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An efficient synthesis of uracil derivatives from 2-alkyl-Δ^2-oxazolines and nitriles

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ABSTRACT

An efficient and convenient synthesis of new fluorinated and non-fluorinated uracils is described herein. The condensation of nitriles with enolates generated from 2-alkyl-Δ^2-oxazolines (I) affords fluorinated β-enamino acid derivatives, which react with triphosgene to give an isomeric mixture of oxazolopyrimidinones. These can then be easily transformed into a single C-6 pyrimidindione derivative through reaction with a suitable nucleophile.

1. Introduction

The disruption of the biological mechanisms associated with nucleic acids is a major field in drug discovery research, especially that focussed on the development of effective antitumoral and/or antiviral agents. In this context, the preparation of molecules that mimic the structures of nucleic acids or their building blocks has led to many examples of therapeutically useful compounds [1]. Moreover, it has been shown that the introduction of fluorine atoms into organic molecules usually promotes dramatic changes in their biological properties and, as a result, this strategy has been successfully applied to the synthesis of biologically active fluorinated nucleotides and nucleosides [2,3]. Emblematic examples include 5-fluorouracil and trifluridine (Fig. 1), both potent inhibitors of thymidylate synthase. While the former is widely used in the treatment of several types of cancer, the latter has proven to be an effective antiviral agent against *Herpes simplex* infections. In other drugs, such as the antitumoral compound gemcitabine, the fluorine atoms are positioned in the sugar moiety. The potential of this class of compounds, however, is not limited to the field of medicine. C-6 Fluorinated uracils, for example, have found important applications as agrochemicals [4].

2. Results and discussion

In previous articles we described several synthetic routes for the efficient preparation of C-6 fluoroalkylated uracils **1** starting from fluorinated nitriles (R_FCN) **2** (Scheme 1). In our strategy, the target uracils (X = O) or thiouracils (X = S) **1** are obtained in two steps from nitriles **2** and esters **3** *via* the corresponding β-enamino esters **4** with the aid of both solution (R^3 = Et) and solid-phase (R^3 = Wang's resin) techniques [5], as well as through fluorous synthesis [6]. In addition, when suitable olefin substituents are introduced into the β-enamino esters, a ring closing metathesis reaction can be performed to afford bicyclic fluorinated uracils **6** and **7** [7]. Our second methodology, which was initially published as a communication [8], allows for the preparation of uracils **1** from 2-alkyl-Δ^2-oxazolines **8** and fluorinated nitriles **2**. This paper will give a full account of the development of this latter strategy, which we have also applied to the preparation of non-fluorinated uracils with various substitution patterns at R^2.

Our first synthetic approach (via compounds **4**, Scheme 1) did not allow for the preparation of uracils with a $-CH_2CH_2Cl$ substituent on the N atom [5,8]. When the corresponding isocyanate ($NCO-CH_2CH_2Cl$) was used in the condensation reaction with the β-enamino ester **4**, only ill-defined mixtures were formed, perhaps because the highly basic reaction conditions promote elimination in either the isocyanate or in the uracil after its formation. Still, these types of compounds seemed to constitute an interesting synthetic target, as the functionalized side chain would permit the introduction of further functionality. We thus devised a second strategy for the preparation of these compounds.

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[1] X-ray analysis.

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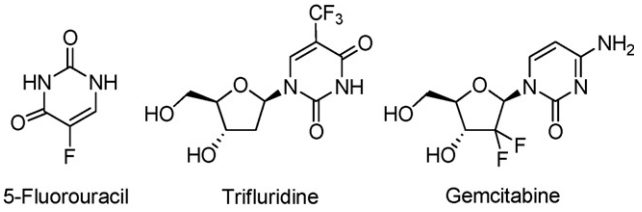


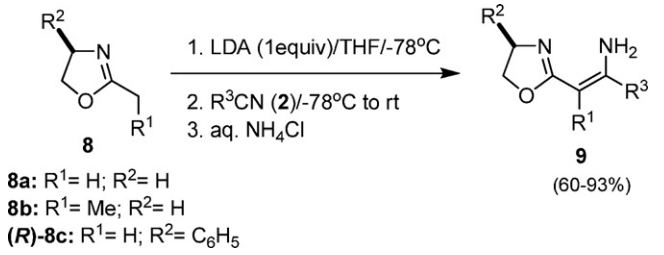
Fig. 1. Some biologically active fluorinated uracil-based compounds.

The starting materials used in this new approach were two commercial oxazolines, namely 2-methyl-Δ^2-oxazoline (**8a**) and 2-ethyl-Δ^2-oxazoline (**8b**), as well as (*R*)-2-methyl-4-phenyl-Δ^2-oxazoline (**8c**). This last compound, although not yet commercially available, can be easily prepared by following methods described in the literature [9]. Additional starting materials included both aromatic and aliphatic, fluorinated and non-fluorinated nitriles **2**. While all the aromatic fluorinated nitriles were commercially available, only one of the aliphatic fluorinated nitriles (**2c**, perfluorooctanenitrile) could be purchased. For that reason, **2e** [10], **2b** [10,11], and **2a** [11,12] were prepared in accordance with procedures previously described in the literature.

In the first step of the synthesis, 2-alkyl-Δ^2-oxazolines **8** were treated with 1 equiv. of LDA at −78 °C to afford their lithium enolates. These were then condensed with different fluorinated and non-fluorinated nitriles **2**, which, after hydrolysis, gave the oxazoline-protected β-enamino acids **9** in yields ranging from 60 to 93% (Scheme 2). Both fluorinated and non-fluorinated compounds **9** appeared exclusively in the enamino form [13]. In this fashion, then, a variety of chiral and achiral compounds **9** were prepared (see Table 1). The yields of this condensation reaction are good to excellent and seem to be independent of whether the nitrile is fluorinated (entries 1–11, Table 1) or not (entries 12–15, Table 1).

The second step consisted of a condensation with either phosgene or triphosgene [14]. These reagents have previously been used in reactions with *N*,*N*′-binucleophiles such as diamines or aminocarboxyamides to afford cyclic ureas (imidazol-2-ones) or related heterocycles with 5 or 6-membered rings [14]. Triphosgene has also been used with 1-azadiene derivatives to give 2-(1*H*)-pyrimidones in good yields [15]. In our synthesis, triphosgene reacted with the protected, fluorinated β-enamino acids **9** to give a mixture of isomeric oxazolopyrimidinones **14** and **15** in yields ranging from 70 to 95% (Scheme 3; Table 2) after quenching of the crude reaction with 5 M aqueous KOH solution.

Because substituting phosgene for triphosgene did not affect the yields and since triphosgene is easier to work with, we chose to use one molar equivalent of triphosgene in each reaction. We were also able to determine that an excess of triphosgene influenced neither the yields nor the proportion of the final products.



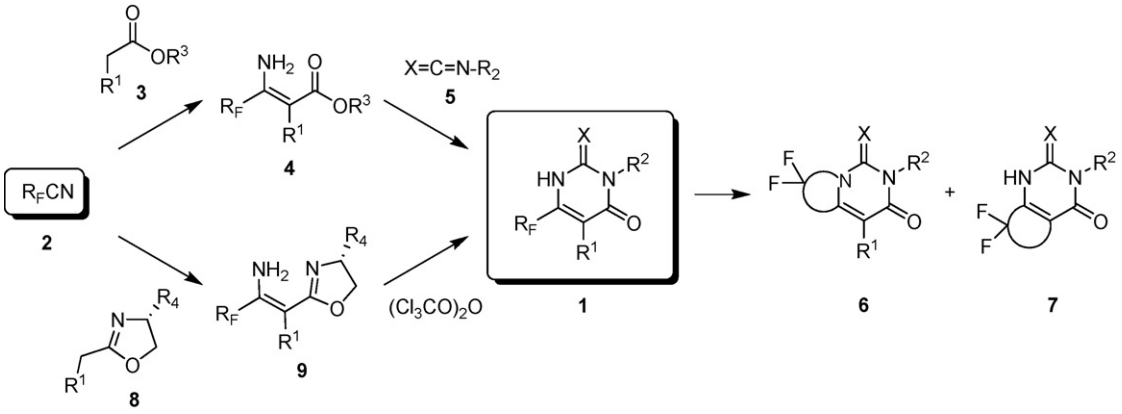
Scheme 2. The condensation of oxazolines **8** and nitriles **2** affords oxazoline-protected β-enamino acids **9**.

Table 1
Results for the reaction between oxazolines **8** and nitriles **2**

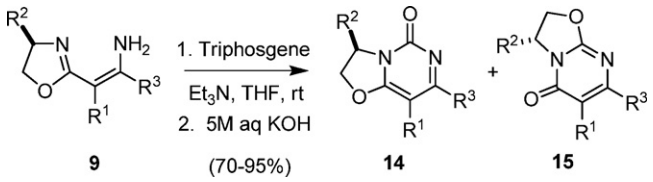
Entry	8	R^1	R^2	2	R^{3a}	Product (9)	Yield (%)[b]
1	**8a**	H	H	**2e**	$CF_2(\beta\text{-}C_{10}H_7)$	**9a**	84
2	**8a**	H	H	**2b**	$CF_2(\alpha\text{-}C_{10}H_7)$	**9b**	80
3	**8a**	H	H	**2a**	$CF_2C_6H_5$	**9c**	70
4	**8a**	H	H	**2c**	$(CF_2)_6CF_3$	**9d**	60
5	**8b**	CH_3	H	**2e**	$CF_2(\beta\text{-}C_{10}H_7)$	**9e**	76
6	**8c**	H	C_6H_5	**2e**	$CF_2(\beta\text{-}C_{10}H_7)$	**9f**	74
7	**8c**	H	C_6H_5	**2b**	$CF_2(\alpha\text{-}C_{10}H_7)$	**9g**	65
8	**8a**	H	H	**2f**	$2,4\text{-}F_2C_6H_3$	**9h**	70
9	**8a**	H	H	**2g**	$p\text{-}CF_3C_6H_4$	**9i**	93
10	**8a**	H	H	**2h**	$p\text{-}FC_6H_4$	**9j**	70
11	**8c**	H	C_6H_5	**2h**	$p\text{-}FC_6H_4$	**9k**	72
12	**8a**	H	H	**2i**	$p\text{-}CH_3C_6H_4$	**9l**	81
13	**8a**	H	H	**2j**	C_6H_5	**9m**	78
14	**8a**	H	H	**2k**	$p\text{-}CH_3OC_6H_4$	**9n**	85
15	**8a**	H	H	**2l**	Thiophenyl	**9o**	80

[a] $\beta\text{-}C_{10}H_7$ = β-naphtyl; $\alpha\text{-}C_{10}H_7$ = α-naphtyl.
[b] Yields for purified products.

In most cases, pyrimidinone derivatives **15** were the predominant products of the condensation reaction. In many cases, both oxazolopyrimidinones **14** and **15** were isolated and purified, but in some instances only **15** was isolated (entries 2, 3, 5, 6, and 9). The results for the reactions with non-fluorinated compounds (entries 11–14, Table 2) indicate that the outcome of this reaction is not dependent on whether the starting oxazoline-protected β-enamino acid is fluorinated or not. However, while isomer **15** is the main product in the reaction of fluorinated compounds **9** with triphosgene (Table 2, entries 1–10), in the same reaction with non-fluorinated compounds **9**, isomer **14** is the major product obtained.



Scheme 1. Previous strategies for the preparation of uracil derivatives developed by our group.



Scheme 3. The reaction of compounds **9** with triphosgene affords a mixture of compounds **14** and **15** after aqueous basic work-up.

Table 2
Preparation of compounds **14** and **15**

Entry[a]	9	R^1	R^2	R^3	Yield (%)[b]	14/15[c]	Isolated products[d]
1	**9a**	H	H	$CF_2(\beta\text{-}C_{10}H_7)$	80	30/70	**14a**, **15a**
2	**9b**	H	H	$CF_2(\alpha\text{-}C_{10}H_7)$	82	10/90	**15b**
3	**9c**	H	H	$CF_2C_6H_5$	72	5/95	**15c**
4	**9d**	H	H	$(CF_2)_6CF_3$	70	10/90	**14d** + **15d**[e]
5	**9e**	CH_3	H	$CF_2(\beta\text{-}C_{10}H_7)$	85	20/80	**15e**
6	**9f**	H	(*R*)-Ph	$CF_2(\beta\text{-}C_{10}H_7)$	90	10/90	**15f**
7	**9h**	H	H	2,4-$F_2C_6H_3$	95	35/65	**14g**, **15g**
8	**9i**	H	H	*p*-$CF_3C_6H_4$	89	30/70	**14h**, **15h**
9	**9j**	H	H	*p*-FC_6H_4	82	35/65	**15i**
10	**9k**	H	(*R*)-Ph	*p*-FC_6H_4	87	30/70	**14j**, **15j**
11	**9l**	H	H	*p*-$CH_3C_6H_4$	85	60/40	**14k**, **15k**
12	**9m**	H	H	C_6H_5	80	50/50	**14l**, **15l**
13	**9n**	H	H	*p*-$CH_3OC_6H_4$	78	65/35	**14m**, **15m**
14	**9o**	H	H	Thiophenyl	84	75/25	**14n**, **15n**

[a] $\beta\text{-}C_{10}H_7$ = β-naphthyl; $\alpha\text{-}C_{10}H_7$ = α-naphthyl.
[b] Yield of **14** + **15** crude mixture.
[c] Proportion **14**/**15** in the crude reaction mixture, as determined through ^1H and/or ^{19}F NMR analysis.
[d] Isolated and purified products; see Experimental Section for individual isolated yields.
[e] It was not possible to separate this mixture.

The structures for isomeric compounds **14** and **15** were unambiguously confirmed by means of X-ray diffraction techniques. Single crystals suitable for X-ray analysis for compounds **14h** (entry 8, Table 2) and **15k** (entry 11, Table 2) were obtained by slow ethyl acetate/*n*-hexane and chloroform/*n*-hexane liquid diffusion, respectively. The corresponding crystal structures indicate that, whereas compound **14h** displays a fluorinated oxazolo[3,2-*c*]pyrimidinone structure (Fig. 2), **15k** is an oxazolo[3,2-*a*]pyrimidinone (Fig. 3).

