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PII: S0960-894X(17)30029-X
DOI: http://dx.doi.org/10.1016/j.bmcl.2017.01.017
Reference: BMCL 24593

To appear in: *Bioorganic & Medicinal Chemistry Letters*

Received Date: 7 November 2016
Revised Date: 6 January 2017
Accepted Date: 8 January 2017

Please cite this article as: Paparin, J-L., Amador, A., Badaroux, E., Bot, S., Caillet, C., Convard, T., Da Costa, D., Dukhan, D., Griffe, L., Griffon, J-F., LaColla, M., Leroy, F., Liuzzi, M., Giulia Loi, A., McCarville, J., Mascia, V., Milhau, J., Onidi, L., Pierra, C., Rahali, R., Rosinosky, E., Sais, E., Seifer, M., Surleraux, D., Standring, D., Dousson, C.B., Discovery of Benzophosphadiazine Drug Candidate IDX375: A Novel Hepatitis C Allosteric NS5B RdRp Inhibitor, *Bioorganic & Medicinal Chemistry Letters* (2017), doi: http://dx.doi.org/10.1016/j.bmcl.2017.01.017

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Bioorganic & Medicinal Chemistry Letters
journal homepage: www.elsevier.com

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ARTICLE INFO

Article history:
Received
Revised
Accepted
Available online

Keywords:
Hepatitis C virus
Direct-acting antivirals
NS5B non-nucleoside inhibitors
Allosteric inhibitors
Phosphadiazines
Phophorylated bioisosteres
Thiadiazine bioisosteres
IDX375

ABSTRACT

Hepatitis C virus (HCV) NS5B RNA-dependent RNA polymerase (RdRp) plays a central role in virus replication. NS5B has no functional equivalent in mammalian cells, and as a consequence is an attractive target for selective inhibition. This paper describes the discovery of a novel family of HCV NS5B non-nucleoside inhibitors inspired by the bioisosterism between sulfonamide and phosphonamide. Systematic structural optimization in this new series led to the identification of IDX375, a potent non-nucleoside inhibitor that is selective for genotypes 1a and 1b. The structure and binding domain of IDX375 were confirmed by X-ray co-crystalisation study.

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Chronic hepatitis C virus (HCV) infection is a significant medical concern globally, and was first identified in 1989 as a positive-stranded RNA virus of the Flaviridae family.[1] According to the World Health Organization, HCV has already infected approximately 180 million people (around 3% of the worldwide population) and nearly 4 million new infections occur annually.[2]

A majority of HCV infections progress to chronic liver problems such as cirrhosis and hepatocellular carcinoma requiring liver transplantation, with morbidity and mortality rates projected to double in this decade.[3] Recent reviews have comprehensively described the current state of research in the field and emphasize the critical growing medical need for the development of combination therapies.[4]

Drugs targeting three major classes of HCV drug target have reached clinical trials: NS3/4A serine protease inhibitors, NS5A phosphoprotein inhibitors, and two main categories of HCV NS5B RdRp inhibitors, which include active site nucleoside prodrugs and allosteric non-nucleoside inhibitors.[5]

In 2002, GlaxoSmithKline reported several new classes of non-nucleoside benzothiadiazine-substituted quinolinedione HCV polymerase inhibitors (Figure 1, **1)** with nanomolar IC_{50}'s.[6] These molecules bind to the ''palm" region of NS5B, also now known as the allosteric site 4, located within the β-hairpin loop (Palm site II) and in close proximity to the active site, thought to be involved in primer-independent initiation of RNA replication.[7]

A parallel synthetic effort was reported subsequently by researchers at Roche, highlighting the discovery of tetramic acid derivatives as potential mimetics for the quinolinone moiety (Figure 1, **2)**.[8]

