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Article

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Discovery of a Novel Series of Imidazo[1,2-*a*]pyrimidine Derivatives as Potent and Orally Bioavailable Lipoprotein-Associated Phospholipase A_2 Inhibitors

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ABSTRACT

Inhibition of lipoprotein-associated phospholipase A_2 (Lp-PLA_2) has been suggested to be a promising therapeutic strategy for several inflammation-associated diseases, including atherosclerosis, Alzheimer's disease, and diabetic macular edema. Herein, we report the discovery of a novel series of Lp-PLA_2 inhibitors constructed on an imidazo[1,2-*a*]pyrimidine scaffold through a conformational restriction strategy. Structure-activity relationship (SAR) analysis resulted in identification of several compounds with high potency *in vitro* and good metabolic stability in liver S9 fractions. Compounds **7c** and **14b** selected for further exploration *in vivo* demonstrated excellent pharmacokinetic profiles and exhibited significant inhibitory efficacy in SD rats upon oral dosing.

INTRODUCTION

Lipoprotein-associated phospholipase A_2 (Lp-PLA_2) previously known as platelet-activating factor acetylhydrolase (PAF-AH), is a member of the phospholipase A_2 superfamily.[1] Lp-PLA_2 is produced mainly by macrophages, monocytes, T-lymphocytes, and mast cells.[2–4] In human plasma, Lp-PLA_2 circulates mainly with low-density lipoprotein[5] and can hydrolyze oxidized modified phosphatidylcholine to generate oxidized free fatty acids and lysophosphatidylcholine (lyso-PC),[6] and both products have been shown to induce inflammatory responses.[7, 8] Lyso-PC, for example, has been found to be involved in leukocyte activation, induction of apoptosis, and mediation of endothelial dysfunction.[9, 10] Consistent with these results, Lp-PLA_2 has been considered to be a promising therapeutic target for atherosclerosis.[11–13] Very recently, it was reported that inhibition of Lp-PLA_2 might protect against the damage to the blood-brain barrier caused by hyperglycemia and hypercholesterolemia, suggesting that inhibition of Lp-PLA_2 could be used for treating neurodegenerative diseases.[14] In addition, inhibition of Lp-PLA_2 was recently reported to have beneficial effects against diabetic macular edema (DME),[15, 16] a severe complication whose pathogenesis is directly related to the breakdown of the blood-retinal barrier.[17, 18]

To date, a number of Lp-PLA_2 inhibitors have been reported, including azetidinones,[19] oximes,[20, 21] amides of xanthurenic acid,[22, 23] carbamates,[24] and pyrimidones.[25–39] Among them, several compounds have progressed into clinical trials (Figure 1), and darapladib has been the most rapidly developed.[40] Although darapladib

was ineffective in two phase-III trials focusing on coronary heart diseases,[41, 42] another phase-II trial revealed that oral administration of darapladib for 3 months modestly reduced macular edema and enhanced vision acuity in center-involved DME patients.[16] Two other compounds, rilapladib (once also in phase-II trial for atherosclerosis[43]) and GSK2647544 (structure not disclosed), which are in phase-II and phase-I trials, respectively, are in development for the treatment of Alzheimer's disease.

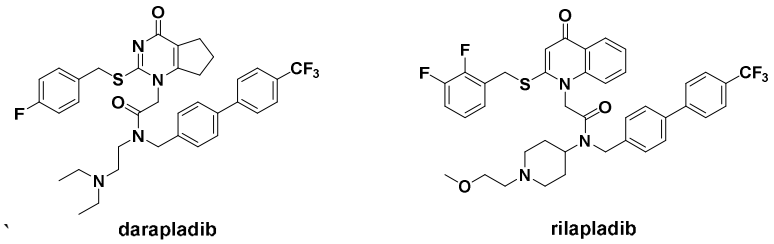


Figure 1. Chemical structures of Lp-PLA_2 inhibitors in clinical trials.

Previously, our research team reported a series of darapladib analogs with high potency *in vitro*.[44, 45] However, high oral efficacy through further structural modifications was hard to obtain because of low plasma exposure. Likewise, darapladib as the initial compound also shows relatively low oral plasma exposure because of low oral bioavailability.[31, 46] We postulated that the limited oral plasma exposure of darapladib and its analogs should be mainly due to their large molecular sizes and high lipophilicity (darapladib: molecular weight (MW), 666.78; cLogP, 8.33).[47] Therefore, we sought to develop a new class of Lp-PLA_2 inhibitors with lower MW and cLogP to obtain better pharmacokinetic properties, so that sufficient plasma concentrations of these compounds could be achieved to effectively inhibit Lp-PLA_2 enzyme in plasma after oral administration.

In our ongoing exploration of novel molecular scaffolds of Lp-PLA_2 inhibitors, we recently undertook rational drug design on compound **1** (Figure 2A), which was newly developed by GlaxoSmithKline (GSK) scientists, and reported to have high potency *in vitro*.[32] Moreover, compound **1** provided a smaller molecular size as well as lower lipophilicity (MW, 502.88; cLogP, 4.48) compared with darapladib, and our preliminary pharmacokinetic experiments revealed that compound **1** demonstrated greater plasma exposure than darapladib when dosed orally to SD rats (Table 1). Nevertheless, besides these virtues, compound **1** showed limited elimination half-life *in vivo* ($t_{1/2}$ = 2.08 h). Through further evaluation of metabolic stability in rat liver S9 fractions, we confirmed that the high clearance of compound **1** in vivo was mainly due to its poor metabolic stability (CL_{int} = 74.4 mL/min/kg). Structural restriction has been reported to contribute to greater metabolic stability,[48–51] and bicyclic structures, such as imidazo[1,2-*a*]pyrimidine, have been commonly used as a versatile building block in medicinal chemistry,[52–54] so we were tempted to use a structural restriction strategy to replace the pyrimidone group in compound **1** with a new imidazo[1,2-*a*]pyrimidine scaffold (Figure 2A). Based on this design, the first-prepared compound (**7a**) demonstrated better metabolic stability in human and rat liver S9 fractions as compared with compound **1,** and displayed good potency against recombinant human Lp-PLA_2 (rhLp-PLA_2). Encouraged by these results, we undertook systematic structure-activity relationship (SAR) explorations of imidazo[1,2-*a*]pyrimidine derivatives.

Herein, we describe the discovery of imidazo[1,2-*a*]pyrimidine derivatives as a novel

class of Lp-PLA$_2$ inhibitors. These compounds are potent *in vitro*, metabolically stable, and exhibit excellent pharmacokinetic profiles and high inhibitory efficacy *in vivo*. The synthesis and pharmacological evaluation are reported.

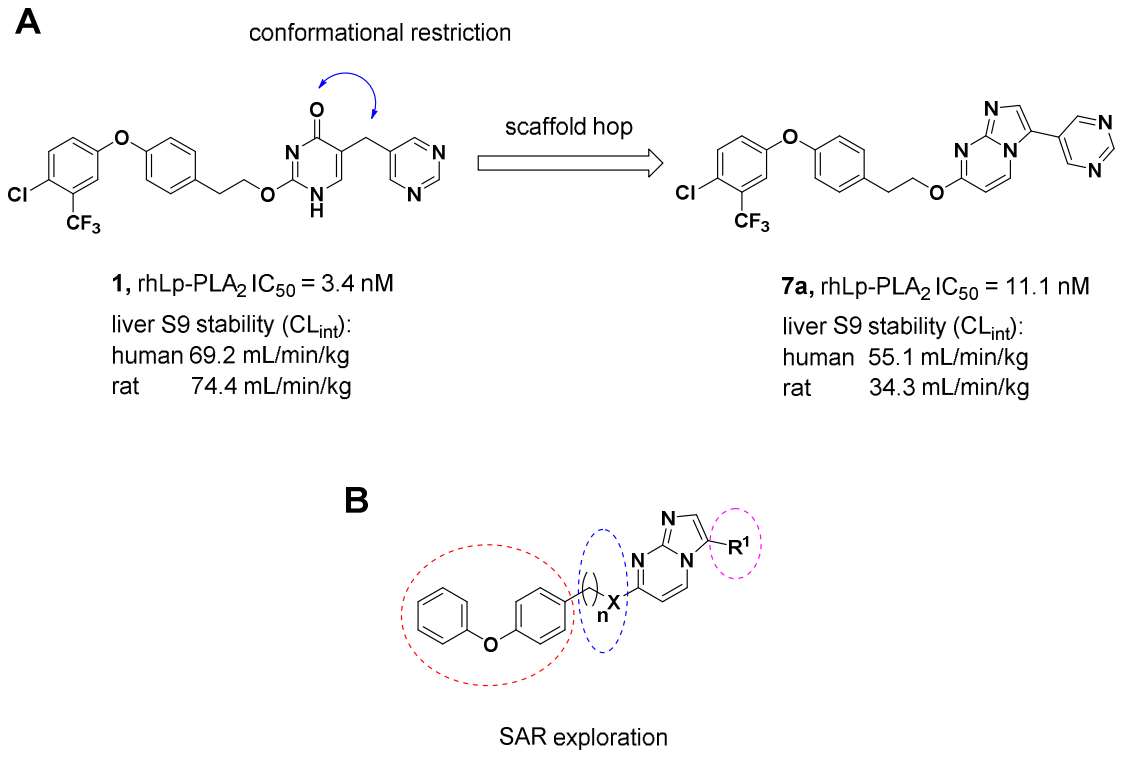


Figure 2. (A) Design of imidazo[1,2-*a*]pyrimidine derivatives as Lp-PLA$_2$ inhibitors. (B) Systematic SAR explorations of imidazo[1,2-*a*]pyrimidine derivatives.

Table 1. Pharmacokinetic parameters of compound 1 and darapladib after oral administration to SD rats[a]

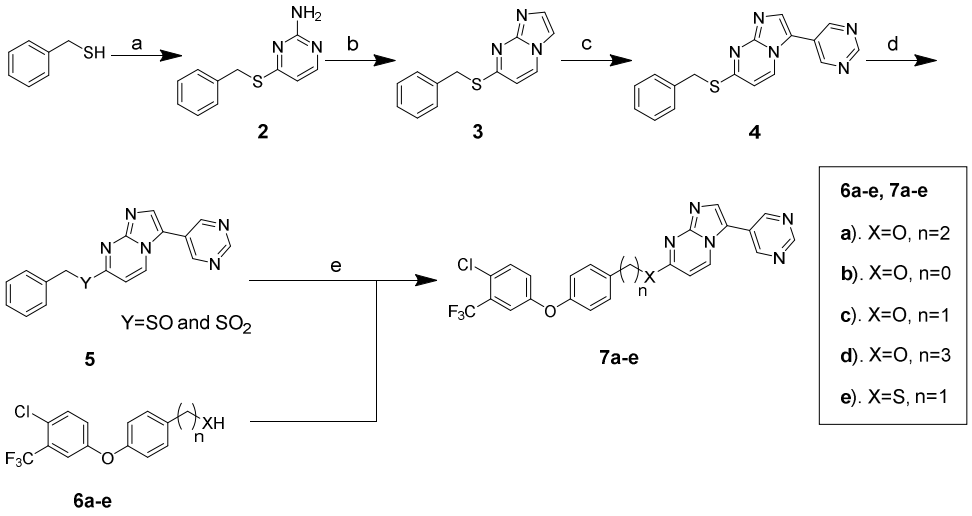
compd	$AUC_{0-\infty}$ (μg·h/mL)	$t_{1/2}$ (h)	C_{max} (μg/mL)
1[b]	3.38	2.08	0.78
darapladib[c]	2.11	11.50	0.15

[a]n = 5 animals/group; [b]administered at 25 mg/kg; [c]administered at 50 mg/kg. Data are the mean.

