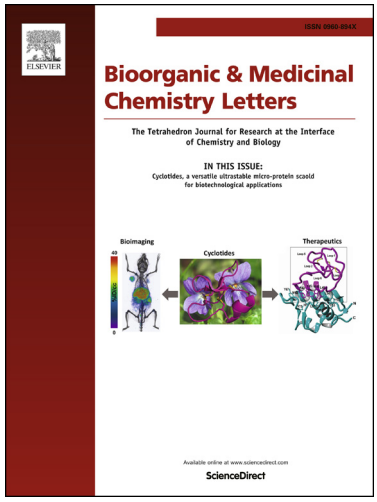

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Regioselectivity of Thiouracile Alkylation: Application to Optimization of Darapladib Synthesis

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ABSTRACT

Darapladib is one of the most potent Lp-PLA$_2$ (Lipoprotein-associated phospholipase A$_2$) inhibitor with an IC$_{50}$ of 0.25 nM. We demonstrate that a crucial step of Darapladib synthesis was not correctly described in the literature, leading to the production of wrong regioisomers. Moreover we show that the inhibitory activity is directly linked to the position on *N1* since compounds bearing alkylation on different sites have potentially less interaction within the active site of Lp-PLA$_2$.

Atherosclerosis is characterized by an accumulation of lipids and leukocytes within the vascular wall of large arteries, leading to their occlusion and subsequent clinical events such as myocardial infarction and ischemic stroke. In western countries, atherosclerotic complications are responsible for about 50% of death.[1] Hydrolysis of oxidized phospholipids in low density lipoproteins (LDL) mediated by lipoprotein-associated phospholipase A$_2$ (Lp-PLA$_2$)[2] plays an important role in atheroma plaque development by promoting the recruitment of leukocytes. Clinical studies have shown that plasma Lp-PLA[2] levels were correlated with cardiovascular events.[3] *In situ*, the expression of Lp-PLA$_2$ was higher in carotid atherosclerotic plaques from symptomatic than asymptomatic patients. This enzyme thus became a particularly valuable biomarker candidate for assessment of the cardiovascular risk as well as a promising therapeutic target.[4] GSK was among the first company to design Lp-PLA$_2$ inhibitors.[5]

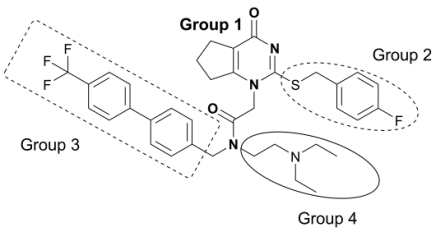


Figure 1. Four moieties of Darapladib involved in Lp-PLA$_2$ recognition.

In 2003, GSK discovered a new and highly potent (IC$_{50}$ = 0.25 nM) candidate, named Darapladib (**14**)[6] (**Figure 1**). After the publication of these results, many groups worked on the synthesis of analogs of **14**, in order to test their Lp-PLA$_2$ inhibitory effect in biological systems[7] or even designed new classes of compounds.[8] Unfortunately, in coronary heart disease patients, **14** did not meet Phase III endpoints in clinical trials.[9] However, recent studies have shown promising results using another Lp-PLA$_2$ inhibitor on the progression of Alzheimer disease[10] or diabetic macular edema.[11] Since Lp-PLA$_2$ inhibitors may be used to thwart the deleterious effect of this enzyme in different pathologies, we have synthesized our own series of inhibitors using the key structure of **14**. There are currently three different synthetic pathways reported to produce **14** (**Figure 2**).

