is absent, the cell dies. Thus, small-molecule inhibitors of PARP1 standalone can be an efficient targeted therapy for these cancer patients. Because of the high homology between PARP-1 and PARP-2, many of the reported PARP-1 inhibitors actually inhibit PARP-2 to a similar extent. Inhibitors of PARP-1 are most likely also inhibitors of PARP2-4, so the amount of polyADP(ribosylation) is completely shut down.[7] In fact, some clinical evidences have shown that drugs targeting PARP show promise as treatments for some of the most aggressive and difficult-to-treat forms of breast cancer.[8]

As shown in Figure 1, at least six major series of small molecule PARP inhibitors have been developed in the past decade, and have advanced into different stages of clinic trials.[6] While earlier PARP-1 inhibitors were investigated primarily in non-oncological indications, the more recent efforts have been focused on the use both as mono-anticancer therapy in specific patient populations (e.g. BRCA-deficient) and in combination with various chemotherapeutics.

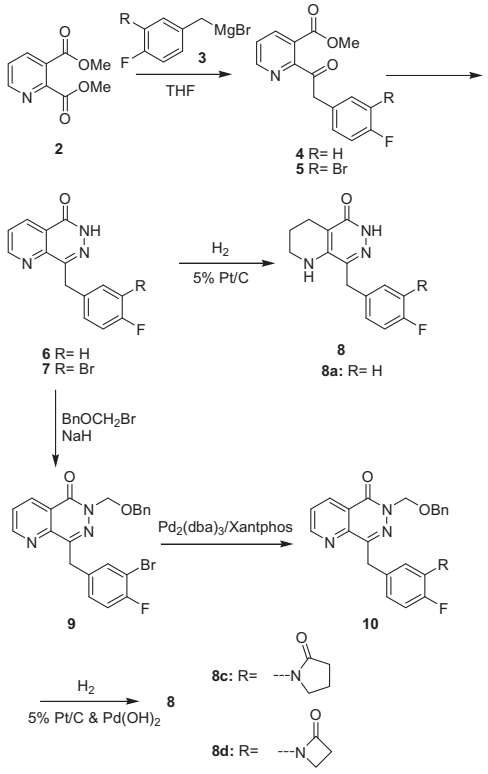
We have previously reported our efforts in identifying a series of potent benzimidazole-containing PARP inhibitors, including the leading candidate **1c** (ABT-888, veliparib), now in Phase II clinical trials.[9] This compound demonstrated significant oral efficacy in a number of preclinical rodent tumor models, potentiating the efficacy of cytotoxic agents such as temozolomide (TMZ), cisplatin, carboplatin, and cyclophosphamide, as well as radiation. In this report, we describe the discovery and SAR of a series of novel and orally efficacious tetrahydropyridopyridazinone PARP inhibitors. A number of these analogs displayed excellent in vitro potency in both intrinsic and cellular assays, adequate pharmacokinetic properties as well as oral efficacy in mouse xenograft models.

2. X-ray Co-crystal structure of veliparib and computer modeling of a tetrahydropyridopyridazinone PARP inhibitor

Figure 2 displays an X-ray co-crystal structure of veliparib (**1c**) overlaid with a tetrahydropyridopyridazinone PARP inhibitor (**8c**). Consistent with our previous reports,[9] as well as others, three key hydrogen-bond interactions between the carboxamide group of veliparib with Ser-904 and Gly-863 in the PARP-1 catalytic domain were observed. The carboxamide group was restricted into an optimal orientation for the hydrogen-bond interaction through formation of an intramolecular hydrogen bond with the 3-nitrogen of the imidazole moiety. In addition to a characteristic π-stacking interaction for PARP inhibitors between the benzimidazole ring and Tyr-907, the 1-NH of the benzimidazole ring appears to be involved in a water-mediated hydrogen bond (W1) with Glu-988 of the protein. While olaparib (**1b**) has demonstrated certain success in clinical trials, an overlay (not shown in the figure but similar to **8c**) with veliparib shows that this compound lacks a hydrogen bond donor as for the "NH" of veliparib benzimidazole that forms a hydrogen bond interaction with W1. As modeling suggests in Figure 2, the proposed tetrahydropyridopyridazinone, in which a 5-NH is incorporated into the ring structure, would provide additional molecular interaction as compared to olaparib. There is also a water molecule in the vicinity of the pyrrolidine-NH near the "northern pocket", displacement of this W2 with a pyrrolidinone carbonyl would increase the potency through potential interaction with Tyr896. We have chosen a fluorine atom at the *para*-position of the 4-benzyl group as for the case of olaparib due to a limited space available at this position in the X-ray structure.

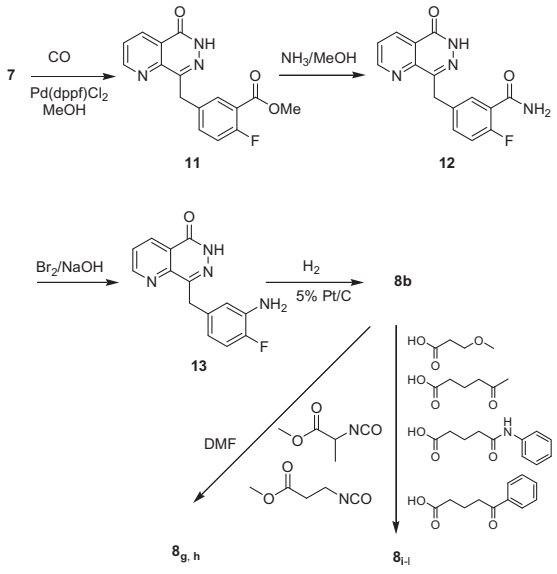
3. Chemistry

The tetrahydropyridopyridazinone pharmacophore was constructed through a selective Grignard addition of a properly functionalized benzylmagnesium bromide to the 2-carboxylate of a commercially available dimethyl pyridine-2,3-dicarboxylate (2), followed by a pyridazinone ring closure and pyridine saturation (Scheme 1). There is no literature precedence for the high selectivity observed, and it appears that the presence and position of the ring nitrogen of pyridine 2,3-dicarboxylate 2 is critical for the mono-Grignard addition. Lack of or shift of the ring nitrogen failed to provide reasonable selectivity. Heating the ketoester **4** or **5** with hydrazine as the mono HCl salt provided pyridopyridazinone **6** or **7** in good yields. Hydrogenation of the pyridopyridazinone ring in the presence of 5% platinum on charcoal under acidic conditions furnished desired product **8a**. A direct Buchwald amidation of the bromide 7 failed to provide the coupled product **8c** or **8d**. However, after protecting the free lactam NH as benzyloxymethyl ether to give **9**, the Buchwald coupling reaction proceeded smoothly by using Xantphos as ligand under microwave conditions. Hydrogenation of **10** with a mixture of platinum and palladium hydroxide on carbon removed the benzyloxymethyl group and saturated the pyridine ring simultaneously.

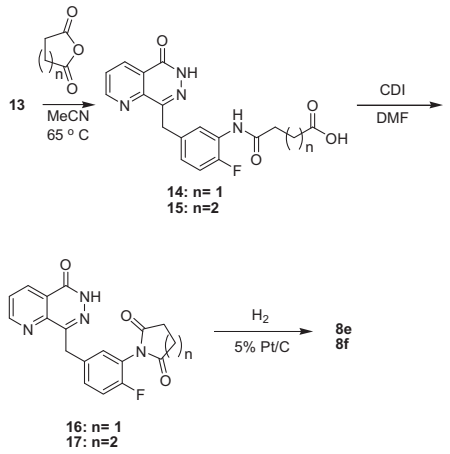


Scheme 1.

As shown in Schemes 2 and 3, the carboxamides **8b**, **8e** through **8l** were prepared in a straightforward fashion. Carboxylation of compound 7 in the presence of Pd(dppf)Cl_2 smoothly afforded **11** that, upon treatment with an ammonia solution in methanol, furnished **12**. A Hoffman rearrangement of amide **12** provided a key intermediate **13** that was hydrogenated on platinum on charcoal under acidic conditions to give **8b**. The imidazolidinedione analog **8g** and dihydropyrimidinedione **8h** were prepared through heating equal molar equivalent of **8b** with methyl 2- or 3-isocyanotopropanoate at 65 °C in DMF overnight (Scheme 2). Amide coupling



Scheme 2.

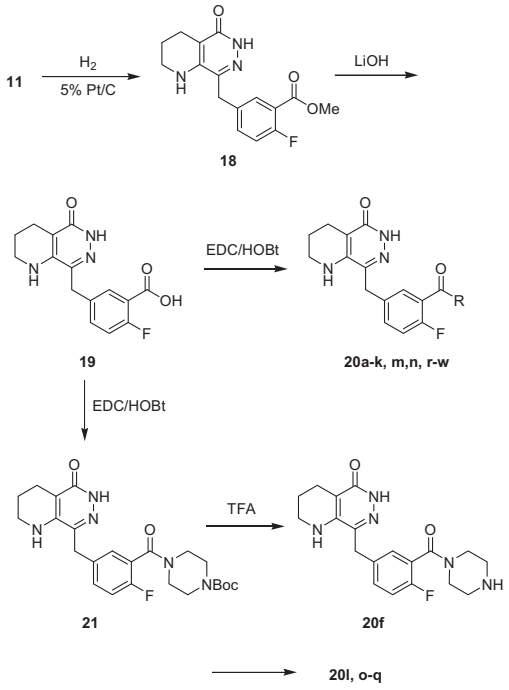


Scheme 3.

of **8b** with appropriate acids in the presence of HATU and Hünig's base smoothly afforded **8i-l**.

