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Endocyclic Enamides Derived from Aza-Diketopiperazines as Olefin Partners in Povarov Reaction: An Access to Tetracyclic N-Heterocycles

Timothé Maujean,^[a] Isabelle Chataigner,^{[b],[c]} Nicolas Girard,*^[a] Mihaela Gulea,*^[a] and Dominique Bonnet*^[a]

[a]	T. Maujean, Dr. N. Girard, Dr. M. Gulea, Dr. D. Bonnet
	Université de Strasbourg, CNRS, Laboratoire d'Innovation Thérapeutique, LIT UMR 7200, LabEx Medalis, ITI InnoVec,
	F-67000 Strasbourg, France
	E-mail: nicolas.girard@unistra.fr; gulea@unistra.fr; dbonnet@unistra.fr
[b]	Pr. I. Chataigner
	Normandie Université, INSA Rouen, CNRS, COBRA UMR 6014,
	F-76000 Rouen, France
	E-mail: isabelle.chataigner@univ-rouen.fr
[c]	Pr. I. Chataigner
	Sorbonne Université, CNRS, Laboratoire de Chimie Théorique, LCT UMR 7616,
	F-75005 Paris, France
ORCI	Ds:
I. Cha	aigner: 0000-0001-6302-7831
N. Gir	ard: 0000-0003-4610-9872
M. Gu	lea: 0000-0002-2945-0078
D. Boi	inet: 0000-0002-8252-9199

Supporting information for this article (computational data and NMR spectra) is given via a link at the end of the document.

Abstract: Original endocyclic enamides based on a bicyclic azadiketopiperazine (aza-DKP) structure have been used as dienophile partners in the Povarov reaction. The reported method represents a successful strategy for the structural diversification of the aza-DKP scaffold, giving access to a new family of fused tetracyclic *N*heterocycles, which contain at least four nitrogen atoms in the heterocyclic structure. Depending on the nature of the aldehyde partner, the cycloadditions have been performed either as a twocomponent or a three-component reaction (2CR or 3CR), in the presence of BF₃ as a Lewis acid catalyst. With aliphatic aldehydes the reaction proceeds with high diastereoselectivities in favor of the cis compounds. Some mechanistic aspects of this cycloaddition have been examined computationally.

Introduction

Discovered by Povarov in the 1960s,^[1] the Povarov reaction was widely developed and represents nowadays a powerful tool in heterocyclic synthesis. Several reviews have been devoted to its applications in synthetic^[2] or medicinal chemistry.^[3] The Povarov reaction has been successfully used in diversity-oriented synthesis, as well as in target-oriented synthesis, to access tetrahydroquinolines (THQs),^[4] which represent a valuable class of heterocyclic compounds. There are two currently available versions of the Povarov reaction: the two-component reaction (2CR) that involves an electron-rich olefin and an *N*-aryl imine, and the three-component reaction (3CR) that consists in reacting directly the olefin, the *N*-aryl amine, and the aldehyde. A literature survey revealed that among the different electron-rich olefins, endocyclic enamides have been sparsely reported as partners in

the Povarov reaction. However, they represent attractive substrates to access various *N*-polyheterocycles of pharmaceutic interest. In Figure 1 are illustrated the few published examples of 4-,^[5] 5-,^[6] and 6-membered ring^[7] endocyclic enamides or enecarbamates **I-III**, and 6-membered ring unsaturated lactams derivatives **IV**.^[8] In this context, we decided to investigate the azadiketopiperazine (aza-DKP) derivative represented by the general structure **V**, as a new type of endocyclic enamide. This substrate represents an interesting case, due to its unique bicyclic structure including a 1,2,4-triazine-3,6-dione subunit.



Figure 1. Endocyclic enamide-type substrates in Povarov reaction.

Aza-diketopiperazines are aza analogues of the well-known 2,5diketopiperazines (DKPs)^[9] and have been reported as an emerging scaffold with potential application in medicinal chemistry. They have been the subject of several studies in our laboratory^[10] and showed promising drug-likeness properties.^{10a-c} Most of reported in the literature aza-DKPs are monocyclic, however some fused bicyclic and tricyclic aza-DKPs (Figure 2) were obtained either from cyclic precursors (such as cyclic amino acids or hydrazine derivatives)^[11] or from a monocyclic aza-DKP by post-synthetic transformation.^{10c,d} To our knowledge, only one example of fused tetracyclic aza-DKP (Figure 2) was reported so far, an aza-analogue of tadalafil PDE5 inhibitor.^[12]



Figure 2. General structure of an aza-DKP and selected examples of polycyclic derivatives.

In this context, the Povarov reaction appeared as an interesting and versatile strategy to access a new family of fused tetracyclic aza-DKPs using endocyclic enamides **V** as olefin partners. The obtained tetracyclic *N*-heterocycles **VI** will combine in their structure two interesting scaffolds of interest in medicinal chemistry, a tetrahydroquinoline and an aza-diketopiperazine (Scheme 1).



Scheme 1. Aza-DKPs as partners in Povarov reaction.

Results and Discussion

We first synthesized the bicyclic aza-DKP precursor 1 as a simple and achiral endocyclic enamide substrate. In a first step, N-benzyl glycine ethyl ester reacted with N-allyl tert-butylcarbazate and triphosgene to furnish in 58% yield the desired allyl-aza-DKP. The latter was then placed under rhodium-catalyzed cyclohydrocarbonylation conditions to afford product 1 (Scheme 2). The transformation was first performed with 2 mol% of Rhsource and 6 mol% of BiPhePhos ligand and product 1 was isolated in 74% yield. As both the Rh-source and the ligand are expensive, we attempted to decrease the catalytic charge, while trying to perform the reaction on gram-scale. Finally, we succeeded in decreasing the amount of Rh-catalyst down to 0.25 mol% when performing the reaction on a 1.4 grams scale, while maintaining a good 70% yield in 1.



As a first assay, the reactivity of enamide 1 toward Nbenzylideneaniline was tested in commonly used two-component Povarov reaction (2CR) conditions, with an excess of imine (1.4 equiv), in the presence of 1 equiv of BF₃.Et₂O as Lewis acid to promote the reaction, in acetonitrile, at room temperature (Table 1, entry 1). Reaction completion was total after 18 h and the expected product 2a was obtained as a mixture of two diastereoisomers 2aA and 2aB in an approximative 1:1 ratio (determined by HPLC on the crude mixture), together with a little amount of the side-product 2a' resulting from the dehydrogenative aromatization of 2a. We were able to separate the diastereomers by reversed-phase chromatography and unambiguously assign by NMR NOESY-2D experiments the cis-configuration to 2aA and the trans-configuration to 2aB (see SI: for 2aA correlation spots between the three protons of the contiguous CH of the tetrahydroquinoline system and for 2aB correlation spots only between the two vicinal CH protons of the hexahydropyridazine heterocycle). The formation of 2a' was probably due to the excess of the imine, which plays the role of oxidant and is reduced to the corresponding N-benzylaniline.[13] The total isolated yield was 45% and the two diastereomers were separated using reversedphase chromatography. This purification technique was crucial for an optimal yield and separation (see experimental section), as the use of normal-phase chromatography or crystallization led to partial degradation and dramatically decreased the yield. Simple replacement of acetonitrile by dichloromethane led to an incomplete conversion after 18 h and more of the undesired product 2a' was formed (Table 1, entry 2). Performing the reaction at 50 °C afforded again more side-product 2a' (Table 1. entry 3). By reducing the amount of imine to 1 equiv in the conditions of the first experiment, the formation of 2a' was suppressed and a higher yield of 69% was obtained (Table 1, entry 4). On the other hand, reducing the amount of the BF₃ catalyst to 0.3 equiv, led to a slower process and the reaction time had to be extended to 2 days for a total conversion, while the vield dropped to 39% (Table 1. entry 5). Other Lewis acids such as Sc(OTf)₃, Yb(OTf)₃, and Dy(OTf)₃, which are known to be efficient in some Povarov reactions, were tested using a 30 mol% catalytic charge.2b Although the yields were similar to those obtained with BF₃.Et₂O. the reaction time had to be extended to 3-4 days for a total completion (Table 1, entries 6 to 8). Finally, the trifluoroacetic acid (TFA) and the diphenyl phosphate were also envisaged as Brønsted acids catalysts, leading respectively to 41% yield of 2a, or to recovering the starting material (Table 1, entries 9 and 10).

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Entry	Catalyst	Ratio 1/imine/cat.	Time	Ratio ^[a] 1/2a/2a'	Yield (%) ^[b]
1	BF ₃ .Et ₂ O	1/1.4/1	18 h	0/9/1	45
2 ^[c]	BF3.Et2O	1/1.4/1	18 h	1/1/1	nd ^[d]
3 ^[e]	BF ₃ .Et ₂ O	1/1.4/1	18 h	0/3/2	nd
4	BF3.Et2O	1/1/1	18 h	0/1/0	69
5	BF3.Et2O	1/1/0.3	2 d	0/1/0	39
6	Sc(OTf) ₃	1/1/0.3	4 d	0/1/0	60
7	Yb(OTf) ₃	1/1/0.3	3 d	0/1/0	64
8	Dy(OTf)₃	1/1/0.3	3 d	0/1/0	65
9	TFA	1/1/1	3 d	0/1/0	41
10	(PhO) ₂ PO ₂ H	1/1/0.3	2 d	1/0/0	nd

[a] Measured by HPLC on crude mixture. [b] Total isolated yield of **2a** (**A** + **B**). [c] DCM used as solvent. [d] Not determined. [e] Reaction performed at 50 °C.

The optimized conditions for this 2CR version for the synthesis of 2a, were then transposed in a 3CR version, by reacting enamide 1 with aniline and benzaldehyde (Table 2, entries 1 and 2). This time, an excess of BF₃.Et₂O (1.5 equiv) was necessary to reach reaction completion and a slightly lower yield was obtained (59% vs 69%). The A/B ratio remained the same (\approx 1:1) in both cases. Having fixed the reaction conditions for the two versions (2CR and 3CR), we next investigated the scope and limitation of the Povarov reaction of enamide 1 varying first the aldehyde component (Table 2). As in the previous case, the 2CR version proved more efficient. The imines were prepared from aniline and different aromatic aldehydes.^[14] The influence of the electronic nature and position of the substituents on the aromatic ring has been examined. Electron-rich systems bearing a methyl or a bromo substituent in para position led to a drastic loss of reactivity and the desired cycloadducts were not detected (Table 2, entries 3 and 4). In contrast, the reaction with 3-bromobenzaldehyde proved efficient in the three-component reaction conditions, with a complete conversion after 7 hours. The expected product 2h was obtained in a 40:60 A/B ratio and in a moderate yield of 41% (Table 2, entry 10). In all cases, the presence of an electron withdrawing group (i.e. CO₂Me, NO₂, CF₃), whatever their position on the aromatic ring, led to faster reactions. Isolated yields were around 60% with diastereomeric ratios remaining close to 1:1 (Table 2, entries 5, 6, 8, 9, and 11). Expectedly, the fastest reactions occurred with the imines derived from 4nitrobenzaldehyde and from 3,5-bis(trifluoromethyl)benzaldehyde, as only 2 hours were needed to reach completion. Adducts 2e and 2j were isolated in 61% and 74% yield, respectively (Table 2, entries 6 and 12). Here again, performing the reaction in the threecomponent version led to a slightly lower yield (Table 2, entry 7).