CHEMISTRY

The synthesis of imidazo[1,2-*a*]pyrimidine derivatives **7a-e** is summarized in Scheme 1. A nucleophilic substitution reaction between benzyl mercaptan and 4-chloropyrimidin-2-amine in the presence of sodium hydride yielded intermediate **2**, and subsequent cyclization of **2** provided intermediate **3**.[55] Direct arylation of **3** with 5-bromopyrimidine using palladium(II) acetate as a catalyst gave intermediate **4**,[56] which was oxidized using *m*-CPBA to provide **5** as a mixture of the sulphone and sulfoxide. A nucleophilic substitution reaction between **5** and hydroxyl or thiol derivatives **6a-e** (**6a-e**: see Supporting Information for synthesis details) using sodium hydride as a base afforded compounds **7a-e**.

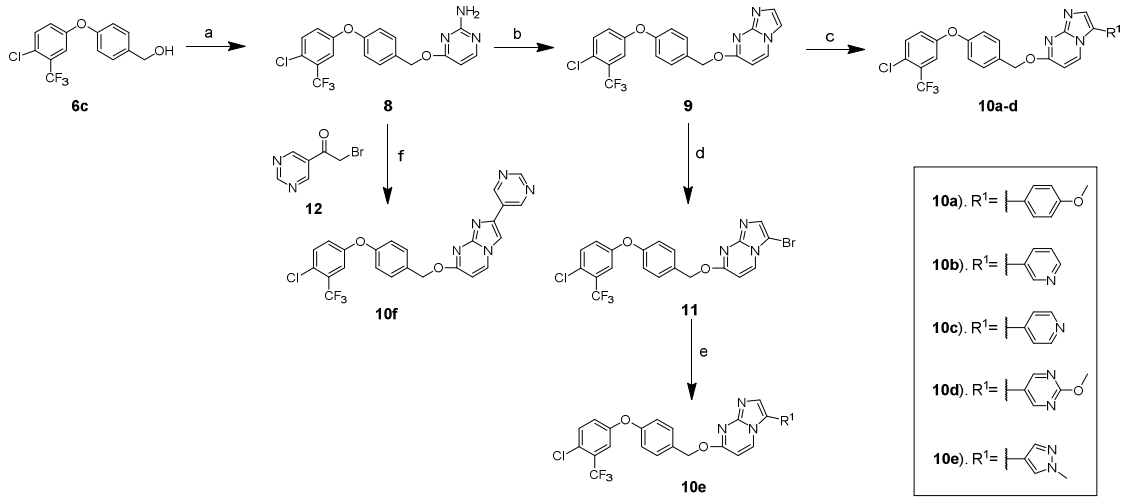
Scheme 1. **Synthesis of analogs 7a-e**[a]



[a]Reagents and conditions: (a) 4-chloropyrimidin-2-amine, sodium hydride, THF, rt; (b) 2-bromoacetaldehyde diethyl acetal, 48% HBr aqueous solution, 80 °C, 6 h, then rt, $NaHCO_3$, **2**, 70 °C, 2 h; (c) 5-bromopyrimidine, $Pd(OAc)_2$, KOAc, DMA, 140 °C; (d) *m*-CPBA, DCM, rt; (e) sodium hydride, THF, rt.

Compounds **10a-d** were synthesized starting from benzyl alcohol **6c** and 4-chloropyrimidin-2-amine using a method similar to that described for intermediate **4** (Scheme 2). Compound **10e** was obtained by an alternative route: bromination of **9** gave intermediate **11**, and subsequent Suzuki coupling of **11** and (1-methyl-1H-pyrazol-4-yl)boronic acid using bis(triphenylphosphine)palladium(II) dichloride as a catalyst gave the desired compound **10e**. The synthesis of **10f** was commenced by a cyclization reaction between **8** and **12** in ethanol.

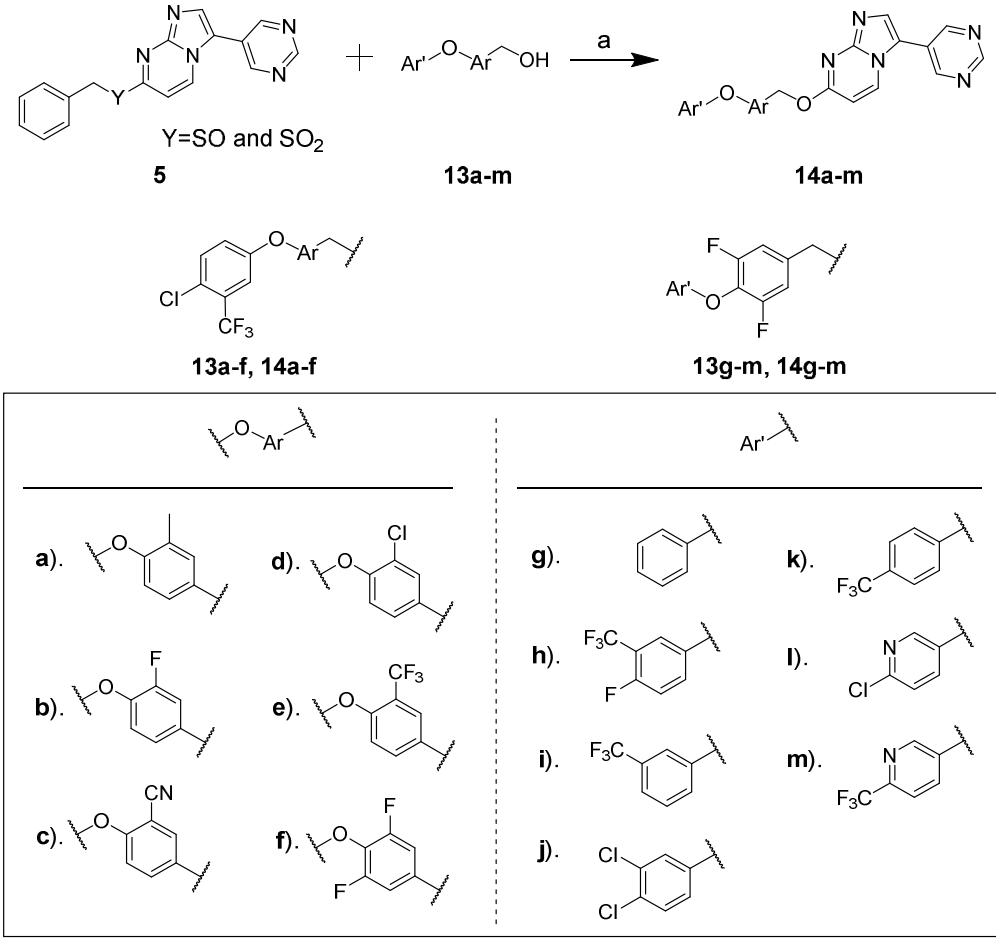
Scheme 2. **Synthesis of compounds 10a-f**[a]



[a]Reagents and conditions: (a) 4-chloropyrimidin-2-amine, sodium hydride, THF, rt; (b) 2-bromoacetaldehyde diethyl acetal, 48% HBr aqueous solution, 80 °C, 6 h, then rt, $NaHCO_3$, **8**, 70 °C, 2 h; (c) R^1Br, $Pd(OAc)_2$, KOAc, DMA, 140 °C; (d) NBS, THF, rt; (e) (1-methyl-1H-pyrazol-4-yl)boronic acid, $PdCl_2(PPh_3)_2$, Na_2CO_3, dioxane, H_2O, microwave, 150 °C, 30 min; (f) ethanol, H_2O, reflux.

As shown in Scheme 3, the biaryl analogs **14a**-**m** were synthesized in a manner similar to that described for compounds **7a**-**e** starting from **5** and the corresponding benzyl alcohol **13a**-**m** (**13a**-**m**: see Supporting Information for synthesis details).

Scheme 3. Synthesis of biaryl analogs 14a-m[a]



[a]Reagents and conditions: (a) sodium hydride, THF, rt.

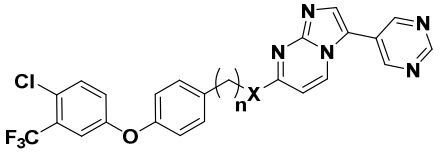
RESULTS AND DISCUSSION

SAR *in vitro*. Compounds were first evaluated for their inhibitory activity against rhLp-PLA_2 at two concentrations (100 nM and 10 nM) *in vitro*, and rhLp-PLA_2 activity was measured using 2-thio-PAF as the substrate. IC_{50} values against rhLp-PLA_2 for those compounds with an acceptable inhibitory activity (>30% at 10 nM) were tested to ascertain their inhibitory potency precisely.

SAR analyses mainly focused on the influences of three regions on rhLp-PLA_2 inhibitory activity (Figure 2B): the linker between the imidazo[1,2-*a*]pyrimidine moiety and diphenyl ether moiety; substituents at the 3-position of imidazo[1,2-*a*]pyrimidine (R^1); diphenyl ether moiety.

Effects of the linker were first explored (Table 2). Compound **7b** with the oxygen atom directly connected to the diphenyl ether moiety showed a complete loss of potency, and elongation of the linker to three carbon atoms (**7d**) was also not tolerated. Compound **7c** with a single methylene spacer demonstrated comparable potency with the initial hit compound **7a**. Replacement of the oxygen atom with a sulfur atom (**7e**) reduced potency markedly. These results suggested that rhLp-PLA_2 inhibitory activity was affected considerably by the length of the linker and linking atom.

Table 2. SAR of the linker



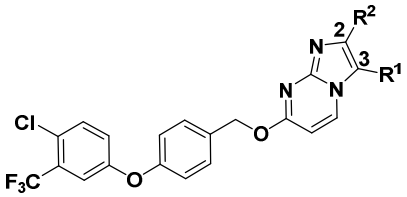
compd	X	n	% inhibition against rhLp-PLA$_2$		IC_{50} （nM）
			100 nM	10 nM	
7a	O	2	87	55	11.1
7b	O	0	0		
7c	O	1	89	55	10.6
7d	O	3	19		
7e	S	1	28		
1			98	78	3.4
darapladib			92	88	0.7[a]

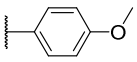
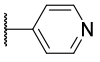
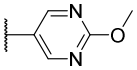
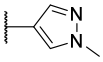
[a]Reported IC_{50} = 0.25 nM.

On the basis of the high inhibitory activity, **7c** was selected for further optimization. Our next objective was to investigate the influences of R^1 on potency, and representative compounds are shown in Table 3. Among the modifications, we found that removal of the pyrimidine ring resulted in a loss of potency (**9**). Replacement of the pyrimidine ring with a *p*-methoxy-phenyl ring was not well tolerated (**10a**), whereas the pyridine derivatives **10b** and **10c** restored potency to a certain degree. These SARs suggested that an aromatic

ring and hydrogen-bond acceptor(s) were required at this moiety in the molecule. This hypothesis was further confirmed by the 2-methoxy-pyrimidine compound **10d** and 1-methyl-pyrazole compound **10e**: both compounds were more potent than the *p*-methoxy-phenyl compound **10a.** Loss of potency after relocation of the pyrimidine ring to the 2-position (**10f**) suggested that substitution at the 3-position was favored for potency.