As shown in Scheme 3, treating the amine **13** with succinic anhydride ($n = 1$) or dihydro-2*H*-pyran-2,6(3*H*)-dione ($n = 2$) in acetonitrile provided either **14** or **15** that upon exposure to carbonyldiimidazole (CDI) furnished compounds **16** or **17**. A pyridine ring saturation under acidic conditions afforded compounds **8e** or **8f** in the presence of 5% platinum on carbon.

Scheme 4 illustrates an alternative protocol in which the pyridine ring of the tetrahydropyridopyridazinone core structure was first saturated, followed by an amide elaboration. Thus, hydrogenation of **11**, in the presence of platinum on carbon and one equivalent of HCl, afforded **18**. Saponification of the ester **18**, followed by amide coupling with appropriate amines under the standard EDC/HOBt conditions, provided **20a–k**, **20m,n**, and **20r-w**. For syntheses of piperazine derivatives **20l** and **20o-q**, acid **19** was coupled to *N*-Boc-piperazine to give **21**. An acid-mediated deprotection of **21** led to compound **20f** which upon further elaboration to give **20l** and **20o-q**.

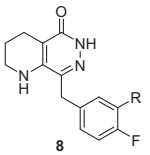


Scheme 4.

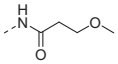
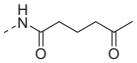
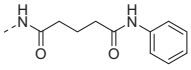
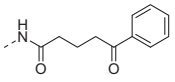
4. Results and discussion

We initiated the SAR exploration of the novel tetrahydropyridopyridazinone pharmacophore with a more optimized 4-fluorobenzyl substituent at the C4 position of the pyridazinone, based on previous reports for olaparib and related series.[10–12] Consistent with the SAR in the phthalazinone series, both unsubstituted (**8a**) and amino analog **8b** displayed a low submicromolar potency in a PARP1 assay (Table 1). In an attempt to exploit potential binding interactions in the 'Northern Pocket' (Fig. 2) for the tetrahydropyridopyridazinone series, we have incorporated a lactam-like carbonyl as illustrated by compounds **8c** through **8h**. These modifications provided a series of low single-digit nanomolar PARP inhibitors with **8f** displaying the highest potency both in intrinsic and cellular assays. Among these cyclic carbonyl substituents, the imide analogs (**8e**, **8f**) appeared to be more potent than the lactams (**8c** and **8d**) in the enzyme but not in the cellular assay, and imidazolidine-2,4-dione (**8g** and **8h**) were least active. Good activity was also observed for acyclic amide substituents (**8i**–**8l**), particularly for those with another carbonyl group at the remote end of the carboxylates, rendering a potential hydrogen bond interaction deeper into the adenosine-ribose binding region.

Table 1
Enzyme and cellular assays of compound **8**



8

Compd	R	PARP-1 (K_i, nM)	Cellular[a] (EC_{50}, nM)
a	H	118	ND
b	NH_2	112	ND
c		6	11
d		3	22
e		1.4	56
f		0.7	6
g		9	271
h		17	ND
i		12	134
j		4	27
k		1.4	16
l		1.3	16

[a] Average of at least two determinations.

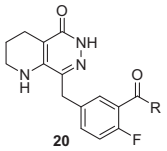
Carboxamides with diverse structures have also been synthesized and evaluated for PARP inhibitory and pharmaceutical properties (Table 2). While primary and secondary amides displayed modest to good enzyme activity, as exemplified by **20a**–**20g**, their potency in cellular settings varied from poor to modest, and relatively poor correlations were observed between their intrinsic and cellular activities. We were not clear whether the relatively poor cellular activity observed for some compounds (e.g. **20e**–**g**, **8g**) is due to low cellular permeability and/or because they are MDR substrate. In an attempt to improve cellular potency, the same strategy as for the benzimidazole series of PARP inhibitors,[13] for which introduction of basic amines was beneficial, was utilized. As shown in Table 2, a blend of cellular data, however, was obtained for these modifications. It appeared that incorporation of a tertiary amine (e.g. **20d**, **20i** and **20j**) or sterically hindered secondary amine (e.g. **20h**) is beneficial to the cellular activity, while those primary amines (e.g. **20f**, **20g**) or diamines (**20e**) were less active. Nevertheless, all compounds displayed excellent intrinsic activity against PARP1, presumably due to a large binding pocket at this area of the protein. To explore an impact of the basicity of the molecule, we synthesized a number of amides (e.g. **20k**–**20o**), urea (**20p**) and sulfonamide (e.g. **20q**) analogs. Overall these modifications led to increased potency in cellular assays. Lastly, weakly basic amine analogs **20r**–**20w** with an aryl- or heteroaryl group at the *para*-nitrogen of **20f** were also evaluated and resulted in a series of the most active PARP inhibitors to date with **20w** being the most potent (PARP1 K_i = 0.4 nM, cellular EC_{50} = 1 nM).

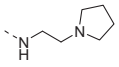
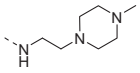
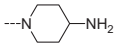
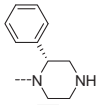
Pharmacokinetic evaluation of tetrahydropyridopyridazinone series of PARP inhibitors started from a quick screening protocol, due to the large number of potent PARP inhibitors we identified. All compounds for the mouse screening PK were dosed orally at 10 mg/kg and the plasma concentrations were determined up to 3 h, seeking orally efficacious PARP inhibitors. Compounds **8f**, **20m**, and **20n** had AUCs in range of 0.07–0.19 μg-h/mL in this screening PK protocol, while a subset analogs **20r**, **20u**, and **20w** showed a slight improvement in oral exposure with AUCs of 2.9–6.82 μg-h/mL. Presence of an extra aryl group appeared to improve pharmacokinetic property within the series.

Mouse pharmacokinetic parameters from a standard protocol for selected compounds were obtained and shown in Table 3. These compounds were dosed orally at 10 mg/kg and intravenously at 3 mg/kg, and the plasma concentrations were determined up to 8 h. A head-to-head comparison of the tetrahydropyridyl series (**8c** or **20u** and **20w** highlighted) with the tetrahydrophenyl series (**23**)[14] indicates that the presence of a NH functionality is beneficial for an improved pharmacokinetic property in this series of PARP inhibitors. All compounds with a ring-nitrogen (e.g. **8c**, **20u**, and **20w**) displayed significantly higher plasma exposure in a mouse pharmacokinetic evaluation with an oral AUC_{0-8h} of 3.11, 5.95, and 9.06 μg-h/mL respectively, versus an oral AUC_{0-8h} of 0.33, 2.70, and 2.38 μg-h/mL for the corresponding compounds, (**23c**, **23u**, and **23w)** lacking this nitrogen.

Considering a balanced in vitro potency, pharmacokinetic and pharmaceutical properties and structural diversity, compounds **8c** and **20u** were evaluated in a murine B16F10 syngeneic melanoma model (Figs. 3A and 3B). This B16F10 model, while relatively resistant to most chemotherapeutics, is moderately sensitive to TMZ and the sensitivity can be enhanced with PARP inhibitors. It also closely corresponds with the actual clinical setting of TMZ used for melanoma. Compound **8c** was administered orally on days 5–10 at doses of 10, 30 and 60 mg/kg/day, bid, while TMZ was administered orally at 50 mg/kg/day, qd, from day 5 to day 10. As displayed in Figure 3A, **8c** significantly potentiated the efficacy of TMZ in a dose-dependent manner. Significant potentiation was observed as early as day 12, with TGI (tumor growth inhibition) values (vs. vehicle control) of 57, 59, and 69 for the 10, 30, and

Table 2
Enzyme and cellular assays of compound **20**



Compd	R	PARP-1 (K_i, nM)	Cellular [a] (EC_{50}, nM)
a	NH_2	17	122
b	NHEt	6	45
c		14	82
d		9	111
e		3.5	290
f		1.8	4400
g		1.6	2400
h		7	22
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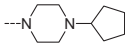
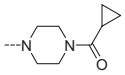
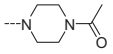
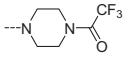
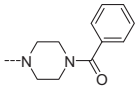
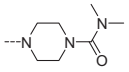
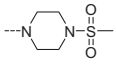
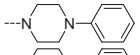
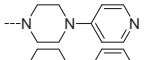
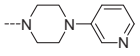
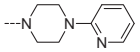
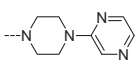
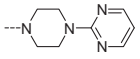
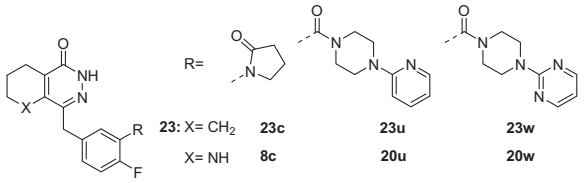
j		2.5	7
k		0.9	190
l		1.3	22
m		1.3	180
n		0.9	6
o		0.9	11
p		1.2	50
q		0.7	150
r		1.2	1.7
s		1.2	39
t		0.9	9
u		0.9	1.4
v		0.4	3.3
w		0.4	1

[a] Average of at least two determinations.

60 mg/kg/day **8c** combination groups, respectively, compared to 30% for TMZ alone. All three dosing groups continued to differentiate from the TMZ alone group out to end of the trial at day 21. The **8c**-TMZ combination was well tolerated for the 10 and 30 mg/kg dose groups with minimal loss of body weight. For the 60 mg/kg

Table 3
Standard mouse pharmacokinetic parameters for **8c**, **20u**, **20w**, and **23c, 23u, 23w**



Compd	% F[a] (po)	$T_{1/2}$[b] (iv)	AUC[c]	C_{max}[d]	V_{ss}[e]	CL[f]
8c	106	0.49	3.11	1.50	5.25	7.43
23c	13	0.28	0.33	0.14	4.78	11.72
20u	67	2.6	5.95	2.01	7.66	2.04
23u	74	1.10	2.70	1.09	9.48	5.92
20w	36	3.86	9.06	5.60	4.99	0.89
23w	48	0.36	2.38	1.03	2.33	4.55

[a] 10 mg/kg PO dose, 3 mg/pk IV dose.
[b] h.
[c] po, μg-h/mL.
[d] po, μg/mL.
[e] L/kg.
[f] L/h/kg.