Heteroaromatic aldehydes can also be involved as partners in the 3CR version of the cycloaddition. Reactions of 3- and 4-pyridyl aldehydes required the use of a larger 2.5 equiv of catalyst, as 1 equiv is coordinated to the pyridine nitrogen, and led to the expected products 2k and 2l, in 50% and 47% yield, respectively (Table 2, entries 13 and 14). The A/B ratios were similar in these two cases, around 70:30. The reaction with 4-pyridyl aldehyde proved much faster than the one with the 3-pyridyl derivative (3 vs 48 hours), as expected from electronic properties. In the case of 3-thiophenecarboxaldehyde the reaction led to the formation of a complex mixture and the desired product 2m was not detected (Table 2, entry 15). It is to notice that despite the low stereoselectivity of the reaction, we were able however to isolate each diastereomer by reversed-phase chromatography in all cases except for 2g. The set of results obtained is consistent with the putative inverse electron-demand aza-Diels-Alder nature of the Povarov reaction, showing a better reactivity of the enamide electron-rich partner 1 towards electron-depleted iminodienes.

We then envisaged to extend the scope of the reaction to aliphatic aldehydes. Owing to the instability of the corresponding imines, we turned again to the 3CR version. No reaction took place in the presence of butyraldehyde (Table 2, entry 16), while isobutyraldehyde and cyclic derivatives such as cyclohexyl and cyclopropyl aldehydes afforded the desired corresponding products (Table 2, entries 17-19). Gratifyingly, higher stereoselectivities were observed in these cases (ratios ranging from 72:28 to 99:1), and the major **A** stereoisomer (*cis*) was isolated in moderate to high yields (47 to 90% yield). The *cis* configuration was assigned by NOESY NMR experiments for compounds **2o** and **2p** (see SI).



Entry	Product	Method ^[a]	Time (h)	Ratio ^[b] A/B	Yield (%) (A ; B) ^[c]
1	2a	2CR	18	48:52	69 (29; 40)
2	2a	3CR	18	44:56	59 (23; 36)



3	2b	2CR	48	-	nd ^[e]
4	2c	3CR	24	-	nd ^[e]
5	2d	2CR	6	50:50	63 (24; 39)
6	2e	2CR	2	49:51	61 (26; 35)
7	2e	3CR	3	53:47	38 (13; 25)
8	2f	2CR	4	57:43	66 (35; 31)
9	2g	2CR	4	50:50	75 ^[f]
10	2h	3CR	7	40:60	41 (11; 30)
11	2 i	2CR	7	47:53	60 (24; 36)
12	2j	2CR	2	42:58	74 (32; 42)
13 ^[d]	2k	3CR	48	75:25	50 (37; 13)
14 ^[d]	21	3CR	3	71:29	47 (37; 10)
15	2m	3CR	24	67:33	nd ^[e]
16	2n	3CR	96	-	0
17	20	3CR	48	99:1	70 (70; 0)
18	2р	3CR	28	90:10	90 (90; 0)
19	2q	3CR	96	72:28	47 (47; 0)

[a] 2CR: ratio 1/imine/BF₃ 1/1/1; 3CR: ratio 1/aniline/aldehyde/BF₃ 1/1/1/1.5. [b] Determined by HPLC at the reaction completion. [c] Total isolated yield; in brackets isolated yields of **A** and **B**. [d] 2.5 equiv of BF₃ used. [e] not determined. [f] Inseparable mixture of **A** and **B**.

The scope of the reaction in regard to the variation of the aryl amine partner was next investigated in the presence of the cyclohexyl aldehyde (Table 3). Three commercially available anilines functionalized in different positions have been envisaged: the 3-(trifluoromethyl)aniline, the 2-iodoaniline, and the 4morpholinoaniline. The reactions proceeded smoothly and led to the expected cycloadducts with higher diastereoselectivities than in aromatic series, the major A-isomer being isolated in all cases in good yields (Table 3, entries 2-4). It is to notice that product 2sA is the regioisomer resulting from the cyclization on the 6position of the 3-(trifluoromethyl)aniline. Formation of the other regioisomer, cyclized on the 2-position, was not observed. 3-Aminopyridine was finally used as an N-heteroaryl amine partner. requiring here again 2.5 equiv of BF₃.Et₂O. It led to the desired product 2u, as a unique regioisomer. It was, however, isolated in a disappointing 18% yield (A-isomer) from a 86:14 mixture of A/B diastereomers (Table 3, entry 5).

 Table 3. Scope and limitation of the Povarov reaction of enamide 1: arylamine variation.



Entry	Product	Time (h)	Ratio ^[a] A/B	Yield (%) ^[b]
1	2р	28	90:10	90
2	2r 🛌	5	89:11	62
3	2s	7	85:15	56
4	2t	10	94:6	86
5 ^[c]	2u	24	86:14	18

[a] Determined by HPLC at the reaction completion. [b] Isolated yield for the major product **2A**; **2B** not isolated. [c] 2.5 equiv of BF_3 used.

Finally, in order to study an asymmetric version of the reaction, we prepared the enantiopure endocyclic enamide 3 using Lphenylalanine.^{12a} The reaction was first attempted with aniline and isobutyraldehyde (3CR) but no product was formed after 24 h. We then turned to the more reactive (4-nitrophenyl)-Nphenylmethanimine and this time the reaction with 3 proved efficient and led, after 7 h, to the expected cycloadduct, formed as a mixture of four stereoisomers, and isolated in 21% yield (Scheme 3). The ratio A/B was 1:1 (like in the case of 2e) and a diastereomeric ratio of 4:1 resulted from the chiral induction for each stereoisomer A and B. Despite our efforts, only one of the major stereoisomers could be isolated. The analysis by NMR spectrometry (NOESY experiment) indicated that it corresponded to a stereoisomer B (trans). Discrimination between 4B and 4'B was unfortunately impossible at this stage in the absence of an Xray crystallographic structure.



Scheme 3. Asymmetric version: use of enantiopure enamide 3.

Theoretical study

In order to get a better insight into the mechanistic details of these reactions, we examined the course of this Povarov reaction by computational means. DFT calculations were performed at the M062X/6-31+G(d,p) level of theory, which proved appropriate for many organic transformations and has been shown to provide accurate energies for cycloaddition reactions.[15],[16] Solvation by acetonitrile was taken into account by using a solvation model based on density (SMD) (for the computational details and benchmark of the method, see SI). The Povarov reaction has been studied computationally in a few cases, involving different dienophiles, most of the time simpler monosubstituted ones.[17-21] The cycloaddition part of the process was also shown to preferably proceed through involvement of the iminium aza-diene, in a two-step mechanism. The final 1,3-hydrogen shift leading to a highly favorable rearomatization was reported to be an easy step. We thus considered only the cycloaddition step of the Povarov reaction in our study. Calculations were first envisaged with the electron-rich N-methyl dienophile D, considered as a good model of the N-benzyl substrate 1 used in the experimental part, and the unsubstituted electron-poor aza-diene I (Scheme 4).



Scheme 4. Povarov reaction of dienophile D and N-phenyl imines I

First the processes involving the uncomplexed imine I_1 and its complexed BF3-I1 iminium form were compared. Noteworthy, the optimized aza-diene conformation displayed a slightly bent C=N-C=C dihedral angle of 44° for I1. A similar 41° distorsion was observed for the complexed iminium derivative BF3-I1. Evaluation of the frontier orbitals energies confirmed the preferential interaction between the HOMO of the dienophile D with the LUMO of the aza-diene I1 or BF3-I1, and thus the inverse electron demand character of the cycloaddition process. The energy difference between the reacting molecular orbitals (dienophile HOMO and diene LUMO) was lower when taking the complexed BF₃-I₁ diene (6.2 eV vs 7 eV for I₁), a preliminary data suggesting a more favorable Lewis acid assisted cycloaddition. In each case, the LUMO coefficients proved bigger on the terminal N=CH₂ part of the aza-diene. Quantitative evaluation of the preferred pathway on the activation energy was then undertaken, by localization of the transition states (TS) of the cycloaddition. Two orientations, corresponding to the endo/exo approaches were considered (Table 4). The computed reaction profiles proved different. Indeed, the imine derivative I1 displayed an asynchronous concerted mechanism (1.7 vs 2.7-2.8 Å, in the TS, for the CH-CH₂ and CH-CHAr bonds, respectively). In contrast, a two-steps cycloaddition process was computed in the presence of the BF3-I1 iminium, with the formation of an intermediate zwitterion Zl1, before cyclization involving a Friedel-Crafts type reaction. The first step was the rate determining one, since the energy difference between TSb and Zl1 was lower than the one between TS_a and the substrates. Even if non determining, the Friedel-Crafts type cyclization proved much easier in the case of an *endo* approach ($\Delta G^{\ddagger} = 2.8 \text{ kcal.mol}^{-1} \text{ vs}$ 13.5 for the *exo* approach). Comparing the activation energies of the rate determining step in the uncomplexed/complexed case (compare entries 1-2 with 3-4) showed that with a much higher energy was required when the imine uncomplexed aza-diene was involved ($\Delta\Delta G^{\ddagger} = 16.5 \text{ kcal.mol}^{-1}$). The Lewis-acid catalyzed cycloaddition is thus, expectedly, the most favored process.