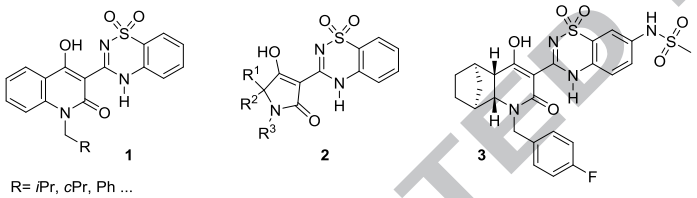


Figure 1. Thiadiazines Inhibitors of HCV polymerase

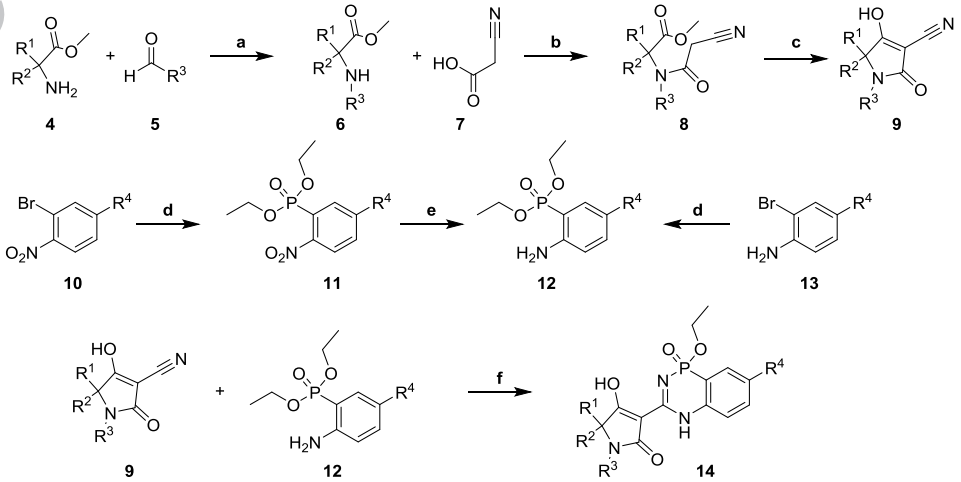
In 2009, still Roche reported[9] the synthesis and evaluation of benzothiazine analogs and published a crystal structure confirming that these thiazines bind in the "palm" site of the NS5B polymerase near the catalytic site. The quinolinedione phenyl projects into an hydrophobic pocket formed by Met414 and Gly410, and the methyl sulfonamide group incorporated at at C-7 significantly improves the polymerase binding affinity of the whole series.[9c] In the same year, Setrobuvir (**3**, ANA-598) demonstrated efficacy in Phase I clinical trials,[10a] but its structure was only disclosed in 2011 when Roche acquired Anadys[10b] and a review was published on this chemotype. [10c]

In 2011, Idenix disclosed[11] a novel series of HIV-1 non-nucleoside reverse transcriptase inhibitors, among other phosphorous-based bioisosteres, featuring a 3-arylphosphoindole bearing a key phosphinate moiety as a sulfonamide replacement.[12] This work led to the discovery of NNRTI Fosdevirine (IDX899) and demonstrated the potential of the phosphorous chemistry as bioisostere strategy. The replacement of key pharmacophores with bioisosteres is an important tool in medicinal chemistry that can be leveraged to improve potency, selectivity, physicochemical properties and the pharmacokinetic profile of key compounds.[12]

When we started this HCV project in 2006, we chose to explore a novel phosphodiazine series based on thiadiazine **2**, seeking to alter the physicochemical properties of the scaffold and to harness the chiral center of the phosphorous atom to further probe the polymerase binding site. We report herein the synthesis and optimization of this benzophosphodiazine series, which led to the discovery of IDX375.

When we initiated our efforts, few synthetic examples describing this scaffold class were reported.[13] To this end, we developed a short and convergent synthetic route, first inspired by Palacios publications,[13a,b] to access this new family of products.[14] The key step of the synthesis features a condensation between a phosphinate and a nitrile (obtained from chiral aminoester), activated with trimethyl aluminium. Our general convergent route for the preparation of substituted benzophosphodiazines is presented in Scheme 1.

The synthesis of the tetramic acid moeity starts with a reductive amination between diverse amino acid methyl esters **4** and aldehydes **5**. Condensation with cyanoacetic acid **7** and cyclisation of intermediate **8** under basic conditions yield the desired substituted cyano-tetramic acid **9**. The synthesis of the second moiety begins with substituted 1-nitro-2-phenyl compound **10** or directly from the corresponding bromo-aniline **13**, with palladium-catalyzed substitution providing the desired phosphinate moiety **12**. Finally, the benzophosphodiazine core **14** is obtained as a mixture of diastereomers by condensation of **9** and **12** in the presence of trimethyl aluminium.