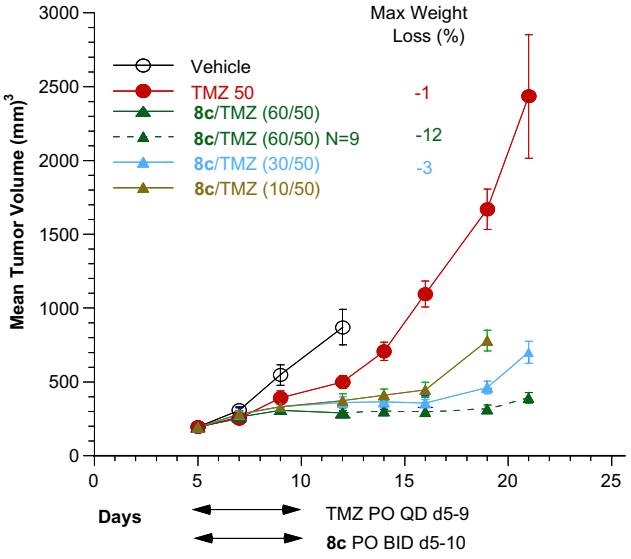


Fig. 3A. B16F10 model: **8c** in combination with TMZ.

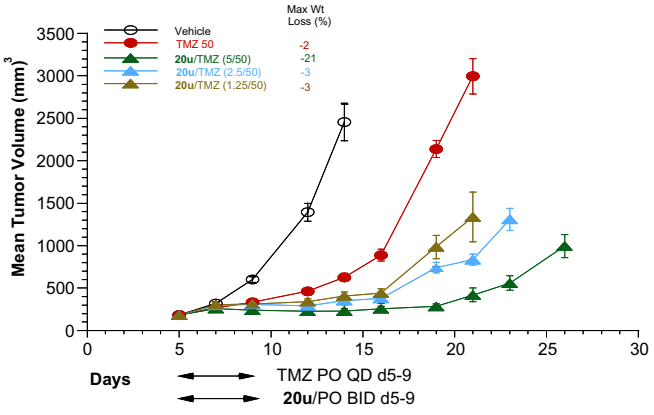


Fig. 3B. B16F10 model: **20u** in combination with TMZ.

group, however, an average of body weight loss of 12% was observed. One animal was euthanized and the data showed reflected the rest of animals.

Similar to **8c**, compound **20u** demonstrated significant potentiation of the TMZ efficacy but at much lower doses. Compound **20u** was administered orally on days 5–9 at doses of 1.25, 2.5 and 5 mg/kg/day, bid, while TMZ was administered orally at 50 mg/kg/day once a day during the same period. As displayed in Figure 3B, **20u** significantly potentiated the efficacy of TMZ in a dose-dependent manner, and all combination groups continued to differentiate from the TMZ alone group through the entire study period. Like compound **8c**, the **20u**-TMZ combination was well tolerated at lower doses with an average body weight loss similar to the TMZ monotherapy group. Significant body weight loss was, however, observed at the 5 mg/kg combination groups.

5. Conclusion

In summary, we have discovered and characterized a novel tetrahydropyridopyridazinone series of PARP inhibitors for the treatment of cancer. Some of the compounds described herein are among the most potent PARP inhibitors to date in both intrinsic and cellular assays. Compounds **8c** and **20u** have demonstrated significant efficacy in a B16 murine xenograft model, significantly potentiating the efficacy of TMZ. Pharmacokinetic characterization through a head-to-head comparisons has demonstrated that the presence of the NH in the tetrahydropyridyl ring is important for improved oral exposure. Compound **20u** represents a promising drug candidate for further pre-clinical characterization.

6. Experimental

6.1. General

NMR spectra were obtained on Varian M-300, Bruker AMX-400, Varian U-400, or Varian Unity Inova 500 magnetic resonance spectrometers with indicated solvent and internal standard. Chemical shifts are given in delta (δ) values and coupling constants (J) in Hertz (Hz). The following abbreviations are used for peak multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broadened. Mass spectra were performed as follows: ESI (electrospray ionization) was performed on a Finnigan SSQ7000 MS run as a flow injection acquisition; DCI (desorption chemical ionization) was performed on a Finnigan SSQ7000 MS using a direct exposure probe with ammonia gas; APCI (atmospheric pressure chemical ionization) was performed on a Finnigan Navigator MS run as flow injection acquisition. Elemental analyses were performed by Quantitative Technologies Inc. Whitehouse, New Jersey. All manipulations were performed under nitrogen atmosphere unless otherwise noted. All solvents and reagents were obtained from commercial sources and used without further purification. HPLC purifications were carried out using a Zorbax C-18, 250 × 2.54 column and a eluting with a 0-100% gradient of mobile phase A (0.1% trifluoroacetic acid (TFA) in water) and mobile phase B (0.1% TFA in CH_3CN).

6.1.1. PARP enzyme assay

Enzyme assay was conducted in buffer containing 50 mM Tris pH 8.0, 1 mM DTT, and 4 mM $MgCl_2$. PARP reactions contained 1.5 μM [^{3}H]-NAD$^+$ (1.6 μCi/mmol), 200 nM biotinylated histone H1, 200 nM slDNA, and 1 nM PARP-1 or 4 nM PARP-2 enzyme. Auto reactions utilizing SPA bead-based detection were carried out in 100 μL volumes in white 96 well plates. Reactions were initiated by adding 50 L of 2× NAD$^+$ substrate mixture to 50 L of 2× enzyme mixture containing PARP and DNA. These reactions were terminated by the addition of 150 L of 1.5 mM benzamide (~1000-fold over its IC_{50}). 170 L of the stopped reaction mixtures were transferred to streptavidin-coated Flash Plates, incubated for 1 h, and counted using a TopCount microplate scintillation counter. K_i data was determined from inhibition curves at various substrate concentrations.

6.1.2. Cellular PARP assay

C41 cells were treated with test compound for 30 min in a 96-well plate. PARP was activated by damaging DNA with 1 mM H_2O_2 for 10 min. Cells were washed with ice-cold PBS once and fixed with pre-chilled methanol/acetone (7:3) at −20°C for 10 min. After air-drying, plates were rehydrated with PBS and blocked using 5% non-fat dry milk in PBS-tween (0.05%) (blocking solution) for 30 min at room temperature. Cells were incubated with anti-PAR antibody 10H (1:50) in blocking solution at room temperature for 60 min followed by washing with PBS-Tween20 5 times, and incubation with goat anti-mouse fluorescein 5(6)-isothiocyanate (FITC) -coupled antibody (1:50) and 1 μg/ml 4′,6-diamidino-2-phenylindole (DAPI) in blocking solution at room temperature for 60 min. After washing with PBS-Tween20 5 times, analysis was performed using an fmax Fluorescence Microplate Reader set at the excitation and emission wavelength for FITC or the excitation and emission wavelength for DAPI. PARP activity (FITC signal) was normalized with cell numbers (DAPI).

6.1.3. B16F10 tumor model

For B16F10 syngeneic studies, 6×10^4 cells were mixed with 50% matrigel (BD Biosciences, Bedford, MA) and inoculated by s.c. injection into the flank of 6–8 week old female C57BL/6 mice, 20 g (Charles River Laboratories, Wilmington, MA). Mice were injection-order allocated to treatment groups and PARP inhibitor therapy was initiated on day 5 following inoculation, with temozolomide treatment also starting on day 5.

6.2. Synthesis of compound 8a–l

6.2.1. Methyl 2-(2-(4-fluorophenyl)acetyl)nicotinate (4)

To a solution of dimethyl pyridine-2,3-dicarboxylate (1.0 g, 5.1 mmol) in anhydrous THF (50 ml) was added (4-fluorobenzyl)magnesium chloride (0.25 M in THF, 20 mL, 5.1 mmol) through a syringe at −78 °C. The reaction mixture was stirred at the same temperature for 30 min and was quenched with addition of water. After warming up to room temperature, the reaction mixture was partitioned between ethyl acetate and brine. The organic phase was washed with brine and concentrated. The residue was purified by flash chromatography (15% ethyl acetate in hexane) to give 0.45 g of the title compound. Yield: 33%. MS (DCI/NH_3) m/z 274 (M+H)$^+$; ^{1}H NMR. (300 MHz, $CDCl_3$): δ 3.88 (s, 3H), 4.38 (s, 2H), 6.94–7.12 (m, 2H), 7.25–7.39 (m, 2H), 7.48 (dd, J = 7.80, 4.75 Hz, 1H), 8.04 (dd, J = 7.97, 1.53 Hz, 1H), 8.74 (dd, J = 4.75, 1.70 Hz, 1H).

6.2.2. 8-(4-Fluorobenzyl)pyrido[3,2-*d*]pyridazin-5(6*H*)-one (6)

A solution of **4** (0.46 g, 1.68 mmol) in ethanol (20 mL) was treated with hydrazine (108 mg, 3.37 mmol) at room temperature for 5 hours. The reaction mixture was concentrated to about 5 mL. The formed solid was collected by filtration, washed with ethanol and dried to provide 0.39 g of title compound. Yield: 91%. MS (DCI/NH_3) m/z 256 (M+H)$^+$; ^{1}H NMR. (300 MHz, DMSO-d_6): δ 4.36 (s, 2H), 6.99–7.13 (m, 2H), 7.29–7.39 (m, 2H), 7.85 (dd, J = 8.13, 4.56 Hz, 1H), 8.59 (dd, J = 8.13, 1.78 Hz, 1H), 9.16 (dd, J = 4.56, 1.78 Hz, 1H).