We next considered the involvement of a substituted iminium azadiene BF₃-I₂, bearing a methyl group, as a model of the alkyl derivatives used experimentally. Here again, the dienic moiety of the optimized structure was not planar (dihedral angle of 56° for the E isomer) and this raised the problem of the E/Z geometry of the iminium. The optimized E isomer indeed proved less stable than the Z isomer, even if the energy difference remained small $(\Delta\Delta G = 0.7 \text{ kcal.mol}^{-1})$. The Z isomer displayed an even larger dienic CCNC dihedral angle of 81°, meaning quasi perpendicular methyl and phenyl groups. Four approaches were next envisaged for the cycloaddition (E/Z geometries and endo/exo approaches, Table 4, entries 5-8). Here again, two-steps transformations were computed, with the formation of a zwitterionic intermediate adduct Zl₂, and a subsequent Friedel-Crafts cyclization. The first addition step of this formal cycloaddition process was, here again, the rate determining one. The process required higher activation energies than in the unsubstituted case, because of the larger steric hindrance in this case. The endo approaches were slightly preferred to the exo ones ($\Delta\Delta G^{\ddagger}$ = 1.9 kcal.mol⁻¹, compare entries 5 and 6). Even if the E-iminium is less stable, the TS involving this geometry proved slightly more favorable ($\Delta\Delta G^{\ddagger} = 0.8 \text{ kcal.mol}^{-1}$ for the most favored endo approach, compare entries 5 and 7). This is probably due to the more unfavorable steric effects with the Z isomer. The most favored approach was thus the E-endo one, that would lead to the formation if the cis-P2 cycloadduct, as experimentally observed. However, the activation energy differences remained relatively small in this case, involving a methyl substituent. It is probable that the iPr or Cy substituent used experimentally would induce greater differences between the E and Z approaches and this explains the higher diastereoselectivity observed in these cases. The endergonicity of these cycloadditions is the reflect of a dearomatization process that is not thermodynamically favored. The re-aromatization occurring next, through the 1,3-hydrogen shift, is most probably the driving force of the process, and shifts the process toward the formation of the re-aromatized cycloadduct P2, that is, experimentally, the only type of product isolated. The cis-P2 cycloadduct proved computationally to be slightly more stable than the trans-P2 one, by 0.18 kcal.mol⁻¹, in line with the experimental data, which showed the preferred formation of the cis isomer in the aliphatic aldehyde series.



Entry	R	х	Approach	ΔG^{\ddagger} TS _a ^[a]	ΔG_r ZI ^[a,b]	ΔG^{\ddagger} TS _b ^[a,c]	$\begin{array}{c} \Delta G_r \\ \pmb{C}^{[a,d]} \end{array}$
1	н	-	endo	36.8	-	-	5.6
2	Н	-	ехо	38.1	-	-	5.0
3	Н	BF₃	endo	20.8	13.3	16.0	-1.8
4	Н	BF₃	ехо	20.3	13.8	27.3	>-1.6
5	Ме	BF₃	E-endo	29.7	23.6	26.2	11.2
6	Ме	BF₃	E-exo	31.6	22.8	34.3	4.8
7	Me	BF₃	Z-endo	30.5	23.2	26.4	6.5
8	Me	BF₃	Z-exo	32.6	28.9	37.4	13.8

[a] Gibbs Free Energy differences relative to the separated substrates, in kcal.mol⁻¹. [b] zwitterionic adduct ZI. [c] TSb transition state for the second step.^[d] cycloadduct C.

In order to get more insight on the high cis-diastereoselectivity observed with aliphatic aldehydes, we also examined, computationally, the 3D-structures of *cis*-**Po** and *trans*-**Po** analogues of compounds **2o** in which the N-Bn was replaced by an N-Me (Figure 3). Interestingly, the calculation showed, here again, that the *cis*-isomer is slightly more stable than the *trans*-isomer by 0.35 kcal/mol. Even if the difference remains small, this lower energy for the *cis*-isomer is in line with the experimental data and can be understood considering the isopropyl substituent, which occupies a *pseudo*-equatorial position in *cis*-**Po** and a *pseudo*-axial position in *trans*-**Po** (see SI for details).





Figure 3. Computed conformations for cis and trans Po.

The conformations of the analogues P4 of structures 4 in which the two Bn groups were replaced by Me groups and the $4-NO_2-C_6H_4$ by a Ph group (Figure 4), were also optimized (see in SI the four corresponding stereoisomers). The Me-substituent on the stereogenic carbon was found in pseudo-equatorial position in the four cases, while the Ph-substituent occupied a pseudoequatorial position in P4'A and P4B, and a pseudo-axial position in P4A and P4'B. The analysis of some computed distances in P4B and P4'B, of around 4 Å (see in SI), could explain why some expected dipolar couplings were not observed by NMR NOESYexperiment on product 4B or 4'B, and thus the difficulties encountered in the assignment of the relative configuration of the isolated stereoisomer.



Figure 4. Structures P4 used for the calculations (see in SI).

Conclusion

In summary, we succeeded in the application of the Povarov reaction to endocyclic enamides based on a bicyclic azadiketopiperazine (aza-DKP) structure as original dienophiles partners. The cycloaddition tolerated various aldehydes and anilines and has been performed in the presence of BF₃ as the Lewis acid catalyst, either as a two-component or a threecomponent reaction (2CR or 3CR), depending on the nature of the aldehyde partner. With aromatic aldehydes the reaction showed a low *cis/trans* selectivity, but the two diastereomers could be separated by column chromatography. On the other

hand, with aliphatic aldehydes the reaction was highly *cis*diastereoselective. The method represents an efficient strategy for the structural diversification of the aza-DKP scaffold. It allowed the synthesis of a new family of molecules combining in a fused tetracyclic N-heterocyclic structure two interesting scaffolds for medicinal chemistry, a tetrahydroquinoline and a bicyclic azadiketopiperazine. Mechanistic details of the cycloadditions have been examined by computational means. This confirmed the role of the catalyst in lowering the energy barriers and showed that the cycloaddition was a stepwise process. Even if small energy differences were observed between the approaches considered in the presence of methyl substituted iminium, the conclusions were in full agreement with the experimental results.

Experimental Section

General information. Reagents were obtained from commercial sources and used without any further purification. Thin layer chromatography was performed on silica gel 60 F254 plates.

NMR spectra were recorded at 400 or 500 MHz for ¹H and at 100 or 125 MHz for ¹³C. Chemical shifts are reported in parts per million (ppm) relative to residual solvent and coupling constants (J) are reported in hertz (Hz). CDCI_3 was filtered previously on basic alumina. Assignments of $^1\mathsf{H}$ and $^{13}\mathsf{C}$ signals were made by DEPT, COSY, HSQC, HMBC, NOESY-2D experiments for compounds 2aA, 2aB, 2oA, 2pA, 4B (or 4'B). HRMS were performed with quadrupole /time-of-flight (Q-TOF) analysers, using either electrospray ionization (ESI) at T_{source} = 340 °C, V_{cap} = 4000 V, or atmospheric pressure chemical ionization (APCI) at T_{gas} = 300 °C, T_{vap} = 380 °C, V_{corona} = 4µA. The purification on reversed-phase chromatography was performed on a Gilson PLC 2020 apparatus equipped with Interchim Flash chromatography column PF-30C18HP-F0025. The solvents used were Solvent A (0.1% TFA in MeCN, v/v) and Solvent B (0.1% TFA in H2O, v/v). The program started with a 5 min plateau at 10% of Solvent A, then a gradient for 30 minutes from 10% to 100% of Solvent A and a 5 min plateau at 100% of Solvent A.

Synthesis of the enamide precursor 1:

Step 1. In a dry RBF (round-bottom flask) under argon, to a solution of triphosgene (1.05 g, 0.335 equiv) in anhydrous THF (61.9 mL), was added dropwise over 5 minutes a solution of ethyl 2-(benzylamino)acetate (2 g, 10.3 mmol) and DIEA (3.78 mL, 2.1 equiv) in anhydrous THF (13 mL) and DCM (13 mL). The mixture was stirred at room temperature for 15 min. A solution of N'-(prop-2-en-1-yl)(tert-butoxy)carbohydrazide (1.78 g, 1 equiv) and DIEA (1.88 mL, 1.1 equiv) in anhydrous THF (15 mL) was added dropwise and the mixture was heated at 40°C overnight. The mixture was filtered and evaporated in vacuo. A mixture TFA/water: 95/5 (13 mL) was added and the mixture was stirred at room temperature for 1 h before being evaporated. The crude mixture was purified on silica gel eluting with 70% ethyl acetate in heptane to afford the 2-allyl-4-benzyl-1,2,4-triazinane-3,6-dione as a yellowish solid (1.45 g, 57%).

¹**H NMR** (400 MHz, CDCl₃) δ 7.37-7.23 (m, 5H), 5.82 (ddt, *J* = 17.2, 10.2, 6.2 Hz, 1H), 5.32 (br d, *J* = 17.2 Hz, 1H), 5.29 (bs d, *J* = 10.2 Hz, 1H), 4.51 (s, 2H), 4.17 (bs d, *J* = 6.5 Hz, 2H), 3.67 (s, 2H). ¹³**C NMR** (100 MHz, CDCl₃) δ 163.9, 154.5, 135.8, 131.3, 129.1, 128.5, 128.3, 120.7, 51.0, 50.5, 48.8.

Step 2. A solution of Rh(CO)₂(acac)₂ (3.55 mg, 0.25 mol%) and Biphephos (32.5 mg, 0.75 mol%) in anhydrous THF (2 mL), prepared in a Schlenk glassware under an argon atmosphere, was introduced under argon into a stainless steel autoclave containing the 2-allyl-4-benzyl-1,2,4-triazinane-3,6-dione (1.35 g, 1 equiv) and pyridinium *p*-toluenesulfonate (1.38 g, 1 equiv) in anhydrous THF (49 mL). The reactor was purged three time with

H₂/CO (1:1, 5 bars) and filled with H₂/CO (1:1, 5 bars). The reactor was heated to 70 °C and stirred for 16 h. The reactor was then cooled to ambient temperature and vented to ambient pressure. The reaction mixture was evaporated. The residue was retaken in EtOAc and washed with brine, the organic phase was then dried over Na₂SO₄ and concentrated. The crude product was purified on gel silica eluting with 50% ethyl acetate in heptane to afford product **1** as a yellowish solid (1 g, 71%).

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Povarov reaction

General Procedure A (two-component reaction): To a round bottom flask under argon was placed the imine (0.18 mmol, 1 equiv) in acetonitrile (1 mL) and BF₃·OEt₂ (22 µL, 1 equiv) was added to the reaction mixture which was stirred for 5 min at room temperature. Enamide **1** (46 mg, 0.18 mmol, 1 equiv) in acetonitrile (1 mL) was then added to the solution and stirred at room temperature until completion (monitored by HPLC). The solvent was removed under vacuo and DMSO (500 µL) was added and the crude product **2** obtained as a mixture of two diastereoisomers **A** and **B** was purified by reversed-phase chromatography (H₂O/MeCN + 0.1% TFA) to afford separated pure products **2A** and **2B**.

General Procedure B (three-component reaction): To a round bottom flask under argon was placed enamide **1** (37.4 mg, 0.15 mmol, 1 equiv) in acetonitrile (1 mL), the aldehyde (0.15 mmol, 1 equiv) and the aniline (0.15 mmol, 1 equiv) with acetonitrile (1 mL). BF₃·OEt₂ (28 μ L, 1.5 equiv) was then added to the reaction mixture which was stirred until completion (monitored by HPLC) at room temperature. The solvent was removed under vacuo and DMSO (500 μ L) was added and the crude product **2** obtained as a mixture of two diastereoisomers **A** and **B** was purified by reversed-phase chromatography (H₂O/MeCN + 0.1% TFA) to afford separated pure products **2A** and **2B**.