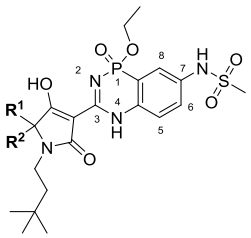


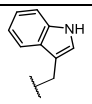
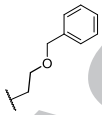
Scheme 1. Convergent synthesis of benzophosphodiazines. Reagents and conditions: (a) $NaBH_3CN$, TEA, MeOH, rt; (b) DCC, CH_2Cl_2, DMF, rt; (c) *t*BuOK, *t*BuOH, rt, 1h; (d) $P(OEt)_3$, $Pd(OAc)_2$, CH_3CN, 160°C, 30min microwaves; (e) H_2, Pd/C, MeOH, rt; (f) $AlMe_3$, dioxane, 80°C, 3h.

Scheme 1 presents the synthesis with ethylphosphinate derivatives only as they were found to provide the most active compounds (see Figure 2). In addition, their improved chemical stability over methyl phosphinate derivatives and their potential to liberate ethanol as a benign metabolite provided additional support for this core.

As exemplified in Table 1, a large range of core substitutions were evaluated off the tetramic acid. Monosubstitution with cycloalkyl groups (Table 1, Entries **27–30**) and alkyl groups (Table 1, Entries **31–34**) were discovered to be the only functionalities providing acceptable 1b-HCV polymerase inhibition. However, this discovery was made subsequent to our initial optimization studies. As such, we learned that large aromatic moieties and polar groups (Table 1, Entries **15–20**) yielded poor potencies. Additionally, disubtituted tetrameric acids bearing cycloalkyl and alkyl disubstitution (Table 1, Entries **21–26**), although lipophilic, exhibited poor potency in the cell replicon assay. Finally, we idenitified *t*-butyl to be an optimal substituent, and favoured in the cell replicon assay, with **34** exhibiting an EC_{50} = 0.009 μM.

Table 1. R^1, R^2 substitution-based SAR



	R^1	R^2	EC_{50}[a] (μM)	SI[d]	IC_{50}[b] (μM) Gt-1a	IC_{50}[c] (μM) Gt-1b
15		H	>8.300	>9	1.143	0.300
16		H	>8.300	>9	2.597	0.490
17		H	>8.300	>9	0.972	0.200
18		H	>8.300	>9	4.540	0.021
19		H	>8.300	>9	1.311	0.055
20		H	>8.300	>9	n.d.	0.915
21		Me	4.390	>17	1.363	0.064
22	Et	Me	>8.300	>9	n.d.	0.800
23	CF_3	Me	>8.300	>9	>10.000	0.183
24	Me	Me	>8.300	>9	n.d.	1.370
25			5.514	>13	5.327	0.187
26			0.185	278	0.186	0.006
27		H	1.204	>62	0.206	0.012
28		H	0.055	>1500	0.067	0.008
29		H	0.216	>350	0.097	0.007
30		H	5.510	>13	0.728	0.040
31	Me	H	6.950	>10	0.961	0.021
32		H	0.610	>123	0.227	0.024
33		H	0.842	>89	0.247	0.012
34		H	0.009	>8333	0.059	0.012

[a] Inhibition of HCV replication cells in the HCV Replicon Luciferase assay; EC_{50} values were determined from 50% inhibition versus concentration data.

[b] Biochemical assay for inhibition capacity on the 1a-H77 HCV NS5B polymerase; IC_{50} values were determined from the percent inhibition versus concentration data.

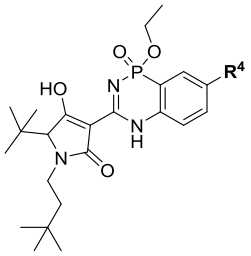
[c] Biochemical assay for inhibition capacity on the 1b-J4 HCV NS5B polymerase; IC_{50} values were determined from the percent inhibition versus concentration data.