6.2.3. 8-(4-Fluorobenzyl)-1,2,3,4-tetrahydropyrido[3,2-*d*]pyridazin-5(6*H*)-one (8a)

A mixture of compound **6** (150 mg, 0.6 mmol), 5% platinum on carbon (30 mg), concentrated aqueous HCl (50 μL) and DMF

(5 mL) in a pressure vessel was stirred at room temperature under 50 psi of hydrogen for 16 h. The reaction mixture was filtered, and the filtrate was concentrated. The residual solid was purified by HPLC (Zorbax C-18, 0.1% TFA/CH_3CN/H_2O) to provide **8** as TFA salt. Yield: 126 mg (83%). MS (ESI) *m*/*z* 260 $(M+H)^+$; ^1H NMR. (300 MHz, DMSO-d_6): δ *1.55–1.80 (m, 2H), 2.35 (t, J = 6.27 Hz, 2H), 3.10–3.25 (m, 2H),* 3.81 (s, 2H), 7.06–7.18 (m, 2H), 7.20–7.31 (m, 2H).

6.2.4. Methyl 2-(2-(3-bromo-4-fluorophenyl)acetyl)nicotinate (5)

A mixture of magnesium turnings (880 mg, 37 mmol) and 2-bromo-4-(bromomethyl)-1-fluorobenzene (1.0 g, 3.7 mmol) in anhydrous diethyl ether (15 ml) was treated with a piece of iodine. The mixture was then heated to gentle reflux until the color of the mixture disappeared, after which the heating continued for additional hour. The suspension was cooled to room temperature, and cannulated into a solution of dimethyl pyridine-2,3-dicarboxylate (1.0 g, 5.1 mmol) in tetrahydrofuran (50 ml) at −78 °C. The reaction mixture was maintained at the same temperature for 30 min, and was quenched with addition of water. After warming up to room temperature, the reaction mixture was partitioned between ethyl acetate and brine. The organic phase was washed with brine and concentrated. The residue was purified by flash chromatography (15% ethyl acetate in hexane) to provide the title compound. Yield: 500 mg (38%). MS (DCI/NH_3) *m*/*z* 353 $(M+H)^+$; ^1H NMR. (300 MHz, METHANOL-D4) δ 3.88 (s, 3H), 4.38 (s, 2H), 7.09–7.20 (m, 1H), 7.24–7.34 (m, 1H), 7.57 (dd, *J* = 6.61, 2.20 Hz, 1H), 7.63 (dd, *J* = 7.97, 4.92 Hz, 1H), 8.18 (dd, *J* = 7.80, 1.70 Hz, 1H), 8.77 (dd, *J* = 4.92, 1.53 Hz, 1H).

6.2.5. 8-(3-Bromo-4-fluorobenzyl)pyrido[3,2-*d*]pyridazin-5(6*H*)-one (7)

Compound **7** was prepared according to the procedure for compound **4** and **6** substituting (3-bromo-4-fluorobenzyl)magnesium chloride for (4-fluorobenzyl)magnesium chloride. Yield: 180 mg (38%). MS (DCI/NH_3) *m*/*z* 335 $(M+H)^+$. ^1H NMR. (300 MHz, DMSO-d_6): δ 3.31 (s, 2H), 7.27 (t, *J* = 8.65 Hz, 1H), 7.30–7.41 (m, 1H), 7.66 (dd, *J* = 6.78, 2.37 Hz, 1H), 7.86 (dd, *J* = 7.97, 4.58 Hz, 1H), 8.60 (dd, *J* = 7.97, 1.86 Hz, 1H), 9.17 (dd, *J* = 4.58, 1.86 Hz, 1H).

6.2.6. Methyl 4-[(4-oxo-3,4,5,6,7,8-hexahydrophthalazin-1-yl)methyl]pyridine-2-carboxylate (11)

A 250 mL high pressure vessel was charged with **7** (4.5 g, 13.47 mmol), a mixture of MeOH (50 mL) and DMF (50 mL), $Pd(dppf)_2Cl_2{\cdot}CH_2Cl_2$ (0.099 g, 0.135 mmol) and NEt_3 (3.75 ml, 26.9 mmol). The mixture was purged and pressurized with carbon monoxide (60 psi), and stirred at 100 °C for 5 h. Solid material was filtered off, and the filtrate was concentrated. The formed solid was collected by filtration, washed with MeOH, and dried to give the title product. Yield: 3.8 g (90%). MS (DCI/NH_3) *m*/*z* 314 $(M+H)^+$; ^1H NMR. (300 MHz, DMSO-d_6): δ 3.88 (s, 3H), 3.98 (s, 2H), 7.21 (t, *J* = 8.65 Hz, 1H), 7.31–7.47 (m, 1H), 7.61 (dd, *J* = 6.98, 2.37 Hz, 1H), 7.87 (dd, *J* = 8.07, 4.58 Hz, 1H), 8.60 (dd, *J* = 8.07, 1.86 Hz, 1H), 9.17 (dd, *J* = 4.58, 1.86 Hz, 1H).

6.2.7. 2-Fluoro-5-[(5-oxo-5,6-dihydropyrido[2,3-*d*]pyridazin-8-yl)methyl]benzamide (12)

A solution of compound **11** (1 g, 3.2 mmol) in 7 N ammonia in methanol (5 ml) was heated at 70 °C overnight, and cooled to room temperature. The formed solid was collected by filtration, washed with methanol and dried to provide the title compound. Yield: 20 mg (28%). MS (DCI/NH_3) *m*/*z* 299 $(M+H)^+$; ^1H NMR. (300 MHz, DMSO-d_6): δ 4.39 (s, 2H), 7.17 (dd, *J* = 10.51, 8.53 Hz, 1H), 7.31–7.52 (m, 1H), 7.59 (dd, *J* = 7.14, 2.38 Hz, 1H), 7.85 (dd, *J* = 8.13, 4.56 Hz, 1H), 8.59 (dd, *J* = 7.93, 1.98 Hz, 1H), 9.16 (dd, *J* = 4.56, 1.78 Hz, 1H).

6.2.8. 8-(3-Amino-4-fluorobenzyl)pyrido[2,3-*d*]pyridazin-5(6*H*)-one (13)

A mixture of 1.5 N aqueous KOH solution (2 mL) and 3 g of ice was treated with bromine (80 mg, 0.5 mmol) at −10 °C for 10 min. Compound **12** (100 mg, 0.3 mmol) was then added. The reaction mixture was stirred at −10 °C for an additional 10 min, and was then allowed to warm up to 65 °C for 1 h. After cooling, the mixture was partitioned between ethyl acetate and brine. The organic phase was washed with brine, and concentrated to about 10 mL. The formed solid was collected by filtration, washed with methanol, and dried to provide**13**. Yield: 50 mg (77%). MS (DCI/NH_3) *m*/*z* 271 $(M+H)^+$. ^1H NMR. (300 MHz, DMSO-d_6): δ 4.20 (s, 2H), 4.99 (s, 2H), 6.31–6.54 (m, 1H), 6.67 (dd, *J* = 8.82, 2.03 Hz, 1H), 6.83 (dd, *J* = 11.53, 8.14 Hz, 1H), 7.84 (dd, *J* = 7.97, 4.58 Hz, 1H), 8.59 (dd, *J* = 8.14, 1.70 Hz, 1H), 9.14 (dd, *J* = 4.58, 1.86 Hz, 1H).

6.2.9. 8-(3-Amino-4-fluorobenzyl)-2,3,4,6-tetrahydropyrido[2,3-*d*]pyridazin-5(1*H*)-one (8b)

Compound **8b** was prepared as TFA salt according to procedure for compound **8**, substituting compound **13** for **6**. Yield: 56 mg (55%). MS (ESI) *m*/*z* 275 $(M+H)^+$; ^1H NMR (300 MHz, DMSO-d_6): 1.62–1.74 (m, 2H), 2.35 (t, *J* = 6.27 Hz, 2H), 3.10–3.23 (m, 2H), 3.69 (s, 2H), 4.91 (s, 2H), 6.25 (s, 1H), 6.45–6.54 (m, 1H), 6.64 (dd, *J* = 8.82, 2.03 Hz, 1H), 6.92 (dd, *J* = 11.53, 8.48 Hz, 1H), 11.93 (s, 1H).

6.2.10. 6-(Benzyloxymethyl)-8-(3-bromo-4-fluorobenzyl)pyrido[3,2-*d*]pyridazin-5(6*H*)-one (9)

A solution of compound **7** (100 mg, 0.3 mmol) in anhydrous dimethylformamide (10 mL) was treated with potassium *t*-butoxide (1 N solution in tetrahydrofuran, 0.3 mL, 3 mmol) at room temperature for 30 min. Benzyloxychloromethane (52 mg, 0.3 mmol) was then added, and the mixture was stirred at room temperature overnight. After quenching with water, the reaction mixture was partitioned between ethyl acetate and brine. The organic layer was washed with brine, and concentrated. The residue was purified by flash chromatography (85% ethyl acetate in hexane) to provide **9**. Yield: 100 mg (74%). MS (DCI/NH_3) *m*/*z* 454 $(M+H)^+$; ^1H NMR. (300 MHz, CD_3OD): δ 4.42 (s, 2H), 4.69 (s, 2H), 5.63 (s, 2H), 7.02–7.28 (m, 6H), 7.34–7.47 (m, 1H), 7.69 (dd, *J* = 6.74, 1.98 Hz, 1H), 7.79 (dd, *J* = 8.13, 4.56 Hz, 1H), 8.60–8.70 (m, 1H), 9.11 (dd, *J* = 4.56, 1.78 Hz, 1H).