3-benzyl-8-phenyl-2,3,6,7,7a,8,9,13b-octahydro-[1,2,4]triazino[2',1':1,2] pyridazino[4,3-c]quinoline-1,4-dione (**2a**) was obtained according to the general procedure A, performed on a 0.18 mmol scale (53 mg, 69%) and according to the general procedure B, performed on a 0.15 mmol scale (35 mg, 69%).

2aA: white amorphous solid (by procedure A: 22 mg, 29%; by procedure B: 13 mg, 23%). ¹**H NMR** (400 MHz, CDCl₃): δ 7.45-7.30 (m, 10H), 7.10 (tdd, *J* = 7.1, 1.6, 0.8 Hz, 1H), 6.80 (dt, *J* = 7.8, 1.3 Hz, 1H), 6.71 (ddd, *J* = 7.9, 7.3, 1.2 Hz, 1H), 6.62 (dd, *J* = 8.0, 1.1 Hz, 1H), 6.16 (d, *J* = 5.1 Hz, 1H, NC<u>H</u>CH), 4.84 (d, *J* = 2.5 Hz, 1H, CHPh), 4.75 (d, *J* = 14.7 Hz, 1H, NC<u>H</u>2Ph), 4.35 (ddd, *J* = 12.5, 4.9, 2.4 Hz, 1H), NC<u>H</u>2CH₂), 4.22 (d, *J* = 14.7 Hz, 1H, NC<u>H</u>2Ph), 3.90 (d, *J* = 15.8 Hz, 1H), 3.82 (d, *J* = 15.8 Hz, 1H), 2.92 (td, *J* = 12.7, 3.0 Hz, 1H, NC<u>H</u>2CH₂), 2.17 (dddd, J = 11.9, 5.1, 3.8, 2.6 Hz, 1H, C<u>H</u>CH₂), 1.92 (qd, *J* = 13.0, 4.9 Hz, 1H), 1.37 (dd, *J* = 13.6, 3.1 Hz, 1H). ¹³**C NMR** (101 MHz, CDCl₃): δ 163.8 (C=O), 155.8 (C=O), 144.6 (Cq), 140.3 (Cq), 136.0 (Cq), 128.9 (CAr), 128.73 (CAr), 128.68 (CAr), 128.5 (CAr), 128.07 (CAr), 128.02 (CAr), 126.8 (CAr), 126.5 (CAr), 118.7 (CAr), 116.1 (Cq), 115.0 (CAr), 58.8 (CH), 52.2 (CH), 50.4 (CH₂), 48.3 (CH₂), 45.0 (CH₂), 37.7 (CH), 19.2 (CH₂). **HRMS** (ESI-TOF): Calculated for C₂₇H₂₇N4O₂ [M+H]⁺: 439.2134; Found: 439.2124.

2aB: white amorphous solid (by procedure A: 31 mg, 40%; by procedure B: 22 mg, 36%). ¹**H NMR** (400 MHz, CDCl₃): δ 7.48-7.18 (m, 10H), 7.13 (dddd, *J* = 7.8, 6.8, 2.0, 0.8 Hz, 1H), 6.72-6.62 (m, 3H), 5.99 (bs, 1H), 5.43 (d, *J* = 5.0 Hz, 1H, NC<u>H</u>2CH), 4.73 (d, *J* = 14.7 Hz, 1H, NC<u>H</u>2Ph), 4.52-4.40 (m, 2H), 4.25 (d, *J* = 14.7 Hz, 1H, NC<u>H</u>2Ph), 3.87 (d, *J* = 15.7 Hz, 1H), 3.80 (d, *J* = 15.7 Hz, 1H), 3.16 (td, *J* = 12.7, 3.1 Hz, 1H), 2.25 (dddd, *J* = 12.4, 5.0, 3.9, 2.3 Hz, 1H, C<u>H</u>CH₂), 2.03 (qd, *J* = 12.8, 4.7 Hz, 1H), 1.87 (dd, *J* = 13.4, 3.3 Hz, 1H). ¹³**C NMR** (101 MHz, CDCl₃): δ 163.5 (C=O), 155.9

 $\begin{array}{l} (C=O), \ 143.7 \ (C_q), \ 143.3 \ (C_q), \ 135.8 \ (C_q), \ 128.98 \ (C_{Ar}), \ 128.93 \ (C_{Ar}), \\ 128.88 \ (C_{Ar}), \ 128.5 \ (C_{Ar}), \ 128.1 \ (C_{Ar}), \ 127.6 \ (C_{Ar}), \ 126.4 \ (C_{Ar}), \ 125.5 \ (C_{Ar}), \\ 117.7 \ (C_{Ar}), \ 114.7 \ (C_q), \ 113.6 \ (C_{Ar}), \ 58.7 \ (CH), \ 50.5 \ (CH), \ 48.3 \ (CH_2), \ 48.0 \ (CH_2), \ 44.9 \ (CH_2), \ 37.1 \ (CH), \ 26.2 \ (CH_2). \ \textbf{HRMS} \ (ESI-TOF): \ Calculated \ for \\ C_{27}H_{27}N_4O_2 \ [M+H]^+: \ 439.2134; \ Found: \ 439.2115. \end{array}$

Methyl 4-(3-benzyl-1,4-dioxo-1,2,3,4,6,7,7a,8,9,13b-decahydro-[1,2,4]triazino[2',1':1,2]pyrid-azino[4,3-c]quinolin-8-yl)benzoate (2d) was obtained according to the general procedure A, performed on a 0.16 mmol scale (52 mg, 63%).

2dA: white amorphous solid (20 mg, 24%). **1H NMR** (400 MHz, CDCl₃) δ 8.10 (d, J = 1.8 Hz, 1H), 8.01 (dt, J = 7.8, 1.4 Hz, 1H), 7.63 (dt, J = 7.9, 1.7 Hz, 1H), 7.49 (t, J = 7.7 Hz, 1H), 7.42-7.30 (m, 5H), 7.12 (dddd, J = 8.0, 7.2, 1.6, 0.8 Hz, 1H), 6.81 (dt, J = 7.8, 1.3 Hz, 1H), 6.73 (td, J = 7.5, 1.1 Hz, 1H), 6.66 (dd, J = 8.1, 1.2 Hz, 1H), 6.16 (d, J = 5.1 Hz, 1H), 4.89 (d, J = 2.5 Hz, 1H), 4.73 (d, J = 14.8 Hz, 1H), 4.41-4.29 (m, 1H), 4.23 (d, J = 14.8 Hz, 1H), 3.95 (s, 3H), 3.92-3.85 (m, 1H), 3.81 (d, J = 15.8 Hz, 1H), 3.24 (bs, 1H), 2.90 (td, J = 12.7, 3.0 Hz, 1H), 2.23-2.14 (m, 1H), 1.92 (qd, J = 12.9, 4.8 Hz, 1H), 1.28 (dd, J = 13.5, 3.4 Hz, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 166.8, 163.8, 155.7, 144.3, 140.8, 135.9, 131.2, 130.7, 129.3, 128.9, 128.8, 128.8, 128.5, 128.1, 127.8, 126.5, 119.1, 116.2, 115.2, 58.5, 52.3, 52.1, 50.5, 48.3, 44.9, 37.6, 19.1. HRMS (ESI-TOF): Calculated for C₂₉H₂₉N₄O₄ [M+H]⁺: 497.2189; Found: 497.2173.

2dB: white amorphous solid (32 mg, 39%). ¹**H NMR** (400 MHz, CDCl₃) δ 7.81 (dd, J = 6.3, 1.6 Hz, 2H), 7.35 (dt, J = 7.8, 1.7 Hz, 1H), 7.31-7.19 (m, 6H), 7.06-6.99 (m, 1H), 6.64-6.60 (m, 1H), 6.56 (dd, J = 8.1, 6.9 Hz, 2H), 5.25 (d, J = 5.0 Hz, 1H), 4.62 (d, J = 14.7 Hz, 1H), 4.43-4.31 (m, 2H), 4.13 (d, J = 14.7 Hz, 1H), 3.79 (s, 3H), 3.72 (d, J = 15.6 Hz, 1H), 3.65 (d, J = 15.6 Hz, 1H), 3.04 (td, J = 12.6, 3.0 Hz, 1H), 2.22-2.13 (m, 1H), 2.01-1.87 (m, 1H), 1.75 (dd, J = 13.4, 3.4 Hz, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 166.8, 163.5, 155.7, 144.2, 143.0, 135.9, 130.7, 130.1, 129.1, 129.1, 128.9, 128.8, 128.7, 128.5, 128.2, 128.1, 126.9, 126.4, 117.9, 114.7, 113.7, 58.2, 52.2, 50.5, 48.3, 47.6, 44.8, 37.0, 26.1. HRMS (ESI-TOF): Calculated for C₂₉H₂₉N₄O₄ [M+H]*: 497.2189; Found: 497.2179.

3-benzyl-8-(4-nitrophenyl)-2,3,6,7,7a,8,9,13b-octahydro-

[1,2,4]triazino[2',1':1,2]pyridazino[4,3 -c]quinolone-1,4-dione (2e) was obtained according to the general procedure A, performed on a 0.17 mmol scale (50 mg, 61%) and according to the general procedure B, performed on a 0.17 mmol scale (31 mg, 38%).

2eA: yellow amorphous solid (by procedure A: 21 mg, 26%; by procedure B: 10 mg, 13%). ¹H NMR (400 MHz, CDCl₃) δ 8.32-8.24 (m, 2H), 7.67-7.60 (m, 2H), 7.43-7.30 (m, 5H), 7.13 (dddd, *J* = 7.9, 7.1, 1.7, 0.8 Hz, 1H), 6.83 (dt, *J* = 7.9, 1.3 Hz, 1H), 6.80-6.72 (m, 1H), 6.67 (dd, *J* = 8.1, 1.1 Hz, 1H), 6.17 (d, *J* = 5.1 Hz, 1H), 4.94 (d, *J* = 2.5 Hz, 1H), 4.73 (d, *J* = 14.7 Hz, 1H), 4.35 (ddd, *J* = 12.6, 4.9, 2.3 Hz, 1H), 4.23 (d, *J* = 14.7 Hz, 1H), 3.89 (d, *J* = 15.8 Hz, 1H), 3.82 (d, *J* = 15.8 Hz, 1H), 2.91 (td, *J* = 12.7, 2.9 Hz, 1H), 2.20 (dt, *J* = 15.3 Hz, 1H), 1.93 (qd, *J* = 12.9, 4.8 Hz, 1H), 1.58 (bs, 1H), 1.24 (d, *J* = 15.3 Hz, 1H). ¹³C NMR (101 MHz, CDCl₃): δ 163.9, 155.7, 147.8, 143.9, 135.9, 129.0, 128.9, 128.5, 128.1, 127.7, 126.6, 124.0, 119.6, 116.3, 115.5, 58.5, 51.9, 50.5, 48.3, 44.8, 37.6, 19.2. HRMS (ESI-TOF): Calculated for C₂₇H₂₆N₅O4 [M+H]⁺: 484.1985; Found: 484.1974.