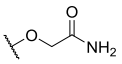
[d] Selectivity index (CC_{50}/ EC_{50})

n.d.: not determined

With optimal substitution identifed at R^1 and R^2, we examined the SAR of the C7 R^4 position based on our most potent lead, **34**. While we identified interesting analogs exhibiting H-bond donor properties (Table 2, Entries **42–46**), none of these substituents provided any improvement in compound Gt1a,1b potency, as shown in Table 2.

Table 2. R^4 substitution-based SAR



	R^4	EC_{50}[a] (μM)	SI[d]	IC_{50}[b] (μM) Gt-1a	IC_{50}[c] (μM) Gt-1b
35	H	3.418	5	3.534	0.044
36	F	4.800	6	3.609	0.116
37	OMe	6.158	3	n.d.	0.707
38	NH_2	3.269	>20	3.727	0.114
39	Me	4.400	4	>10.000	0.451
40	CF_3	>8.300	3<	n.d.	>10.000
41	CN	3.180	12	4.959	0.085
42		7.930	>9	2.951	0.279
43		0.130	>576	0.182	0.017
45		0.019	>3947	0.817	0.065
46	$NHSO_2NH_2$	0.056	>1339	n.d.	0.008

[a] Inhibition of HCV replication cells in HCV Replicon Luciferase assay; EC_{50} values were determined from 50% inhibition versus concentration data.

[b] Biochemical assay for inhibition capacity on the 1a-H77 HCV NS5B polymerase; IC_{50} values were determined from the percent inhibition versus concentration data.

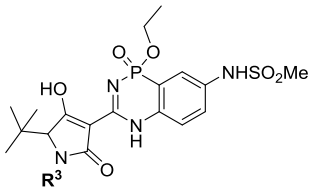
[c] Biochemical assay for inhibition capacity on the 1b-J4 HCV NS5B polymerase; IC_{50} values were determined from the percent inhibition versus concentration data.

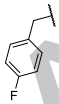
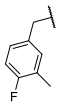
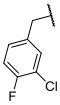
[d] Selectivity index (CC_{50}/ EC_{50})

n.d.: not determined

Finally, we turned our attention to optimization of the R^3 position. Diverse substituted benzyl groups were evaluated along with simple alkyl chains in order to optimally occupy the aforementioned hydrophobic pocket. As shown in Table 3, all compounds displayed reasonable activity. Interestingly, the benzyl subseries (Table 3, Entried **50–56**) was favored in the polymerase enzymatic assay while the replicon cell-based assay indicated a slight advantage to the neohexyl chain (Table 3, Entry **34**). It is noteworthy that changing from a terminal isopropyl (Table 3, Entry **49**) to a *t*-butyl (Table 3, Entry **34**) provided a 10- fold improvement in activity in the replicon assay, providing our optimal lead benzophosphadiazine. More polar heteroaryl replacements of the phenyl were detrimental to the replicon activity, likely due to poor cell penetration.

Table 3. R^3 substitution-based SAR



	R^3	EC_{50}[a] (μM)	SI[d]	IC_{50}[b] (μM) Gt-1a	IC_{50}[c] (μM) Gt-1b
47		1.003	>75	0.167	0.007
48		0.126	>595	0.080	0.014
49		0.095	>789	0.040	0.010
50		0.090	>833	0.057	0.008
51		0.044	>1704	0.031	0.015
52		0.162	>462	0.104	0.006
53		0.018	>4166	0.015	0.005
54		0.015	>5000	0.017	0.005
55		0.031	>2419	0.028	0.006
56		0.039	>1923	0.020	0.009
57		>8.300	>9	1.002	0.065
58		>8.300	>9	8.126	0.091

[a] Inhibition of HCV replication cells in HCV Replicon Luciferase assay; EC_{50} values were determined from 50% inhibition versus concentration data.

[b] Biochemical assay for inhibition capacity on the 1a-H77 HCV NS5B polymerase; IC_{50} values were determined from the percent inhibition versus concentration data.

[c] Biochemical assay for inhibition capacity on the 1b-J4 HCV NS5B polymerase; IC_{50} values were determined from the percent inhibition versus concentration data.

[d] Selectivity index (CC_{50}/ EC_{50})

Through our optimization efforts, we generated a large array of compounds all of which were evaluated for *in vitro* potency in the NS5B polymerase and replicon assay. An overview of our structure activity relationship (SAR) studies based on EC_{50} is presented in Figure 2.