6.2.11. 8-[4-Fluoro-3-(2-oxopyrrolidin-1-yl)benzyl]-2,3,4,6-tetrahydropyrido[2,3-*d*]pyridazin-5(1*H*)-one (8c)

A microwave tube was charged with tris(dibenzylideneacetone)dipalladium(0) (50 mg, 0.05 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos) (50 mg, 0.085 mmol), **9** (250 mg, 0.55 mmol), pyrrolidin-2-one (95 mg, 1.1 mmol) and Cs_2CO_3 (270 mg, 0.85 mmol). Anhydrous dioxane (10 mL) was added, and the suspension was heated in a microwave reactor (CEM Discover) at 200 °C for 60 min. After concentration, the residue was partitioned between ethyl acetate and brine. The organic phase was concentrated. The residual solid was separated by flash chromatography on silica gel (100% ethyl acetate) to provide a coupled product. This product was mixed with 5% platinum on carbon (25 mg), 5% $Pd(OH)_2$ on carbon (25 mg), concentrated aqueous HCl (66 μL) and dimethylformamide (10 ml), and pressurized under 40 psi of hydrogen at rt for 48 h. The volatiles were removed, and the residue was separated by HPLC (Zorbax C-18, 0.1% TFA/CH_3CN/H_2O) to provide compound **8c** as TFA salt. Yield: 58 mg. MS (ESI) *m*/*z* 343 $(M+H)^+$; ^1H NMR (300 MHz, DMSO-d_6): δ 1.57–1.81 (m, 2H), 2.01–2.18 (m, 2H), 2.26–2.46 (m, 4H), 3.17 (m, 2H), 3.72 (t, *J* = 6.94 Hz, 2H), 3.84 (s, 2H), 6.39 (s, 1H), 7.16–7.19 (m, 1H), 7.18–7.25 (m, 1H), 7.29 (dd, *J* = 7.54, 1.98 Hz, 1H), 11.89 (s, 1H).

6.2.12. 8-(4-Fluoro-3-(2-oxoazetidin-1-yl)benzyl)-1,2,3,4-tetrahydropyrido[3,2-*d*]pyridazin-5(6*H*)-one (8d)

Compound **8d** was prepared according to procedure for**8c**, substituting azitidinone for pyrrolidin-2-one. MS (ESI) *m*/*z* 329 $(M+H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.61–1.76 (m, 2H), 2.33 (t, *J* = 6.35 Hz, 2H), 3.12 (t, *J* = 4.56 Hz, 2H), 3.17 (m, 2H), 3.77 (s, 2H), 3.81 (q, *J* = 4.36 Hz, 2H), 6.32 (s, 1H), 6.87–7.01 (m, 1H), 7.17 (dd, *J* = 11.90, 8.33 Hz, 1H), 7.78 (dd, *J* = 7.54, 2.38 Hz, 1H), 11.80 (s, 1H).

6.2.13. 1-(2-Fluoro-5-((5-oxo-5,6-dihydropyrido[3,2-*d*]pyridazin-8-yl)methyl)phenyl)pyrrolidine-2,5-dione 16)

To a solution of **13** (300 mg, 1.1 mmol)) in acetonitrile (20 mL) was added succinic anhydride (167 mg, 1.7 mmol) and stirred at 80 °C for 18 h. The reaction mixture was heated at 90 °C for an additional three days. After cooling, the mixture was concentrated. The crude solid was dissolved in DMF (100 mL) and treated with CDI (180 mg, 1.1 mmol) and stirred at 80 °C for 16 h. The reaction mixture was partitioned between ethyl acetate and brine. The organic layer was washed with brine and concentrated. The residue was purified by HPLC (Zorbax C-8, 0.1% TFA/CH_3CN/H_2O) to provide the title product. Yield: 260 mg (67%). MS (ESI) *m*/*z* 353 $(M+H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.34–2.53 (m, 4H), 4.40 (s, 2H), 7.21–7.34 (m, 2H), 7.41–7.51 (m, 1H), 7.86 (dd, *J* = 8.13, 4.56 Hz, 1H), 8.57–8.63 (m, 1H), 9.15 (dd, *J* = 4.56, 1.78 Hz, 1H).

6.2.14. 1-{2-Fluoro-5-[(5-oxo-1,2,3,4,5,6-hexahydropyrido[2,3-*d*]pyridazin-8-yl)methyl]phenyl}pyrrolidine-2,5-dione (8e)

Compound **8e** was prepared as TFA salt according to the procedure for compound **8**, substituting compound **16** for **6**. Yield: 38%. MS (ESI) *m*/*z* 357 $(M+H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.58–1.78 (m, 2H), 2.33 (t, *J* = 6.27 Hz, 2H), 2.72–2.90 (m, 4H), 3.07–3.23 (m, 2H), 3.84 (s, 2H), 6.34 (s, 1H), 7.13 (dd, *J* = 6.95, 2.20 Hz, 1H), 7.27–7.37 (m, 1H), 7.37–7.43 (m, 1H), 11.83 (s, 1H).

6.2.15. 1-(2-Fluoro-5-((5-oxo-5,6-dihydropyrido[3,2-*d*]pyridazin-8-yl)methyl)phenyl)piperidine-2,6-dione (17)

Compound **17** was prepared according to the procedure for **16**, substituting dihydro-2*H*-pyran-2,6(3*H*)-dione for succinic anhydride. MS (ESI) *m*/*z* 367 $(M+H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.72–2.15 (m, 2H), 2.74 (t, *J* = 6.54 Hz, 4H), 4.37 (s, 2H), 7.10–7.28 (m, 2H), 7.33–7.47 (m, 1H), 7.86 (dd, *J* = 8.13, 4.56 Hz, 1H), 8.60 (dd, *J* = 8.13, 1.78 Hz, 1H), 9.15 (dd, *J* = 4.56, 1.78 Hz, 1H), 12.83 (s, 1H).

6.2.16. 1-{2-Fluoro-5-[(5-oxo-1,2,3,4,5,6-hexahydropyrido[2,3-*d*]pyridazin-8-yl)methyl]phenyl}piperidine-2,6-dione (8f)

To a solution of compound **17** (200 mg, 0.546 mmol) in DMF (20 mL) in a 100 mL pressure bottle was added 5% Pt/C (60.0 mg, 0.308 mmol) and concentrated HCl (55 μl, 1.2 equiv). The reaction mixture was purged and pressurized with hydrogen (30 psi), and stirred at rt for 3 days. Additional 60 mg of 5% Pt/C and 40 μL of concentrated HCl were then added, and the mixture was stirred at rt for 3 days. Solid material was filtered off, and the filtrate was concentrated. The residue was separated by HPLC (Zorbax C-18, 0.1% TFA/CH_3CN/H_2O) to provide **8f** as a TFA salt. Yield: 80 mg (40%). MS (DCI/NH_3) *m*/*z* 371 $(M+H)^+$; ^{1}H NMR (DMSO-d_6): δ 1.58–1.78 (m, 2H), 1.82–2.10 (m, 2H), 2.34 (t, *J* = 6.15 Hz, 2H), 2.76 (t, *J* = 6.35 Hz, 4H), 3.81 (s, 2H), 3.79–4.01 (m, 2H), 6.37 (s, 1H), 7.07 (dd, *J* = 7.14, 2.38 Hz, 1H), 7.18–7.28 (m, 1H), 7.28–7.38 (m, 1H), 11.88 (s, 1H).

6.2.17. 3-{2-Fluoro-5-[(5-oxo-1,2,3,4,5,6-hexahydropyrido[2,3-*d*]pyridazin-8-yl)methyl]phenyl}-5-methylimidazolidine-2,4-dione (8g)

A suspension of compound **8b** (50 mg, 0.18 mmol) in CH_3CN (15 mL) was heated until a transparent solution formed. After cooling, methyl 2-isocyanatopropanoate (23 mg, 0.18 mmol) was added, and the mixture was stirred at 65 °C overnight. The reaction mixture was concentrated, and the residue was dissolved in DMF (10 mL). 2 N NaOH solution (1 mL) was added, and the mixture was stirred at room temperature overnight. Solvent was removed, and the residue was purified by HPLC (Zorbax C-8, 0.1% TFA/CH_3CN/H_2O) to provide **8g** as the TFA salt. Yield: 14 mg (23%). MS (DCI/NH_3) *m*/*z* 372 $(M+H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.29 (d, *J* = 7.46 Hz, 3H), 1.59–1.79 (m, 2H), 2.27–2.36 (m, 2H), 3.17 (d, *J* = 4.41Hz, 2H), 3.74 (s, 2H), 4.04–4.23 (m, 1H), 6.28 (s, 1H), 6.74–6.88 (m, 1H), 6.97 (d, *J* = 7.12 Hz, 1H), 7.08 (dd, *J* = 11.53, 8.48 Hz, 1H), 8.01 (dd, *J* = 7.97, 2.20 Hz, 1H), 8.39 (d, *J* = 2.37 Hz, 1H).

6.2.18. 3-{2-Fluoro-5-[(5-oxo-1,2,3,4,5,6-hexahydropyrido[2,3-*d*]pyridazin-8-yl)methyl]phenyl}dihydropyrimidine-2,4(1H,3H)-dione (8h)

The title compound was prepared as the TFA salt according to the procedure for compound **8g**, substituting methyl 3-isocyanatopropanoate for methyl 2-isocyanatopropanoate. Yield: 9 mg (9%). MS (DCI/NH_3) *m*/*z* 372 $(M+H)^+$; ^{1}H NMR (DMSO-d_6) δ 1.68 (m, 2H), 2.27–2.37 (m, 2H), 2.40 (t, *J* = 6.27 Hz, 2H), 3.17 (m, 2H), 3.33 (m, 2H), 3.73 (s, 2H), 6.24 (s, 1H), 6.66–6.82 (m, 2H), 7.05 (dd, *J* = 11.36, 8.31Hz, 1H), 8.31 (s, 1H), 11.79 (s, 1H).