The X-ray molecular structure of **14h** (Fig. 2) shows an essentially planar conformation for the oxazolo[3,2-*c*]pyrimidinone system (mean deviation 0.017 Å). The planarity of the nine

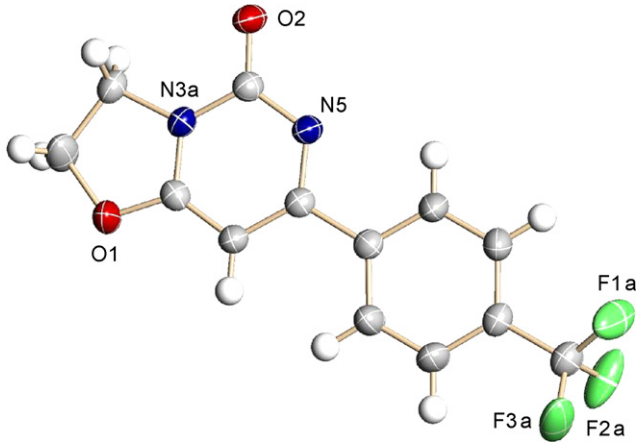


Fig. 2. Ellipsoid plot of compound **14h** (50% probability level).

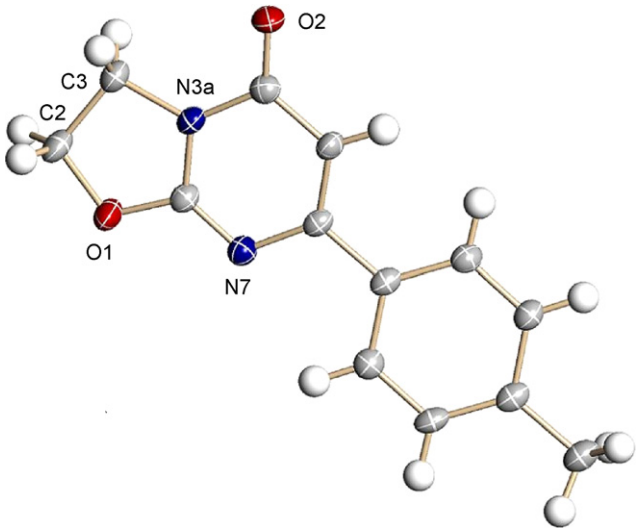


Fig. 3. Ellipsoid plot of compound **15k** (50% probability level).

member fused system determines an eclipsed conformation for the C(2)–C(3) bond. The *p*-CF_3–C_6H_4 moiety is coplanar respect to the molecular main plane (dihedral angle 1.10°).

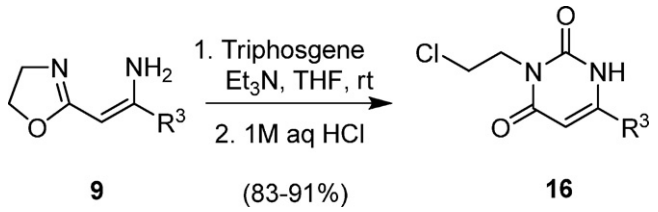
The molecular structure of **15k** (Fig. 3) displays a non planar oxazolo[3,2-*a*]pyrimidinone conformation. The five-membered C1–C2–C3–N3(A)–C7(A) ring is slightly folded in an envelope conformation with the C(2) atom 0.179(3) Å out of the plane. The *p*-tolyl group forms a dihedral angle of 11.13° with the oxazolo[3,2-*a*]pyrimidinone main plane.

In these reactions, we were able to determine which type of aqueous reaction work-up conditions led to specific compounds being isolated as the final products. Thus, when the crude reaction mixture was treated with water or aqueous bicarbonate solution, a mixture of compounds **14**, **15**, and **16** was obtained (see Tables 2 and 3). However, as discussed above, when the reaction mixture was quenched with 5 M aqueous KOH solution, only compounds **14** and **15** were isolated. Finally, when the crude reaction mixture was treated with 1 M aqueous HCl solution, only compounds **16** were isolated in good to excellent yields (85–91%) (Scheme 4). Table 3 shows several examples of the direct preparation of compounds **16** from enaminooxazolines **9**.

Taking all these facts into account, the formation of compounds **14**, **15**, and **16** can be rationalized as depicted in Scheme 5. The nucleophilic attack of the enamine moiety to triphosgene would give rise to an intermediate, which, after loss of HCl, would evolve to the corresponding non-isolated carbamyl chloride. This compound, in turn, would cyclize to compound **14** (Scheme 5). Protonation of the carbonyl oxygen of **14** would favor the nucleophilic attack of chloride anion on the α carbon relative to the oxazoline ring oxygen atom, thus generating a halogenated intermediate **16**. The heterocyclization of this compound with concomitant HCl elimination would then afford the oxazolopyrimidone **15** [16].

Table 3
Preparation of compounds **16**

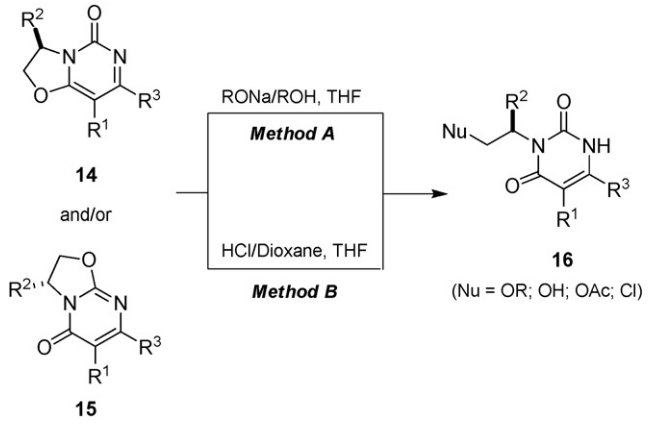
Entry	9	R^3	Yield (%)	Isolated product
1	**9c**	$C_6H_5CF_2$	88	**16a**
11	**9l**	*p*-$CH_3C_6H_4$	88	**16b**
12	**9m**	C_6H_5	85	**16c**
13	**9n**	*p*-$CH_3OC_6H_4$	83	**16d**
14	**9o**	Thiophenyl	91	**16e**



Scheme 4. The reaction of compounds **9** with triphosgene affords compounds **16** after aqueous acidic work-up.

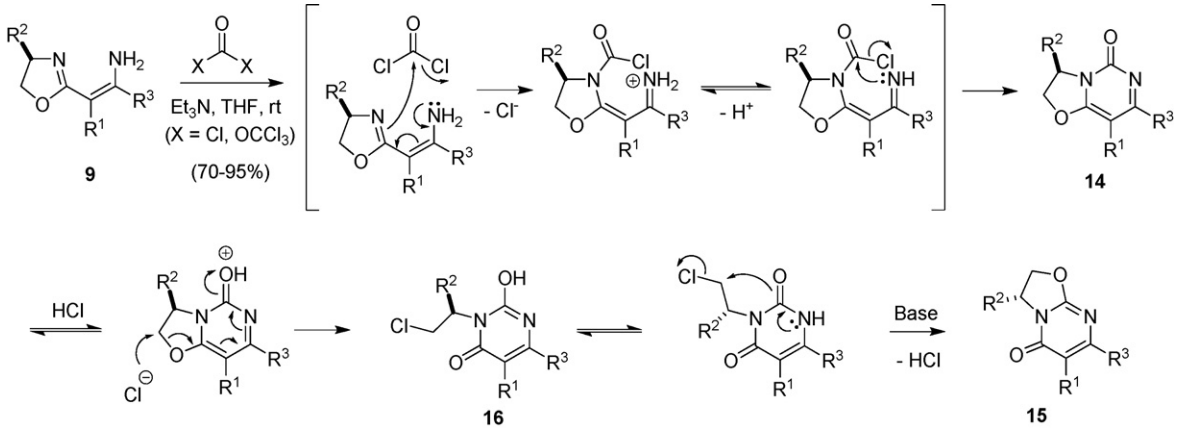
The last step in the synthesis consisted of an oxazoline ring-opening reaction by a nucleophile. Although this type of process is infrequent, there are precedents for such reactions in the literature [17–19]. We thus decided to study the reactivity of pyrimidinones **14** and **15** with nucleophiles such as MeOH, EtOH, H_2O, AcOH, and HCl – under basic or acidic conditions – to determine what combination of factors would give rise to compounds **16** most efficiently (Scheme 6).

The oxazoline ring-opening reaction of **14** and **15** under basic conditions took place in refluxing THF and was followed by hydrolysis with an aqueous solution of NH_4Cl to give uracils **16** (method A, Scheme 6 and Table 4).



Scheme 6. Compounds **14** and **15** are efficient precursors of derivatives **16**.

Alternatively, when compounds **14** and/or **15** were dissolved in THF and treated with 1.2 equiv. of 4 M HCl in dioxane at room temperature, subsequent hydrolysis with NH_4Cl aqueous solution also afforded uracils **16** (Nu = Cl; method B, Scheme 6 and Table 4) [20].

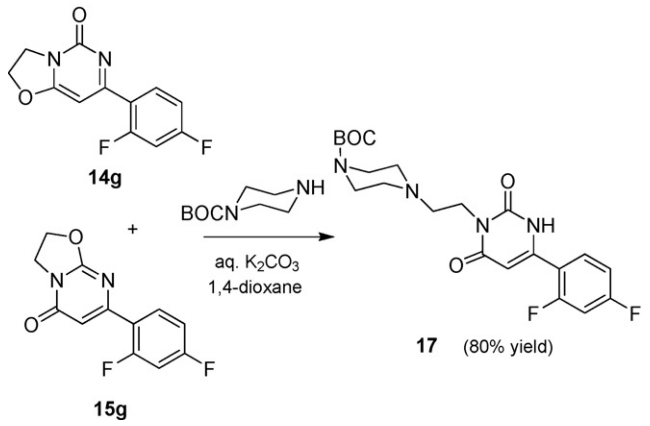


Scheme 5. A possible mechanism for the formation of compounds **14**–**16**.

Table 4
Results for the ring-opening reaction of pyrimidinones **14** and/or **15** with nucleophiles

Entry[a]	Substrate	R^1	R^2	R^3	Nu	Method[b]	Yield (%)[c]	Product
1	**15c**	H	H	$CF_2C_6H_5$	Cl	B	96	**16a**
2	**15b**	H	H	$CF_2(\alpha\text{-}C_{10}H_7)$	OMe	A	80	**16f**
3	**14a**, **15a**	H	H	$CF_2(\beta\text{-}C_{10}H_7)$	Cl	B	98	**16g**
4	**14d** + **15d**	H	H	$(CF_2)_6CF_3$	OH	A	72	**16h**
5	**15e**	CH_3	H	$CF_2(\beta\text{-}C_{10}H_7)$	Cl	B	95	**16i**
6	**15f**	H	(*R*)-Ph	$CF_2(\beta\text{-}C_{10}H_7)$	Cl	B[d]	92	**16j**
7	**14g**, **15g**	H	H	2,4-$F_2C_6H_3$	OH	A	75	**16k**
8	**14g**, **15g**	H	H	2,4-$F_2C_6H_3$	Cl	B	91	**16l**
9	**14h**, **15h**	H	H	*p*-$CF_3C_6H_4$	OMe	A	78	**16m**
10	**14h**, **15h**	H	H	*p*-$CF_3C_6H_4$	OH	A	72	**16n**
11	**15i**	H	H	*p*-FC_6H_4	OEt	A	78	**16o**
12	**14j**, **15j**	H	(*R*)-Ph	*p*-FC_6H_4	Cl	B[d]	92	**16p**
13	**14k**, **15k**	H	H	*p*-$CH_3C_6H_4$	OAc	A	75	**16q**
14	**14k**, **15k**	H	H	*p*-$CH_3C_6H_4$	Cl	B	80	**16b**
15	**14k**, **15k**	H	H	*p*-$CH_3C_6H_4$	OH	A	79	**16r**
16	**14k**, **15k**	H	H	*p*-$CH_3C_6H_4$	OMe	A	70	**16s**
17	**14k**, **15k**	H	H	*p*-$CH_3C_6H_4$	F[e]	A	70	**16t**

Synthesis of uracils **16**.
[a] $\beta\text{-}C_{10}H_7$ = β-naphthyl; $\alpha\text{-}C_{10}H_7$ = α-naphthyl.
[b] Method A: RONa/ROH, THF, reflux. Method B: HCl/dioxane, THF, rt.
[c] Yield of purified product.
[d] At 50 °C.
[e] 0.5 M solution of TBAF in THF under reflux was used as reagent.



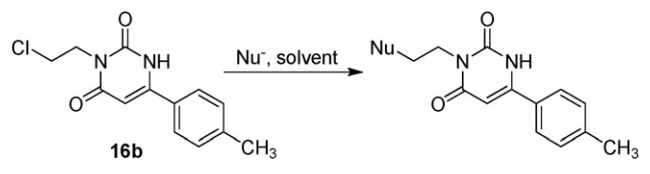
Scheme 7. An example of the use of compounds **14** and **15** as substrates for nucleophilic ring-opening.

It is worth noting that the same uracil **16** was obtained regardless of whether compound **14**, **15**, or a mixture thereof was used, thus making this method quite useful from a synthetic point of view. In all cases, the ring-opening reaction in acidic medium was faster (0.5–2 h) and produced better yields (80–98%) than the corresponding reactions under basic conditions (5–7 h; 72–80%). In cases in which the oxazoline ring had a substituent ($R^2 \neq H$, entries 6 and 12, Table 4), the ring-opening reaction under acidic conditions occurred more slowly and the temperature had to be raised to 50 °C to obtain the corresponding uracils **16j** and **16p**, respectively.

To confirm the validity of our approach as a general method of introducing a nucleophile into these systems, we attempted to do so with the cyclic amine *t*-butyl 1-piperazinecarboxylate (Scheme 7). We chose this compound not only because it would allow for the introduction of other groups after *N*-BOC deprotection, but also because analogous systems form part of several pharmaceutically significant compounds, including Ketanserine [19], a 5-HT_2 serotonin antagonist drug, and Zopiclone [21], an ansiolytic drug that acts as a benzodiazepine receptor agonist.

We found that when a solution of a mixture of **14g** and **15g** in 1,4-dioxane was slowly added to a solution of *N*-BOC-piperazine in a 1:1 mixture of aqueous K_2CO_3 and 1,4-dioxane and stirred at 100 °C for 24 h, the desired compound **17** was obtained in 80% yield, thus proving the validity of our approach (Scheme 7).