2eB: yellow amorphous solid (by procedure A: 29 mg, 35%; by procedure B: 21 mg, 25%). **¹H NMR** (400 MHz, CDCl₃) δ 8.17 (d, *J* = 8.8 Hz, 1H), 7.45-7.30 (m, 7H), 7.16 (dddd, *J* = 7.7, 6.6, 2.2, 0.8 Hz, 1H), 6.75-6.66 (m, 3H), 5.34 (d, *J* = 5.0 Hz, 1H), 4.71 (d, *J* = 14.7 Hz, 1H), 4.55 (d, *J* = 2.2 Hz, 1H), 4.46 (ddd, *J* = 12.6, 4.8, 2.3 Hz, 1H), 4.25 (d, *J* = 14.7 Hz, 1H), 3.84 (d, *J* = 15.7 Hz, 1H), 3.77 (d, *J* = 15.7 Hz, 1H), 3.55 (bs, 1H), 3.16 (td, *J* = 12.6, 3.1 Hz, 1H), 2.30-2.20 (m, 1H), 2.05 (qd, *J* = 12.8, 4.8 Hz, 1H), 1.88 (dd, *J* = 13.4, 3.2 Hz, 1H). ¹³C NMR (101 MHz, CDCl₃): δ 163.5, 155.8, 151.0, 147.5, 142.5, 135.7, 129.3, 128.9, 128.5, 128.2, 126.7, 126.5, 124.3, 118.4, 114.5, 113.8, 58.2, 50.8, 48.2, 47.5, 44.8, 36.7, 26.0. HRMS (ESI-TOF): Calculated for C₂₇H₂₆N₅O4 [M+H]⁺: 484.1985; Found: 484.1980.

3-benzyl-8-(4-(trifluoromethyl)phenyl)-2,3,6,7,7a,8,9,13b-octahydro-[1,2,4]triazino[2',1':1,2] pyridazino[4,3-c]quinoline-1,4-dione (2f). was obtained according to the general procedure A, performed on a 0.16 mmol scale (53 mg, 66%).

2fA: white amorphous solid (28 mg, 36%). **¹H NMR** (400 MHz, CDCI₃) δ 7.67 (d, J = 8.1 Hz, 2H), 7.59-7.54 (m, 2H), 7.44-7.28 (m, 6H), 7.12 (dddd, J = 7.9, 7.1, 1.6, 0.8 Hz, 1H), 6.81 (dt, J = 7.8, 1.3 Hz, 1H), 6.75 (ddd, J =7.8, 7.1, 1.1 Hz, 1H), 6.65 (dd, J = 8.1, 1.1 Hz, 1H), 6.17 (d, J = 5.1 Hz, 1H), 4.90 (d, J = 2.5 Hz, 1H), 4.74 (d, J = 14.7 Hz, 1H), 4.35 (ddd, J = 12.6, 4.9, 2.3 Hz, 1H), 4.23 (d, J = 14.8 Hz, 1H), 3.90 (d, J = 15.8 Hz, 1H), 3.82 (d, J = 15.8 Hz, 1H), 2.92 (td, J = 12.7, 2.9 Hz, 1H), 2.46 (bs, 1H), 2.18 (dt, J = 11.9, 5.8 Hz, 1H), 1.93 (qd, J = 12.9, 4.8 Hz, 1H), 1.33-1.27 (m, 2H). 1³C NMR (101 MHz, CDCI₃) δ 163.9, 155.7, 144.4, 144.2, 135.8, 128.90, 128.89, 128.5, 128.2, 127.2, 126.5, 125.7 (q, J = 3.9 Hz), 119.3, 116.1, 115.3, 58.6, 52.1, 50.5, 48.2, 44.9, 37.6, 19.1. ¹⁹F NMR (376 MHz, CDCI₃) δ -63.23. HRMS (ESI-TOF): Calculated for C₂₈H₂₆F₃N₄O₂ [M+H]⁺: 507.2008; Found: 507.1991.

2fB: white amorphous solid (25 mg, 31%). ¹**H NMR** (400 MHz, CDCl₃) δ 7.56 (d, J = 8.1 Hz, 2H), 7.42-7.29 (m, 8H), 7.14 (dddd, J = 8.0, 7.1, 1.7, 0.8 Hz, 1H), 6.74 (dt, J = 7.8, 1.4 Hz, 1H), 6.71-6.63 (m, 2H), 5.38 (d, J =5.0 Hz, 1H), 4.71 (d, J = 14.7 Hz, 1H), 4.54-4.42 (m, 2H), 4.26 (d, J = 14.7Hz, 1H), 3.84 (d, J = 15.7 Hz, 1H), 3.77 (d, J = 15.7 Hz, 1H), 3.15 (td, J =12.6, 3.1 Hz, 1H), 2.99 (bs, 1H), 2.30-2.19 (m, 1H), 2.05 (qd, J = 12.9, 4.9 Hz, 1H), 1.87 (dd, J = 13.3, 3.1 Hz, 1H). ¹³**C NMR** (101 MHz, CDCl₃) δ 163.6, 155.9, 147.6, 142.8, 135.6, 129.2, 128.9, 128.5, 128.2, 126.4, 126.1, 126.0 (q, J = 3.7 Hz), 118.1, 114.4, 113.7, 58.3, 50.6, 48.2, 47.8, 44.87, 36.8, 26.1. ¹⁹**F NMR** (376 MHz, CDCl₃) δ -63.17. **HRMS** (ESI-TOF): Calculated for C₂₈H₂₆F₃N₄O₂ [M+H]⁺: 507.2008; Found: 507.1999.

3-benzyl-8-(2-(trifluoromethyl)phenyl)-2,3,6,7,7a,8,9,13b-octahydro-[1,2,4]triazino[2',1':1,2] pyridazino[4,3-c]quinoline-1,4-dione (2gB) & (7aS,8S,13bS)-3-benzyl-8-(2-(trifluoromethyl)phenyl)-2,3,6,7,7a,8,9,13boctahydro-[1,2,4] triazino [2',1':1,2]pyridazino[4,3-c]quinoline-1,4-dione (2gA) was obtained according to the general procedure A as a mixture of diastereomers, performed on a 0.2 mmol scale (75 mg, 75%).

2gA & 2gB: white amorphous solid. ¹H NMR (400 MHz, CDCl₃) δ 7.97 (d, J = 7.9 Hz, 1H, 2gA), 7.78-7.71 (m, 1H, 2gA), 7.64 (q, J = 7.7 Hz, 2H), 7.54-7.27 (m, 14H), 7.13 (dt, J = 9.9, 7.4 Hz, 2H), 6.81-6.66 (m, 4H), 6.64-6.57 (m, 2H), 6.14 (d, J = 5.1 Hz, 1H, 2gA), 5.61 (d, J = 5.0 Hz, 1H, 2gB), 5.21 (s, 1H), 4.84 (s, 1H), 4.77 (d, J = 14.7 Hz, 1H, 2gB), 4.74 (d, J = 14.8 Hz, 1H, **2gA**), 4.42 (tdd, J = 13.1, 4.9, 2.4 Hz, 2H), 4.28 (d, J = 14.7 Hz, 1H, 2gB), 4.22 (d, J = 14.8 Hz, 1H, 2gA), 3.94 (d, J = 15.8 Hz, 1H, 2gA), 3.87 (d, J = 15.7 Hz, 1H, 2gB), 3.86 (d, J = 15.9 Hz, 1H, 2gA), 3.82 (d, J = 15.8 Hz, 1H, 2gB), 3.13 (td, J = 12.7, 3.2 Hz, 1H, 2gB), 2.96 (td, J = 12.8, 2.9 Hz, 1H, 2gA), 2.29-2.13 (m, 2H), 2.11-1.89 (m, 2H), 1.84 (dd, J = 13.4, 3.4 Hz, 1H, 2gB), 1.46 (dd, J = 13.3, 3.4 Hz, 1H, 2gA). ¹³C NMR (101 MHz, CDCl₃) δ 163.8, 163.7, 159.0, 158.6, 158.1, 157.8, 157.74, 156.01, 156.0, 144.6, 143.3, 143.1, 138.5, 135.6, 135.5, 132.7, 131.8, 129.2, 129.1, 129.0, 128.9, 128.6, 128.5, 128.3, 127.8, 127.8, 126.6, 126.6, 126.5, 126.1, 119.3, 117.9, 116.1, 116.1, 115.4, 113.6, 113.4, 54.6, 52.6 (2gA), 50.62, 50.55, 48.1, 47.8 (2gB), 45.1 (2gB), 44.86 (2gA), 36.0, 35.9, 26.2 (2gB), 19.5 (2gA). ¹⁹F NMR (376 MHz, CDCl₃) δ -58.89, -59.09. HRMS (ESI-TOF): Calculated for C₂₈H₂₆F₃N₄O₂ [M+H]⁺: 507.2008; Found: 507.1999.

3-benzyl-8-(3-bromophenyl)-2,3,6,7,7a,8,9,13b-octahydro-

[1,2,4]triazino[2',1':1,2]pyridazino-[4,3-c]quinoline-1,4-dione (**2h**) was obtained according to the general procedure B, performed on a 0.19 mmol scale (39 mg, 41%).

2hA: white amorphous solid (11 mg, 11%). **¹H NMR** (400 MHz, CDCl₃) δ 7.59 (t, J = 1.9 Hz, 1H), 7.47 (ddd, J = 7.8, 2.1, 1.2 Hz, 1H), 7.44-7.22 (m, 7H), 7.11 (dddd, J = 7.9, 7.1, 1.6, 0.8 Hz, 1H), 6.81 (dt, J = 7.8, 1.4 Hz, 1H), 6.77-6.70 (m, 1H), 6.64 (dd, J = 8.0, 1.1 Hz, 1H), 6.14 (d, J = 5.1 Hz, 1H), 4.79 (d, J = 2.6 Hz, 1H), 4.74 (d, J = 14.7 Hz, 1H), 4.36 (ddd, J = 12.5, 4.9, 2.3 Hz, 1H), 4.22 (d, J = 14.7 Hz, 1H), 3.89 (d, J = 15.8 Hz, 1H), 3.81

(d, J = 15.7 Hz, 1H), 3.19 (bs, 1H), 2.92 (td, J = 12.7, 2.9 Hz, 1H), 2.22-2.10 (m, 1H), 1.89 (qd, J = 13.0, 4.9 Hz, 1H), 1.32 (dd, J = 14.0, 3.0 Hz, 1H). ¹³**C NMR** (101 MHz, CDCl₃) δ 163.8, 155.8, 144.2, 142.7, 135.9, 131.2, 130.3, 129.8, 128.9, 128.8, 128.5, 128.1, 126.5, 125.4, 122.9, 119.1, 116.1, 115.2, 58.3, 52.1, 50.5, 48.2, 44.9, 37.6, 19.1. **HRMS** (ESI-TOF): Calculated for C₂₇H₂₆BrN₄O₂ [M+H]⁺: 517.1239; Found: 517.1224.