Table 3. **Influences of R^1 on the inhibitory activity of rhLp-PLA_2**

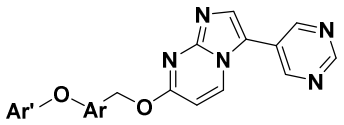


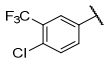
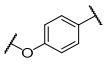
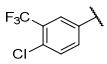
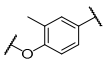
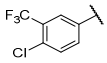
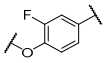
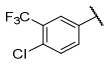
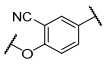
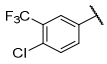
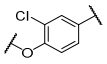
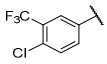
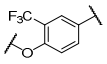
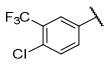
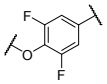
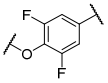
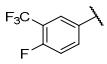
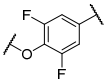
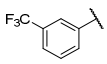
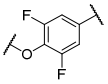
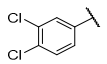
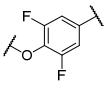
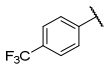
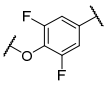
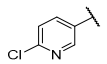
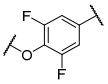
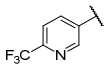
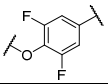
compd	R^1	R^2	% inhibition against rhLp-PLA_2		IC_{50} （nM）
			100 nM	10 nM	
7c		H	89	55	10.6
9	H	H	26		
10a		H	58	25	
10b		H	76	34	19.3
10c		H	78	32	16.0
10d		H	79	44	13.4
10e		H	78	32	16.9
10f	H		12		

Finally, we explored the effects of the diphenyl ether moiety. As shown in Table 4, we first investigated the influences of the central benzene ring. Introduction of a methyl substituent *ortho* to the diphenyl ether linkage resulted in a decrease in potency (**14a**). In contrast, introduction of a small, electron-withdrawing fluorine group (**14b**) or cyano group (**14c**) increased the activity as compared to **7c**. Encouraged by the results of **14b** and **14c**, we then turned our attention to the introduction of electron-withdrawing groups in the central benzene ring. However, compounds with a bulkier substituent such as a chloro group (**14d**) or trifluoromethyl group (**14e**) were less potent. In addition, further incorporation of a fluorine group in the fluorine-substituted derivative **14b** maintained inhibitory potency (**14f**). However, replacement of the central benzene ring with a pyridine ring or five-membered heteroaromatic ring provided a lower cLogP value was not tolerated (data not shown). These SARs led us to speculate that slight electron deficiency and hydrophobicity of the central aromatic ring was beneficial for the binding to the Lp-PLA_2 enzyme. Next, keeping the di-fluorine benzene ring constant, we examined the effects of the terminal benzene ring. Representative compounds are shown in Table 4. A benzene ring without substituents (**14g**) was less active than compound **14f**. Replacement of the chlorine atom with a fluorine atom (**14h**) or removal of the chlorine atom (**14i**) resulted in compounds with slightly decreased potency. Replacement of the trifluoromethyl group with a chlorine atom (**14j**) also resulted in a slight decrease in potency, and migration of the trifluoromethyl group to the *para* position (**14k**) was poorly tolerated. As with the central benzene ring, alteration of the terminal benzene ring to the

pyridine ring also resulted in low-activity compounds (**14l** and **14m**). Thus, we speculated that the terminal benzene ring played a key role in hydrophobic interactions with Lp-PLA_2 enzyme, and Lp-PLA_2 inhibitory activity was obviously affected by the substituents on the terminal benzene ring.

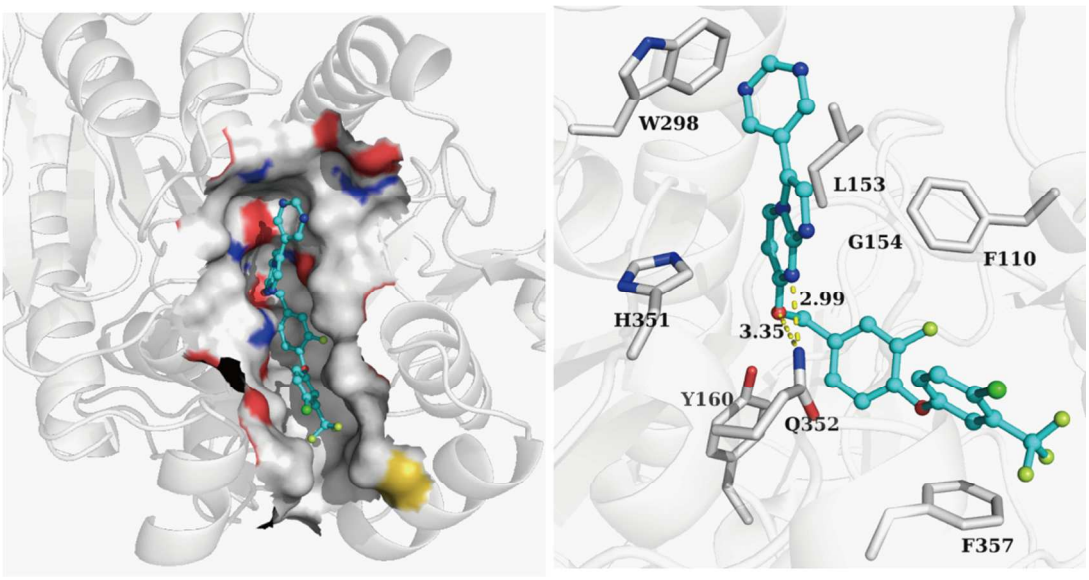
Table 4. **Effects of the diphenyl ether on the inhibitory activity of rhLp-PLA$_2$**



compd	Ar'	O-Ar	% inhibition against rhLp-PLA$_2$ 100 nM	% inhibition against rhLp-PLA$_2$ 10 nM	IC_{50} （nM）
7c			89	55	10.6
14a			70	15	
14b			95	78	3.7
14c			97	68	2.9
14d			74	11	
14e			3		
14f			100	82	2.3
14g			47		
14h			96	66	6.5
14i			91	47	10.9
14j			94	57	6.3
14k			79	29	
14l			57	8	
14m			21		

To further gain insight into the binding interactions of these

imidazo[1,2-*a*]pyrimidine derivatives with Lp-PLA_2 enzyme, docking studies were then performed to investigate the docking pose of compound **14b** into Lp-PLA_2 (Figure 3). Key interactions between this compound and Lp-PLA_2 are hydrogen bonds and several hydrophobic interactions. Q352 formed two hydrogen bonds with **14b**. The pyrimidine ring in position R^1 formed an edge-to-face π-π stacking interaction with W298. In the case of imidazo[1,2-a]pyrimidine ring, the pyrimidine moiety formed hydrophobic interactions with H351 and L153. The central and terminal benzene rings are participated in a number of hydrophobic interactions, most notably to F110, G154, Y160, and F357.



(A) (B)

Figure 3. Docking pose of compound **14b** showing key interactions with Lp-PLA_2 binding site. Carbon, oxygen, nitrogen, fluorine and chlorine atoms are colored cyan, red, blue, limon, and green, respectively. Compound **14b** is represented as a ball-and-stick model. The protein is shown as light grey cartoons. (A) The binding pocket is shown by molecular surface. (B) Interactions between **14b** and Lp-PLA_2. Hydrogen bonds are depicted as dotted lines. Key residues at the binding site are shown as sticks.

To account for any non-specific binding effects in plasma, selected compounds with relatively good activity against rhLp-PLA_2 were further evaluated for their potency against Lp-PLA_2 in human plasma. As shown in Table 5, potency against Lp-PLA_2 in human plasma correlated well with potency against rhLp-PLA_2. For example, compounds **14c** and **14f** act as the most potent compounds against rhLp-PLA_2, displayed rather high potency against Lp-PLA_2 in human plasma, and potency against rhLp-PLA_2 of **14c** and

14f (**14c**, 68% at 10 nM; **14f**, 82% at 10 nM) were similar to their potency against Lp-PLA_2 in human plasma (**14c**, 83% at 10 nM; **14f**, 87% at 10 nM). These findings suggested that non-specific binding had a negligible effect on the binding affinity between these imidazo[1,2-a]pyrimidine derivatives and Lp-PLA_2 enzyme in human plasma. Before we evaluated efficacy *in vivo*, we also assessed the activity of selected compounds against Lp-PLA_2 in rat and mouse plasma (Table 5). Surprisingly, potency in the plasma of rats and mice differed from the potency observed in human plasma for these imidazo[1,2-*a*]pyrimidine derivatives. For instance, compound **14f** displayed a high activity against Lp-PLA_2 in human plasma (87% at 10 nM), but showed a relatively low activity in rat plasma (26% at 100 nM). In addition, in mouse plasma, all of these imidazo[1,2-*a*]pyrimidine derivatives showed quite low potency against the Lp-PLA_2 enzyme. Despite this species difference, most of these imidazo[1,2-*a*]pyrimidine derivatives provided ＞50% inhibition of Lp-PLA_2 in rat plasma at 100 nM, which were better than that observed for compound **1**.

Table 5. Inhibitory activity against Lp-PLA$_2$ in human plasma, rat plasma, and mouse plasma

compd	% inhibition in plasma					
	human		rat		mouse	
	100 nM	10 nM	100 nM	10 nM	1 μM	100 nM
7a	87	56	49		53	2
7c	91	58	76	10	56	10
10e	85	42	64	13	28	
14b	84	60	70	11	13	
14c	94	83	68	14	0	
14f	96	87	26		8	
1	96	86	48		91	18
darapladib	100	93	98	84	99	96

Metabolic stability tests in liver S9 fractions. Compounds with relatively good activity against rhLp-PLA$_2$ were also selected to evaluate their metabolic stability in human and rat liver S9 fractions (Table 6). Compound **7c** with a single methylene spacer displayed much better metabolic stability compared with the hit compound **7a**. Replacement of the pyrimidine ring with 1-methyl-pyrazole (**10e**) also resulted in good metabolic stability. Compounds with different substituents in the central benzene ring demonstrated different metabolic stability. The cyano-substituted derivative **14c** showed relatively poor

metabolic stability, whereas the fluorine-substituted derivatives **14b** and **14f** were quite stable in human and rat liver S9 fractions.

Table 6. Metabolic stability in liver S9 fractions of selected compounds

compd	liver S9 stability ($t_{1/2}$, min)	
	human	rat
7a	42	110
7c	116	348
10e	180	NC[a]
14b	331	169
14c	106	40
14f	212	196
1	33	51

[a]NC = cannot be calculated. The half-life was too long to be calculated in this system.

Pharmacokinetic evaluation. For assessment of the pharmacokinetic properties of these imidazo[1,2-*a*]pyrimidine derivatives *in vivo*, compounds **7c**, **14b**, and **14c** were selected for evaluation in male SD rats through oral administration. The concentration-time curves are shown in Figure 4 (with the data of compound **1** and darapladib included for comparison), and the key pharmacokinetic parameters are summarized in Table 7. Pharmacokinetic studies showed that the *in vivo* half-lives of these compounds correlated well with the metabolic stability in rat liver S9 fractions. With good metabolic stability in rat liver S9 fractions, *in vivo* half-lives of **7c** and **14b** were 9.44 h and 13.34 h,

respectively, much longer than that of compound **1** (2.08 h). Compound **14c** was less stable in rat liver S9 fractions, and displayed a shorter *in vivo* half-life (3.24 h). Furthermore, **7c**, **14b**, and **14c** achieved a maximum concentration (C_{max}) of 3.52, 2.60 and 1.40 μg/mL, respectively, whereas the C_{max} of compound **1** was 0.78 μg/mL. Consequently, AUC values for **7c** (88.05 μg·h/mL), **14b** (78.14 μg·h/mL), and **14c** (16.13 μg·h/mL) were higher than that for compound **1** (3.38 μg·h/mL). Taken together, these data suggested that imidazo[1,2-*a*]pyrimidine derivatives possess promising pharmacokinetic profiles *in vivo*.

Table 7. Pharmacokinetic parameters of selected compounds after oral administration to SD rats[a]

compd	$AUC_{0-\infty}$ (μg·h/mL)	$t_{1/2}$ (h)	C_{max} (μg/mL)
7c	88.05	9.44	3.52
14b	78.14	13.34	2.60
14c	16.13	3.24	1.40

[a]n = 5 animals/group, administered at 25 mg/kg. Data are the mean.