Compounds **16** also constitute suitable substrates for further derivatization through obvious nucleophilic attack. As an example of this, compound **16b** was treated with sodium methoxide in methanol and with TBAF in THF to afford the corresponding derivatives **16s** and **16t**, in 65 and 67% yields, respectively (Scheme 8).



Nu^-	solvent	product	yield
MeO^-	MeOH	**16s**	65%
F^- (TBAF)	THF	**16t**	67%

Scheme 8. Transformation of compound **16b** into derivatives **16s** and **16t** through nucleophilic substitution.

3. Conclusions

In summary, we have described a convenient procedure for the preparation of both fluorinated and non-fluorinated uracil derivatives **14**, **15**, and **16** from oxazolines **8** and nitriles **2** in only three steps and with good chemical yields. The ring-opening reaction of intermediate oxazolopyrimidinones **14** and **15** by a number of different nucleophiles allows for the preparation of a variety of potentially bioactive uracils. Compounds **16** are also suitable substrates for nucleophilic substitution reactions, thus increasing the versatility of this family of compounds.

4. Experimental

4.1. General experimental procedures

All reactions were performed with magnetic stirring in flame-dried glassware under an argon atmosphere with dry, distilled solvents. Tetrahydrofuran (THF) was distilled over Na–K alloy. Dichloromethane (CH_2Cl_2) was distilled over CaH_2. Acetonitrile (CH_3CN) was distilled over P_2O_5 and collected under inert atmosphere over molecular sieves (4 Å). All other commercially obtained solvents or reagents were used as received. All reactions were monitored with thin layer chromatography (TLC) in which precoated 250 μm softlayer silica gel GF uniplates (Merck) were used. TLC plates were visualized with UV light (254 nm), vanillin, or cerium molybdate stains. Flash chromatography was performed with the indicated solvent system on 60 (230–400 mesh, particle size 0.040–0.063 mm) normal phase silica gel. In several cases, all of which are clearly identified in the text, the silica gel for column chromatography was deactivated prior to the actual separation through overnight treatment with a 2% solution of triethylamine in hexane, followed by equilibration with the solvent mixture finally employed. 'Concentrated' refers to the removal of solvent with a rotary evaporator at normal water aspirator pressure followed by further evacuation with a two-stage mechanical pump. Yields refer to chromatographically and spectroscopically pure compounds. All new compounds were determined to be at least 95% pure by means of NMR. All melting points were determined with an open capillary. Chemical shifts were reported in δ values relative to tetramethylsilane in ^1H NMR standard, fluorotrichloromethane in ^{19}F NMR, and the solvent peak in ^{13}C NMR. ^1H NMR was measured at 300 MHz, ^{19}F NMR at 282.4 MHz, and ^{13}C NMR at 75.5 MHz. The units for coupling constants are Hertz (Hz). Peak splitting patterns in NMR are reported as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 684059 and 684060. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

4.2. Preparation of compounds 9

4.2.1. General procedure

To a solution of diisopropylamine (14 mmol) in THF (10 mL) at −20 °C, *n*-butyllithium (17.5 mmol, 2.5 M in hexane) was slowly added. The mixture was stirred for 30 min at that temperature, after which the temperature was lowered to −78 °C. Then, a solution of the oxazoline (**8a**, **8b**, or (*R*)-**8c**; 15.0 mmol) in THF (15 mL) was added dropwise and the reaction mixture was stirred 1 h at that temperature to allow azaenolate formation. A solution of the nitrile **7** (14 mmol) in THF (10 mL) was added slowly. The reaction progress was monitored by means of TLC, and after *ca.* 2 h

it was quenched with satd. aq. NH_4Cl solution and extracted with CH_2Cl_2 (3 × 25 mL). The organic layers were pooled together, washed with brine, dried over anh. Na_2SO_4, and concentrated to give crude product **8**, which was purified in each case as described below.

*4.2.2. (Z)-1-Difluoro(2-naphthyl)methyl-2-(4,5-dihydro-1,3-oxazol-2-yl)-1-ethenylamine (**9a**)*

Flash chromatography of the crude reaction product [*n*-hexane:EtOAc (3:1)] on deactivated silica gel (Et_3N 2%) gave a brownish solid (84%): mp 79–81 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 3.82 (t, J = 9.4 Hz, 2H), 4.03 (t, J = 9.8 Hz, 2H), 4.85 (s, 1H), 6.36 (br s, 2H), 7.41–7.51 (m, 3H), 7.76–7.78 (m, 3H), 7.98 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 54.3 (t), 65.7 (t), 82.9 (t, $^3J_{CF}$ = 6.0 Hz), 118.2 (t, $^1J_{CF}$ = 243.9 Hz), 122.3 (t, $^3J_{CF}$ = 5.1 Hz), 125.5 (t, $^3J_{CF}$ = 6.9 Hz), 126.7 (d), 127.4 (d), 127.6 (d), 128.5 (d), 128.6 (d), 131.8 (t, $^2J_{CF}$ = 31.6 Hz), 132.2 (s), 133.9 (s), 150.3 (t, $^2J_{CF}$ = 28.7 Hz), 165.6 (s); ^{19}F NMR (282 MHz, $CDCl_3$) δ −98.34 (s, 2F). HRMS calcd for $C_{16}H_{14}F_2N_2O$ 288.1074, found 288.1069.

*4.2.3. (Z)-1-Difluoro(1-naphthyl)methyl-2-(4,5-dihydro-1,3-oxazol-2-yl)-1-ethenylamine (**9b**)*

Flash chromatography of the crude reaction product [*n*-hexane:EtOAc (4:1)] on deactivated silica gel (Et_3N 2%) gave a yellow solid (80% yield): mp 67–68 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 3.86 (t, J = 9.2 Hz, 2H), 4.05 (t, J = 9.9 Hz, 2H), 4.72 (s, 1H), 6.46 (br s, 2H), 7.41–7.46 (m, 3H), 7.76–8.04 (m,4H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 54.2 (t), 65.6 (t), 83.3 (t, $^3J_{CF}$ = 6.1 Hz), 119.2 (t, $^1J_{CF}$ = 243.7 Hz), 124.2 (d), 124.8 (d), 125.5 (t, $^3J_{CF}$ = 8.6 Hz), 126.1 (d), 127.0 (d), 128.6 (d), 129.4 (t, $^2J_{CF}$ = 24.7 Hz), 129.7 (s), 131.7 (d), 133.8 (s), 150.4 (t, $^2J_{CF}$ = 27.5 Hz), 165.6 (s); ^{19}F NMR (282 MHz, $CDCl_3$) δ −94.19 (s, 2F). HRMS calcd for $C_{16}H_{14}F_2N_2O$ 288.1074, found 288.1073.

*4.2.4. (Z)-1-Difluoro(phenyl)methyl-2-(4,5-dihydro-1,3-oxazol-2-yl)-1-ethenylamine (**9c**)*

Flash chromatography of the crude reaction product [*n*-hexane:EtOAc (4:1)] on deactivated silica gel (Et_3N 2%) gave a yellowish solid (70% yield): mp 33–5 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 3.83 (t, J = 9.3 Hz, 2H), 4.04 (t, J = 9.4 Hz, 2H), 4.79 (s, 1H), 6.32 (br s, 2H), 7.31–7.48 (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 54.2 (t), 65.7 (t), 82.6 (t, $^3J_{CF}$ = 5.7 Hz), 118.0 (t, $^1J_{CF}$ = 244.3 Hz), 125.4 (d), 128.4 (d), 130.4 (d), 134.6 (t, $^2J_{CF}$ = 27.0 Hz), 150.3 (t, $^2J_{CF}$ = 28.7 Hz), 165.5 (s); ^{19}F NMR (282 MHz, $CDCl_3$) δ −98.85 (s, 2F). HRMS calcd for $C_{12}H_{12}F_2N_2O$. 238.0917, found 238.0936.

*4.2.5. (Z)-2-(4,5-dihydro-1,3-oxazol-2-yl)-1-(1,1,2,2,3,3,4,4,7,7,8,8,7,7-pentadecafluoro heptyl)-1-ethenylamine (**9d**)*

Flash chromatography of the crude reaction product [*n*-hexane:EtOAc (4:1] on deactivated silica gel (Et_3N 2%) gave a yellow solid (60% yield): mp 64–6 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 3.91 (t, J = 9.3 Hz, 2H), 4.15 (t, J = 9.1 Hz, 2H), 5.01 (s, 1H), 6.38 (br s, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 54.3 (t), 66.0 (t), 85.3 (t, $^3J_{CF}$ = 7.2 Hz), 108–119 (signals from the group C_7F_{15} were obscured because of their low intensity), 142.3 (t, $^2J_{CF}$ = 25.0 Hz), 165.0 (s); ^{19}F NMR (282 MHz, $CDCl_3$) δ −81.3 (s, 3F), −118.5 (s, 2F), −122.1 (s, 2F), −122.5 (s, 2F), −123.0 (s, 2F), −123.2 (s, 2F), −126.6 (s, 2F).CI HRMS calcd for $C_{12}H_8F_{15}N_2O$ (M^++1) 481.0397, found 481.0406.

*4.2.6. (Z)-[1-Difluoro(2-naphthyl)methyl]-2-(4,5-dihydro-1,3-oxazol-2-yl)-1-propenylamine (**9e**)*

Flash chromatography of the crude reaction product [*n*-hexane:EtOAc (4:1)] on deactivated silica gel (Et_3N 2%) gave a yellowish oil (76% yield). ^1H NMR (300 MHz, $CDCl_3$) δ 1.53 (t, J = 2.3 Hz, 3H), 3.97 (t, J = 8.9 Hz, 2H), 4.10–4.16 (m, 2H), 7.00 (br s, 2H), 7.43–7.51 (m, 2H), 7.60–7.64 (m, 1H), 7.78–7.84 (m, 3H), 8.02 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 12.6 (c), 54.5 (t), 65.6 (t), 90.0 (t, $^3J_{CF}$ = 3.4 Hz), 118.9 (t, $^1J_{CF}$ = 243.4 Hz), 122.3 (t, $^3J_{CF}$ = 4.3 Hz), 125.7 (t, $^3J_{CF}$ = 6.0 Hz), 126.7 (d), 127.4 (d), 127.7 (d), 128.7 (d), 128.8 (d), 132.4 (s), 132.5 (t, $^2J_{CF}$ = 27.0 Hz), 134.1 (s), 146.0 (t, $^2J_{CF}$ = 25.3 Hz), 168.3 (s); ^{19}F NMR (282 MHz, $CDCl_3$) δ −90.57 (s, 2F). HRMS calcd for $C_{17}H_{16}F_2N_2O$ 302.1230, found 302.1220.

*4.2.7. (Z)-1-[Difluoro(2-naphthyl)methyl]-2-[(4R)-4-phenyl-(4,5-dihydro-1,3-oxazol-2-yl)]-1-ethenylamine (**9f**)*

Flash chromatography of the crude reaction product [*n*-hexane:EtOAc (5:1)] on deactivated silica gel (Et_3N 2%) gave a yellow oil (74% yield). $[\alpha]_D^{25}$ − 76.6 (*c* 1.35, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 4.02–4.09 (m, 1H), 4.56–4.63 (m, 1H), 5.16 (s, 1H), 5.38 (t, J = 9.1 Hz, 1H), 6.71 (br s, 2H), 7.37–7.46 (m, 5H), 7.62–7.75 (m, 3H), 7.90–7.99 (m, 3H), 8.23 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 69.5 (d), 72.9 (t), 82.3 (t, $^3J_{CF}$ = 5.7 Hz), 118.2 (t, $^1J_{CF}$ = 244.9 Hz), 122.3 (t, $^3J_{CF}$ = 5.1 Hz), 125.5 (t, $^3J_{CF}$ = 8.2 Hz), 126.5 (d), 126.7 (d), 127.3 (d), 127.4 (d), 127.6 (d), 128.5 (d), 128.6 (d), 128.6 (d), 132.0 (t, $^2J_{CF}$ = 24.7 Hz), 132.2 (s), 133.9 (s), 143.0 (s), 151.0 (t, $^2J_{CF}$ = 27.5 Hz), 165.9 (s); ^{19}F NMR (282 MHz, $CDCl_3$) δ −97.78 (d, J = 258.8 Hz, 1F), −98.80 (d, J = 256.7 Hz, 1F); HRMS calcd for $C_{22}H_{18}F_2N_2O$ 364.1387, found 364.1387.

*4.2.8. (Z)-[1-Difluoro(1-naphthyl)methyl]-2-[(4R)-4-phenyl-(4,5-dihydro-1,3-oxazol-2-yl)-1-ethenylamine (**9g**)*

Flash chromatography of the crude reaction product [*n*-hexane:EtOAc (4:1)] on deactivated silica gel (Et_3N 2%) gave an orange oil (65% yield). $[\alpha]_D^{25}$ − 106.0 (*c* 1.05, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 3.85 (t, J = 8.2 Hz, 2H), 4.42 (dd, J = 9.8 Hz, J = 8.5 Hz, 2H), 4.78 (s, 1H), 5.20 (t, J = 9.0 Hz, 2H), 6.60 (br s, 2H), 7.17–7.46 (m, 8H), 7.78–8.09 (m, 4H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 69.5 (d), 73.0 (t), 82.7 (t, $^3J_{CF}$ = 6.0 Hz), 119.2 (t, $^1J_{CF}$ = 243.7 Hz), 124.2 (d), 124.9 (d), 125.5 (t, $^3J_{CF}$ = 8.2 Hz), 126.1 (d), 126.5 (d), 127.0 (d), 127.3 (d), 128.5 (d), 128.6 (d), 129.4 (t, $^2J_{CF}$ = 24.7 Hz), 129.8 (s), 131.8 (d), 133.9 (s), 143.0 (s), 151.0 (t, $^2J_{CF}$ = 27.5 Hz), 165.9 (s); ^{19}F NMR (282 MHz, $CDCl_3$) δ −93.38 (d, J = 268.7 Hz, 1F), −94.35 (d, J = 268.6 Hz, 1F); HRMS calcd for $C_{22}H_{18}F_2N_2O$ 364.1387, found 364.1374.