2hB: white amorphous solid (29 mg, 30%). **1H NMR** (400 MHz, CDCl₃) δ 7.44-7.29 (m, 7H), 7.18-7.10 (m, 3H), 6.74-6.61 (m, 3H), 5.39 (d, *J* = 5.0 Hz, 1H), 4.73 (d, *J* = 14.7 Hz, 1H), 4.57 (bs, 1H), 4.50-4.40 (m, 2H), 3.86 (d, *J* = 15.7 Hz, 1H), 3.80 (d, *J* = 15.7 Hz, 1H), 3.16 (td, *J* = 12.6, 3.1 Hz, 1H), 2.31-2.21 (m, 1H), 2.01 (qd, *J* = 12.8, 4.7 Hz, 1H), 1.84 (dd, *J* = 13.4, 3.2 Hz, 1H). ¹³**C NMR** (101 MHz, CDCl₃) δ 163.6, 156.0, 146.0, 142.8, 135.6, 130.8, 130.6, 129.2, 128.9, 128.8, 128.5, 128.2, 126.3, 124.2, 123.0, 118.0, 114.4, 113.7, 58.1, 50.6, 48.2, 47.9, 44.9, 36.9, 26.0. **HRMS** (ESI-TOF): Calculated for C₂₇H₂₆BrN₄O₂ [M+H]⁺: 517.1239; Found: 517.1218.

3-benzyl-8-(3-(trifluoromethyl)phenyl)-2,3,6,7,7a,8,9,13b-octahydro-

[1,2,4]*triazino*[2',1':1,2] pyridazino[4,3-c]quinoline-1,4-dione (**2i**) was obtained according to the general procedure A, performed on a 0.16 mmol scale (48 mg, 60%).

2iA: white amorphous solid (19 mg, 24%). ¹**H NMR** (400 MHz, CDCl₃) δ 7.62 (d, J = 2.0 Hz, 1H), 7.55 (td, J = 7.7, 1.9 Hz, 2H), 7.46 (t, J = 7.7 Hz, 1H), 7.32 (tt, J = 6.8, 1.2 Hz, 2H), 7.30-7.23 (m, 3H), 7.08-7.02 (m, 1H), 6.73 (dt, J = 7.8, 1.4 Hz, 1H), 6.67 (td, J = 7.5, 1.1 Hz, 1H), 6.60 (dd, J = 8.0, 1.1 Hz, 1H), 6.09 (d, J = 5.1 Hz, 1H), 4.80 (d, J = 2.5 Hz, 1H), 4.66 (d, J = 14.7 Hz, 1H), 4.28 (ddd, J = 12.6, 4.9, 2.3 Hz, 1H), 4.15 (d, J = 14.7 Hz, 1H), 3.83 (d, J = 15.8 Hz, 1H), 3.76 (d, J = 15.9 Hz, 1H), 3.45 (s, 1H), 2.85 (td, J = 12.7, 2.9 Hz, 1H), 1.27-1.13 (m, 1H). ¹³**C** NMR (101 MHz, CDCl₃) δ 163.9, 155.8, 144.2, 141.4, 135.8, 131.0 (q, J = 32.4 Hz), 130.2, 129.2, 128.89, 128.87, 128.5, 128.3, 128.1, 126.5, 124.9 (d, J = 3.8 Hz), 123.5 (d, J = 3.9 Hz), 119.3, 116.2, 115.4, 58.6, 52.1, 50.5, 48.2, 44.9, 37.6, 19.0. ¹⁹**F** NMR (376 MHz, CDCl₃) δ -63.18. HRMS (ESI-TOF): Calculated for C₂₈H₂₆F₃N₄O₂ [M+H]*: 507.2008; Found: 507.1999.

2iB: white amorphous solid (29 mg, 36%). ¹**H NMR** (400 MHz, CDCl₃) δ 7.47-7.43 (m, 1H), 7.40 (d, J = 2.0 Hz, 1H), 7.39-7.22 (m, 7H), 7.10-7.05 (m, 1H), 6.65-6.57 (m, 3H), 5.31 (d, J = 5.0 Hz, 1H), 4.76 (s, 1H), 4.66 (d, J = 14.7 Hz, 1H), 4.43 (d, J = 2.2 Hz, 1H), 4.38 (ddd, J = 12.6, 4.8, 2.3 Hz, 1H), 4.17 (d, J = 14.7 Hz, 1H), 3.79 (d, J = 15.7 Hz, 1H), 3.72 (d, J = 15.8 Hz, 1H), 3.10 (td, J = 12.7, 3.1 Hz, 1H), 2.19 (dddd, J = 12.4, 5.0, 3.8, 2.2 Hz, 1H), 1.96 (qd, J = 12.9, 4.9 Hz, 1H), 1.84-1.76 (m, 1H). ¹³C NMR (101 MHz, Chloroform-*d*) δ 163.6, 156.0, 144.7, 142.8, 135.5, 131.2 (q, J = 32.2 Hz), 129.6, 129.2, 128.9, 128.5, 128.2, 126.3, 124.6 (q, J = 3.8 Hz), 122.5 (q, J = 3.8 Hz), 118.1, 114.3, 113.7, 58.2, 50.6, 48.2, 47.8, 44.9, 36.9, 26.0. ¹⁹F NMR (376 MHz, CDCl₃) δ -63.01. HRMS (ESI-TOF): Calculated for C₂₈H₂₆F₃N₄O₂ [M+H]⁺: 507.2008; Found: 507.2008.

3-benzyl-8-(3,5-bis(trifluoromethyl)phenyl)-2,3,6,7,7a,8,9,13b-octahydro-[1,2,4]triazino[2',1':1,2]pyridazino[4,3-c]quinoline-1,4-dione (2j) was obtained according to the general procedure A, performed on a 0.17 mmol scale (74 mg, 74%).

2jA: white amorphous solid (32 mg, 32%). ¹**H NMR** (400 MHz, CDCI₃) δ 8.20 (d, J = 1.7 Hz, 2H), 8.09 (s, 1H), 7.45-7.29 (m, 5H), 7.12-7.03 (m, 1H), 6.82-6.76 (m, 1H), 6.71-6.57 (m, 2H), 6.42 (s, 1H), 6.03 (d, J = 5.0 Hz, 1H), 5.10 (d, J = 2.4 Hz, 1H), 4.61 (d, J = 14.9 Hz, 1H), 4.20 (d, J = 14.9 Hz, 1H), 4.13 (d, J = 15.5 Hz, 1H), 4.04 (ddd, J = 12.6, 5.0, 2.2 Hz, 1H), 3.78 (d, J = 15.5 Hz, 1H), 2.98 (td, J = 12.8, 2.9 Hz, 1H), 2.33-2.22 (m, 1H), 1.52 (qd, J = 13.0, 4.9 Hz, 1H), 1.01 (dd, J = 13.4, 3.8 Hz, 1H). ¹³C NMR (101 MHz, CDCI₃) δ 163.8, 155.7, 143.7, 143.2, 135.8, 132.2 (d, J = 33.3 Hz), 129.0, 128.9, 128.5, 128.1, 127.0, 126.6, 122.1, 119.9, 116.4, 115.7, 58.4, 51.8, 50.5, 48.2, 44.7, 37.6, 19.0. ¹⁹F NMR (376 MHz, CDCI₃) δ -62.77. HRMS (ESI-TOF): Calculated for C₂₉H₂₅F₆N₄O₂ [M+H]⁺: 575.1882; Found: 575.1898.

2jB: white amorphous solid (42 mg, 42%). ¹**H** NMR (400 MHz, CDCl₃) δ 8.04 (s, 1H), 7.99 (s, 2H), 7.44-7.36 (m, 2H), 7.32 (dt, *J* = 9.0, 3.0 Hz, 3H), 7.11 (ddd, *J* = 8.4, 6.3, 2.3 Hz, 1H), 6.85 (s, 1H), 6.80 (d, *J* = 8.1 Hz, 1H), 6.60-6.51 (m, 2H), 4.98 (d, *J* = 5.1 Hz, 1H), 4.72 (s, 1H), 4.60 (d, *J* = 14.8 Hz, 1H), 4.23-4.12 (m, 2H), 4.05 (d, *J* = 15.5 Hz, 1H), 3.72 (d, *J* = 15.5 Hz, 1H), 3.28-3.17 (m, 1H), 2.44-2.37 (m, 1H), 1.93 (d, *J* = 13.1 Hz, 1H), 1.61 (qd, *J* = 12.8, 4.9 Hz, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 163.5, 155.6, 146.5, 142.1, 135.9, 132.3 (d, *J* = 33.5 Hz), 129.4, 128.9, 128.5, 128.1, 126.6, 126.0, 124.2, 122.0, 118.7, 114.5, 113.8, 58.0, 50.5, 48.3, 47.3, 44.6, 36.9, 26.1. ¹⁹F NMR (376 MHz, CDCl₃) δ -62.79. HRMS (ESI-TOF): Calculated for C₂₉H₂₅F₆N₄O₂ [M+H]⁺: 575.1882; Found: 575.1891.

3-benzyl-8-(pyridin-3-yl)-2,3,6,7,7a,8,9,13b-octahydro-

[1,2,4]*triazino*[2',1':1,2]*pyridazino*[4,3-*c*]*quinoline*-1,4-*dione* (**2k**) was obtained as a TFA salt according to the general procedure B (2.5 equiv of $BF_3 \cdot Et_2O$ were used for this example), performed on a 0.16 mmol scale (46 mg, 50%).

2kA: yellowish amorphous solid isolated as a TFA salt (38 mg, 41%). ¹**H NMR** (400 MHz, DMSO- d_6) δ 8.86 (d, J = 2.1 Hz, 1H), 8.75 (dd, J = 5.3, 1.5 Hz, 1H), 8.32 (dt, J = 8.1, 1.8 Hz, 1H), 7.82 (dd, J = 8.0, 5.3 Hz, 1H), 7.49-7.13 (m, 6H), 7.11-6.99 (m, 1H), 6.75 (dd, J = 8.1, 1.1 Hz, 1H), 6.70-6.55 (m, 2H), 6.39 (bs, 1H), 6.02 (d, J = 5.1 Hz, 1H), 5.05 (d, J = 2.5 Hz, 1H), 4.60 (d, J = 14.9 Hz, 1H), 4.19 (d, J = 14.9 Hz, 1H), 4.14 (d, J = 15.5 Hz, 1H), 4.04 (ddd, J = 12.4, 4.9, 2.2 Hz, 1H), 3.78 (d, J = 15.5 Hz, 1H), 2.97 (td, J = 12.7, 2.8 Hz, 1H), 2.28-2.18 (m, 1H), 1.52 (qd, J = 13.0, 4.9 Hz, 1H), 1.09 (dd, J = 13.2, 3.5 Hz, 1H). ¹³**C NMR** (101 MHz, DMSO- d_6) δ 164.1, 155.8, 145.7, 145.2, 144.9, 140.2, 139.1, 137.5, 129.0, 128.7, 128.5, 128.0, 126.1, 125.6, 117.7, 116.3, 115.7, 55.2, 51.3, 49.9, 48.7, 44.6, 36.3, 19.3. **HRMS** (ESI-TOF): Calculated for C₂₆H₂₆N₅O₂ [M+H]⁺: 440.2097; Found: 440.2077.