6.2.19. *N*-{2-Fluoro-5-[(5-oxo-1,2,3,4,5,6-hexahydropyrido[2,3-*d*]pyridazin-8-yl)methyl]phenyl}-3-methoxypropanamide (8i)

A mixture of 3-methoxypropanoic acid (19 mg, 0.18 mmol), HATU (69 mg, 0.18 mmol) and Hunnig's base (24 mg, 0.18 mmol) in DMF (0.4 ml) was stirred at room temperature for 10 min. Then 8-(3-Amino-4-fluorobenzyl)-1,2,3,4-tetrahydropyrido[3,2-d]pyridazin-5(6*H*)-one (50 mg, 0.18 mmol) was added into the reaction. The mixture was stirred at the same temperature for overnight. After filtration, the mixture was dissolved in a 1:1 mixture of dimethylsulfoxide/methanol, and separated by HPLC (Waters Sunfire C-8, 0.1% trifluoroacetic acid/water/CH_3CN) to provide **8i**. Yield: 10 mg (15%). MS (ESI) *m*/*z* 361 $(M+H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.64–1.73 (m, 2H), 2.33 (t, *J* = 6.15 Hz, 2H), 2.60 (t, *J* = 6.15 Hz, 2H), 3.17 (t, *J* = 5.16 Hz, 2H), 3.24 (s, 3H), 3.59 (t, *J* = 6.15 Hz, 2H), 3.77 (s, 2H), 6.33 (s, 1H), 6.90–7.05 (m, 1H), 7.14 (dd, *J* = 10.91, 8.53 Hz, 1H), 7.68–7.81 (m, 1H), 9.63 (s, 1H), 11.85 (s, 1H).

6.2.20. *N*-{2-Fluoro-5-[(5-oxo-1,2,3,4,5,6-hexahydropyrido[2,3-*d*]pyridazin-8-yl)methyl]phenyl}-5-oxohexanamide (8j)

The title compound was prepared as TFA salt according to the procedure for compound **8i**, substituting 5-oxohexanoic acid for 3-methoxypropanoic acid. MS (ESI) *m*/*z* 387 $(M+H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6): 1.64–1.80 (m, 4H), 2.08 (s, 3H), 2.27–2.39 (m, 4H), 2.42–2.50 (m, 2H), 3.10–3.23 (m, 2H), 3.77 (s, 2H), 6.34 (s, 1H), 6.94–7.04 (m, 1H), 7.13 (dd, *J* = 10.85, 8.48 Hz, 1H), 7.66–7.71 (m, 1H), 9.58 (s, 1H), 11.86 (s, 1H).

6.2.21. *N*-{2-fluoro-5-[(5-oxo-1,2,3,4,5,6-hexahydropyrido[2,3-*d*]pyridazin-8-yl)methyl]phenyl}-*N*′-phenylpentanediamide (8k)

The title compound was prepared as TFA salt according to the procedure for compound **8i**, substituting 5-oxo-5-(phenylamino)pentanoic acid for 3-methoxypropanoic acid. Yield: 13 mg. MS (ESI) *m*/*z* 464 $(M+H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.62–1.75 (m, 2H), 1.81–1.96 (m, 2H), 2.34 (t, *J* = 7.12 Hz, 4H), 2.42 (t, *J* = 8.14 Hz, 2H), 3.09–3.22 (m, 2H), 3.77 (s, 2H), 6.30 (s, 1H), 6.93–7.07 (m, 1H), 7.14 (dd, *J* = 10.85, 8.48 Hz, 1H), 7.22–7.34 (m, 3H), 7.59 (d, *J* = 7.80 Hz, 2H), 7.68–7.77 (m, 1H), 9.62 (s, 1H), 9.87 (s, 1H), 11.82 (s, 1H).

6.2.22. *N*-{2-fluoro-5-[(5-oxo-1,2,3,4,5,6-hexahydropyrido[2,3-*d*]pyridazin-8-yl)methyl]phenyl}-4-oxo-4-phenylbutanamide (8l)

The title compound was prepared according to the procedure for compound **8i**, substituting 4-oxo-4-phenylbutanoic acid for 3-methoxypropanoic acid. MS (ESI) *m*/*z* 435 $(M+H)^+$; ^1H NMR (300 MHz, DMSO-d_6): δ 1.63–1.73 (m, 2H), 2.32 (t, *J* = 5.95 Hz, 2H), 2.75–2.79 (m, 2H), 3.08–3.19 (m, 2H), 3.27–3.36 (m, 2H), 3.75 (s, 2H), 6.27 (s, 1H), 6.91–7.04 (m, 1H), 7.14 (dd, *J* = 10.91, 8.53 Hz, 1H), 7.54 (t, *J* = 7.54 Hz, 2H), 7.59–7.69 (m, 1H), 7.70–7.77 (m, 1H), 7.94–8.03 (m, 2H), 9.74 (s, 1H), 11.78 (s, 1H).

6.3. Synthesis of compound 20

6.3.1. Methyl 2-fluoro-5-[(5-oxo-1,2,3,4,5,6-hexahydropyrido[2,3-*d*]pyridazin-8-yl)methyl]benzoate (18)

In a 250 mL high pressure vessel, compound **11** (3.3 g, 10.53 mmol) and 5% Pt/C (0.330 g, 1.692 mmol) were suspended in 30 mL of AcOH. This suspension was purged and pressurized with 30 psi of hydrogen, and stirred at ambient temperature for 32 h. Solid material was filtered off, and the filtrate was concentrated. The formed solid was collected by filtration, washed with MeOH and dried to give **18**. Yield: 2.8 g (84%). MS (ESI) *m*/*z* 318 $(M+H)^+$; ^1H NMR (300 MHz, DMSO-d_6): δ 1.61–1.75 (m, 2H), 2.34 (t, *J* = 6.15 Hz, 2H), 3.17 (m, 2H), 3.44 (s, 3H), 3.84 (s, 2H), 6.39 (s, 1H), 7.27 (dd, *J* = 10.91, 8.53 Hz, 1H), 7.46–7.56 (m, 1H), 7.76 (dd, *J* = 7.14, 2.38 Hz, 1H), 11.84 (s, 1H).

6.3.2. 2-Fluoro-5-[(5-oxo-1,2,3,4,5,6-hexahydropyrido[2,3-*d*]pyridazin-8-yl)methyl]benzoic acid (19)

Compound **18** (2.8 g, 8.8 mmol) was dissolved in hot THF (150 mL), and was treated with LiOH (253 mg, 10.6 mmol) in water (20 mL) at 50 °C overnight. After cooling to room temperature, the reaction mixture was acidified with diluted HCl to a pH4, and concentrated to about 10 mL. The formed solid material was collected by filtration, washed with water and dried to provide **19**. Yield: 2.4 g (85%). MS (ESI) *m*/*z* 304 $(M+H)^+$; ^1H NMR (300 MHz, DMSO-d_6): δ 1.61–1.77 (m, 2H), 2.34 (t, *J* = 6.10 Hz, 2H), 3.06–3.25 (m, 2H), 3.84 (s, 2H), 6.36 (s, 1H), 7.22 (dd, *J* = 10.85, 8.48 Hz, 1H), 7.39–7.52 (m, 1H), 7.73 (dd, *J* = 7.12, 2.37 Hz, 1H), 11.82 (s, 1H) 13.19 (s, 1H).

6.3.3. General procedure for the syntheses of compounds 20

To a solution of compound **19** (100 mg, 0.33 mmol) in anhydrous DMF (3 mL) was added appropriate amine (0.43 mmol), EDC (82 mg, 0.43 mmol), 1-hydroxybenzotriazole monohydrate (66 mg, 0.43 mmol), and triethylamine (43 mg, 0.43 mmol). The reaction mixture was stirred at rt overnight, and partitioned between methylene chloride and brine. The organic phase was washed with brine, water, and concentrated. The residue was separated by HPLC to provide compounds **20**. For compounds **20f**, **20g**, and **20h** whose syntheses involved the use of BOC-protected amine, the coupling product was then treated with TFA (0.5 ml) in CH_2Cl_2 (2 mL) at rt for 1 h. Removal of the volatiles provided the crude **20** that can be further purified by HPLC to give the title products.

6.3.4. 2-Fluoro-5-((5-oxo-1,2,3,4,5,6-hexahydropyrido[2,3-*d*]pyridazin-8-yl)methyl)benzamide (20a)

MS (ESI) *m*/*z* 303 $(M+H)^+$; ^1H NMR (300 MHz, DMSO-d_6): δ 1.58–1.81 (m, 2H), 2.34 (t, *J* = 6.15 Hz, 2H), 3.12–3.23 (m, 2H), 3.84 (s, 2H), 7.27 (dd, *J* = 10.91, 8.53 Hz, 1H), 7.40–7.64 (m, 1H), 7.76 (dd, *J* = 7.14, 2.38 Hz, 1H).