*4.2.9. (Z)-1-(2,4-Difluorophenyl)-2-(4,5-dihydro-1,3-oxazol-2-yl)-1-ethenylamine (**9h**)*

Flash chromatography of the crude reaction product [*n*-hexane:EtOAc (4:1)] on deactivated silica gel (Et_3N 2%) gave a yellowish solid (70% yield): mp 83–85 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 3.92 (t, J = 9.3 Hz, 2H), 4.12 (t, J = 9.8 Hz, 2H), 4.75 (s, 1H), 6.55 (br s, 2H), 6.75–6.86 (m, 2H), 7.35–7.45 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 54.3 (t), 65.5 (t), 83.6 (d, $^4J_{CF}$ = 2.3 Hz), 104.6 (dd, $^2J_{CF}$ = 26.4 Hz, $^2J_{CF}$ = 26.4 Hz), 111.6 (d, $^2J_{CF}$ = 21.2 Hz), 121.9 (d, $^2J_{CF}$ = 16.0 Hz), 130.4 (dd, $^3J_{CF}$ = 9.1 Hz, $^3J_{CF}$ = 9.1 Hz), 149.9 (s), 159.7 (dd, $^1J_{CF}$ = 252.9 Hz, $^3J_{CF}$ = 12.0 Hz), 163.2 (dd, $^1J_{CF}$ = 252.9 Hz, $^3J_{CF}$ = 12.0 Hz), 166.3 (s); ^{19}F NMR (282 MHz, $CDCl_3$) δ −108.58 (m, 1F), −111.19 (m, 1F). HRMS calcd for $C_{11}H_{10}F_2N_2O$ 224.0761, found 224.0754.

*4.2.10. (Z)-2-(4,5-Dihydro-1,3-oxazol-2-yl)-1-(4-trifluoromethylphenyl)-1-ethenylamine (**9i**)*

Recrystallization of the crude reaction product from *n*-hexane-EtOH (9:1) gave a yellowish solid (93% yield): mp 119–121 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 3.94 (t, J = 9.0 Hz, 2H), 4.15 (t, J = 9.0 Hz, 2H), 4.90 (s, 1H), 6.55 (br s, 2H), 7.59 (s, 4H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 54.3 (t), 65.7 (t), 82.8 (d), 124.3 (q, $^1J_{CF}$ = 290.0 Hz), 125.7

(d), 131.2 (d), 132.6 (q, $^2J_{CF}$ = 33.0 Hz), 141.4 (s), 153.9 (s), 166.5 (s); ^{19}F NMR (282 MHz, $CDCl_3$) δ −63.29 (s, 3F). HRMS calcd for $C_{12}H_{11}F_3N_2O$ 256.0823, found 256.0782.

4.2.11. (Z)-2-(4,5-Dihydro-1,3-oxazol-2-yl)-1-(4-fluorophenyl)-1-ethenylamine (9j)

Recrystallization of the crude reaction mixture from *n*-hexane-EtOH (9:1) gave a yellow solid (70% yield): mp 89–90 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.92 (t, *J* = 9.2 Hz, 2H), 4.13 (t, *J* = 9.1 Hz, 2H), 4.81 (s, 1H), 6.44–6.56 (br s, 2H), 6.89–7.04 (m, 2H), 7.44–7.46 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 54.3 (t), 65.5 (t), 81.5 (d), 115.6 (d, $^2J_{CF}$ = 21.6 Hz), 127.8 (d), 134.1 (s), 154.6 (s), 163.4 (d, $^1J_{CF}$ = 249.3 Hz), 166.6 (s); ^{19}F NMR (282 MHz, $CDCl_3$) δ −111.70 (m, 1F). HRMS calcd for $C_{11}H_{10}FN_2O$ 205.0777, found 205.0777.

4.2.12. (Z)-1-(4-Fluorophenyl)-2[(4R)-4-phenyl-4,5-dihydro-1,3-oxazol-2-yl-(4-fluoromethylphenyl)-1-ethenylamine (9k)

Flash chromatography of the crude reaction product [*n*-hexane:EtOAc (4:1)] on deactivated silica gel (Et_3N 2%) gave a yellow solid (72% yield): mp 106–8 °C. $[\alpha]_D^{25}$ − 205.3 (*c* 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.92 (t, *J* = 8.2 Hz, 2H), 4.48 (dd, *J* = 9.8 Hz, *J* = 8.1 Hz, 2H), 4.86 (s, 1H), 5.25 (dd, *J* = 9.8 Hz, *J* = 8.0 Hz, 2H), 6.45–6.66 (br s, 2H), 6.99–7.05 (m, 2H), 7.18–7.33 (m, 5H), 7.46–7.51 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 69.6 (d), 72.9 (t), 81.0 (d), 115.7 (d, $^2J_{CF}$ = 21.3 Hz), 126.6 (d), 127.3 (d), 127.9 (d, $^3J_{CF}$ = 8.0 Hz), 128.6 (d), 134.1 (d, $^4J_{CF}$ = 3.4 Hz), 143.6 (s), 155.2 (d), 163.5 (d, $^1J_{CF}$ = 249.4 Hz), 166.9 (s); ^{19}F NMR (282 MHz, $CDCl_3$) δ −111.70 (m, 1F). HRMS calcd for $C_{17}H_{15}FN_2O$ 282.1168, found 282.1127.

4.2.13. (Z)-2-(4,5-Dihydro-1,3-oxazol-2-yl)-1-(4-methylphenyl)-1-ethenylamine (9l)

Flash chromatography of the crude reaction product [*n*-hexane:EtOAc (4:1)] on deactivated silica gel (Et_3N 2%) gave a yellow solid (81% yield): mp 85–87 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.37 (s, 3H), 4.00 (t, *J* = 6.7 Hz, 2H), 4.22 (t, *J* = 6.7 Hz, 2H), 4.95 (s, 1H), 7.20 (d, *J* = 6.3, 2H), 7.49 (d, *J* = 6.3, 2H); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 54.2 (q), 55.1 (t), 65.3 (t), 80.2 (d), 113.8 (d), 127.1 (d), 130.1 (s), 155.2 (s), 160.5 (s), 166.7 (s). MS (*m*/*z*): 202 (M^+), 201 (100%); Elemental analysis calcd for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.93; N, 13.86. Found: C, 71.25; H, 6.96; N, 13.90.

4.2.14. (Z)-2-(4,5-Dihydro-1,3-oxazol-2-yl)-1-phenyl-1-ethenylamine (9m)

Flash chromatography of the crude reaction product [*n*-hexane:EtOAc (4:1)] on deactivated silica gel (Et_3N 2%) gave a yellow solid (78% yield): mp 56–58; ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.97 (t, *J* = 6.7 Hz, 2H), 4.16 (t, *J* = 6.7 Hz, 2H), 4.94 (s, 1H), 6.50 (NH_2, 2H), 7.36–7.52 (m, 5H); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 54.2 (t), 65.4 (t), 81.2 (d), 128.6 (d), 128.9 (d), 129.4 (d), 137.9 (s), 155.5 (s), 164.0 (s). MS (*m*/*z*): 188 (M^+), 187 (100%); Elemental analysis calcd for $C_{11}H_{12}N_2O$: C, 70.21; H, 6.66; N, 14.89. Found: C, 70.18; H, 6.70; N, 14.92.

4.2.15. (Z)-2-(4,5-Dihydro-1,3-oxazol-2-yl)-1-(4-methoxyphenyl)-1-ethenylamine (9n)

Flash chromatography of the crude reaction product [*n*-hexane:EtOAc (4:1)] on deactivated silica gel (Et_3N 2%) gave a yellow solid (85% yield): mp 66–68 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.82 (s, 3H), 3.98 (t, *J* = 6.8 Hz, 2H), 4.19 (t, *J* = 6.7 Hz, 2H), 4.90 (s, 1H), 6.91 (d, *J* = 6.3, 2H), 7.49 (d, *J* = 6.3, 2H); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 54.2 (q), 55.1 (t), 65.3 (t), 80.2 (d), 113.8 (d), 127.1 (d), 130.1 (s), 155.2 (s), 160.5 (s), 166.7 (s). MS (*m*/*z*): 218 (M^+), 217 (100%); Elemental analysis calcd for $C_{12}H_{14}N_2O_2$: C, 66.05; H, 6.42; N, 12.84. Found: C, 66.07; H, 6.44; N, 12.85.

4.2.16. (Z)-2-(4,5-Dihydro-1,3-oxazol-2-yl)-1-(2-thiophenyl)-1-ethenylamine (9o)

Flash chromatography of the crude reaction product [*n*-hexane:EtOAc (4:1)] on deactivated silica gel (Et_3N 2%) gave a yellow solid (80% yield): mp 89–91 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.87 (t, *J* = 6.8 Hz, 2H), 4.08 (t, *J* = 6.7 Hz, 2H), 4.98 (s, 1H), 6.96 (m, 1H), 7.19 (m, 2H); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 54.6 (t), 65.8 (t), 81.8 (d), 125.0 (d), 126.5 (d), 127.8 (d), 141.0 (s), 148.8 (s), 166.6 (s). HRMS calcd for $C_9H_{10}N_2SO$ 194.0513, found 193.9971.

4.3. Preparation of compounds 14 and 15

4.3.1. General procedure

To a solution of triphosgene (1.0 mmol) in toluene (1 mL) and THF (5 mL), a solution of compound **9** (1.0 mmol) in THF (5 mL) was slowly added, followed by triethylamine (2.0 mmol). The mixture was stirred at room temperature. When TLC showed that the reaction was complete (between 3 and 7 h) it was quenched with 5 M aq. KOH soln. at 0 °C and extracted with CH_2Cl_2 (3 × 25 mL). The organic layers were pooled together, dried on anh. $MgSO_4$, and the solvent removed under vacuum. The resulting crude reaction mixture consisted of a mixture of compounds **14** and **15**, which was purified and separated as indicated in each case.

4.3.2. 7-Difluoro(2-naphthyl)methyl-2,3-dihydro-5H-[1,3]oxazolo[3,2-c]pyrimidin-5-one (14a)

The crude yield of the mixture **14a** + **15a** was 80%. Flash chromatography [*n*-hexane:EtOAc (1:1)] on deactivated silica gel (Et_3N 2%) gave **14a** as a yellow solid (20% isolated yield): mp 149–150 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.20 (t, *J* = 8.9 Hz, 2H), 4.75 (t, *J* = 8.7 Hz, 2H), 6.24 (s, 1H), 7.44–7.63 (m, 3H), 7.78–7.83 (m, 3H), 8.08 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 43.7 (t), 69.6 (t), 81.9 (d), 117.1 (t, $^1J_{CF}$ = 245.5 Hz), 122.3 (t, $^3J_{CF}$ = 5.1 Hz), 125.7 (t, $^3J_{CF}$ = 6.9 Hz), 126.6 (d), 127.3 (d), 127.6 (d), 128.4 (d), 128.6 (d), 131.9 (t, $^2J_{CF}$ = 27.0 Hz), 132.3 (s), 133.9 (s), 154.1 (s), 165.9 (s), 172.3 (t, $^2J_{CF}$ = 30.7 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −100.68 (s, 2F). HRMS calcd for $C_{17}H_{12}F_2N_2O_2$ 314.0866, found 314.0863.

4.3.3. 7-Difluoro(2-naphthyl)methyl-2,3-dihydro-5H-[1,3]oxazolo[3,2-a]pyrimidin-5-one (15a)

Flash chromatography [*n*-hexane:EtOAc (1:1)] of the mixture of **14a** + **15a** on silica gel gave **15a** as a yellow solid (50% isolated yield): mp 182–4 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.18 (t, *J* = 8.7 Hz, 2H), 4.63 (t, *J* = 8.5 Hz, 2H), 6.52 (s, 1H), 7.44–7.55 (m, 3H), 7.77–7.85 (m, 3H), 8.04 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 42.1 (t), 66.4 (t), 104.7 (t, $^3J_{CF}$ = 4.9 Hz), 117.4 (t, $^1J_{CF}$ = 245.5 Hz), 122.3 (t, $^3J_{CF}$ = 5.1 Hz), 125.7 (t, $^3J_{CF}$ = 6.9 Hz), 126.7 (d), 127.3 (d), 127.6 (d), 128.4 (d), 128.6 (d), 131.9 (t, $^2J_{CF}$ = 27.0 Hz), 132.2 (s), 133.9 (s), 160.2 (s), 160.7 (s), 161.3 (t, $^2J_{CF}$ = 31.6 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −100.87 (s, 2F). HRMS calcd for $C_{17}H_{12}F_2N_2O_2$ 314.0866, found 314.0863.

4.3.4. 7-Difluoro(1-naphthyl)methyl-2,3-dihydro-5H-[1,3]oxazolo[3,2-a]pyrimidin-5-one (15b)

Flash chromatography [*n*-hexane:EtOAc (1:1)] on silica gel of the crude reaction mixture **14b** + **15b** gave **10b** as a colorless oil (70% isolated yield). Compound **14b** could not be isolated. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.16 (t, *J* = 8.7 Hz, 2H), 4.59 (t, *J* = 8.5 Hz, 2H), 6.52 (s, 1H), 7.39–7.48 (m, 3H), 4.78–8.00 (m, 4H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 42.1 (t), 66.3 (t), 105.6 (d), 118.4 (t, $^1J_{CF}$ = 245.5 Hz), 124.4 (d), 124.5 (d), 125.6 (t, $^3J_{CF}$ = 9.1 Hz), 125.9 (d), 126.8 (d), 128.8 (d), 129.1 (s), 129.6 (t, $^2J_{CF}$ = 24.1 Hz), 131.5 (d), 133.8 (s), 160.1 (s), 160.7 (s), 161.4 (t, $^2J_{CF}$ = 30.4 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −95.65 (s, 2F). HRMS calcd for $C_{17}H_{12}F_2N_2O_2$ 314.0866, found 314.0863.

*4.3.5. 7-Difluoro(1-phenyl)methyl-2,3-dihydro-5H-[1,3]oxazolo[3,2-a]pyrimidin-5-one (**15c**)*

Flash chromatography [*n*-hexane:EtOAc (1:1)] on silica gel of the crude reaction mixture **14c** + **15c** gave compound **15c** as a colorless oil in 60% isolated yield. Compound **14c** could not be isolated. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.22 (t, J = 8.6 Hz, 2H), 4.68 (t, J = 8.6 Hz, 2H), 6.46 (s, 1H), 7.35–7.57 (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 42.2 (t), 66.4 (t), 104.6 (t, $^3J_{CF}$ = 4.9 Hz), 117.2 (t, $^1J_{CF}$ = 245.1 Hz), 125.6 (t, $^3J_{CF}$ = 6.3 Hz), 128.4 (d), 129.3 (d), 134.6 (t, $^2J_{CF}$ = 20.0 Hz), 160.2 (s), 160.7 (s), 161.3 (t, $^2J_{CF}$ = 31.6 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −101.09 (s, 2F). HRMS calcd for $C_{13}H_{10}F_2N_2O_2$ 264.0710, found 264.0709.