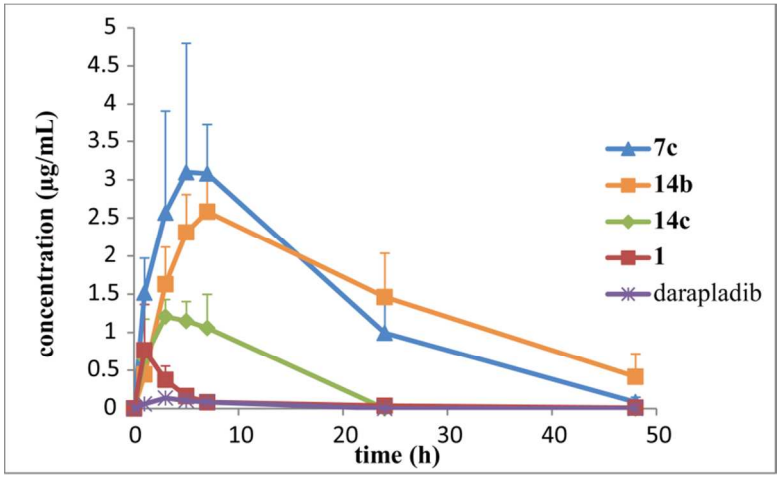


Figure 4. Concentration-time curves of selected compounds after oral administration to SD rats (n=5). Compounds **7c**, **14b**, **14c** and **1** were administrated at 25 mg/kg, darapladib was administered at 50 mg/kg.

Assessment of the inhibitory activity of Lp-PLA$_2$ *in vivo*. Based on their very promising profiles, compounds **7c** and **14b** were selected for evaluating inhibitory activity in male SD rats through oral administration at a single dose of 25 mg/kg, with the data for compound **1** and darapladib included for comparison (Figure 5). The relatively low inhibitory activity of compound **1** *in vivo* could be due to its modest pharmacokinetic profile and relatively low potency against Lp-PLA$_2$ in rat plasma *in vitro*. With much better pharmacokinetic properties and slightly greater potency against Lp-PLA$_2$ in rat plasma *in vitro*, **7c** and **14b** exhibited much better inhibitory activity *in vivo* when compared with compound **1**. Both compounds produced ≈75% inhibition of Lp-PLA$_2$ activity after 5 h and could effectively inhibit Lp-PLA$_2$ activity over 24 h.

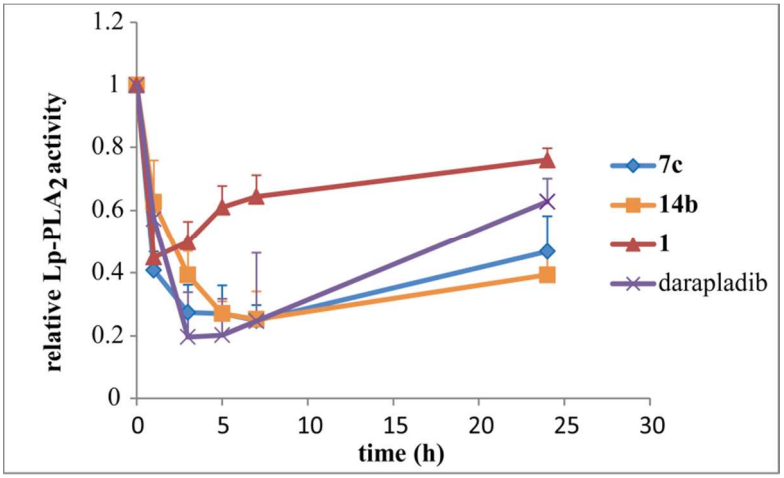


Figure 5. Relative activity of Lp-PLA$_2$ in the serum of SD rats after a single oral dose of 25 mg/kg (n = 5).

CONCLUSION

Among reported Lp-PLA$_2$ inhibitors, darapladib has been the most rapidly developed compound. However, darapladib demonstrated low oral bioavailability due to its physicochemical properties, such as high values of MW (666.78) and cLogP (8.33). In an effort to find potent and orally bioavailable Lp-PLA$_2$ inhibitors, we focused on the development of compounds with lower values of MW and cLogP.

In this work, we chose compound **1** (MW, 502.88; cLogP, 4.48) from GSK as a starting point. In view of the poor metabolic stability of compound **1**, structural modification using conformational restriction yielded imidazo[1,2-*a*]pyrimidine as a novel scaffold. SAR explorations resulted in identification of several imidazo[1,2-*a*]pyrimidine derivatives with good inhibitory activity *in vitro* and favorable metabolic stability in liver S9 fractions. Several compounds that proceeded to pharmacokinetic evaluation *in vivo* showed much better pharmacokinetic profiles

compared with those observed for darapladib and compound **1**. Compounds **7c** and **14b** selected for efficacy assessment *in vivo* demonstrated robust inhibitory potency in male SD rats at a single oral dose of 25 mg/kg, this activity was comparable with that for darapladib and much better than that for compound **1**.

Taken together, results generated so far suggest that imidazo[1,2-*a*]pyrimidine derivatives with reasonable physicochemical properties, are potent, and orally bioavailable Lp-PLA_2 inhibitors. In this way, they can serve as valuable probes to further study the role of Lp-PLA_2 *in vivo* across various inflammation-associated diseases. We also observed a species difference across humans, rats and mice. Additional studies on identification of compounds to overcome this species difference are underway.

EXPERIMENTAL SECTION

***In vitro* assay to measure the inhibitory activity of Lp-PLA_2.**[57] Activities against recombinant human Lp-PLA_2 (rhLp-PLA_2), human plasma, rat plasma and mouse plasma Lp-PLA_2 were measured using 2-thio-PAF as the substrate. Briefly, 10 μL of the rhLp-PLA_2 enzyme (or plasma) and 10 μL of a DMSO solution of the compound were added to 0.1 mol/L Tris-HCl (pH 7.2) containing 1 mmol/L EGTA, 50 μmol/L 2-thio-PAF and 10 μL of 2 mmol/L 5,5′-dithiobis (2-nitrobenzoic acid) in a total volume of 200 μL. The assay was carried out using a plate reader to obtain absorbance values at 414 nm every minute for 10 min. Percent inhibition was determined using the following equation:

$$\text{Inhibition (\%)} = 1 - \frac{\text{Vmax}_{\text{compound}} - \text{Vmax}_{\text{blank}}}{\text{Vmax}_{\text{positive}} - \text{Vmax}_{\text{blank}}} \times 100\%$$

Vmax: slope of absorbance values for 10 min, calculated by MolecularDevice, SpectraMax M2e. The blank sample contained no rhLp-PLA_2 enzyme (or plasma) or test compound in assay buffer. The positive sample contained no test compound.

This study has been approved and supervised by Institutional Animal Care and Use Committee (IACUC), Shanghai Institute of Materia Medica, Chinese Academy of Sciences (IACUC Approval Number: SIMM-2014-08-WYP-18) and the Ethics Committee of Shanghai Xuhui Central Hospital.

Metabolic stability tests in human and rat liver S9 fractions. The test compound was dissolved in DMSO and diluted to the desired concentration with an aqueous solution of 0.1% BSA. Liver S9 (0.33 mg/mL; pooled human liver S9 purchased from Celsis In Vitro Technologies; Wistar rat liver S9 purchased from Research Institute for Liver Diseases), test compounds (0.1 μM), $MgCl_2$ (5.0 mM), BSA (0.005%), and NADPH (1.0 mM) in Tris buffer (0.1 M, pH 7.4) were incubated in a 96-well plate at 37 °C. An aliquot was removed at each time point and the enzymatic reaction stopped by protein precipitation in cold methanol. Half-lives of the compounds in liver S9 fractions were calculated based on the first-order rate constants that were measured. Intrinsic clearance was calculated using the following equation:

$$\mathrm{CL_{int}} = \frac{0.693}{in\ vitro\ \mathrm{t_{1/2}}} \times \frac{\text{mL of incubation}}{\text{mg of liver S9 protein}} \times \frac{\text{mg of liver S9 protein}}{\text{g of tissue}} \times \frac{\text{g of tissue}}{\text{kg of weight}}$$

Scaling factors for the human liver (145-mg S9 protein/g liver and 24.3-g liver/kg body weight) and rat liver (179-mg S9 protein/g liver and 40-g liver/kg body weight) were employed in this calculation.

Docking protocols. A crystal structure of Lp-PLA_2 (PDB ID: 3D59) was used as the receptor structure. The active site was defined according to the crystal structure of Lp-PLA_2 in complex with its substrate (PDB ID: 3D5E).[58] Water molecules and ions were deleted. Receptor was prepared using Protein Preparation and Grid Preparation tools in the Schrödinger Maestro interface. The 3D structures of substrate were generated with the Schrödinger program LigPrep. Automated docking was performed with Glide 5.5.[59] Standard Precision (SP) calculations were carried out with default settings. The OPLS-2005 force field was used for minimization and grid generation, while OPLS-2001 force field was used for docking. The docked conformation of the compound with the lowest energy was selected for study.

Animals. Male Sprague−Dawley (SD) rats were obtained from Shanghai SLAC Laboratory Animal Co. Ltd. (Shanghai, China). Animal experiments were approved by Animal Care and Use Committee, Shanghai Institute of Materia Medica, Chinese Academy of Sciences.

Pharmacokinetic studies. Test compounds (0.5% carboxymethylcellulose sodium) were subjected to pharmacokinetic studies on male SD rats with five animals in each group. Test compounds were administered via the oral route by gavage at 25 mg/kg. Serial specimens were collected pre-dose as well as 1, 3, 5, 7, 24 and 48 h after administration and quantified by liquid chromatography-mass spectrometry. Pharmacokinetic parameters were calculated from the mean serum concentration by non-compartmental analyses using DAS software 2.1.1.

Assay to measure the inhibitory activity of Lp-PLA$_2$ *in vivo*. A group of five male SD rats were fasted overnight, and administered test compounds by gavage at 25 mg/kg. Test compounds were formulated in 0.5% carboxymethylcellulose sodium. Blood samples were drawn pre-dose as well as 1, 3, 5, 7 and 24 h after administration to measure Lp-PLA$_2$ activity in serum. Lp-PLA$_2$ activity in the serum of SD rats was measured according to the method described for measurement of Lp-PLA$_2$ inhibitory activity *in vitro*.

Materials and methods. All reagents were purchased from commercial suppliers and used without further purification unless otherwise stated. Yields were not optimized. Microwave reactions were performed in a Biotage Initiator. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian-Mercucy Plus-300 or a Bruker AC400 or a Bruker AC500 NMR spectrometer using tetramethylsilane as an internal reference. Low-resolution mass spectra were determined on Agilent liquid-chromatography mass spectrometer system that consisted of an Agilent 1260 infinity LC coupled to Agilent 6120 Quadrupole mass spectrometer (electrospray positive ionization; ESI). High-resolution mass spectra were conducted on a triple TOF 5600$^+$ MS/MS system (AB Sciex, Concord, Ontario, Canada) in the positive ESI mode. The purity of test compounds was determined by HPLC (Agilent ChemStation, Agilent Eclipse XDB-C18, 5 μM, 4.6×150 mm, 30 °C, UV 240 nM, flow rate = 1.0 mL/min) with aqueous CH_3CN (50-90%) containing ammonium formate (10 mmol/L) for 25 min. All the assayed compounds possess ≥95% purity. Column chromatography was performed on silica gel

(200-300 mesh), preparative TLC was performed on HSGF 254 (0.4-0.5 mm thickness; Yantai Jiangyou Company, Yantai, Shangdong, China).

4-(benzylthio)pyrimidin-2-amine (2). To a suspension of 4-chloropyrimidin-2-amine (2.00 g, 15.44 mmol) and sodium hydride (1.85 g, 46.25 mmol, 60% in mineral oil) in THF (50 mL) at 0 °C，was added benzyl mercaptan (1.60 mL, 13.65 mmol) dropwise over a period of 0.5 h, the reaction mixture was stirred at rt overnight. Then the reaction was quenched with NH_4Cl solution, diluted with ethyl acetate (50 mL). The organic layer was separated, washed with brine, part of the organic solvent was evaporated under reduced pressure, the precipitates formed were collected by filtration to give **2** as a white solid (1.80 g, 54%).^{1}H NMR (400 MHz, Chloroform-d) δ 7.85 (d, J = 5.5 Hz, 1H), 7.41 (d, J = 7.5 Hz, 2H), 7.32−7.18 (m, 3H), 6.50 (d, J = 5.5 Hz, 1H), 4.40 (s, 2H). MS (ESI): *m/z* 218 $[M+H]^+$.