6.3.5. *N*-Ethyl-2-fluoro-5-[(5-oxo-1,2,3,4,5,6-hexahydropyrido[2,3-*d*]pyridazin-8-yl)methyl]benzamide (20b)

MS (ESI) *m*/*z* 331 $(M+H)^+$; ^1H NMR (300 MHz, DMSO-d_6): 1.09 (t, *J* = 7.14 Hz, 3H), 1.58–1.74 (m, 2H), 2.34 (t, *J* = 6.15 Hz, 2H), 3.12–3.20 (m, 2H), 3.20–3.29 (m, 2H), 3.82 (s, 2H), 6.39 (s, 1H), 7.19 (dd, *J* = 10.31, 8.33 Hz, 1H), 7.30–7.38 (m, 1H), 7.47 (dd, *J* = 6.74, 2.38 Hz, 1H), 8.17–8.29 (m, 1H), 11.88 (s, 1H).

6.3.6. *N*-Cyclopropyl-2-fluoro-5-[(5-oxo-1,2,3,4,5,6-hexahydropyrido[2,3-*d*]pyridazin-8-yl)methyl]benzamide (20c)

MS (ESI) *m*/*z* 343 $(M+H)^+$; ^1H NMR (300 MHz, DMSO-d_6): 0.44–0.59 (m, 2H), 0.63–0.76 (m, 2H), 1.60–1.78 (m, 2H), 2.34 (t, *J* = 6.35 Hz, 2H), 2.74–2.90 (m, 1H), 3.09–3.22 (m, 2H), 3.81 (s, 2H), 6.39 (s, 1H), 7.03–7.25 (m, 1H), 7.25–7.37 (m, 1H), 7.42 (dd, *J* = 6.74, 2.38 Hz, 1H), 8.33 (d, *J* = 3.97 Hz, 1H), 11.89 (s, 1H).

6.3.7. 2-Fluoro-5-[(5-oxo-1,2,3,4,5,6-hexahydropyrido[2,3-*d*]pyridazin-8-yl)methyl]-*N*-(2-pyrrolidin-1-ylethyl)benzamide (20d)

MS (ESI) *m*/*z* 400 $(M+H)^+$; ^1H NMR (300 MHz, DMSO-d_6): δ 1.63–1.76 (m, 2H), 1.76–1.93 (m, 2H), 1.93–2.10 (m, 2H), 2.34 (t, *J* = 6.10 Hz, 2H), 2.61–2.76 (m, 2H), 2.96–3.12 (m, 2H), 3.12–3.22 (m, 2H), 3.25–3.40 (m, 2H), 3.52–3.68 (m, 2H), 3.84 (s, 2H), 6.35 (s, 1H,) 7.25 (dd, *J* = 10.85, 8.48 Hz, 1H), 7.33–7.49 (m, 1H), 7.57 (dd, *J* = 7.12, 2.37 Hz, 1H), 8.31–8.50 (m, 1H), 11.84 (s, 1H).

6.3.8. 2-Fluoro-*N*-[2-(4-methylpiperazin-1-yl)ethyl]-5-[(5-oxo-1,2,3,4,5,6-hexahydropyrido[2,3-*d*]pyridazin-8-yl)methyl]benzamide (20e)

MS (DCI/NH_3) *m*/*z* 429 (M+H); ^1H NMR (300 MHz, DMSO-d_6): δ 1.66–1.72 (m, 2H), 2.34 (t, *J* = 6.27 Hz, 2H), 2.80 (s, 3H), 2.83–2.96 (m, 2H), 3.05–3.31 (m, 6H), 3.47 (q, *J* = 6.22 Hz, 6H), 3.83 (s, 2H), 6.39 (s, 1H), 7.23 (dd, *J* = 10.68, 8.65 Hz, 1H), 7.38–7.45 (m, 1H), 7.51 (dd, *J* = 7.12, 2.37 Hz, 1H), 8.28 (d, *J* = 3.39 Hz, 1H), 11.88 (s, 1H).

6.3.9. 8-[4-fluoro-3-(piperazin-1-ylcarbonyl)benzyl]-2,3,4,6-tetrahydropyrido[2,3-*d*]pyridazin-5(1*H*)-one (20f)

MS (DCI/NH_3) *m*/*z* 372 $(M+H)^+$; ^1H NMR (300 MHz, DMSO-d_6): δ 1.60–1.77 (m, 2H), 2.35 (t, *J* = 6.27 Hz, 2H), 3.08 (s, 2H), 3.12–3.31 (m, 4H), 3.44 (s, 2H), 3.77–3.82 (m, 2H), 3.83 (s, 2H), 7.15–7.33 (m, 2H), 7.33–7.44 (m, 1H).

6.3.10. 8-{3-[(4-Aminopiperidin-1-yl)carbonyl]-4-fluorobenzyl}-2,3,4,6-tetrahydropyrido[2,3-d]pyridazin-5(1*H*)-one (20g)

MS (DCI/NH_3) *m*/*z* 386 $(M+H)^+$; ^1H NMR (300 MHz, CD_3OD): δ 1.44–1.70 (m, 2H), 1.71–1.88 (m, 2H), 1.91–2.04 (m, 1H), 2.12 (d, *J* = 11.53 Hz, 1H), 2.51 (t, *J* = 6.27 Hz, 2H), 2.80–3.00 (m, 1H), 3.14–3.34 (m, 2H), 3.32–3.51 (m, 2H), 3.58–3.73 (m, 1H), 3.91 (s, 2H), 4.74 (d, *J* = 13.90 Hz, 1H), 7.08–7.26 (m, 2H), 7.31–7.47 (m, 1H).

6.3.11. 8-(4-Fluoro-3-{[(2*R*),-2-phenylpiperazin-1-yl]carbonyl}benzyl),-2,3,4,6-tetrahydropyrido[2,3-*d*]pyridazin-5(1*H*),-one (20h)

MS (DCI/NH_3) *m*/*z* 448 $(M+H)^+$; ^1H NMR (DMSO-d_6): δ 1.48–1.86 (m, 2H), 2.14–2.42 (m, 2H), 3.02–3.37 (m, 2H), 3.40–3.73 (m, 2H), 3.87 (m, 4H), 3.84 (s, 2H), 4.63 (m, 1H), 6.37 (s, 1H), 7.20–7.37 (m, 3H), 7.37–7.47 (m, 2H), 7.48–7.63 (m, 3H), 9.56 (s, 1H), 11.86 (s, 1H).

6.3.12. 8-{4-Fluoro-3-[(4-methylpiperazin-1-yl)carbonyl]benzyl}-2,3,4,6-tetrahydropyrido[2,3-*d*]pyridazin-5(1*H*)-one (20i)

MS (DCI/NH_3) *m*/*z* 386 $(M+H)^+$; ^1H NMR (DMSO-d_6): δ 1.52–1.78 (m, 2H), 2.35 (t, *J* = 6.10 Hz, 2H), 2.84 (s, 3H), 2.92–3.25 (m, 6H), 3.39 (m, 2H), 3.57 (m, 2H), 3.83 (s, 2H), 6.37 (s, 1H), 7.06–7.36 (m, 2H), 7.33–7.51 (m, 1H), 11.86 (s, 1H).

6.3.13. 8-{3-[(4-Cyclopentylpiperazin-1-yl)carbonyl]-4-fluorobenzyl}-2,3,4,6-tetrahydropyrido[2,3-*d*]pyridazin-5(1*H*)-one (20j)

MS (DCI/NH_3) *m*/*z* 440 $(M+H)^+$; ^1H NMR (DMSO-d_6): δ 1.29–1.86 (m, 8H), 2.01 (m, 2H), 2.35 (t, *J* = 6.10 Hz, 2H), 2.98 (m, 1H), 3.03–3.29 (m, 4H), 3.43 (m, 2H), 3.56 (m, 4H), 3.83 (s, 2H), 6.38 (s, 1H), 7.04–7.34 (m, 2H), 7.34–7.54 (m, 1H), 11.86 (s, 1H).

6.3.14. 8-{4-Fluoro-3-[(3-oxopiperazin-1-yl)carbonyl]benzyl}-2,3,4,6-tetrahydropyrido[2,3-*d*]pyridazin-5(1*H*)-one (20k)

MS (DCI/NH_3) *m*/*z* 386 $(M+H)^+$; ^1H NMR (DMSO-d_6): δ 1.47–1.78 (m, 2H), 2.34 (t, *J* = 6.10 Hz, 2H), 3.07–3.24 (m, 2H), 3.39 (m, 2H), 3.69–3.81 (m, 2H), 3.83 (s, 2H), 4.11 (s, 2H), 6.38 (s, 1H), 7.04–7.30 (m, 2H), 7.31–7.41 (m, 1H), 8.13 (s, 1H), 11.89 (s, 1H).

6.3.15. 8-(3-{[4-(Cyclopropylcarbonyl)piperazin-1-yl]carbonyl}-4-fluorobenzyl)-2,3,4,6-tetrahydropyrido[2,3-*d*]pyridazin-5(1*H*)-one (20l)

MS (DCI/NH_3) *m*/*z* 440 $(M+H)^+$; ^1H NMR (DMSO-d_6) δ 0.60–0.82 (m, 4H), 1.59–1.79 (m, 2H), 1.94 (m, 1H), 2.34 (t, *J* = 6.27 Hz, 2H), 3.00–3.35 (m, 4H), 3.38–3.79 (m, 2H), 3.82 (s, 2H), 3.83–4.11 (m, 4H), 6.37 (s, 1H), 7.15–7.27 (m, 1H), 7.24–7.30 (m, 1H), 7.30–7.40 (m, 1H), 11.87 (s, 1H).

6.3.16. 8-{3-[(4-Acetylpiperazin-1-yl)carbonyl]-4-fluorobenzyl}-2,3,4,6-tetrahydropyrido[2,3-*d*]pyridazin-5(1*H*)-one (20m)

MS (DCI/NH_3) *m*/*z* 412 (M+H); ^1H NMR (300 MHz, DMSO-d_6): δ 1.66–1.76 (m, 2H), 2.04 (s, 3H), 2.35 (t, *J* = 6.27 Hz, 2H), 3.12–3.30 (m, 4H), 3.36–3.46 (m, 2H), 3.52 (d, *J* = 5.09 Hz, 2H), 3.58 (d, *J* = 5.09 Hz, 1H), 3.66 (d, *J* = 5.09 Hz, 1H), 3.83 (s, 2H), 7.14–7.29 (m, 2H), 7.30–7.43 (m, 1H).