*4.3.6. 7-(1,1,2,2,3,3,4,4,5,5,6,6,7,7,7-Pentadecafluoroheptyl)-2,3-dihydro-5H-[1,3] oxazolo[3,2-a]- and [3,2-c]pyrimidin-5-one (**14d** + **15d**)*

Flash chromatography [*n*-hexane:EtOAc (1:1)] on silica gel gave a mixture of **14d** and **15d** as a colorless oil (80% yield) in proportion 10:90 as deduced from the ^{19}F NMR spectrum. This mixture could not be separated. **14d**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.30 (t, J = 8.6 Hz, 2H), 4.78 (t, J = 8.6 Hz, 2H), 6.44 (s, 1H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −81.2 (s, 3F), −116.6 (s, 2F), −121.8 (s, 2F), −122.0 (s, 2F), −122.4 (s, 2F), −123.2 (s, 2F), −126.5 (s, 2F). **15d**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.34 (t, J = 8.9 Hz, 2H), 4.88 (t, J = 8.6 Hz, 2H), 6.15 (s, 1H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −81.1 (s, 3F), −116.4 (s, 2F), −121.7 (s, 2F), −121.8 (s, 2F), −122.3 (s, 2F), −123.1 (s, 2F), −126.5 (s, 2F). HRMS calcd for $C_{13}H_5F_{15}N_2O_2$ (**14d** + **15d**) 506.0111, found 506.0093.

*4.3.7. 7-Difluoro(2-naphthyl)methyl-6-methyl-2,3-dihydro-5H-[1,3]oxazolo[3,2-a] pyrimidin-5-one (**15e**)*

Flash chromatography [*n*-hexane:EtOAc (1:1)] on silica gel of the crude reaction mixture **14e** + **15e** gave compound **15e** as a yellow solid in 62% yield. Compound **14e** could not be isolated. Mp 125–7 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.08 (t, J = 3.1Hz, 3H), 4.22 (t, J = 8.5 Hz, 2H), 4.66 (t, J = 8.5 Hz, 2H), 7.44–7.59 (m, 3H), 7.77–7.88 (m, 3H), 7.99 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 10.5 (c), 42.7 (t), 66.3 (t), 116.1 (s), 118.8 (t, $^1J_{CF}$ = 245.6 Hz), 122.4 (t, $^3J_{CF}$ = 5.1 Hz), 125.3 (t, $^3J_{CF}$ = 6.3 Hz), 126.7 (d), 127.3 (d), 127.7 (d), 128.5 (d), 128.7 (d), 132.4 (s), 132.9 (t, $^2J_{CF}$ = 27.0 Hz), 133.9 (s), 154.7 (t, $^2J_{CF}$ = 29.3 Hz), 156.9 (s), 162.2 (s); ^{19}F NMR (282 MHz, $CDCl_3$) δ −93.3 (s, 2F). HRMS calcd for $C_{18}H_{14}F_2N_2O_2$ 328.1023, found 328.1011.

*4.3.8. (3R)-7-Difluoro(2-naphthyl)methyl-3-phenyl-2,3-dihydro-5H-[1,3]oxazolo[3,2-a] pyrimidin-5-one (**15f**)*

Flash chromatography [*n*-hexane:EtOAc (1:1)] on silica gel of the crude reaction mixture **14f** + **15f** gave **15f** as a yellowish solid (78% yield). Compound **14f** could not be isolated. Mp 160–2 °C. $[\alpha]_D^{25}$ − 44.48 (*c* 1.03, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.50 (dd, J = 9.2 Hz, J = 4.3 Hz, 1H), 4.82 (t, J = 9.1 Hz, 1H), 5.53 (dd, J = 9.0 Hz, J = 4.3 Hz, 1H), 6.46 (s, 1H), 7.16–7.29 (m, 5H), 7.45–7.60 (m, 3H), 7.73–7.83 (m, 3H), 8.06 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 58.3 (d), 74.2 (t), 105.6 (d), 117.5 (t, $^1J_{CF}$ = 245.5 Hz), 122.4 (t, $^3J_{CF}$ = 5.4 Hz), 125.8 (t, $^3J_{CF}$ = 6.3 Hz), 126.3 (d), 126.7 (d), 127.3 (d), 127.3 (d), 127.6 (d), 128.4 (d), 128.7 (d), 129.3 (d), 131.9 (t, $^2J_{CF}$ = 27.1 Hz), 132.4 (s), 133.9 (s), 136.2 (s), 160.0 (s), 160.1 (s), 161.2 (t, $^2J_{CF}$ = 31.9 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −100.03 (d, J = 250.5 Hz, 1F), −101.25 (d, J = 250.5 Hz, 1F). HRMS calcd for $C_{23}H_{16}F_2N_2O_2$ 390.1179, found 390.1186.

*4.3.9. 7-(2,4-Difluorophenyl)-2,3-dihydro-5H-[1,3]oxazolo[3,2-c]pyrimidin-5-one (**14g**)*

Flash chromatography [*n*-hexane:EtOAc (1:1)] on silica gel of the crude reaction mixture **14g** + **15g** (crude yield 95%) gave **14g** as a white solid (28%): mp 172–4 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.31 (t, J = 8.8 Hz, 2H), 4.80 (t, J = 8.7 Hz, 2H), 6.41 (s, 1H), 6.77–6.94 (m, 2H), 8.16–8.24 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 43.7 (t), 69.2 (t), 85.7 (d), 104.4 (dd, $^2J_{CF}$ = 27.0 Hz, $^2J_{CF}$ = 25.3 Hz), 112.0 (dd, $^2J_{CF}$ = 21.3 Hz, $^4J_{CF}$ = 3.4 Hz), 121.1 (d, $^2J_{CF}$ = 13.8 Hz), 133.1 (d, $^3J_{CF}$ = 10.3 Hz), 154.4 (s), 161.3 (dd, $^1J_{CF}$ = 253.0 Hz, $^3J_{CF}$ = 12.7 Hz), 165.1 (dd, $^1J_{CF}$ = 252.9 Hz, $^3J_{CF}$ = 12.7 Hz), 166.3 (s), 168.3 (s); ^{19}F NMR (282 MHz, $CDCl_3$) δ −105.18 (m, 1F), −109.15 (m, 1F). HRMS calcd for $C_{12}H_8F_2N_2O_2$ 250.0553, found 250.0554.

*4.3.10. 7-(2,4-Difluorophenyl)-2,3-dihydro-5H-[1,3]oxazolo[3,2-a]pyrimidin-5-one (**15g**)*

Flash chromatography [*n*-hexane:EtOAc (1:1)] on silica gel of the crude reaction mixture **14g** + **15g** (crude yield 95%) gave **15g** as a white solid (55% isolated yield): mp 142–4 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.28 (t, J = 8.6 Hz, 2H), 4.72 (t, J = 8.6 Hz, 2H), 6.59 (s, 1H),6.78–6.92 (m, 2H), 7.93–8.01 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 42.7 (t), 66.5 (t), 104.6 (dd, $^2J_{CF}$ = 27.0 Hz, $^2J_{CF}$ = 25.3 Hz), 107.5 (d, $^3J_{CF}$ = 13.7 Hz), 112.1 (dd, $^2J_{CF}$ = 20.7 Hz, $^4J_{CF}$ = 3.4 Hz), 121.1 (d, $^2J_{CF}$ = 13.8 Hz), 132.3 (d, $^3J_{CF}$ = 9.7 Hz), 157.7 (s), 159.7 (s), 161.7 (dd, $^1J_{CF}$ = 253.0 Hz, $^3J_{CF}$ = 12.7 Hz), 162.6 (s), 164.4 (dd, $^1J_{CF}$ = 252.9 Hz, $^3J_{CF}$ = 12.7 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −106.80 (m, 1F), −108.25 (m, 1F). HRMS calcd for $C_{12}H_8F_2N_2O_2$ 250.0553, found 250.0551.

*4.3.11. 7-(4-Trifluoromethylphenyl)-2,3-dihydro-5H-[1,3]oxazolo[3,2-c]pyrimidin-5-one (**14h**)*

Flash chromatography [*n*-hexane:EtOAc (1:1)] on silica gel of the crude reaction mixture **14h** + **15h** (89% crude yield) gave **14h** as a white solid (59% isolated yield): mp 164–6 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.32 (t, J = 8.8 Hz, 2H), 4.82 (t, J = 8.7 Hz, 2H), 6.2 (s, 1H), 7.64 (d, J = 8.3 Hz, 2H), 8.0 (d, J = 8.1 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 43.7 (t), 69.3 (t), 82.3 (d), 127.4 (q, $^1J_{CF}$ = 275.3 Hz), 125.6 (d), 128.1 (d), 133.1 (q, $^2J_{CF}$ = 32.7 Hz), 139.8 (s), 154.6 (s), 165.3 (s), 171.7 (s); ^{19}F NMR (282 MHz, $CDCl_3$) δ −63.32 (s, 3F). HRMS calcd for $C_{13}H_9F_3N_2O_2$ 263.0632, found 263.0682.

Crystal data for **14h**: $C_{13}H_9F_3N_2O_2$, M = 282.22, monoclinic, a = 17.0270(20), b = 8.1299(12), c = 8.7201(14) Å, β = 101.934(6)°, V = 1181.0(3) Å^3, T = 133(2) K, space group $P2_1/c$, Z = 4, μ(Mo Kα) = 0.140 mm^{-1}, 7133 reflections measured, 2407 unique (Rint = 0.039), direct primary solution and refinement on F^2 (SHELXL-97, G.M. Sheldrick, University of Göttingen, 1997), 209 parameters, the CF_3 group is disordered over two sites, hydrogen atoms refined as riding, $R_1[I > 2\sigma(I)] = 0.0383$, wR_2(all data) = 0.1061.

*4.3.12. 7-(4-Trifluoromethylphenyl)-2,3-dihydro-5H-[1,3]oxazolo[3,2-a]pyrimidin-5-one (**15h**)*

Flash chromatography [*n*-hexane:EtOAc (1:1)] on silica gel of the crude reaction mixture **14h** + **15h** (89% crude yield) gave **15h** as a white solid (22% isolated yield): mp 262–4 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.30 (t, J = 8.6 Hz, 2H), 4.76 (t, J = 8.6 Hz, 2H), 6.51 (s, 1H), 7.63 (d, J = 8.1 Hz, 2H), 7.97 (d, J = 8.3 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 42.3 (t), 66.3 (t), 103.9 (d), 124.6 (q, $^3J_{CF}$ = 3.6 Hz), 126.3 (d), 159.7 (s), 161.3 (s), 161.7 (s), the rest of the signals were obscured because of their low intensity; ^{19}F NMR (282 MHz, $CDCl_3$) δ −63.25 (s, 3F). HRMS calcd for $C_{13}H_9F_3N_2O_2$ 263.0632, found 263.0759.

*4.3.13. 7-(4-Fluorophenyl)-2,3-dihydro-5H-[1,3]oxazolo[3,2-a]pyrimidin-5-one (**15i**)*

Flash chromatography [*n*-hexane:EtOAc (1:1)] on silica gel of the crude reaction mixture **14i** + **15i** (82% crude yield) gave **10i** as a white solid (50% isolated yield). Compound **14i** could not be

isolated. Mp 91–3 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.28 (t, J = 8.4 Hz, 2H), 4.73 (t, J = 8.4 Hz, 2H), 6.41 (s, 1H), 7.02–7.09 (m, 3H), 7.83–7.88 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 42.6 (t), 66.6 (t), 102.7 (d), 116.1 (d, $^2J_{CF}$ = 21.8 Hz), 129.5 (d, $^3J_{CF}$ = 8.6 Hz), 132.0 (s), 159.9 (s), 161.9 (d, $^4J_{CF}$ = 3.4 Hz), 162.6 (s), 164.8 (d, $^1J_{CF}$ = 251.1 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −110.09 (s, 1F). HRMS calcd for $C_{12}H_9FN_2O_2$ 232.0648, found 232.0646.

4.3.14. (3R)-7-(Fluorophenyl)-3-phenyl-2,3-dihydro-5H-[1,3]oxazolo[3,2-c]pyrimidin-5-one (14j)

Flash chromatography [*n*-hexane:EtOAc (9:1)] on silica gel of the crude reaction mixture **14j** + **15j** (87% crude yield) gave **14j** as a yellow solid (20% isolated yield): mp 170–3 °C. $[\alpha]_D^{25}$ − 224.1 (*c* 1.16, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.66 (dd, J = 9.0 Hz, J = 3.7 Hz, 1H), 5.00 (t, J = 8.9 Hz, 1H), 5.68 (dd, J = 8.8 Hz, J = 3.7 Hz, 1H), 6.29 (s, 1H), 7.03–7.09 (m, 2H), 7.19–7.31 (m, 5H), 7.99–8.03 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 59.3 (d), 77.3 (t), 81.3 (d), 115.6 (d, $^2J_{CF}$ = 21.8 Hz), 126.2 (d), 129.1 (d), 129.3 (d), 130.1 (d, $^3J_{CF}$ = 8.6 Hz), 132.7 (d, $^4J_{CF}$ = 3.4 Hz), 136.7 (s), 153.8 (s), 164.9 (s), 165.0 (d, $^1J_{CF}$ = 252.4 Hz), 172.0 (s); ^{19}F NMR (282 MHz, $CDCl_3$) δ −108.55 (m, 1F). HRMS calcd for $C_{18}H_{13}FN_2O_2$ 308.0961, found 308.0957.

4.3.15. (3R)-7-(Fluorophenyl)-3-phenyl-2,3-dihydro-5H-[1,3]oxazolo[3,2-a]pyrimidin-5-one (15j)

Flash chromatography [*n*-hexane:EtOAc (9:1)] on silica gel of the crude reaction mixture **14j** + **15j** (87% crude yield) gave **15j** as a yellow solid (58% isolated yield): mp 165–7 °C. $[\alpha]_D^{25}$: −33.0 (*c* 1.02, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.56 (dd, J = 9.0 Hz, J = 3.9 Hz, 1H), 4.92 (t, J = 9.0 Hz, 1H), 5.64 (dd, J = 8.8 Hz, J = 3.9 Hz, 1H), 6.36 (s, 1H), 7.00–7.07 (m, 2H), 7.24–7.40 (m, 5H), 7.83–7.88 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 58.2 (d), 74.0 (t), 103.0 (d), 115.6 (d, $^2J_{CF}$ = 21.9 Hz), 126.1 (d), 129.0 (d), 129.2 (d), 129.3 (d, $^3J_{CF}$ = 9.8 Hz), 132.1 (s), 136.9 (s), 159.4 (s), 160.7 (s), 161.9 (s), 164.4 (d, $^1J_{CF}$ = 251.8 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −110.05 (m, 1F). HRMS calcd for $C_{18}H_{13}FN_2O_2$ 308.0961, found 308.0960.