7-(benzylthio)imidazo[1,2-a]pyrimidine (3). A solution of 2-bromoacetaldehyde diethyl acetal (7.80 mL, 66.00 mmol) and HBr (2.70 mL, 24.02 mmol, 48% aqueous solution) in 95% ethanol (40 mL) was heated at 80 °C for 6 h. After the solution was cooled down to rt, solid $NaHCO_3$ (3.50 g, 41.66 mmol) was added in small portions, follow by **2** (1.80 g, 8.29 mmol), the mixture was further stirred at 70 °C for 3 h. After the reaction was complete, the solvent was evaporated under reduced pressure, DCM (50 mL) was added to the residue, dried over $MgSO_4$, filtered, and concentrated. The residue was purified with column chromatography (DCM/MeOH = 20:1) to yield **3** (684 mg, 34%) as

a yellow solid. ^{1}H NMR (400 MHz, Chloroform-d) δ 8.10 (d, *J* = 7.0 Hz, 1H), 7.62 (s, 1H), 7.55−7.28 (m, 6H), 6.66 (d, *J* = 7.0 Hz, 1H), 4.57 (s, 2H). MS (ESI): *m/z* 242 $[M+H]^+$.

7-(benzylthio)-3-(pyrimidin-5-yl)imidazo[1,2-a]pyrimidine (4). To a solution of **3** (684 mg, 2.84 mmol), 5-bromopyrimidine (496 mg, 3.12 mmol) in DMA (15 mL), was added $Pd(OAc)_2$ (64 mg, 0.28 mmol), KOAc (556 mg, 5.67 mmol), the mixture was heated at 140 °C under nitrogen for 2 h. After the solution was cooled down, diluted with water (50 mL), and extracted with DCM (50 mL × 3), the organic layers were combined, washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified with column chromatography (DCM/MeOH = 20:1) to yield **4** (370 mg, 41%) as a yellow solid. ^{1}H NMR (300 MHz, Chloroform-d) δ 9.27 (s, 1H), 8.93 (s, 2H), 8.22 (d, *J* = 7.2 Hz, 1H), 7.83 (s, 1H), 7.49 (d, *J* = 7.3 Hz, 2H), 7.39−7.28 (m, 3H), 6.78 (d, *J* = 7.5 Hz, 1H), 4.62 (s, 2H). MS (ESI): *m/z* 320 $[M+H]^+$.

Intermediate 5. To a solution of **4** (370 mg, 1.16 mmol) in DCM (60 mL) was added *m*-CPBA (715 mg, 2.90 mmol, 70% purity) at 0 °C, the mixture was stirred at 0 °C for 3 h. Then the reaction was quenched with sodium bicarbonate solution, the organic layer was separated, and washed with sodium bicarbonate solution, dried over Na_2SO_4, filtered, and concentrated. Intermediate **5** (240 mg) was obtained as a mixture, and can be used in next step without purification. MS (ESI): *m/z* 352$[M+H]^+$, *m/z* 336$[M+H]^+$.

General Synthetic Procedure for 7a-e. To a solution of **5** (0.10 mmol) and

corresponding alcohol (0.10 mmol) in THF (2 mL) was added sodium hydride (0.25 mmol) at 0 °C. The reaction was stirred at rt for 1 h, and then quenched with NH_4Cl solution, extracted with ethyl acetate (5 mL × 3), washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue obtained was purified with preparative TLC (DCM/MeOH = 30:1) to yield the desired compound.

7-(4-(4-chloro-3-(trifluoromethyl)phenoxy)phenethoxy)-3-(pyrimidin-5-yl)imidazo[1,2-a]pyrimidine (7a). The title compound was obtained as a white solid from **5** and **6a** according to the general procedure in 72% yield. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.26 (s, 1H), 8.92 (s, 2H), 8.30 (d, *J* = 7.4 Hz, 1H), 7.72 (s, 1H), 7.42 (d, *J* = 8.8 Hz, 1H), 7.32 (m, 3H), 7.06 (d, *J* = 9.0 Hz, 1H), 6.98 (d, *J* = 8.0 Hz, 2H), 6.54 (d, *J* = 8.3 Hz, 1H), 4.74 (t, *J* = 6.5 Hz, 2H), 3.16 (t, *J* = 6.4 Hz, 2H). ^{13}C NMR (126 MHz, Chloroform-d) δ 162.83, 157.99, 156.30, 155.05 (2C), 154.49, 149.72, 134.12, 133.05, 132.63, 132.26, 130.65 (2C), 129.51 (q, *J* = 31.9 Hz), 125.55, 123.71, 123.40 (q, *J* = 273.9 Hz), 122.11, 119.56 (2C), 117.49 (q, *J* = 5.3 Hz), 117.25, 102.62, 67.68, 34.25. HRMS (ESI): *m/z* $[M+H]^+$ calculated for $C_{25}H_{18}ClF_3N_5O_2$: 512.1096, found: 512.1111.

7-(4-(4-chloro-3-(trifluoromethyl)phenoxy)phenoxy)-3-(pyrimidin-5-yl)imidazo[1,2-a]pyrimidine (7b). The title compound was obtained as a white solid from **5** and **6b** according to the general procedure in 65% yield. ^{1}H NMR (400 MHz, Chloroform-d) δ 9.29 (s, 1H), 8.95 (s, 2H), 8.45 (d, *J* = 7.4 Hz, 1H), 7.76 (s, 1H), 7.47 (d, *J* = 8.8 Hz, 1H), 7.41 (d, *J* = 2.7 Hz, 1H), 7.29 (d, *J* = 8.9 Hz, 2H), 7.14 (dd, *J* = 8.8, 2.7 Hz, 1H), 7.08 (d,

J = 8.9 Hz, 2H), 6.81 (d, *J* = 7.3 Hz, 1H). ^{13}C NMR (126 MHz, Chloroform-d) δ 162.24, 158.12, 156.11, 155.12 (2C), 153.37, 149.06, 148.26, 133.83, 133.08, 132.75, 129.65 (q, *J* = 31.4 Hz), 125.90, 123.63, 123.41 (2C), 122.38 (q, *J* = 274.0 Hz), 122.18, 120.40 (2C), 117.87 (q, *J* = 5.3 Hz), 117.53, 102.26. HRMS (ESI): *m/z* $[M+H]^+$ calculated for $C_{23}H_{14}ClF_3N_5O_2$: 484.0783, found: 484.0786.

7-((4-(4-chloro-3-(trifluoromethyl)phenoxy)benzyl)oxy)-3-(pyrimidin-5-yl)imidazo[1,2-a]pyrimidine (7c). The title compound was obtained as a white solid from **5** and **6c** according to the general procedure in 75% yield. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.27 (s, 1H), 8.93 (s, 2H), 8.33 (d, *J* = 7.4 Hz, 1H), 7.76 (s, 1H), 7.54 (d, *J* = 8.6 Hz, 2H), 7.45 (d, *J* = 8.8 Hz, 1H), 7.34 (d, *J* = 2.9 Hz, 1H), 7.10 (dd, *J* = 8.8, 2.8 Hz, 1H), 7.04 (d, *J* = 8.6 Hz, 2H), 6.61 (d, *J* = 7.4 Hz, 1H), 5.55 (s, 2H). ^{13}C NMR (126 MHz, Chloroform-d) δ 162.47, 157.94, 156.09, 155.80, 155.03 (2C), 149.61, 133.26, 132.73, 132.42, 131.81, 130.72 (2C), 129.62 (q, *J* = 31.8 Hz), 126.00, 123.78, 122.53, 122.35 (q, *J* = 273.9 Hz), 119.31 (2C), 117.89 (q, *J* = 5.3 Hz), 117.31, 102.49, 68.34. HRMS (ESI): *m/z* $[M+H]^+$ calculated for $C_{24}H_{16}ClF_3N_5O_2$: 498.0939, found: 498.0945.

7-(3-(4-(4-chloro-3-(trifluoromethyl)phenoxy)phenyl)propoxy)-3-(pyrimidin-5-yl)imidazo[1,2-a]pyrimidine (7d). The title compound was obtained as a yellow solid from **5** and **6d** according to the general procedure in 35% yield. ^{1}H NMR (400 MHz, Chloroform-d) δ 9.26 (s, 1H), 8.93 (s, 2H), 8.31 (d, *J* = 7.4 Hz, 1H), 7.72 (s, 1H), 7.42 (d, *J* = 8.8 Hz, 1H), 7.31 (s, 1H), 7.24 (d, *J* = 8.5 Hz, 2H), 7.05 (dd, *J* = 8.8, 2.8 Hz, 1H),

6.95 (d, *J* = 8.5 Hz, 2H), 6.56 (d, *J* = 7.4 Hz, 1H), 4.54 (t, *J* = 6.5 Hz, 2H), 2.81 (t, *J* = 8.4 Hz, 2H), 2.21−2.13 (m, 2H). ^{13}C NMR (126 MHz, Chloroform-d) δ 162.89, 157.88, 156.45, 154.99 (2C), 153.97, 149.87, 137.54, 133.16, 132.60, 132.17, 130.06 (2C), 129.46 (q, *J* = 31.9 Hz), 125.40, 123.85, 122.42 (q, *J* = 274.0 Hz), 121.98, 119.56 (2C), 117.41 (q, *J* = 5.5 Hz), 117.17, 102.52, 66.60, 31.48, 30.17. HRMS (ESI): *m/z* $[M+H]^+$ calculated for $C_{26}H_{20}ClF_3N_5O_2$: 526.1252, found: 526.1269.

7-((4-(4-chloro-3-(trifluoromethyl)phenoxy)benzyl)thio)-3-(pyrimidin-5-yl)imidazo[1,2-a]pyrimidine (7e). The title compound was obtained as a yellow solid from **5** and **6e** according to the general procedure in 38% yield. ^{1}H NMR (400 MHz, Chloroform-d) δ 9.28 (s, 1H), 8.93 (s, 2H), 8.24 (d, *J* = 7.2 Hz, 1H), 7.83 (s, 1H), 7.51 (d, *J* = 8.6 Hz, 2H), 7.42 (d, *J* = 8.8 Hz, 1H), 7.32 (d, *J* = 2.9 Hz, 1H), 7.06 (dd, *J* = 8.8, 2.8 Hz, 1H), 6.96 (d, *J* = 8.6 Hz, 2H), 6.80 (d, *J* = 7.2 Hz, 1H), 4.61 (s, 2H). ^{13}C NMR (126 MHz, Chloroform-d) δ 161.93, 158.11, 155.92, 155.26, 154.13 (2C), 149.98, 133.94, 133.05, 132.67, 131.09 (2C), 129.73, 129.07, 125.72, 123.57, 122.93 (q, *J* = 298.6 Hz), 122.38, 119.38 (2C), 117.83 (q, *J* = 6.3 Hz), 117.44, 109.44, 33.46. HRMS (ESI): *m/z* $[M+H]^+$ calculated for $C_{24}H_{16}ClF_3N_5OS$: 514.0711, found: 514.0705.

4-((4-(4-chloro-3-(trifluoromethyl)phenoxy)benzyl)oxy)pyrimidin-2-amine (8). To a solution of **6c** (3.00 g, 9.91 mmol) in anhydrous THF (100 mL) was added sodium hydride (0.80 g, 27.73 mmol, 60% in mineral oil) at 0 °C, 4-chloropyrimidin-2-amine (0.85 g, 6.56 mmol) was added after the mixture was stirred at 0 °C for 0.5 h, the mixture

was stirred at rt overnight. Then the reaction was quenched with NH_4Cl solution, extracted with ethyl acetate (100 mL × 3), washed with brine, dried over $NaSO_4$, filtered and concentrated, the residue obtained was purified with column chromatography (petroleum ether/ethyl acetate = 2:1) to yield intermediate **8** as a white solid (2.40 g, 93%). ^{1}H NMR (400 MHz, Chloroform-d) δ 8.04 (d, *J* = 5.7 Hz, 1H), 7.44 (d, *J* = 8.6 Hz, 3H), 7.34 (d, *J* = 2.9 Hz, 1H), 7.09 (dd, *J* = 8.8, 2.9 Hz, 1H), 7.02 (d, *J* = 8.6 Hz, 2H), 6.15 (d, *J* = 5.7 Hz, 1H), 5.32 (s, 2H), 4.93 (s, 2H). MS (ESI): *m/z* 396 $[M+H]^+$.