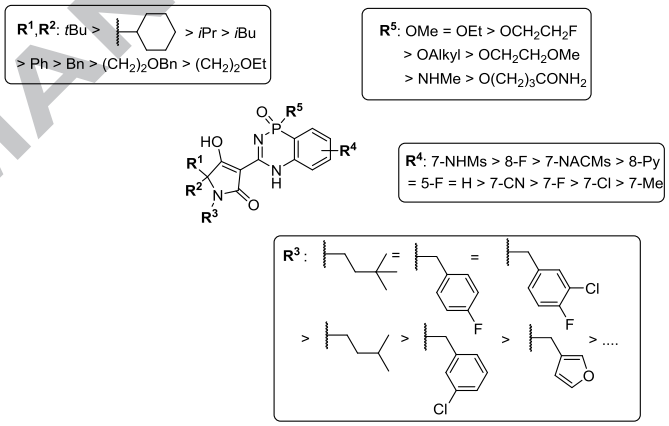


Figure 2. General benzophosphadiazine SAR

We have found this qualitative SAR as a useful tool for structure optimization. Indeed, we can see clearly that R^1= *t*-Bu is prefered over all alkyls across substitution patterns. In addition, the SAR at R^4 directed us toward hydrogen bond donors in position 7, with a simple methanesulfonyl group being optimal. Finally, further R^5 optimization guided us to select the ethyl phosphonate as optimal, as previously discussed in this publication.

Ultimately, the mixture of isomers of **34** was separated by chiral preparative purification and yielded four individual diastereoisomers (compounds **59**-**62**) whose the stereochemistry was confirmed by X-ray crystallography (*vide infra*).

Table 4. Selection of the optimal diastereoisomer for preclinical studies

Compound	Stereo-chemistry	EC_{50}[a] (μM)	SI[d]	IC_{50}[b] (μM) Gt-1a	IC_{50}[c] (μM) Gt-1b
59	R, Sp	1.397	>53	1.757	0.012
60	S, Sp	0.003	>25000	0.015	0.005
61	R, Rp	0.568	>132	0.324	0.014
62	S, Rp	1.390	>53	1.757	0.701

[a] Inhibition of HCV replication cells in HCV Replicon Luciferase assay; EC_{50} values were determined from 50% inhibition versus concentration data.

[b] Biochemical assay for inhibition capacity on the 1a-H77 HCV NS5B polymerase; IC_{50} values were determined from the percent inhibition versus concentration data.

[c] Biochemical assay for inhibition capacity on the 1b-J4 HCV NS5B polymerase; IC_{50} values were determined from the percent inhibition versus concentration data.

[d] Selectivity index (CC_{50}/ EC_{50})

We found the most potent diastereoisomer to be compound **60** which was elected as lead candidate and named IDX375: IC_{50} 1a&1b = 0.015 μM & 0.005 μM with EC_{50} = 0.003 μM and was inactive against all tested human cellular polymerases (>75μM).

In order to study its interactions with the viral protein, co-crystals were obtained (PDB code: 4EAW) and binding to the "palm" domain was confirmed. The PDB ID: 4EAW (backbone and carbons of residues in cream and ligand colored by elements, water in red) binding interaction is compared to those of PDB ID: 3G86[9c] (backbone, carbons of residues and carbons of ligand in light green, water in blue). These active sites differ in the residue at position 316, which is a Tyr in 4EAW and an Asn in 3G86.

Despite this difference we observe a number of binding similarities in both crystal structures. In particular, the same kind of hydrogen bonding interaction between the nitrogen backbone of Tyr448 and the tetramic acid or the hydroxyl of the phenol are observed in both structures. In addition, both also bind through a water molecule to Gln446 and Gly449. The benzophosphadiazine ring system also interacts in a T-shaped π-stacking mode with Phe193 (which one is also stabilized by two similar T-shaped π-stacking interactions), similar to the benzothiadiazine ring system.