4.3.16. 7-(4-Methylphenyl)-2,3-dihydro-5H-[1,3]oxazolo[3,2-c]pyrimidin-5-one (14k)

Flash chromatography [EtOAc:MeOH (7:3)] on silica gel of the crude reaction mixture **14k** + **15k** (79% crude yield) gave **14k** as a white solid (20% isolated yield): mp 189–191 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.32 (s, 3H), 4.25 (t, J = 8.5 Hz, 2H), 4.69 (t, J = 8.5 Hz, 2H), 6.42 (s, 1H), 7.16 (d, J = 8.1 Hz, 2H), 7.74 (d, J = 8.3 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.4 (q), 41.3 (t), 65.1 (t), 101.0 (d), 125.9 (d), 128.4 (d), 132.2 (d), 140.2 (s), 158.5 (s), 160.7 (s), 162.2 (s). HRMS calcd for $C_{13}H_{12}N_2O_2$ 228.0899, found 228.0894.

4.3.17. 7-(4-Methylphenyl)-2,3-dihydro-5H-[1,3]oxazolo[3,2-a]pyrimidin-5-one (15k)

Flash chromatography [EtOAc] on silica gel of the crude reaction mixture **14k** + **15k** (79% crude yield) gave **15k** as a white solid (49% isolated yield): mp 209–211 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.37 (s, 3H), 3.70 (t, J = 6.8 Hz, 2H), 4.26 (t, J = 6.8 Hz, 2H), 5.95 (d, J = 2.0 Hz, 1H), 7.27 (d, J = 8.1 Hz, 2H), 7.50 (d, J = 8.3 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.9 (q), 40.4 (t), 41.9 (t), 98.3 (d), 126.6 (d), 128.5 (d), 130.5 (d), 143.0 (s), 151.0 (s), 153.5 (s), 163.5 (s). HRMS calcd for $C_{13}H_{12}N_2O_2$ 228.0899, found 228.0889.

Crystal data for **15k**: $C_{13}H_{12}N_2O_2$, M = 228.25, monoclinic, a = 7.0142(2), b = 13.3603(4), c = 11.3277(4) Å, β = 90.982(4)°, V = 1061.38(6) Å^3, T = 110(2) K, space group $P2_1/c$, Z = 4, μ(Cu Kα) = 0.098 mm^{-1}, 5284 reflections measured, 1701 unique (Rint = 0.043), direct primary solution and refinement on F^2 (SHELXL-97), 156 parameters, methyl hydrogen atoms refined as rigid, others riding, $R_1[I > 2\sigma(I)]$ = 0.0512, wR_2(all data) = 0.1526.

4.3.18. 7-Phenyl-2,3-dihydro-5H-[1,3]oxazolo[3,2-c]pyrimidin-5-one (14l)

The crude yield of the mixture **14l** + **15l** was 80%. Flash chromatography [EtOAc/MeOH (4:1)] on silica gel afforded **14l** as a white solid (40% isolated yield): mp 168–170 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.36 (t, J = 8.6 Hz, 2H), 4.84 (t, J = 8.6 Hz, 2H), 6.35 (s, 1H), 7.42–7.51 (m, 3H), 8.04 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 173.6 (s), 165.3 (s), 155.3 (s), 137.0 (s), 132.0 (d), 129.0 (d), 128.2 (d), 82.3 (d), 69.5 (t), 44.1 (t). HRMS calcd for $C_{12}H_{10}N_2O_2$ 214.0742, found 214.0709.

4.3.19. 7-Phenyl-2,3-dihydro-5H-[1,3]oxazolo[3,2-a]pyrimidin-5-one (15l)

Flash chromatography of the crude mixture of **14l** + **15l** on silica gel [EtOAc/MeOH (7:1)] afforded **15l** as a white solid (40% isolated yield): mp 163–165 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.36 (t, J = 8.8 Hz, 2H), 4.91 (t, J = 8.8 Hz, 2H), 6.51 (s, 1H), 7.49–7.52 (m, 3H), 8.04–8.07 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 162.5 (s), 161.3 (s), 160.8 (s), 137.1 (s), 130.7 (d), 128.9 (d), 127.2 (d), 102.2 (d), 67.1 (t), 42.7 (t). HRMS calcd for $C_{12}H_{10}N_2O_2$ 214.0742, found 214.0742.

4.3.20. 7-(4-Methoxyphenyl)-2,3-dihydro-5H-[1,3]oxazolo[3,2-c]pyrimidin-5-one (14m)

The crude yield of the mixture **14m** + **15m** was 78%. Flash chromatography [EtOAc/MeOH (4:1)] on silica gel afforded **14m** as a yellow solid (50% isolated yield): mp 154–156 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.84 (s, 3H), 4.31 (t, J = 8.7 Hz, 2H), 4.80 (t, J = 8.7 Hz, 2H), 6.26 (s, 1H), 6.93 (d, J = 8.8 Hz, 2H), 8.01 (d, J = 8.8 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 171.3 (s), 163.7 (s), 161.6 (s), 154.0 (s), 128.7 (s), 127.9 (s), 112.9 (d), 80.1 (d), 68.1 (t), 54.4 (q), 42.6 (t). HRMS calcd for $C_{13}H_{12}N_2O_3$ 244.0848, found 244.0844.

4.3.21. 7-(4-Methoxyphenyl)-2,3-dihydro-5H-[1,3]oxazolo[3,2-a]pyrimidin-5-one (15m)

Flash chromatography of the crude mixture **14m** + **15m** [EtOAc/MeOH (7:1)] on silica gel afforded **15m** as a yellow solid (28% isolated yield): mp 182–184 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.85 (s, 3H), 4.33 (t, J = 8.7 Hz, 2H), 4.77 (t, J = 8.7 Hz, 2H), 6.45 (s, 1H), 6.93 (d, J = 8.8 Hz, 2H), 7.89 (d, J = 8.8 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 163.3 (s), 162.24 (s), 162.16 (s), 159.8 (s), 129.1 (d), 128.8 (s), 114.4 (d), 101.5 (d), 66.5 (t), 55.8 (q), 42.7 (t). HRMS calcd for $C_{13}H_{12}N_2O_3$ 244.0848, found 244.0838.

4.3.22. 7-(2-Thiophenyl)-2,3-dihydro-5H-[1,3]oxazolo[3,2-c]pyrimidin-5-one (14n)

The crude yield of the mixture **14n** + **15n** was 84%. Flash chromatography [EtOAc/MeOH (4:1)] on silica gel afforded **14n** as a yellow solid (62% isolated yield, method A): mp 185–187 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.33 (t, J = 8.7 Hz, 2H), 4.83 (t, J = 8.7 Hz, 2H), 6.24 (s, 1H), 7.13 (dd, J = 5.1 Hz, J = 4.4 Hz, 1H), 7.56 (d, J = 5.1 Hz, 1H), 7.71 (d, J = 3.4 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 167.0 (s), 164.5 (s), 154.5 (s), 142.2 (s), 132.0 (d), 129.1 (d), 128.1 (d), 80.5 (d), 69.1 (t), 43.6 (t). HRMS calcd for $C_{10}H_8N_2O_2S$ 220.0306, found 220.0271.

4.3.23. 7-(2-Thiophenyl)-2,3-dihydro-5H-[1,3]oxazolo[3,2-a]pyrimidin-5-one (15n)

Flash chromatography of the crude mixture **14n** + **15n** on silica gel [EtOAc/MeOH (7:1)] afforded **15n** as a yellow solid (22%

isolated yield): mp 189–193 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.33 (t, J = 8.7 Hz, 2H), 4.78 (t, J = 8.7 Hz, 2H), 6.42 (s, 1H), 7.11 (dd, J = 5.1 Hz, J = 3.8 Hz, 1H), 7.48 (dd, J = 0.9 Hz, J = 4.9 Hz, 1H), 7.64 (dd, J = 1.1 Hz, J = 3.8 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 165.7 (s), 159.4 (s), 157.8 (s), 141.2 (s), 129.8 (d), 128.3 (d), 127.6 (d), 100.2 (d), 66.2 (t), 42.3 (t). HRMS calcd for $C_{10}H_8N_2O_2S$ 220.0306, found 220.0303.

4.4. Preparation of compounds 16

4.4.1. Method A: Basic conditions

To a solution of compounds **14** and/or **15** (1.5 mmol) in THF (10 mL), a solution of RO^-/ROH (7.5 mmol) diluted in THF (10 mL) was added and then the reaction mixture was refluxed for 5–7 h, until TLC showed completion. The reaction was quenched with satd. aq. NH_4Cl soln. and extracted with CH_2Cl_2 (3 × 25 mL). The organic layers were pooled together, dried over anh. Na_2SO_4, and the solvent removed under vacuum to afford crude **16**, which was then purified as shown below.

4.4.2. Method B: Acidic conditions

To a solution of compounds **14** and/or **15** (1.5 mmol) in THF (10 mL), was added 4N HCl (1.2 eq.) in 1,4-dioxane; the reaction was stirred at room temperature for 0.5–2 h, until TLC showed that it was complete. The reaction was quenched with satd. aq. NH_4Cl soln. and extracted with CH_2Cl_2 (3 × 25 mL). The organic layers were pooled together, dried over anh. Na_2SO_4, and the solvent removed under vacuum to afford crude **16**, which was then purified as shown below.

4.4.3. Directly from compounds 9

To a solution of triphosgene (1.0 mmol) in toluene (1 mL) and THF (5 mL), a solution of compound **9** (1.0 mmol) in THF (5 mL) was slowly added, followed by triethylamine (2.0 mmol). The mixture was stirred at room temperature. When TLC showed that the reaction was complete (between 3 and 7 h) it was quenched with 1 M aq. HCl soln. at 0 °C and extracted with CH_2Cl_2 (3 × 25 mL). The organic layers were pooled together, dried on anh. $MgSO_4$, and the solvent removed under vacuum. The resulting crude reaction mixture consisted of crude compound **16**, which was purified and separated as indicated in each case.

4.4.4. 3-(2-Chloroethyl)-6-[difluoro(phenyl)methyl]-1,2,3,4-tetrahydro-2,4-pyrimidindione (16a)

Recrystallization from *n*-hexane:EtOH (9:1) gave a yellowish solid (96% yield): mp 167–9 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.65 (t, J = 6.7 Hz, 2H), 4.20 (t, J = 6.7 Hz, 2H), 5.80 (s, 1H), 7.44–7.50 (m, 5H), 8.81 (br s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 40.0 (t), 42.1 (t), 101.1 (t, $^3J_{CF}$ = 4.9 Hz), 117.4 (t, $^1J_{CF}$ = 247.5 Hz), 125.5 (t, $^2J_{CF}$ = 32.2 Hz), 125.9 (t, $^3J_{CF}$ = 5.7 Hz), 129.5 (d), 132.2 (d), 142.0 (t, $^2J_{CF}$ = 29.8 Hz), 151.5 (s), 162.5 (s); ^{19}F NMR (282 MHz, $CDCl_3$) δ −100.06 (s, 2F). HRMS calcd for $C_{13}H_{11}F_2ClN_2O_2$ 300.0477, found 300.0464.

4.4.5. 3-(2-Chloroethyl)-6-(4-methylphenyl)-1,2,3,4-tetrahydro-2,4-pyrimidindione (16b)

Flash chromatography [*n*-hexane:EtOAc (1:1)] on silica gel afforded **16b** as a white solid (82% yield): mp 236–8 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.73 (s, 3H), 3.70 (t, J = 6.8 Hz, 2H), 4.26 (t, J = 6.8 Hz, 1H), 5.95 (d, J = 2.1 Hz, 1H), 7.27 (d, J = 8.1 Hz, 2H), 7.50 (d, J = 8.3 Hz, 2H), 9.91 (br s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21,9 (q), 40.4 (t), 41.9 (t), 98.3 (d), 126.6 (d), 128.4 (s), 130.5 (d), 142.9 (s), 151.0 (s), 153.5 (s), 163.5 (s). HRMS calcd for $C_{13}H_{13}N_2O_2Cl$ 264.4421, found 264.4413.

4.4.6. 3-(2-Chloroethyl)-6-phenyl-1,2,3,4-tetrahydro-2,4-pyrimidindione (16c)

Flash chromatography on silica gel (EtOAc) afforded **16c** as a white solid in 85% yield. Mp 205–207 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.76 (t, J = 6.8 Hz, 2H), 4.32 (t, J = 6.8 Hz, 2H), 6.04 (d, J = 2.3, 1H), 7.54 (m, 3H), 7.68 (dd, J = 7.9, J = 1.5, 2H), 10.33 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 162.0 (s), 152.1 (s), 149.6 (s), 130.9 (d), 130.0 (s), 128.4 (d), 125.3 (d), 97.6 (d), 40.6 (t), 39.0 (t). HRMS calcd for $C_{12}H_{11}N_2O_2Cl$ 250.0509, found 250.0498.

4.4.7. 3-(2-Chloroethyl)-6-(4-methoxyphenyl)-1,2,3,4-tetrahydro-2,4-pyrimidindione (16d)

Flash chromatography on silica gel (EtOAc) afforded **16d** as a white solid in 83% yield. Mp 190–193 °C. ^{1}H NMR (300 MHz, DMSO) δ 3.77 (t, J = 6.8 Hz, 2H), 3.88 (s, 3H), 4.33 (t, J = 6.8 Hz, 2H), 5.98 (s, 1H), 7.02 (d, J = 8.8, 2H), 7.62 (d, J = 8.8, 2H), 9.90 (s, 1H); ^{13}C NMR (75.5 MHz, DMSO) δ 163.5 (s), 162.9 (s), 153.2 (s), 150.6 (s), 128.2 (d), 123.4 (s), 115.2 (d), 97.6 (d), 55.9 (q), 41.9 (t), 40.4 (t). HRMS calcd for $C_{13}H_{13}N_2O_3Cl$ 280.0615, found 280.0609.