7-((4-(4-chloro-3-(trifluoromethyl)phenoxy)benzyl)oxy)imidazo[1,2-a]pyrimidine (9). The title compound was obtained as a yellow solid from **8** using a method similar to that described for intermediate **3** in 34% yield. ^{1}H NMR (300 MHz, Chloroform-d) δ 8.19 (d, *J* = 7.3 Hz, 1H), 7.56−7.49 (m, 3H), 7.44 (d, *J* = 8.7 Hz, 1H), 7.36−7.32 (m, 2H), 7.08 (dd, *J* = 8.8, 2.9 Hz, 1H), 7.03 (d, *J* = 8.6 Hz, 2H), 6.47 (d, *J* = 7.2 Hz, 1H), 5.51 (s, 2H). ^{13}C NMR (126 MHz, Chloroform-d) δ 162.08, 159.40, 155.90, 147.91, 134.93, 133.10, 132.70, 132.26, 130.63 (2C), 129.60 (q, *J* = 32.8 Hz), 125.89, 122.44, 122.37 (q, *J* = 274.68 Hz), 119.30 (2C), 117.86 (q, *J* = 5.0 Hz), 110.24, 101.33, 67.90. HRMS (ESI): *m/z* $[M+H]^+$ calculated for $C_{20}H_{14}ClF_3N_3O_2$: 420.0721, found: 420.0748.

7-((4-(4-chloro-3-(trifluoromethyl)phenoxy)benzyl)oxy)-3-(4-methoxyphenyl)imidazo[1,2-a]pyrimidine (10a). The title compound was obtained as a white solid from **9** and 1-bromo-4-methoxybenzene using a method similar to that described for intermediate **4** in 61% yield. ^{1}H NMR (400 MHz, Chloroform-d) δ 8.32 (d, *J* = 7.4 Hz, 1H), 7.54 (d, *J*

= 8.6 Hz, 2H), 7.51 (s, 1H), 7.42 (dd, *J* = 11.0, 8.8 Hz, 3H), 7.34 (d, *J* = 2.9 Hz, 1H), 7.08 (dd, *J* = 8.7, 2.8 Hz, 1H), 7.03 (dd, *J* = 8.6, 1.8 Hz, 4H), 6.47 (d, *J* = 7.4 Hz, 1H), 5.53 (s, 2H), 3.87 (s, 3H). ^{13}C NMR (126 MHz, Chloroform-d) δ 161.72, 159.75, 155.90, 148.03, 132.99, 132.70, 132.33, 130.65 (2C), 130.52, 129.60 (q, *J* = 31.9 Hz), 129.41 (2C), 125.89, 123.90, 122.43, 122.37 (q, *J* = 274.0 Hz), 120.90, 119.31 (2C), 117.86 (q, *J* = 5.4 Hz), 114.80 (2C), 113.23, 101.15, 67.92, 55.43. HRMS (ESI): *m/z* $[M+H]^+$ calculated for $C_{27}H_{20}ClF_3N_3O_3$: 526.1140, found: 526.1168.

7-((4-(4-chloro-3-(trifluoromethyl)phenoxy)benzyl)oxy)-3-(pyridin-3-yl)imidazo[1,2-a]pyrimidine (10b). The title compound was obtained as a white solid from **9** and 3-bromopyridine using a method similar to that described for intermediate **4** in 53% yield. ^{1}H NMR (400 MHz, Chloroform-d) δ 8.80 (d, *J* =1.2 Hz, 2H), 8.68 (dd, *J* = 4.4 Hz, 1.2 Hz, 2H), 8.35 (d, *J* = 7.4 Hz, 1H), 7.82 (dt, *J* = 7.8, 1.8 Hz, 1H), 7.71 (s, 1H), 7.54 (d, *J* = 8.5 Hz, 2H), 7.49−7.41 (m, 2H), 7.34 (d, *J* = 2.8 Hz, 1H), 7.09 (dd, *J* = 8.8, 2.8 Hz, 1H), 7.03 (d, *J* = 8.4 Hz, 2H), 6.56 (d, *J* = 7.4 Hz, 1H), 5.53 (s, 2H). ^{13}C NMR (126 MHz, Chloroform-d) δ 162.31, 156.04, 155.81, 149.53, 148.93, 148.48, 135.09, 132.72, 131.91, 130.79 (2C), 128.61 (q, *J* = 31.6 Hz), 125.98, 125.61, 124.87, 124.12, 122.49, 122.35 (q, *J* = 273.9 Hz), 120.78, 119.30 (2C), 117.88 (q, *J* = 5.3 Hz), 114.98, 102.08, 68.27. HRMS (ESI): *m/z* $[M+H]^+$ calculated for $C_{25}H_{17}ClF_3N_4O_2$: 497.0987, found: 497.0988.

7-((4-(4-chloro-3-(trifluoromethyl)phenoxy)benzyl)oxy)-3-(pyridin-4-yl)imidazo[1,2-a]pyrimidine (10c). The title compound was obtained as a white solid from **9** and

4-bromopyridine using a method similar to that described for intermediate **4** in 48% yield. ^{1}H NMR (400 MHz, Chloroform-d) δ 8.74 (d, *J* = 6.0 Hz, 2H), 8.52 (d, *J* = 7.4 Hz, 1H), 7.81 (s, 1H), 7.54 (d, *J* = 8.4 Hz, 2H), 7.46−7.40 (m, 3H), 7.34 (d, *J* = 2.8 Hz, 1H), 7.09 (dd, *J* = 8.7, 2.8 Hz, 1H), 7.03 (d, *J* = 8.5 Hz, 2H), 6.60 (d, *J* = 7.4 Hz, 1H), 5.54 (s, 2H). ^{13}C NMR (126 MHz, Chloroform-d) δ 162.44, 156.07, 155.79, 150.80 (2C), 149.62, 136.37, 133.35, 133.16, 132.72, 131.79, 130.77 (2C), 129.60 (q, *J* = 31.8 Hz), 125.99, 122.52, 122.34 (q, *J* = 273.9 Hz), 121.56, 120.77 (2C), 119.31 (2C), 117.87 (q, *J* = 5.3 Hz), 102.32, 68.33. HRMS (ESI): *m/z* $[M+H]^+$ calculated for $C_{25}H_{17}ClF_3N_4O_2$: 497.0987, found: 497.0988.

7-((4-(4-chloro-3-(trifluoromethyl)phenoxy)benzyl)oxy)-3-(2-methoxypyrimidin-5-yl)imidazo[1,2-a]pyrimidine (10d). The title compound was obtained as a white solid from **9** and 2-bromo-5-methoxypyrimidine using a method similar to that described for intermediate **4** in 43% yield. ^{1}H NMR (300 MHz, Chloroform-d) δ 8.64 (s, 2H), 8.18 (d, *J* = 7.4 Hz, 1H), 7.62 (d, *J* = 8.7 Hz, 1H), 7.53 (d, *J* = 8.5 Hz, 2H), 7.43 (d, *J* = 8.7 Hz, 1H), 7.33 (d, *J* = 2.8 Hz, 1H), 7.08 (dd, *J* = 8.7, 2.8 Hz, 1H), 7.02 (d, *J* = 8.2 Hz, 2H), 6.57 (d, *J* = 7.1 Hz, 1H), 5.53 (s, 2H), 4.09 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-d) δ 165.40, 162.23, 158.50 (2C), 156.04, 155.85, 149.02, 132.73, 132.35, 132.34, 131.99, 130.69 (2C), 129.64 (q, *J* = 32.3 Hz), 126.00, 122.50, 122.36 (q, *J* = 274.5 Hz), 119.32 (2C), 117.89 (q, *J* = 5.4 Hz), 117.32, 117.04, 102.12, 68.20, 55.39. HRMS (ESI): *m/z* $[M+H]^+$ calculated for $C_{25}H_{18}ClF_3N_5O_3$: 528.1045, found: 528.1039.

7-((4-(4-chloro-3-(trifluoromethyl)phenoxy)benzyl)oxy)-3-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyrimidine (10e). To a solution of **11** (30 mg, 0.06 mmol) and (1-methyl-1H-pyrazol-4-yl)boronic acid (16.3 mg, 0.078 mmol) dissolved in dioxane-H_2O (5 mL:1 mL) in a vial microwave tube, $PdCl_2(PPh_3)_2$ (7.2 mg, 0.0012 mmol) and Na_2CO_3 (19.2 mg, 0.18 mmol) were added. The mixture was microwave irradiated at 150 °C for 0.5 h. After the mixture was cooled down, part of the solvent was evaporated under reduced pressure, the resulting solution was diluted with water, extracted with ethyl acetate (5 mL × 3), washed with brine, dried over $NaSO_4$, filtered, and concentrated. The residue obtained was purified with preparative TLC (DCM/MeOH = 25:1) to yield **10e** as a white solid (17 mg, 56%). ^{1}H NMR (400 MHz, Chloroform-d) δ 8.21 (d, *J* = 7.4 Hz, 1H), 7.67 (s, 1H), 7.58 (s, 1H), 7.53 (d, *J* = 8.4 Hz, 2H), 7.49 (s, 1H), 7.44 (d, *J* = 8.8 Hz, 1H), 7.34 (d, *J* = 2.1 Hz, 1H), 7.08 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.03 (d, *J* = 8.2 Hz, 2H), 6.50 (d, *J* = 7.4 Hz, 1H), 5.52 (s, 2H), 4.01 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-d) δ 161.74, 155.91, 155.89, 147.95, 138.09, 132.95, 132.70, 132.25, 130.85, 130.65 (2C), 129.59 (q, *J* = 32.1 Hz), 128.83, 125.89, 122.44, 122.36 (q, *J* = 274.4 Hz), 119.31 (2C), 117.84 (q, *J* = 5.4 Hz), 115.73, 109.37, 101.30, 67.96, 39.28. HRMS (ESI): *m/z* $[M+H]^+$ calculated for $C_{24}H_{18}ClF_3N_5O_2$: 500.1096, found: 500.1084.

7-((4-(4-chloro-3-(trifluoromethyl)phenoxy)benzyl)oxy)-2-(pyrimidin-5-yl)imidazo[1,2-a]pyrimidine (10f). A solution of **8** (120 mg, 0.30 mmol) and crude **12** (60 mg) in ethanol (20 mL) was refluxed for 8 h. The solution was cooled down, diluted with

$NaHCO_3$ solution, extracted with ethyl acetate (20 mL × 3), dried over Na_2SO_4, filtered, and concentrated. The residue obtained was purified with column chromatography (DCM/MeOH = 30:1) to yield **10f** as a yellow solid (15mg, 10%). ^{1}H NMR (300 MHz, Chloroform-d) δ 9.29 (s, 2H), 9.18 (s, 1H), 8.25 (d, *J* = 7.3 Hz, 1H), 7.76 (s, 1H), 7.52 (d, *J* = 8.5 Hz, 2H), 7.45 (d, *J* = 8.8 Hz, 1H), 7.35 (d, *J* = 2.8 Hz, 1H), 7.10 (dd, *J* = 8.9, 3.0 Hz, 1H), 7.05 (d, *J* = 8.6 Hz, 2H), 6.56 (d, *J* = 7.3 Hz, 1H), 5.55 (s, 2H). ^{13}C NMR (126 MHz, Chloroform-d) δ 162.86, 157.82, 156.11, 155.82, 153.92 (2C), 148.54, 139.18, 134.84, 132.74, 131.81, 130.58 (2C), 129.87 (q, *J* = 35.8 Hz), 127.49, 126.03, 122.53, 122.40 (q, *J* = 285.5 Hz), 119.35 (2C), 117.89 (q, *J* = 5.3 Hz), 106.68, 102.33, 68.34. HRMS (ESI): *m/z* $[M+H]^+$ calculated for $C_{24}H_{16}ClF_3N_5O_2$: 498.0939, found: 498.0948.