The sulfonamide group makes two hydrogen bonds with the carboxamide nitrogen of Asn291 (interatomic distance $d_{O\text{-}N}$= 2.94Å) and the carboxylate group of Asp318 ($d_{O\text{-}O}$= 3.0Å). Finally, in both crystal structures, the neohexyl chain and the the fluorobenzyl moiety are well positioned in the known hydrophobic pocket formed by M414, Cys366 and Tyr415 (Figure 4).

Based on the analysis of these crystal structures, benzophosphadiazines and benzothiadiazines are structurally similar bioisosteres for this binding pocket.

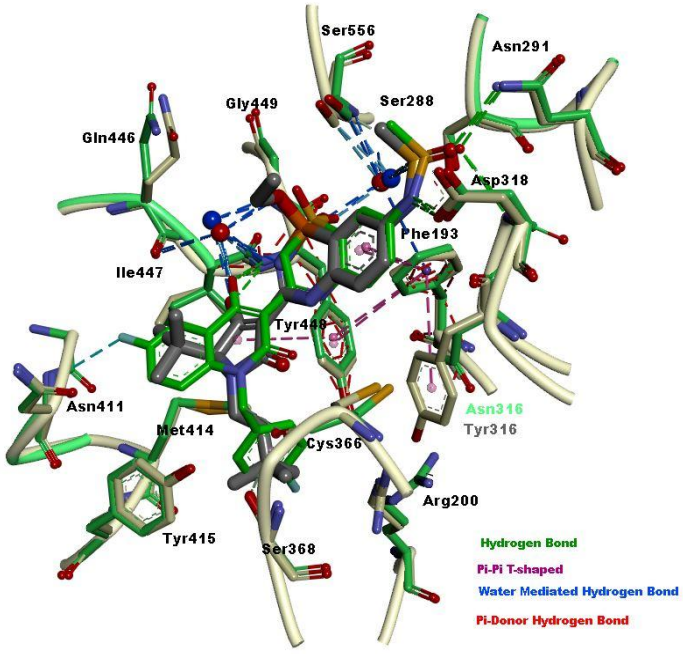


Figure 4. Binding pocket of HCV NS5b (N316Y) containing ligand **IDX375** (PDB code: 4EAW) compared to a benzothidiazine (PDB code: 3G86) [9c].

From preclinical studies, in three days cell-based replicon assay, IDX375 generally showed additivity in combination with the HCV PI IDX320 or the nucleotide IDX184, but exhibited very strong synergy when combined with both classes of direct acting antiviral agents.[15]

According to its promising profile, IDX375 was profiled *in vivo* and PK data were supportive of further development leading to its selection as clinical candidate. Importantly, significant plasma exposures were obtained following oral administration in the rodent and cynomolgus monkey (Table 5).

Table 5. Good PK and exposures levels in rodent and monkey

	Dose (mg/kg)	Cmax (ng/mL)	Tmax (h)	AUCinf/dose (ng*h/mL)	$T_{1/2}$ (h)	Cl (L/h/kg)	F%
Monkey	10	2251	4	11915	5.5	0.84	28
Mouse	15	569	4	3287	5.1	1.58	35
Rat	15	2210	4	4077	1.3	0.61	16

In summary, investigation of benzophosphadiazine derivatives, inspired by their potential to be bioisosteres of thiadiazine analogs, led to the discovery of a new class of potent HCV NS5B inhibitors and a new phosphorylated bioisostere. Systematic optimization around the scaffold led to the discovery of our lead compound **60** (IDX375), which displayed excellent antiviral activity on the genotypes 1a and 1b, and a good PK profile in multiple animal models. Critical interactions with the viral protein at the NS5B PalmII domain were confirmed by co-crystallization X-ray studies. While its further clinical development was discontinued in favour of pan-genotypic direct antiviral agents, IDX375 monotherapy achieved a significant reduction in HCV RNA level (up to 2.7 log) in a 3-day proof of concept study in HCV genotype 1 infected.[16]

Acknowledgments

We thank Proteros Biostructure GmbH, Dr. Martin Augustin for X-ray structure determination of HCV NS5B polymerase in complex with the ligand (**60**). We also thank our many colleagues and our HCV discovery and development teams at Idenix Pharmaceuticals. Finally, J.L. Paparin thanks Izzat Raheem and Sylvie Capelle for their invaluable assistance.

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