4.4.8. 3-(2-Chloroethyl)-6-(4-methylphenyl)-1,2,3,4-tetrahydro-2,4-pyrimidindione (16e)

Flash chromatography on silica gel (EtOAc) afforded **16e** as a white solid in 87% yield. Mp 202–205 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.44 (s, 3H), 3.77 (t, J = 6.8 Hz, 2H), 4.33 (t, J = 6.8 Hz, 2H), 6.00 (d, J = 2.1, 1H), 7.32 (d, J = 8.2, 2H), 7.53 (d, J = 8.2, 2H), 9.51 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 164.5 (s), 154.5 (s), 152.1 (s), 143.9 (s), 131.4 (d), 129.4 (s), 127.6 (d), 99.3 (d), 42.9 (t), 41.4 (t), 22.9 (q). HRMS calcd for $C_{13}H_{13}N_2O_2Cl$ 264.0666, found 264.0655.

4.4.9. 6-[Difluoro(1-naphthyl)methyl]-3-(2-methoxyethyl)-1,2,3,4-tetrahydro-2,4-pyrimidindione (16f)

Recrystallization from *n*-hexane:EtOAc (9:1) gave a white solid (80% yield): mp 131–3 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.25 (s, 3H), 3.52 (t, J = 5.7 Hz, 2H), 4.04 (t, J = 5.6 Hz, 2H), 5.71 (s, 1H), 7.47–7.50 (m, 3H), 7.77–7.98 (m, 4H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 39.7 (c), 58.6 (t), 68.8 (t), 101.6 (t, $^3J_{CF}$ = 4.6 Hz), 117.8 (t, $^1J_{CF}$ = 246.6 Hz), 124.0 (d), 124.3 (d), 125.9 (t, $^3J_{CF}$ = 8.9 Hz), 126.6 (d), 126.7 (t, $^2J_{CF}$ = 29.3 Hz), 127.7 (d), 129.1 (d), 129.2 (s), 132.9 (s), 134.0 (s), 146.1 (t, $^2J_{CF}$ = 31.6 Hz), 151.7 (s), 162.5 (s); ^{19}F NMR (282 MHz, $CDCl_3$) δ −94.79 (s, 2F). HRMS calcd for $C_{18}H_{16}F_2N_2O_3$ 346.1128, found 346.1124.

4.4.10. 3-(2-Chloroethyl)-6-[difluoro(2-naphthyl)methyl]-1,2,3,4-tetrahydro-2,4-pyrimidindione (16g)

Recrystallization from *n*-hexane:EtOAc (10:1) gave a yellow solid (98% yield): mp 182–4 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.63 (t, J = 6.7 Hz, 2H), 4.17 (t, J = 6.8 Hz, 2H), 5.90 (s, 1H), 7.49–7.56 (m, 3H), 7.84–8.02 (m, 4H), 9.46 (br s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 39.6 (t), 41.7 (t), 100.6 (t, $^3J_{CF}$ = 5.2 Hz), 116.3 (t, $^1J_{CF}$ = 247.7 Hz), 121.5 (t, $^3J_{CF}$ = 5.1 Hz), 126.0 (t, $^3J_{CF}$ = 6.9 Hz), 127.4 (d), 127.9 (d), 128.2 (d), 128.7 (d), 129.0 (t, $^2J_{CF}$ = 32.0 Hz), 129.3 (d), 132.2 (s), 134.3 (s), 146.6 (t, $^2J_{CF}$ = 33.3 Hz), 151.6 (s), 162.0 (s); ^{19}F NMR (282 MHz, $CDCl_3$) δ −99.57 (s, 2F). HRMS calcd for $C_{17}H_{13}F_2ClN_2O_2$ 350.0633, found 350.0620.

4.4.11. 3-(2-Hidroxyethyl)-6-(1,1,2,2,3,3,4,4,5,5,6,6,7,7,7-pentadecafluoroheptyl)-1,2,3,4-tetrahydro-2,4-pyrimidindione (16h)

Recrystallization from *n*-hexane:EtOAc (9:1) gave a white solid (72% yield): mp 160–2 °C. ^{1}H NMR (300 MHz, CD_3OD) δ 3.64 (t, J = 6.0 Hz, 2H), 3.97 (t, J = 5.9 Hz, 2H), 6.01 (s, 1H); ^{13}C NMR (75.5 MHz, CD_3OD) δ 44.0 (t), 59.9 (t), 104.1 (d). The signals for the C_7F_{15} group were obscured because of their low intensity, 141.4 (s), 152.8 (s), 164.4 (s); ^{19}F NMR (282 MHz, CD_3OD) δ −82.0 (s, 3F), −118.36 (s, 2F), −122.80 (s, 2F), −123.39 (s, 2F), −123.40 (s, 2F),

−124.15 (s, 2F), −127.74 (s, 2F). HRMS calcd for $C_{13}H_5F_{15}N_2O_2$ (M-H_2O^+) 506.0111, found 506.0087.

*4.4.12. 3-(2-Chloroethyl)-6-[difluoro(2-naphthyl)methyl]-5-methyl-1,2,3,4-tetrahydro-2,4-pyrimidindione (**16i**)*

Recrystallization from *n*-hexane:EtOAc (9:1) gave a yellowish solid (95% yield): mp 135–7 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.79 (t, J = 2.2 Hz, 3H), 3.70 (t, J = 6.7 Hz, 2H), 4.27 (t, J = 6.6 Hz, 2H), 7.49–7.56 (m, 3H), 7.83–7.96 (m, 4H), 8.56 (br s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 10.6 (q), 39.8 (t), 42.2 (t), 109.7 (t, $^3J_{CF}$ = 2.3 Hz), 117.2 (t, $^1J_{CF}$ = 246.0 Hz), 121.3 (t, $^3J_{CF}$ = 4.0 Hz), 125.7 (t, $^3J_{CF}$ = 6.3 Hz), 127.4 (d), 127.8 (d), 128.2 (d), 128.7 (d), 129.5 (d), 130.0 (t, $^2J_{CF}$ = 30.2 Hz),132.4 (s), 134.9 (s), 140.4 (t, $^2J_{CF}$ = 29.3 Hz), 150.1 (s), 163.8 (s); ^{19}F NMR (282 MHz, $CDCl_3$) δ −92.23 (s, 2F).

*4.4.13. 3-[(1R)-2-Chloro-1-phenylethyl)-6-difluoro(1-naphthyl)methyl-1,2,3,4-tetrahydro-2,4-pyrimidindione (**16j**)*

Recrystallization from *n*-hexane:EtOAc (9:1) gave a yellowish solid (92% yield): mp 180–2 °C. $[\alpha]_D^{25}$ − 50.2 (*c* 1.00, $CHCl_3$).^{1}H NMR (300 MHz, $CDCl_3$) δ 4.00 (dd, J = 10.9 Hz, J = 5.6 Hz, 1 H), 4.61 (t, J = 10.6 Hz, 1H), 5.61 (s, 1 H), 6.13 (dd, J = 10.2 Hz, J = 5.6 Hz, 1 H), 7.18–7.51 (m, 8 H), 7.63–8.01 (m, 4 H), 9.69 (br s, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 42.2 (t), 56.9 (d), 102.1 (t, $^3J_{CF}$ = 4.9 Hz), 117.6 (t, $^1J_{CF}$ = 245.1 Hz), 124.2 (t, $^3J_{CF}$ = 3.2 Hz), 124.4 (d), 126.0 (t, $^3J_{CF}$ = 8.9 Hz), 126.7 (d), 126.8 (t, $^2J_{CF}$ = 23.6 Hz), 127.8 (d), 128.4 (d), 128.5 (d), 128.5 (d), 129.1 (d), 129.3 (s), 132.9 (d), 134.0 (d), 135.6 (s), 146.3 (t, $^2J_{CF}$ = 31.0 Hz), 151.9 (s), 162.6 (s); ^{19}F NMR (282 MHz, $CDCl_3$) δ −94.13 (d, J_{FF} = 4.1 Hz, 2F). HRMS calcd for $C_{23}H_{17}FClN_2O_2$ 426.0946, found 426.0922.

*4.4.14. 3-(2-Hidroxyethyl)-6-(2,4-difluorophenyl)-1,2,3,4-tetrahydro-2,4-pyrimidindione (**16k**)*

Recrystallization from *n*-hexane:EtOAc (9:1) gave a yellowish solid (75% yield): mp 185–6 °C. ^{1}H NMR (300 MHz, CD_3OD) δ 3.66 (t, J = 6.2 Hz, 2H), 4.00 (t, J = 6.2 Hz, 2H), 5.73 (s, 1H), 7.02–7.11 (m, 2H), 7.51–7.57 (m, 1H); ^{13}C NMR (75.5 MHz, CD_3OD) δ 43.7 (t), 60.2 (t), 102.2 (d, $^4J_{CF}$ = 2.9 Hz), 106.3 (dd, $^2J_{CF}$ = 26.1 Hz, $^2J_{CF}$ = 26.1 Hz), 113.7 (dd, $^2J_{CF}$ = 22.4 Hz, $^4J_{CF}$ = 4.0 Hz), 132.9 (d, $^3J_{CF}$ = 13.2 Hz), 148.5 (s), 153.8 (s), 166.2 (s), the rest of the signals were obscured because of their low intensity; ^{19}F NMR (282 MHz, CD_3OD) δ −107.53 (m, 1F), −111.43 (m, 1F).

*4.4.15. 3-(2-Chloroethyl)-6-(2,4-difluorophenyl)-1,2,3,4-tetrahydro-2,4-pyrimidindione (**16l**)*

Recrystallization from *n*-hexane:EtOAc (9:1) gave a yellowish solid (91% yield): mp 169–171 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.67 (t, J = 6.7 Hz, 2H), 4.21 (t, J = 6.7 Hz, 2H), 5.95 (s, 1H), 6.90–7.05 (m, 2H), 7.50–7.56 (m, 1H), 10.07 (br s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 39.8 (t), 41.5 (t), 101.6 (d, $^4J_{CF}$ = 5.1 Hz), 105.4 (dd, $^2J_{CF}$ = 25.6 Hz), 112.6 (d, $^2J_{CF}$ = 21.8 Hz, $^4J_{CF}$ = 4.0 Hz), 115.6 (dd, $^2J_{CF}$ = 12.0 Hz, $^4J_{CF}$ = 4.0 Hz), 130.4 (dd, $^3J_{CF}$ = 10.3 Hz, $^5J_{CF}$ = 3.4 Hz), 145.1 (s), 152.7 (s), 160.2 (dd, $^1J_{CF}$ = 256.4, Hz, $^3J_{CF}$ = 12.6 Hz), 162.6 (s), 164.7 (dd, $^1J_{CF}$ = 256.4, Hz, $^3J_{CF}$ = 12.1 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −108.64 (m, 1F), −103.38 (m, 1F). HRMS calcd for $C_{12}H_9F_2ClN_2O_2$ 286.0321, found 286.0320.

*4.4.16. 3-(2-Methoxyethyl)-6-(4-trifluoromethylphenyl)-1,2,3,4-tetrahydro-2,4-pyrimidindione (**16m**)*

Recrystallization from *n*-hexane:EtOAc (9:1) gave a white solid (78% yield): mp 248–9 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.24 (s, 3H), 3.58 (t, J = 5.6 Hz, 2H), 4.13 (t, J = 5.6 Hz, 2H), 6.00 (s, 1H), 7.70 (d, J = 8.5 Hz, 2H), 7.76 (d, J = 8.3 Hz, 2H), 10.65 (br s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 39.7 (t), 58.6 (c), 69.0 (t), 100.0 (d), 123.4 (q, $^1J_{CF}$ = 273.0 Hz), 126.2 (q, $^3J_{CF}$ = 3.8 Hz), 126.9 (d), 133.3 (q, $^2J_{CF}$ = 32.9 Hz), 134.6 (s), 148.9 (s), 153.3 (s), 162.9 (s); ^{19}F NMR (282 MHz, $CDCl_3$) δ −63.47 (s, 3F). HRMS calcd for $C_{14}H_{13}F_3N_2O_3$ 314.0878, found 314.0867.

*4.4.17. 3-(2-Hidroxyethyl)-6-(4-trifluoromethylphenyl)-1,2,3,4-tetrahydro-2,4-pyrimidindione (**16n**)*

Recrystallization from *n*-hexane:EtOAc (9:1) gave a white solid (72% yield): mp 207–9 °C. ^{1}H NMR (300 MHz, CD_3OD) δ 3.66 (t, J = 6.1 Hz, 2H), 4.01 (t, J = 6.1 Hz, 2H), 5.90 (s, 1H), 7.72 (d, J = 8.6 Hz, 2H), 7.77 (d, J = 8.6 Hz, 2H); ^{13}C NMR (75.5 MHz, CD_3OD) δ 43.7 (t), 60.2 (t), 100.5 (d), 125.6 (q, $^1J_{CF}$ = 274.1 Hz), 127.5 (q, $^3J_{CF}$ = 3.8 Hz), 129.2 (d), 134.2 (q, $^2J_{CF}$ = 32.6 Hz), 137.4 (s), 152.5 (s), 154.0 (s), 166.2 (s); ^{19}F NMR (282 MHz, CD_3OD) δ −64.94 (s, 3F). CI HRMS calcd for $C_{13}H_{12}F_3N_2O_3$ (M^+ + H) 301.0800, found 301.0834.

*4.4.18. 3-(2-Ethoxyethyl)-6-(4-fluorophenyl)-1,2,3,4-tetrahydro-2,4-pyrimidindione (**16o**)*

Recrystallization from *n*-hexane:EtOAc (9:1) gave a white solid (78% yield): mp 168–170 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.06 (t, J = 7.0 Hz, 3H), 3.44 (c, J = 7.0 Hz, 2H), 3.61 (t, J = 5.9 Hz, 2H), 4.11 (t, J = 5.8 Hz, 2H), 5.91 (s, 1H), 7.09–7.19 (m, 2H), 7.60–7.63 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 15.0 (q), 39.6 (t), 66.1 (t), 66.7 (t), 98.6 (d), 116.4 (d, $^2J_{CF}$ = 22.4 Hz), 127.4 (d, $^4J_{CF}$ = 2.9 Hz), 128.6 (d, $^3J_{CF}$ = 8.6 Hz), 149.4 (s), 153.4 (s), 163.2 (s), 164.6 (d, $^1J_{CF}$ = 253.5 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −107.96 (m, 1F). HRMS calcd for $C_{14}H_{15}FN_2O_3$ 278.1066, found 278.1057.