3-bromo-7-((4-(4-chloro-3-(trifluoromethyl)phenoxy)benzyl)oxy)imidazo[1,2-a]pyrimidine (11). To a solution of **9** (560 mg, 1.33 mmol) in THF (50 mL) was added NBS (262 mg, 1.33 mmol) at 0 °C, the reaction was stirred at rt for 1 h. After the reaction was complete, the solvent was evaporated under reduced pressure, the resulting residue was purified with column chromatography (petroleum ether/ethyl acetate = 4:1) to yield **11** as a yellow solid (240 mg, 36%). ^{1}H NMR (400 MHz, Chloroform-d) δ 8.19 (d, *J* = 7.3 Hz, 1H), 7.52 (d, *J* = 8.6 Hz, 3H), 7.44 (d, *J* = 8.6 Hz, 1H), 7.34 (d, *J* = 2.7 Hz, 1H), 7.09 (dd, *J* = 8.8, 2.6 Hz, 1H), 7.03 (d, *J* = 8.4 Hz, 2H), 6.58 (d, *J* = 7.3 Hz, 1H), 5.51 (s, 2H). MS (ESI): *m/z* 498 $[M+H]^+$.

2-bromo-1-(pyrimidin-5-yl)ethan-1-one (12). To a mixture of

1-(pyrimidin-5-yl)ethan-1-one (50 mg, 0.41 mmol), TMSOTf (225 μL, 1.23 mmol) and TEA (170 μL, 1.23 mmol) in THF (10 mL) was added NBS (80 mg, 0.45 mmol) at 0 °C, the mixture was stirred at 0 °C for 0.5 h. After the reaction was complete, the solution was diluted with water, extracted with ethyl acetate (10 mL × 3), dried over $MgSO_4$, filtered, and concentrated. The resulting oil (60 mg) was used in next step without further purification.

7-((4-(4-chloro-3-(trifluoromethyl)phenoxy)-3-methylbenzyl)oxy)-3-(pyrimidin-5-yl)imidazo[1,2-a]pyrimidine (14a). The title compound was obtained as a white solid from **5** and **13a** using a method similar to that described for compounds **7a-e** in 38% yield. ^{1}H NMR (400 MHz, Methanol-d_4) δ 9.19 (s, 1H), 9.09 (s, 2H), 8.79 (d, J = 7.4 Hz, 1H), 7.78 (s, 1H), 7.53 (m, 2H), 7.42 (dd, J = 8.2, 1.8 Hz, 1H), 7.25 (d, J = 2.9 Hz, 1H), 7.06 (dd, J = 8.8, 2.9 Hz, 1H), 6.99 (d, J = 8.3 Hz, 1H), 6.72 (d, J = 7.4 Hz, 1H), 5.52 (s, 2H), 2.21 (s, 3H). ^{13}C NMR (126 MHz, Chloroform-d) δ 162.50, 157.97, 156.30, 155.04 (2C), 153.44, 149.66, 133.29, 132.64, 132.42, 132.35, 132.25, 130.40, 129.58 (q, J = 35.9 Hz), 127.97, 125.15, 123.79, 122.41 (q, J = 273.9 Hz), 120.90, 120.01, 117.30, 116.53 (q, J = 5.5 Hz), 102.51, 68.46, 16.13. HRMS (ESI): *m/z* $[M+H]^+$ calculated for $C_{25}H_{18}ClF_3N_5O_2$: 512.1096, found: 512.1126.

7-((4-(4-chloro-3-(trifluoromethyl)phenoxy)-3-fluorobenzyl)oxy)-3-(pyrimidin-5-yl)imidazo[1,2-a]pyrimidine (14b). The title compound was obtained as a white solid from **5** and **13b** using a method similar to that described for compounds **7a-e** in 75%

yield. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 9.27 (s, 1H), 8.93 (s, 2H), 8.35 (d, *J* = 7.4 Hz, 1H), 7.75 (s, 1H), 7.48−7.35 (m, 2H), 7.34−7.29 (m, 2H), 7.13 (t, *J* = 8.2 Hz, 1H), 7.05 (dd, *J* = 8.8, 2.5 Hz, 1H), 6.63 (d, *J* = 7.4 Hz, 1H), 5.56 (s, 2H). ^{13}C NMR (126 MHz, Chloroform-d) δ 162.20, 158.02, 155.88, 155.08 (2C), 153.11, 149.46, 142.246 (d, *J* = 11.8 Hz), 134.30 (d, *J* = 6.4 Hz), 133.38, 132.66, 132.56, 129.57 (q, *J* = 32.1 Hz), 125.92, 125.032 (d, *J* = 3.5 Hz), 123.72, 122.37, 122.32 (q, *J* = 273.9 Hz), 120.77, 117.55, 117.40, 116.33 (q, *J* = 5.4 Hz), 102.31, 67.57. HRMS (ESI): *m/z* $[M+H]^+$ calculated for $C_{24}H_{15}ClF_4N_5O_2$: 516.0845, found: 516.0831.

2-(4-chloro-3-(trifluoromethyl)phenoxy)-5-(((3-(pyrimidin-5-yl)imidazo[1,2-a]pyrimidin-7-yl)oxy)methyl)benzonitrile (14c). The title compound was obtained as a yellow solid from **5** and **13c** using a method similar to that described for compounds **7a-e** in 64% yield. ^{1}H NMR (300 MHz, Chloroform-d) δ 9.28 (s, 1H), 8.93 (s, 2H), 8.36 (d, *J* = 7.4 Hz, 1H), 7.85 (d, *J* = 1.8 Hz, 1H), 7.75 (s, 1H), 7.71 (dd, *J* = 8.6, 2.0 Hz, 1H), 7.54 (d, *J* = 8.8 Hz, 1H), 7.42 (d, *J* = 2.8 Hz, 1H), 7.20 (dd, *J* = 8.7, 2.7 Hz, 1H), 6.94 (d, *J* = 8.6 Hz, 1H), 6.63 (d, *J* = 7.4 Hz, 1H), 5.56 (s, 2H). ^{13}C NMR (101 MHz, Chloroform-d) δ 161.98, 158.07, 158.03, 155.11 (2C), 153.70, 149.29, 134.69, 133.95, 133.42, 133.23, 132.76, 132.42, 129.87 (q, *J* = 29.0 Hz), 128.20 (d, *J* = 1.7 Hz), 123.71, 123.65, 122.12 (q, *J* = 274.8 Hz), 118.47 (q, *J* = 5.4 Hz), 117.79, 117.51, 115.04, 104.82, 102.17, 66.87. HRMS (ESI): *m/z* $[M+H]^+$ calculated for $C_{25}H_{15}ClF_3N_6O_2$: 523.0892, found: 523.0868.

7-((3-chloro-4-(4-chloro-3-(trifluoromethyl)phenoxy)benzyl)oxy)-3-(pyrimidin-5

-yl)imidazo[1,2-a]pyrimidine (14d). The title compound was obtained as a white solid from **5** and **13d** using a method similar to that described for compounds **7a-e** in 36% yield. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.27 (s, 1H), 8.94 (s, 2H), 8.37 (d, *J* = 7.4 Hz, 1H), 7.77 (s, 1H), 7.65 (d, *J* = 1.8 Hz, 1H), 7.44 (m, 2H), 7.29 (d, *J* = 2.9 Hz, 1H), 7.07 (d, *J* = 8.3 Hz, 1H), 7.01 (dd, *J* = 8.8, 2.8 Hz, 1H), 6.65 (d, *J* = 7.4 Hz, 1H), 5.55 (s, 2H). ^{13}C NMR (126 MHz, Chloroform-d) δ 162.21, 158.04, 155.53, 155.09 (2C), 150.97, 149.45, 134.01, 133.36, 132.72, 132.55, 131.07, 129.87 (q, *J* = 36.2 Hz), 128.47, 126.57, 126.05, 123.71, 122.34 (q, *J* = 268.1 Hz), 121.57, 121.20, 117.41, 116.78 (q, *J* = 5.3 Hz), 102.33, 67.48. HRMS (ESI): *m/z* $[M+H]^+$ calculated for $C_{24}H_{15}Cl_2F_3N_5O_2$: 532.0549, found: 532.0539.

7-((4-(4-chloro-3-(trifluoromethyl)phenoxy)-3-(trifluoromethyl)benzyl)oxy)-3-(p yrimidin-5-yl)imidazo[1,2-a]pyrimidine (14e). The title compound was obtained as a white solid from **5** and **13e** using a method similar to that described for compounds **7a-e** in 41% yield. ^{1}H NMR (400 MHz, Chloroform-d) δ 9.27 (s, 1H), 8.93 (s, 2H), 8.36 (d, *J* = 7.4 Hz, 1H), 7.85 (d, *J* = 1.7 Hz, 1H), 7.75 (s, 1H), 7.69 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.48 (d, *J* = 8.8 Hz, 1H), 7.37 (d, *J* = 2.9 Hz, 1H), 7.11 (dd, *J* = 8.8, 2.8 Hz, 1H), 6.99 (d, *J* = 8.5 Hz, 1H), 6.63 (d, *J* = 7.4 Hz, 1H), 5.59 (s, 2H). ^{13}C NMR (126 MHz, Chloroform-d) δ 162.15, 158.06 (2C), 155.10 (2C), 153.89, 149.41, 133.83, 133.39, 132.95, 132.59, 132.03, 129.91 (q, *J* = 32.0 Hz), 127.75 (q, *J* = 4.8 Hz), 127.10, 123.69, 122.86, 122.86 (q, *J* = 273.3 Hz), 122.23 (q, *J* = 273.9 Hz), 122.33 (q, *J* = 30.9 Hz), 119.92, 118.26 (q, *J*

= 5.4 Hz), 117.44, 102.29, 67.49. HRMS (ESI): *m/z* $[M+H]^+$ calculated for $C_{25}H_{15}ClF_6N_5O_2$: 566.0813, found: 566.0830.

7-((4-(4-chloro-3-(trifluoromethyl)phenoxy)-3,5-difluorobenzyl)oxy)-3-(pyrimidin-5-yl)imidazo[1,2-a]pyrimidine (14f). The title compound was obtained as a white solid from **5** and **13f** using a method similar to that described for compounds **7a-e** in 68% yield. ^{1}H NMR (300 MHz, Chloroform-d) δ 9.28 (s, 1H), 8.94 (s, 2H), 8.37 (d, *J* = 7.4 Hz, 1H), 7.76 (s, 1H), 7.42 (d, *J* = 8.8 Hz, 1H), 7.30 (d, *J* = 2.9 Hz, 1H), 7.20 (d, *J* = 8.1 Hz, 2H), 7.03 (dd, *J* = 8.7, 2.7 Hz, 1H), 6.65 (d, *J* = 7.4 Hz, 1H), 5.56 (s, 2H). ^{13}C NMR (101 MHz, Chloroform-d) δ 161.99, 158.10, 155.83, 155.71 (dd, *J* = 253.5, 4.4 Hz, 2C), 155.137 (2C), 149.29, 134.88 (t, *J* = 8.4 Hz), 133.40, 132.78, 132.61, 130.19, 129.53 (q, *J* = 32.2 Hz), 126.00, 123.63, 122.29 (q, *J* = 274.2 Hz), 119.36, 117.53, 115.10 (q, *J* = 5.4 Hz), 112.33 (dd, *J* = 17.3, 5.4 Hz, 2C), 102.18, 67.02. HRMS (ESI): *m/z* $[M+H]^+$ calculated for $C_{24}H_{14}ClF_5N_5O_2$: 534.0751, found: 534.0764.