6.3.17. 8-(4-Fluoro-3-{[4-(trifluoroacetyl)piperazin-1-yl]carbonyl}benzyl)-2,3,4,6-tetrahydropyrido[2,3-*d*]pyridazin-5(1*H*)-one (20n)

MS (DCI/NH_3) *m*/*z* 468 $(M+H)^+$; ^1H NMR (DMSO-d_6): δ 1.57–1.80 (m, 2H), 2.35 (t, *J* = 6.10 Hz, 2H), 3.09–3.26 (m, 2H), 3.35 (m, 2H), 3.57 (m, 2H), 3.67 (m, 2H), 3.74 (m, 2H), 3.83 (s, 2H), 6.42 (s, 1H), 7.03–7.29 (m, 2H), 7.31–7.48 (m, 1H), 11.94 (s, 1H).

6.3.18. 8-{3-[(4-Benzoylpiperazin-1-yl)carbonyl]-4-fluorobenzyl}-2,3,4,6-tetrahydropyrido[2,3-*d*]pyridazin-5(1*H*)-one (20o)

MS (DCI/NH_3) *m*/*z* 476 $(M+H)^+$; ^1H NMR (DMSO-d_6) δ 1.57–1.78 (m, 2H), 2.34 (t, *J* = 6.10 Hz, 2H), 3.17 (m, 4H), 3.21–3.37 (m, 2H), 3.45 (m, 2H), 3.69 (m, 2H), 3.82 (s, 2H), 6.40 (s, 1H), 7.18–7.30 (m, 2H), 7.29–7.38 (m, 1H), 7.39–7.50 (m, 5H), 11.92 (s, 1H).

6.3.19. 4-{2-Fluoro-5-[(5-oxo-1,2,3,4,5,6-hexahydropyrido[2,3-*d*]pyridazin-8-yl)methyl]benzoyl}-*N*,*N*-dimethylpiperazine-1-carboxamide (20p)

MS (DCI/NH_3) *m*/*z* 443 $(M+H)^+$; ^1H NMR (DMSO-d_6): δ 1.37–1.52 (m, 2H), 2.09 (t, *J* = 6.15 Hz, 2H), 2.17–2.29 (m, 2H), 2.75–2.85 (m, 2H), 2.91 (m, 6H), 2.91–3.01 (m, 4H), 3.38 (m, 2H), 3.56 (s, 2H), 6.17 (s, 1H), 6.91–6.99 (m, 1H), 6.97–7.03 (m, 1H), 7.04–7.10 (m, 1H), 11.68 (s, 1H).

6.3.20. 8-(4-Fluoro-3-{[4-(methylsulfonyl)piperazin-1-yl]carbonyl}benzyl)-2,3,4,6-tetrahydropyrido[2,3-*d*]pyridazin-5(1*H*)-one (20q)

MS (DCI/NH_3) *m*/*z* 450 $(M+H)^+$; ^1H NMR (DMSO-d_6): δ 1.63–1.81 (m, 2H), 2.35 (t, *J* = 6.27 Hz, 2H), 2.91 (m, 3H), 3.09 (m, 2H), 3.12–3.24 (m, 4H), 3.32 (m, 2H), 3.74 (m, 2H), 3.82 (s, 2H), 6.38 (s, 1H), 7.17–7.29 (m, 2H), 7.31–7.39 (m, 1H), 11.89 (s, 1H).

6.3.21. 8-{4-Fluoro-3-[(4-phenylpiperazin-1-yl)carbonyl]benzyl}-2,3,4,6-tetrahydropyrido[2,3-*d*]pyridazin-5(1*H*)-one (20r)

MS (DCI/NH_3) *m*/*z* 448 $(M+H)^+$; ^1H NMR (DMSO-d_6): δ 1.52–1.78 (m, 2H), 2.34 (t, *J* = 6.10 Hz, 2H), 3.09 (m, 2H), 3.13–3.26 (m, 4H), 3.35 (m, 2H), 3.68–3.85 (m, 2H), 3.83 (s, 2H), 6.36 (s, 1H), 6.82 (t, *J* = 7.29 Hz, 1H), 6.96 (d, *J* = 7.80 Hz, 2H), 7.22 (d, *J* = 8.48 Hz, 2H), 7.24–7.30 (m, 2H), 7.30–7.39 (m, 1H), 11.85 (s, 1H).

6.3.22. 8-{4-Fluoro-3-[(4-pyridin-4-ylpiperazin-1-yl)carbonyl]benzyl}-2,3,4,6-tetrahydropyrido[2,3-*d*]pyridazin-5(1*H*)-one (20s)

MS (DCI/NH_3) *m*/*z* 449 $(M+H)^+$; ^1H NMR (DMSO-d_6 DMSO-d_6) δ 1.60–1.82 (m, 2H), 2.35 (t, *J* = 6.10 Hz, 2H), 3.09–3.25 (m, 2H), 3.43 (m, 2H), 3.68 (m, 2H), 3.74–3.88 (m, 4H), 3.84 (s, 2H), 6.38 (s, 1H), 7.17 (d, *J* = 7.12 Hz, 2H), 7.21–7.29 (m, 1H), 7.28–7.33 (m, 1H), 7.34–7.42 (m, 1H), 8.30 (d, *J* = 7.46 Hz, 2H), 11.86 (s, 1H).

6.3.23. 8-{4-Fluoro-3-[(4-pyridin-3-ylpiperazin-1-yl)carbonyl]benzyl}-2,3,4,6-tetrahydropyrido[2,3-*d*]pyridazin-5(1*H*)-one (20t)

MS (DCI/NH_3) *m*/*z* 449 $(M+H)^+$; ^1H NMR (DMSO-d_6): δ 1.52–1.80 (m, 2H), 2.35 (t, *J* = 6.10 Hz, 2H), 3.18 (m, 2H), 3.39 (m, 4H), 3.47–3.61 (m, 2H), 3.76–3.84 (m, 2H), 3.84 (s, 2H), 6.44 (s, 1H), 7.05–7.33 (m, 2H), 7.30–7.48 (m, 1H), 7.82 (dd, *J* = 8.98, 5.26 Hz, 1H), 8.02 (dd, *J* = 8.81, 2.37 Hz, 1H), 8.24 (d, *J* = 5.42 Hz, 1H), 8.46 (d, *J* = 2.71Hz, 1H), 11.92 (s, 1H).

6.3.24. 8-{4-Fluoro-3-[(4-pyridin-2-ylpiperazin-1-yl)carbonyl]benzyl}-2,3,4,6-tetrahydropyrido[2,3-*d*]pyridazin-5(1*H*)-one (20u)

MS (DCI/NH_3) *m*/*z* 449 $(M+H)^+$; ^1H NMR (DMSO-d_6 DMSO-d_6): δ 1.60–1.80 (m, 2H), 2.35 (t, *J* = 6.10 Hz, 2H), 3.10–3.24 (m, 2H), 3.39 (m, 2H), 3.55 (m, 2H), 3.68 (m, 2H), 3.73–3.81 (m, 2H), 3.84 (s, 2H), 6.41 (s, 1H), 6.78–6.88 (m, 1H), 7.09 (d, *J* = 8.81Hz, 1H), 7.20–7.28 (m, 1H), 7.26–7.32 (m, 1H), 7.32–7.42 (m, 1H), 7.79 (t, *J* = 7.29 Hz, 1H), 8.00–8.14 (m, 1H), 11.90 (s, 1H).

6.3.25. 8-{4-Fluoro-3-[(4-pyrazin-2-ylpiperazin-1-yl)carbonyl]benzyl}-2,3,4,6-tetrahydropyrido[2,3-*d*]pyridazin-5(1*H*)-one (20v)

MS (DCI/NH_3) *m*/*z* 450 $(M+H)^+$; ^1H NMR (DMSO-d_6): δ 1.61–1.76 (m, 2H), 2.34 (t, *J* = 6.15 Hz, 2H), 3.10–3.24 (m, 2H), 3.34 (m, 2H), 3.54 (m, 2H), 3.67 (m, 2H), 3.74 (m, 2H), 3.83 (s, 2H), 6.43 (s, 1H), 7.20–7.27 (m, 1H), 7.28 (dd, *J* = 6.54, 2.18 Hz, 1H), 7.31–7.38 (m, 1H), 7.87 (d, *J* = 2.78 Hz, 1H), 8.10 (d, *J* = 2.78 Hz, 1H), 8.32 (s, 1H), 11.95 (s, 1H).

6.3.26. 8-{4-Fluoro-3-[(4-pyrimidin-2-ylpiperazin-1-yl)carbonyl]benzyl}-2,3,4,6-tetrahydropyrido[2,3-*d*]pyridazin-5(1*H*)-one (20w)

MS (DCI/NH_3) *m*/*z* 450 $(M+H)^+$; ^1H NMR (DMSO-d_6): δ 1.39–1.85 (m, 2H), 2.33 (t, *J* = 6.10 Hz, 2H), 3.06–3.21 (m, 2H), 3.24–3.35 (m, 2H), 3.55–3.96 (m, 8H), 6.40 (s, 1H), 6.67 (t, *J* = 4.75 Hz, 1H), 7.16–7.26 (m, 1H), 7.24–7.30 (m, 1H), 7.30–7.39 (m, 1H), 8.38 (d, *J* = 4.75 Hz, 2H), 11.91 (s, 1H).

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