*4.4.19. 3-[(1R)-2-Chloro-1-phenylethyl]-6-(4-fluorophenyl)-1,2,3,4-tetrahydro-2,4-pyrimidindione (**16p**)*

Recrystallization from *n*-hexane:EtOAc (9:1) gave a yellowish solid (92% yield): mp 39–41 °C. $[\alpha]_D^{25}$ + 25.26 (*c* 0.95, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.11 (dd, J = 10.9 Hz, J = 5.6 Hz, 1H), 4.69 (t, J = 10.6 Hz, 1H), 5.91 (s, 1H), 6.23 (m, 1H), 7.05–7.31 (m, 7H), 7.57–7.60 (m, 2H), 10.86 (br s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 42.8 (t), 56.8 (d), 99.0 (d), 116.4 (d, $^2J_{CF}$ = 21.8 Hz), 127.2 (d, $^4J_{CF}$ = 2.9 Hz), 127.9 (d), 128.3 (d), 128.4 (d), 128.7 (d, $^3J_{CF}$ = 8.6 Hz), 136.3 (s), 149.8 (s), 153.5 (s), 163.3 (s), 164.6 (d, $^1J_{CF}$ = 253.5 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −107.42 (m, 1F). HRMS calcd for $C_{18}H_{14}FClN_2O_2$ 344.0727, found 344.0722.

*4.4.20. 2-[6-(4-Methylphenyl)-1,2,3,4-tetrahydro-3-pyrimidinyl]ethyl acetate (**16q**)*

Recrystallization from *n*-hexane:EtOAc (7:1) gave a white solid (75% yield): mp 171–3 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.98 (s, 3H), 2.42 (s, 3H), 4.22 (t, J = 4.6 Hz, 2H), 4.38 (t, J = 4.6 Hz, 2H), 6.13 (s, 1H), 7.25 (d, J = 8.1 Hz, 2H), 7.58 (d, J = 8.1 Hz, 2H), 10.21 (br s, 1H); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 20.8 (q), 21.5 (q), 39.4 (t), 61.3 (t), 98.0 (d), 126.1 (d), 126.1 (s), 130.1 (d), 142.5 (s), 150.4 (s), 153.2 (s), 163.4 (s), 171.0 (s). CI HRMS calcd for $C_{15}H_{17}N_2O_4$ (M^+ + 1) 289.1189, found 289.1190.

*4.4.21. 3-(2-Hidroxyethyl)-6-(4-methylphenyl)-1,2,3,4-tetrahydro-2,4-pyrimidindione (**16r**)*

The compound was purified by flash chromatography [EtOAc/MeOH (5:1)] on silica gel, which afforded **9a** as a white solid in 79% yield (method A). Mp 212–214 °C. ^{1}H NMR (300 MHz, DMSO) δ 2.40 (s, 3H), 3.56 (c, J = 6.2 Hz, 2H), 3.93 (t, J = 6.6 Hz, 2H), 4.82 (t, OH), 5.96 (s, 1H), 7.34 (d, J = 8.1, 2H), 7.68 (d, J = 8.3, 2H) 11.34 (s, 1H); ^{13}C NMR (75.5 MHz, DMSO) δ 163.9 (s), 152.8 (s), 151.6 (s), 142.1 (s), 130.4 (d), 129.4 (s), 127.7 (d), 97.8 (d), 58.5 (t), 42.5 (t), 21.8 (q). HRMS calcd for $C_{13}H_{14}N_2O_3$ 246.1004, found 246.1012.

*4.4.22. 3-(2-Methoxyethyl)-6-(4-methylphenyl)-1,2,3,4-tetrahydro-2,4-pyrimidindione (**16s**)*

The compound was purified by flash chromatography [EtOAc/MeOH (5:1)] on silica gel and afforded **9a** as a white solid in 70%

yield from **14k** + **15k** in basic medium (method A, see Scheme 6), 68% yield from **14k** + **15k** in acidic medium (method B, see Scheme 6), and 65% from **16b**. The preparation of **16s** from **16b** was performed as follows: to a solution of **16b** (0.4 mmol) in THF (3 mL), a solution of NaOH (2.8 mmol) in 3 mL of methanol diluted in THF (1 mL) was added and then the reaction mixture was refluxed for 5–7 h, until TLC showed completion. The reaction was quenched with satd. aq. NH_4Cl soln. and extracted with CH_2Cl_2 (3×25 mL). The organic layers were pooled together, dried over anh. Na_2SO_4, and the solvent removed under vacuum to afford crude **9**, which was then purified as indicated above. Mp 204–206 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 2.42 (s, 3H), 3.35 (s, 3H), 3.66 (t, J = 5.6 Hz, 2H), 4.20 (t, J = 5.6 Hz, 2H), 5.99 (s, 1H), 7.29 (d, J = 8.1, 2H), 7.55 (d, J = 8.1, 2H) 9.83 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 163.5 (s), 153.0 (s), 150.1 (s), 142.2 (s), 130.0 (d), 128.4 (s), 126.1 (d), 98.2 (d), 69.2 (t), 58.6 (q), 39.5 (t), 21.4 (q). HRMS calcd for $C_{14}H_{16}N_2O_3$ 260.1161, found 260.1174.

4.4.23. 3-(2-Fluoroethyl)-6-(4-methylphenyl)-1,2,3,4-tetrahydro-2,4-pyrimidindione (16t)

The compound was purified by flash chromatography [EtOAc/MeOH (4:1)] on silica gel and gave **9d** as a white solid in 69% yield from **14k** + **15k** in basic medium (method A, see Scheme 6), and 67% from **16b**. The preparation of **16s** from **16b** was performed as follows: to a solution of **16b** (0.56 mmol) in THF (2 mL), a solution of 1 M TBAF in THF (1.7 mmol, 3 equiv.) was added and then the reaction mixture was refluxed for 3–4 h, until TLC showed completion. The reaction was quenched with satd. aq. NH_4Cl soln. and extracted with CH_2Cl_2 (3×25 mL). The organic layers were pooled together, dried over anh. Na_2SO_4, and the solvent removed under vacuum to afford crude **9**, which was then purified as indicated above. Mp 160–163 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 2.43 (s, 3H), 4.33 (dt, J_1 = 23.3 Hz, J_2 = 5.2 Hz, 2H), 4.69 (dt, J_1 = 47.1 Hz, J_2 = 5.2 Hz, 2H), 6.01 (s, 1H), 7.30 (d, J = 8.1 Hz, 2H), 7.54 (d, J = 8.3 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 163.9 (s), 153.4 (s), 151.2 (s), 142.8 (s), 130.5 (d), 128.8 (s), 126.5 (d), 98.3 (d), 81.1 (t, $J_{C\text{-}F}$ = 170.2 Hz), 40.8 (t, $J_{C\text{-}F}$ = 22.4 Hz), 21.9 (q). HRMS calcd for $C_{13}H_{13}N_2O_2F$ 248.0961, found 248.0958.

4.5. Preparation of compound 17

4.5.1. tert-Butyl 4-{2-[6-(2,4-Difluorophenyl)-2,4-dioxo-1,2,3,4-tetrahydro-2,4-pyrimidinyl] ethyl}-1-piperazinecarboxylate (17)

To a solution of *tert*-butyl 1-piperazinecarboxylate (1.0 mmol) in 2.5 mL of a 10% aq. soln. of K_2CO_3 and 2.5 mL of 1,4-dioxane at 100 °C, a solution of **14g** + **15g** (1.0 mmol) in 1,4-dioxane (4 mL) was slowly added. The reaction mixture was stirred at 100 °C for 24 h, cooled and the volatiles were removed under vacuum. The residue was taken up in 25 mL ethyl acetate. The suspension was dried over anh. Na_2SO_4, filtered, and the solvent removed under vacuum to give crude product **17**. Flash chromatography [*n*-hexane:EtOAc (1:1)] on silica gel gave pure **17** as a yellow oil (80% yield). ^1H NMR (300 MHz, $CDCl_3$) δ 1.38 (s, 9H), 2.38 (t, J = 4.6 Hz, 4H), 2.54 (t, J = 6.8 Hz, 2H), 3.30 (t, J = 4.6 Hz, 4H), 3.98 (t, J = 6.8 Hz, 2H), 5.88 (s, 1H), 6.89–6.97 (m, 2H), 7.46–7.52 (m, 1H), 9.58 (br s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 28.3 (c), 37.6 (t), 52.9 (t), 52.9 (t), 55.1 (t), 79.5 (s), 101.5 (d, $^4J_{CF}$ = 4.0 Hz), 105.4 (dd, $^2J_{CF}$ = 25.9 Hz, $^2J_{CF}$ = 25.9 Hz), 112.7 (dd, $^2J_{CF}$ = 21.8 Hz, $^4J_{CF}$ = 4.0 Hz), 115.9 (dd, $^2J_{CF}$ = 12.1 Hz, $^4J_{CF}$ = 4.0 Hz), 130.5 (dd, $^3J_{CF}$ = 10.2 Hz), 144.6 (s), 152.3 (s), 154.7 (s), 160.2 (dd, $^1J_{CF}$ = 257.0, Hz, $^3J_{CF}$ = 12.6 Hz), 162.9 (s), 164.6 (dd, $^1J_{CF}$ = 260.9, Hz, $^3J_{CF}$ = 12.0 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −103.6 (d, J = 10.3 Hz, 1F), −108.9 (d, J = 10.3 Hz, 1F). HRMS calcd for $C_{21}H_{26}F_2N_4O_4$ 436.1922, found 436.1909.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jfluchem.2008.04.004.

References

[1] C.K. Chu, D.C. Baker (Eds.), Nucleosides and Nucleotides as Antitumor and Antiviral Agents, Plenum Press, New York, 1993.
[2] S. Ozaki, Med. Res. Rev. 16 (1996) 51–86.
[3] (a) I. Ojima, J.R. McCarthy, J.T. Welch, Biomedical Frontiers of Fluorine Chemistry, ACS. Symp. Series, vol. 639, American Chemical Society, Washington, DC, 1996; (b) R. Filler, Y. Kobayashi, Biomedicinal Aspects of Fluorine Chemistry, Elsevier Biomedical Press, New York and Kodansha Ltd., Tokyo, 1982; (c) K.W. Pankiewicz, Carbohydr. Res. 327 (2000) 87–105.
[4] As examples, see:; (a) Y. Tohyama, Y. Sanemitsu, Eur. Pat. Appl. EP 1,122,244 A1 (2001).; (b) G. Theodoridis, S.D. Crawford, (FMC Corporation, USA) US 6,277,847 B1 (2001).; (c) M.-W. Drewes, R. Andree, M. Dollinger, (Bayer A.-G., Germany) Ger. Offen. DE 19,632,005 A1 (1998).; (d) T. Koiso, S. Ono, H. Kondo, T. Asada, (Dainippon Ink and Chemicals, Inc., Japan) Jpn. Kokai Tokkyo Koho JP 09,241,245 (1997).; (e) V. Kameswaran, (American Cyanamid Co. USA) US 6,191,275 B1 (2001). (f) K. Yagi, K. Akimoto, N. Mimori, T. Miyake, M. Kudo, K. Arai, S. Ishii, Pest Manag. Sci. 56 (2000) 65–73.
[5] S. Fustero, J. Piera, J.F. Sanz-Cervera, S. Catalán, C. Ramírez de Arellano, Org. Lett. 6 (2004) 1417–1420.
[6] S. Fustero, S. Catalán, S. Flores, D. Jiménez, C. del Pozo, J.L. Aceña, J.F. Sanz-Cervera, S. Mérida, QSAR Comb. Sci. 25 (2006) 753–760.
[7] S. Fustero, S. Catalán, J. Piera, J.F. Sanz-Cervera, B. Fernández, J.L. Aceña, J. Org. Chem. 71 (2006) 4010–4013.
[8] Preliminary results were published as a communication; see: S. Fustero, E. Salavert, J.F. Sanz-Cervera, J. Piera, A. Asensio, Chem. Commun. (2003) 844–845.
[9] K. Kamata, I. Agata, A.I. Meyers, J. Org. Chem. 63 (1998) 3113–3116.
[10] C.C. Kotoris, M.-J. Chen, S. Taylor, J. Org. Chem. 63 (1998) 8052–8057.
[11] W.J. Middleton, E.M. Bingham, J. Org. Chem. 45 (1980) 2883–2887.
[12] We obtained improved chemical yields (91% vs. 61%) when 2.2 equiv. of Deoxofluor® (dimethoxyethylaminotrifluorosulfurane) were used at room temperature for 24 h instead of DAST. See: G.S. Lal, G.P. Pez, R.J. Pesaresi, F.M. Prozonic, H. Cheng, J. Org. Chem. 64 (1999) 7048–7054.
[13] S. Fustero, D. Díaz, A. Asensio, A. Navarro, J.S. Kong, E. Aguilar, Tetrahedron 55 (1999) 2695–2712.
[14] For a review see: L. Cotarca, P. Delogu, A. Nardelli, V. Sunji, Synthesis, (1996) 553–576.
[15] J. Barluenga, J.F. López-Ortiz, V.J. Gotor, Chem. Soc., Perkin Trans. I (1983) 2273–2276.
[16] A similar behavior has been observed in related systems. See for example: G.R. Brown, J. Chem. Soc. Perkin Trans, 1 (1973) 2022–2024.
[17] R. Lis, T.K. Morgan, A.J. Marisca, R.P. Gómez, J.M. Lind, D.D. Davey, G.B. Philips, M.E. Sullivan, J. Med. Chem. 33 (1990) 2883–2891.
[18] C. Agami, L. Dechoux, L. Hamon, M. Melaimi, J. Org. Chem. 65 (2000) 6666–6669, and references cited therein.
[19] J.L. Herndon, A. Ismaiel, P. Ingher, M. Teitler, R.A. Glennon, J. Med. Chem. 35 (1992) 4903–4910.
[20] It is noteworthy that compounds 16 in which Nu = Cl revert to a mixture 14 + 15 in proportions similar to those observed when they were obtained from 9 upon treatment with a base (i.e. aq. K2CO3/dioxane).
[21] S. Noble, H. Langtry, H.M. Lamb, Drugs 55 (1998) 277–302.