7-((3,5-difluoro-4-phenoxybenzyl)oxy)-3-(pyrimidin-5-yl)imidazo[1,2-a]pyrimidine (14g). The title compound was obtained as a white solid from **5** and **13g** using a method similar to that described for compounds **7a-e** in 48% yield. ^{1}H NMR (400 MHz, Chloroform-d) δ 9.27 (s, 1H), 8.93 (s, 2H), 8.37 (d, *J* = 7.4 Hz, 1H), 7.76 (s, 1H), 7.33−7.28 (m, 2H), 7.17 (d, *J* = 8.0 Hz, 2H), 7.07 (t, *J* = 7.4 Hz, 1H), 6.95 (d, *J* = 8.2 Hz, 2H), 6.65 (d, *J* = 7.4 Hz, 1H), 5.54 (s, 2H). ^{13}C NMR (126 MHz, Chloroform-d) δ 162.05, 158.05, 157.60, 156.14 (dd, *J* = 252.8, 4.8 Hz, 2C), 155.11 (2C), 149.36, 133.72 (t, *J* =

8.4 Hz), 133.39, 132.68, 131.151 (t, *J* = 15.4 Hz), 129.62 (2C), 123.68, 123.01, 117.46, 115.25 (2C), 112.17 (dd, *J* = 18.3, 5.3 Hz, 2C), 102.22, 67.20. HRMS (ESI): *m/z* $[M+H]^+$ calculated for $C_{23}H_{16}F_2N_5O_2$: 432.1267, found: 432.1267.

7-((3,5-difluoro-4-(4-fluoro-3-(trifluoromethyl)phenoxy)benzyl)oxy)-3-(pyrimidin-5-yl)imidazo[1,2-a]pyrimidine (14h). The title compound was obtained as a white solid from **5** and **13h** using a method similar to that described for compounds **7a-e** in 63% yield. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 9.31 (s, 1H), 8.96 (s, 2H), 8.39 (d, *J* = 7.2 Hz, 1H), 7.81 (s, 1H), 7.24−7.08 (m, 5H), 6.73 (d, *J* = 7.3 Hz, 1H), 5.58 (s, 2H). ^{13}C NMR (126 MHz, Chloroform-d) δ 161.96, 158.09, 155.77 (dd, *J* = 252.9, 4.2 Hz, 2C), 155.29 (d, *J* = 250.6 Hz), 155.12 (2C), 153.13, 149.30, 134.66 (t, *J* = 8.1 Hz), 133.43, 132.74, 130.64 (t, *J* = 15.1 Hz), 123.64, 122.03 (q, *J* = 273.0 Hz), 120.30 (d, *J* = 8.2 Hz), 118.11, 117.93, 117.50, 114.14 (d, *J* = 4.3 Hz), 112.32 (dd, *J* = 18.4, 4.8 Hz, 2C), 102.16, 67.02. HRMS (ESI): *m/z* $[M+H]^+$ calculated for $C_{24}H_{14}F_6N_5O_2$: 518.1046, found: 518.1105.

7-((3,5-difluoro-4-(3-(trifluoromethyl)phenoxy)benzyl)oxy)-3-(pyrimidin-5-yl)imidazo[1,2-a]pyrimidine (14i). The title compound was obtained as a white solid from **5** and **13i** using a method similar to that described for compounds **7a-e** in 69% yield. ^{1}H NMR (300 MHz, Chloroform-d) δ 9.30 (s, 1H), 8.95 (s, 2H), 8.39 (d, *J* = 6.5 Hz, 1H), 7.80 (s, 1H), 7.43 (t, *J* = 7.9 Hz, 1H), 7.34 (d, *J* = 7.8 Hz, 1H), 7.21 (d, *J* = 8.3 Hz, 3H), 7.12 (d, *J* = 7.1 Hz, 1H), 6.71 (d, *J* = 6.0 Hz, 1H), 5.58 (s, 2H). ^{13}C NMR (126 MHz, Chloroform-d) δ 162.05, 158.09, 157.55, 155.85 (dd, *J* = 252.8, 4.7 Hz, 2C), 155.13 (2C),

149.30, 134.49 (t, *J* = 8.3 Hz), 133.32, 132.76, 132.16 (q, *J* = 32.9 Hz), 130.37 (t, *J* = 15.4 Hz), 130.29, 123.61, 123.58 (q, *J* = 279.1 Hz), 119.84 (d, *J* = 3.6 Hz), 118.53, 117.51, 112.45, 112.32 (dd, *J* = 19.0, 4.9 Hz, 2C), 102.25, 67.11. HRMS (ESI): *m/z* $[M+H]^+$ calculated for $C_{24}H_{15}F_5N_5O_2$: 500.1140, found: 500.1146.

7-((4-(3,4-dichlorophenoxy)-3,5-difluorobenzyl)oxy)-3-(pyrimidin-5-yl)imidazo[1,2-a]pyrimidine (14j). The title compound was obtained as a white solid from **5** and **13j** using a method similar to that described for compounds **7a-e** in 45% yield. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.28 (s, 1H), 8.94 (s, 2H), 8.37 (d, *J* = 7.4 Hz, 1H), 7.76 (s, 1H), 7.36 (d, *J* = 8.9 Hz, 1H), 7.19 (d, *J* = 8.0 Hz, 2H), 7.04 (d, *J* = 3.2 Hz, 1H), 6.84 (dd, *J* = 9.0, 2.8 Hz, 1H), 6.65 (d, *J* = 7.5 Hz, 1H), 5.56 (s, 2H). ^{13}C NMR (126 MHz, Chloroform-d) δ 161.95, 158.06, 156.34, 155.76 (dd, *J* = 253.0, 4.4 Hz, 2C), 155.10 (2C), 149.29, 134.65(t, *J* = 8.1 Hz), 133.42, 133.20, 132.75, 130.93, 130.36 (t, *J* = 15.1 Hz), 126.62, 123.64, 117.49, 117.38, 115.11, 112.29 (dd, *J* = 18.4, 4.9 Hz, 2C), 102.15, 67.02. HRMS (ESI): *m/z* $[M+H]^+$ calculated for $C_{23}H_{14}Cl_2F_2N_5O_2$: 500.0487, found: 500.0506.

7-((3,5-difluoro-4-(4-(trifluoromethyl)phenoxy)benzyl)oxy)-3-(pyrimidin-5-yl)imidazo[1,2-a]pyrimidine (14k). The title compound was obtained as a white solid from **5** and **13k** using a method similar to that described for compounds **7a-e** in 59% yield. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.28 (s, 1H), 8.94 (s, 2H), 8.38 (d, *J* = 7.4 Hz, 1H), 7.77 (s, 1H), 7.57 (d, *J* = 8.6 Hz, 2H), 7.24−7.17 (m, 2H), 7.02 (d, *J* = 8.6 Hz, 2H), 6.66 (d, *J* = 7.4 Hz, 1H), 5.56 (s, 2H). ^{13}C NMR (126 MHz, Chloroform-d) δ 162.03, 159.77,

158.12, 155.84 (dd, J = 253.0, 4.5 Hz, 2C), 155.15 (2C), 149.29, 134.60, 133.34, 132.75, 130.24 (t, J = 15.0 Hz), 127.17 (q, J = 3.6 Hz, 2C), 125.32 (q, J = 32.8 Hz), 124.03 (q, J = 271.9 Hz), 123.59, 117.52, 115.34 (2C), 112.26 (dd, J = 18.3, 4.8 Hz, 2C), 102.24, 67.09. HRMS (ESI): *m/z* $[M+H]^+$ calculated for $C_{24}H_{15}F_5N_5O_2$: 500.1140, found: 500.1170.

7-((4-((6-chloropyridin-3-yl)oxy)-3,5-difluorobenzyl)oxy)-3-(pyrimidin-5-yl)imidazo[1,2-a]pyrimidine (14l). The title compound was obtained as a white solid from **5** and **13l** using a method similar to that described for compounds **7a-e** in 34% yield. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.28 (s, 1H), 8.94 (s, 2H), 8.37 (d, J = 7.4 Hz, 1H), 8.14 (d, J = 2.8 Hz, 1H), 7.76 (s, 1H), 7.26−7.24 (m, 2H), 7.20 (d, J = 8.1 Hz, 2H), 6.65 (d, J = 7.4 Hz, 1H), 5.56 (s, 2H). ^{13}C NMR (126 MHz, Chloroform-d) δ 161.91, 158.07, 155.54 (dd, J = 252.9, 4.3 Hz, 2C), 155.11 (2C), 153.19, 149.26, 145.00, 137.83, 134.94 (t, J = 8.2 Hz), 133.41, 132.79, 130.27 (t, J = 15.6 Hz), 125.72, 124.68, 123.62, 117.51, 112.32 (dd, J = 18.3, 4.8 Hz, 2C), 102.14, 66.94. HRMS (ESI): *m/z* $[M+H]^+$ calculated for $C_{22}H_{14}ClF_2N_6O_2$: 467.0829, found: 467.0849.

7-((3,5-difluoro-4-((6-(trifluoromethyl)pyridin-3-yl)oxy)benzyl)oxy)-3-(pyrimidin-5-yl)imidazo[1,2-a]pyrimidine (14m). The title compound was obtained as a white solid from **5** and **13m** using a method similar to that described for compounds **7a-e** in 48% yield. ^{1}H NMR (400 MHz, Chloroform-d) δ 9.28 (s, 1H), 8.93 (s, 2H), 8.49 (d, J = 2.7 Hz, 1H), 8.37 (d, J = 7.4 Hz, 1H), 7.76 (s, 1H), 7.64 (d, J = 8.6 Hz, 1H), 7.32 (dd, J = 8.9, 2.5

Hz, 1H), 7.23 (d, *J* = 8.0 Hz, 2H), 6.65 (d, *J* = 7.4 Hz, 1H), 5.57 (s, 2H). ^{13}C NMR (126 MHz, Chloroform-d) δ 161.91, 158.13, 155.49 (dd, *J* = 253.3, 3.9 Hz, 2C), 155.48, 155.15 (2C), 149.3, 138.87, 135.5, 133.44, 132.78, 129.87 (q, *J* = 36.8 Hz), 128.64, 123.62, 122.50, 121.53 (d, *J* = 2.3 Hz), 120.33, 117.55, 112.37 (dd, *J* = 18.6, 4.8 Hz, 2C), 102.13, 66.91. HRMS (ESI): *m/z* $[M+H]^+$ calculated for $C_{23}H_{14}F_5N_6O_2$: 501.1093, found: 501.1132.

ASSOCIATED CONTENT

Supporting information

Experimental procedures for intermediates **6a-e**, **13a-m,** HPLC for all the final compounds, and spectral data of compound **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHER INFORMATION

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Notes

The authors declare no competing financial interest.

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ABBREVIATIONS USED

MW, molecular weight; cLogP, calculated logP; rt, room temperature; *m*-CPBA, 3-chloroperbenzoic acid; NBS, bromosuccinimide; TMSOTf, trimethylsilyl trifluoromethanesulfonate; TEA, triethylamine; DMA, N,N-dimethylacetamide; THF, tetrahydrofuran; DCM, dichloromethane; SD rats, Sprague-Dawley rats; TLC, thin-layer chromatography.

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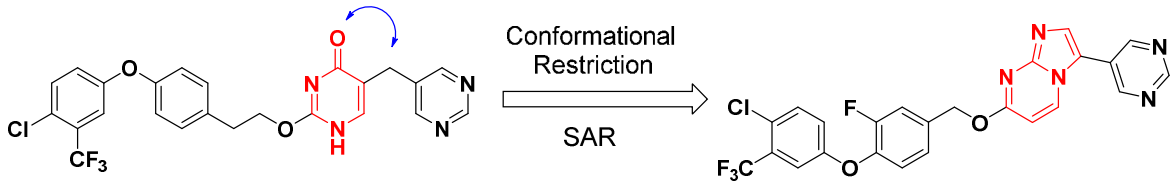
Table of contents graphic



Literature structure