2kB: yellowish amorphous solid isolated as a TFA salt (8 mg, 9%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.64 (dd, *J* = 5.1, 1.7 Hz, 2H), 7.99 (dt, *J* = 8.2, 1.9 Hz, 1H), 7.69 (dd, *J* = 8.0, 5.1 Hz, 1H), 7.46-7.36 (m, 2H), 7.31 (dt, *J* = 5.9, 1.5 Hz, 3H), 7.09 (ddd, *J* = 8.4, 6.5, 2.4 Hz, 1H), 6.77 (dd, *J* = 8.1, 1.0 Hz, 1H), 6.60-6.50 (m, 2H), 5.03 (d, *J* = 5.1 Hz, 1H), 4.66 (s, 1H), 4.57 (d, *J* = 14.8 Hz, 1H), 4.30-4.10 (m, 2H), 4.05 (d, *J* = 15.5 Hz, 1H), 3.73 (d, *J* = 15.4 Hz, 1H), 3.19 (td, *J* = 12.7, 2.9 Hz, 1H), 2.38-2.28 (m, 1H), 1.94-1.86 (m, 1H), 1.62 (qd, *J* = 12.9, 4.8 Hz, 1H). ¹³C NMR (101 MHz, DMSO-*d*₆) δ 164.0, 155.7, 145.8, 144.9, 144.4, 142.0, 138.1, 137.5, 129.2, 129.0, 128.6, 128.0, 126.2, 125.6, 116.6, 114.4, 114.1, 54.6, 49.9, 48.6, 46.7, 44.8, 35.6, 25.6. HRMS (ESI-TOF): Calculated for C₂₆H₂₆N₅O₂ [M+H]⁺: 440.2097; Found: 440.2094.

3-benzyl-8-(pyridin-4-yl)-2,3,6,7,7a,8,9,13b-octahydro-

[1,2,4]triazino[2',1':1,2]pyridazino[4,3-c]quinoline-1,4-dione (2I) was obtained as a TFA salt according to the general procedure B (2.5 equivalents of BF₃·Et₂O were used for this example), performed on a 0.15 mmol scale (38 mg, 46%).

2IA: yellowish amorphous solid isolated as a TFA salt (30 mg, 36%). ¹**H NMR** (400 MHz, DMSO- d_6) δ 8.94-8.86 (m, 1H), 8.04-7.93 (m, 1H), 7.46-7.37 (m, 1H), 7.37-7.29 (m, 2H), 7.09 (ddd, J = 8.5, 6.7, 2.0 Hz, 1H), 6.79 (dd, J = 8.0, 1.1 Hz, 1H), 6.68-6.59 (m, 1H), 6.48 (bs, 1H), 6.05 (d, J = 5.0 Hz, 1H), 5.12 (d, J = 2.6 Hz, 1H), 4.61 (d, J = 14.9 Hz, 1H), 4.20 (d, J = 14.9 Hz, 1H), 4.15 (d, J = 15.5 Hz, 1H), 4.02 (ddd, J = 12.5, 4.8, 2.1 Hz, 1H), 3.79 (d, J = 15.5 Hz, 1H), 2.97 (td, J = 12.7, 2.9 Hz, 1H), 2.31 (ddd, J= 11.6, 6.1, 3.5 Hz, 1H), 1.49 (qd, J = 13.1, 4.9 Hz, 1H), 1.00 (dd, J = 13.7, 3.5 Hz, 1H). ¹³**C NMR** (101 MHz, DMSO) δ 164.1, 155.8, 145.4, 144.4, 137.5, 129.0, 128.7, 128.5, 128.0, 126.1, 124.8, 117.9, 116.3, 115.8, 56.7, 51.3, 49.9, 48.7, 44.6, 36.1, 19.4. **HRMS** (ESI-TOF): Calculated for C₂₆H₂₆N₅O₂ [M+H]⁺: 440.2097; Found: 440.2077.

21B: yellowish amorphous solid isolated as a TFA salt (8 mg, 10%). ¹H NMR (400 MHz, DMSO- d_6) δ 8.82-8.70 (m, 2H), 7.78-7.70 (m, 2H), 7.45-7.35 (m, 2H), 7.31 (dq, *J* = 9.0, 2.3 Hz, 3H), 7.14-7.05 (m, 1H), 6.87 (bs, 1H), 6.80 (d, *J* = 8.1 Hz, 1H), 6.58-6.50 (m, 2H), 4.98 (d, *J* = 5.1 Hz, 1H),

4.71 (s, 1H), 4.57 (d, J = 14.8 Hz, 1H), 4.23-4.10 (m, 2H), 4.05 (d, J = 15.5 Hz, 1H), 3.73 (d, J = 15.5 Hz, 1H), 3.20 (td, J = 12.7, 2.9 Hz, 1H), 2.36 (dq, J = 11.0, 5.6 Hz, 1H), 1.94 (d, J = 13.2 Hz, 1H), 1.62 (qd, J = 12.9, 4.8 Hz, 1H). ¹³**C NMR** (101 MHz, DMSO-*d*₆) δ 164.0, 155.7, 145.4, 144.1, 137.5, 129.3, 129.0, 128.6, 128.0, 126.2, 123.6, 116.8, 114.5, 114.2, 56.3, 49.9, 48.6, 46.7, 44.8, 35.0, 25.7. **HRMS** (ESI-TOF): Calculated for C₂₆H₂₆N₅O₂ IM+H1⁺: 440.2097; Found: 440.2080.

3-benzyl-8-isopropyl-2,3,6,7,7a,8,9,13b-octahydro-

[1,2,4]triazino[2',1':1,2]pyr-idazino[4,3-c]quinoline-1,4-dione (20A) was obtained according to the general procedure B, performed on a 0.16 mmol scale (47 mg, 70%).

20A: white amorphous solid (47 mg, 70%). ¹**H NMR** (400 MHz, CDCl₃) δ 7.73 (bs, 1H), 7.44-7.29 (m, 5H), 7.19-7.10 (m, 1H), 6.85-6.67 (m, 3H), 5.87 (d, *J* = 5.1 Hz, 1H), 4.76 (d, *J* = 14.7 Hz, 1H), 4.39 (ddd, *J* = 12.6, 4.8, 2.5 Hz, 1H), 4.24 (d, *J* = 14.7 Hz, 1H), 3.97 (d, *J* = 16.0 Hz, 1H), 3.89 (d, *J* = 15.9 Hz, 1H), 3.24-3.07 (m, 2H), 2.34-2.28 (m, 1H), 1.95-1.81 (m, 1H), 1.81-1.66 (m, 2H), 1.11 (d, *J* = 6.5 Hz, 3H), 1.00 (d, *J* = 6.7 Hz, 3H). ¹³**C NMR** (101 MHz, CDCl₃) δ 163.9, 156.2, 135.3, 129.1, 129.0, 128.5, 128.3, 126.2, 60.7, 52.3, 50.6, 47.9, 45.1, 32.4, 28.6, 19.8, 18.9. **HRMS** (ESI-TOF): Calculated for C₂₄H₂₉N₄O₂ [M+H]*: 405.2291; Found: 405.2306.

3-benzyl-8-cyclohexyl-2,3,6,7,7a,8,9,13b-octahydro-

[1,2,4]*triazino*[2',1':1,2] pyridazino[4,3-c]quinoline-1,4-dione (**2pA**) was obtained according to the general procedure B, performed on a 0.15 mmol scale, as a white amorphous solid (66 mg, 90%).

¹**H NMR** (400 MHz, CDCl₃) δ 7.43-7.30 (m, 5H), 7.09-7.00 (m, 1H), 6.72 (dt, *J* = 7.8, 1.4 Hz, 1H), 6.65 (td, *J* = 7.5, 1.2 Hz, 1H), 6.52 (dd, *J* = 8.0, 1.1 Hz, 1H), 5.85 (d, *J* = 5.1 Hz, 1H), 4.76 (d, *J* = 14.7 Hz, 1H), 4.39 (ddd, *J* = 12.5, 4.8, 2.4 Hz, 1H), 4.20 (d, *J* = 14.7 Hz, 1H), 3.91 (d, *J* = 15.7 Hz, 1H), 3.82 (d, *J* = 15.8 Hz, 1H), 3.19-3.02 (m, 2H), 2.26-2.10 (m, 1H), 1.95 (d, *J* = 12.6 Hz, 1H), 1.89-1.67 (m, 4H), 1.63 (dd, *J* = 13.7, 3.3 Hz, 1H), 1.49 (tdd, *J* = 11.1, 7.3, 3.2 Hz, 1H), 1.39-1.12 (m, 3H), 0.98 (dqd, *J* = 14.9, 12.1, 11.6, 3.2 Hz, 2H). ¹³**C NMR** (101 MHz, CDCl₃) δ 163.7, 155.9, 144.3, 135.8, 128.9, 128.7, 128.7, 128.5, 128.1, 126.3, 118.3, 116.2, 114.6, 58.8, 52.3, 50.5, 48.2, 45.0, 37.8, 32.0, 28.5, 26.1, 25.8, 25.7, 19.1. **HRMS** (ESITOF): Calculated for C₂₇H₃₃N₄O₂ [M+H]⁺: 445.2604; Found: 445.2591.

3-benzyl-8-cyclopropyl-2,3,6,7,7a,8,9,13b-octahydro-

[1,2,4]*triazino*[2',1':1,2] pyridazino[4,3-c]quinoline-1,4-dione (**2qA**) was obtained according to the general procedure B, performed on a 0.16 mmol scale (30 mg, 47%), as a white amorphous solid (30 mg, 47%).

¹**H NMR** (400 MHz, CDCl₃) δ 7.44-7.29 (m, 5H), 7.14-7.05 (m, 1H), 6.77-6.68 (m, 2H), 6.66-6.59 (m, 1H), 5.85 (d, *J* = 5.2 Hz, 1H), 4.76 (d, *J* = 14.7 Hz, 1H), 4.45 (dt, *J* = 12.5, 3.7 Hz, 1H), 4.24 (d, *J* = 14.7 Hz, 1H), 3.95 (d, *J* = 15.9 Hz, 1H), 3.86 (d, *J* = 15.9 Hz, 1H), 3.29-3.11 (m, 1H), 2.63 (dd, *J* = 9.7, 2.4 Hz, 1H), 2.30-2.17 (m, 1H), 1.98-1.86 (m, 2H), 1.14-0.98 (m, 0H), 0.68 (tt, *J* = 9.1, 4.9 Hz, 1H), 0.59 (tt, *J* = 8.9, 4.8 Hz, 1H), 0.34 (dq, *J* = 9.3, 4.7 Hz, 1H), 0.26 (dq, *J* = 9.7, 4.9 Hz, 1H). ¹³**C NMR** (101 MHz, CDCl₃) δ 163.8, 156.0, 143.9, 135.7, 128.9, 128.8, 128.5, 128.2, 126.4, 118.6, 116.1, 114.6, 60.2, 52.1, 50.5, 48.1, 45.1, 35.1, 19.8, 13.0, 3.9, 1.7. **HRMS** (ESI-TOF): Calculated for C₂₄H₂₇N₄O₂ [M+H]⁺: 403.2134; Found: 403.2124.

3-benzyl-8-cyclohexyl-10-iodo-2,3,6,7,7a,8,9,13b-octahydro-

[1,2,4]*triazino*[2', 1':1,2]*pyridazino*[4,3-*c*]*quinoline*-1,4-*dione* (**2rA**) was obtained according to the general procedure B, performed on a 0.2 mmol scale, as a light-yellow amorphous solid (68 mg, 62%).

 1H), 2.23-2.13 (m, 1H), 2.04 (d, J = 12.8 Hz, 1H), 1.88 (d, J = 13.3 Hz, 1H), 1.84-1.50 (m, 6H), 1.44-1.13 (m, 3H), 1.13-0.90 (m, 2H). ¹³**C** NMR (101 MHz, CDCI₃) δ 163.7, 155.8, 143.6, 138.4, 135.8, 128.9, 128.5, 128.1, 126.5, 119.1, 116.8, 84.4, 59.0, 52.2, 50.5, 48.2, 44.9, 37.7, 31.8, 30.2, 28.5, 26.2, 25.8, 19.1. HRMS (ESI-TOF): Calculated for C₂₇H₃₁IKN₄O₂ [M+K]⁺: 609.1129; Found: 609.1138.

3-benzyl-8-cyclohexyl-11-(trifluoromethyl)-2,3,6,7,7a,8,9,13b-octahydro-[1,2,4]triazino[2',1':1,2]pyridazino[4,3-c]quinoline-1,4-dione (**2sA**) was obtained according to the general procedure B, performed on a 0.16 mmol scale, as a white amorphous solid (48 mg, 58%).

¹**H** NMR (400 MHz, CDCI₃) δ 7.43-7.29 (m, 5H), 6.84-6.75 (m, 2H), 6.75-6.71 (m, 1H), 5.83 (d, *J* = 5.1 Hz, 1H), 4.74 (d, *J* = 14.7 Hz, 1H), 4.44-4.36 (m, 1H), 4.24 (d, *J* = 14.7 Hz, 1H), 3.92 (d, *J* = 15.8 Hz, 1H), 3.83 (d, *J* = 15.8 Hz, 1H), 3.17 (dd, *J* = 9.7, 2.2 Hz, 1H), 3.10 (td, *J* = 12.4, 3.6 Hz, 1H), 2.23 (dd, *J* = 9.0, 4.1 Hz, 1H), 1.94 (d, *J* = 12.7 Hz, 1H), 1.89-1.61 (m, 6H), 1.48 (q, *J* = 10.8 Hz, 1H), 1.39-1.13 (m, 3H), 1.09-0.91 (m, 2H). ¹³C NMR (101 MHz, CDCI₃) δ 163.6, 155.8, 144.7, 135.8, 130.9 (q, *J* = 32.0 Hz), 128.9, 128.5, 128.2, 126.9, 125.4, 119.5, 114.1 (q, *J* = 3.8 Hz), 110.9 (q, *J* = 4.0 Hz), 58.6, 51.8, 50.5, 48.2, 44.9, 37.7, 30.0, 28.5, 26.1, 25.7, 25.7, 19.2. ¹⁹F NMR (376 MHz, CDCI₃) δ -63.7. HRMS (ESI-TOF): Calculated for C₂₈H₃₂F₃N₄O₂ [M+H]⁺: 513.2477; Found: 513.2467.

3-benzyl-8-cyclohexyl-12-morpholino-2,3,6,7,7a,8,9,13b-octahydro-[1,2,4]triazino[2',1':1,2]pyridazino[4,3-c]quinoline-1,4-dione (2tA) was obtained according to the general procedure B, performed on a 0.18 mmol scale, as a purple amorphous solid (80 mg, 86%).

¹**H NMR** (400 MHz, CDCl₃) δ 7.42-7.29 (m, 6H), 7.21 (d, *J* = 8.8 Hz, 1H), 7.03 (s, 1H), 6.54 (d, *J* = 8.7 Hz, 1H), 5.83 (s, 1H), 4.76 (d, *J* = 14.5 Hz, 1H), 4.41-4.31 (m, 2H), 4.09 (bs, 4H), 3.94 (d, *J* = 15.9 Hz, 1H), 3.76 (d, *J* = 15.8 Hz, 1H), 3.38 (bs, 4H), 3.21-3.03 (m, 2H), 2.21 (bs, 1H), 1.97-1.61 (m, 8H), 1.47 (bs, 1H), 1.23 (dt, *J* = 39.9, 12.5 Hz, 4H), 1.01 (d, *J* = 15.0 Hz, 2H). ¹³**C NMR** (101 MHz, CDCl₃) δ 163.63, 156.10, 145.43, 135.56, 132.71, 128.94, 128.90, 128.22, 121.03, 118.94, 117.77, 115.22, 64.34, 58.57, 55.00, 51.46, 50.69, 48.09, 45.39, 37.63, 31.40, 30.03, 28.49, 26.04, 25.72, 25.64, 19.10. **HRMS** (ESI-TOF): Calculated for C₃₁H₄₀N₅O₃ [M+H]⁺: 530.3131; Found: 530.3114.

11-benzyl-6-cyclohexyl-5,6,6a,7,8,11,12,14a-octahydro-

[1,2,4]triazino[2',1':1, 2]pyridazino[4,3-c][1,7]naphthyridine-10,13-dione (**2uA**) was obtained as a TFA salt according to the general procedure B (2.5 equiv of BF₃·Et₂O were used for this example), performed on a 0.19 mmol scale, as a yellowish amorphous solid isolated as a TFA salt (20 mg, 18%).

¹**H NMR** (400 MHz, DMSO-*d*₆) δ 7.85 (dd, *J* = 4.8, 1.4 Hz, 1H), 7.44-7.35 (m, 4H), 7.33-7.25 (m, 2H), 7.22 (q, *J* = 9.4, 5.8 Hz, 1H), 5.82 (d, *J* = 5.2 Hz, 1H), 4.52 (d, *J* = 15.4 Hz, 1H), 4.30 (d, *J* = 15.4 Hz, 1H), 4.11-3.97 (m, 2H), 3.74 (d, *J* = 15.9 Hz, 1H), 3.27 (dd, *J* = 9.7, 2.2 Hz, 1H), 3.16 (td, *J* = 12.6, 2.8 Hz, 1H), 2.25-2.15 (m, 2H), 1.74 (d, *J* = 17.5 Hz, 3H), 1.69-1.60 (m, 2H), 1.48-1.09 (m, 5H), 1.05-0.84 (m, 2H). ¹³**C NMR** (101 MHz, DMSO-*d*₆) δ 164.5, 155.3, 143.3, 137.4, 128.9, 128.1, 127.7, 124.6, 57.8, 49.9, 48.9, 37.8, 30.8, 30.1, 28.4, 26.3, 25.9, 25.8, 19.8. **HRMS** (ESI-TOF): Calculated for C₃₁H₄₀N₅O₃ [M+H]⁺: 530.3131; Found: 530.3114.

Compound (3) was prepared as described in reference [10a].

2,3-dibenzyl-8-(4-nitrophenyl)-2,3,6,7,7a,8,9,13b-octahydro-

[1,2,4]*triazino*[2',1':1,2]*pyridazino*[4,3-*c*]*quinoline*-1,4-*dione* (**4B** or **4'B**) was obtained according to the general procedure A, performed on a 0.09 mmol scale, as a yellow amorphous solid (11 mg, 21%).

¹**H NMR** (500 MHz, C₆D₆) δ 7.60 – 7.42 (m, 2H), 7.21 – 6.97 (m, 11H), 6.93 (d, J = 7.7 Hz, 1H), 6.73 (t, J = 7.5 Hz, 1H), 6.61 – 6.49 (m, 2H), 6.27 (d, J = 8.0 Hz, 1H), 5.55 (d, J = 4.9 Hz, 1H), 5.12 (d, J = 14.8 Hz, 1H), 4.18

 $\begin{array}{l} (t, \textit{J} = 4.7 \text{ Hz}, 1\text{H}), 4.12 - 3.93 \ (m, 1\text{H}), 3.50 \ (d, \textit{J} = 14.8 \text{ Hz}, 1\text{H}), 3.42 \ (d, \textit{J} = 2.1 \text{ Hz}, 1\text{H}), 2.73 \ (qd, \textit{J} = 14.0, 4.6 \text{ Hz}, 2\text{H}), 1.56 \ (ddd, \textit{J} = 11.9, 5.8, 3.4 \text{ Hz}, 1\text{H}), 1.51 - 1.38 \ (m, 2\text{H}), 0.87 \ (d, \textit{J} = 9.7 \text{ Hz}, 1\text{H}). ^{13} \textbf{C} \ \textbf{NMR} \ (126 \text{ MHz}, C_6D_6) \ \delta \ 163.7, 154.1, 150.2, 147.1, 142.7, 136.6, 135.3, 130.2, 128.9, 128.7, 128.6, 128.3, 128.0, 127.2, 126.4, 126.0, 123.6, 118.0, 114.7, 113.5, 60.2, 57.8, 48.9, 47.1, 44.4, 36.5, 36.3, 25.5. \ \textbf{HRMS} \ (\text{ESI-TOF}): Calculated for $C_{34}\text{H}_{32}\text{N}_5\text{O}_4 \ [M+H]^+: 574.2454.; Found: 574.2440. \end{array}$

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An endocyclic enamide having a unique bicyclic structure including a 1,2,4-triazine-3,6-dione subunit was used as an olefin partner in the Povarov reaction. This represents an efficient strategy to access a new family of fused tetracyclic N-heterocycles which combine in their structure two scaffolds of interest in medicinal chemistry, a tetrahydroquinoline (THQ) and an aza-diketopiperazine (aza-DKP).