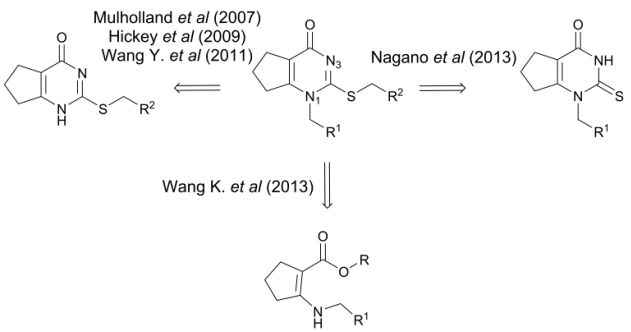
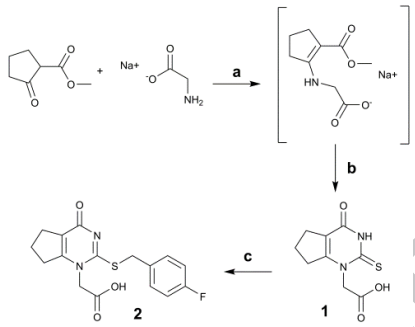


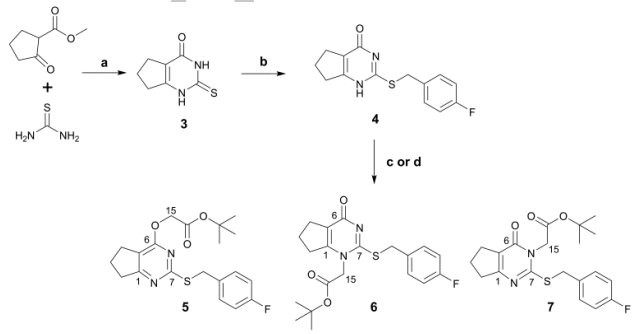
Figure 2. Retrosynthetic pathways leading to alkylated thiouracil ring formation in the synthesis of **14**.

The first one, described in 2003 by Therkelsen *et al.*[12], uses a convergent method, ending with the pyrimidinone ring closure followed by substitution by the sulfur. It was then adapted to **14** in 2013 by Wang K. *et al.*[13]. Two other routes were described using a divergent approach. In 2011, Cardwell *et al.* patented a synthesis that allowed *N1*-alkylation of the thiouracile ring.[14] In 2013, Nagano *et al.* used this method for the synthesis of their analogs,[7] but the reproducibility was lower than that obtained by GSK. The second process developed by Hickey *et al.* involves thiouracile ring closure followed by the alkylation of the *N1* position.[15] The literature is not consistent concerning the reaction conditions used to obtain this substitution. Whereas Shen *et al.* worked in refluxing THF,[16] Azad et al. and Wang Y. et al. performed the alkylation in DMF or MeCN.[17,18] Perumal *et al.* and Achaiah *et al.* worked in DMF and THF with thiouracile analogs close to groups 1 and 2 structure.[19,20] To optimize every step of our synthesis, we looked for the best route by comparing existing methods, tested in parallel. We demonstrate here that one of these three pathways leads to alkylation on the wrong site of the thiouracile ring. Divergent synthesis of **14** allows various changes of the original structure on all groups 1, 2, 3 or 4 (**Figure 1**). In this article, focus will be given on the cyclopentapyrimidine ring and fluorobenzyl sulfane moieties since diethylpropan-amine and trifluoromethyl-biphenyl moieties are obtained without ambiguity.[7] The first synthesis proposed is summarized in **Scheme 1**.



Scheme 1. Synthesis of Groups 1 and 2 using *N1*-substituted key intermediate **1**. Reagents and conditions: (a) NMP, 60°C; (b) NaSCN, TMSCl, 120°C, 58%; (c) 4-fluorobenzyl chloride, KOH, K_2CO_3, H_2O/IPA, 40°C, 60%.

The condensation of the glycine sodium salt on methyl 2-oxocyclopentanecarboxylate leads to the non-isolated enamine that reacts with sodium thiocyanate to yield compound **1** (58%). Intermediate **2** is obtained via substitution on the free sulfur by 4-fluorobenzyl chloride in 60% yield.



Scheme 2. Synthesis of groups 1 and 2 involving differences in selectivity of compound **4**. Reagents and conditions: (a) DBU, MeCN, reflux, 65%; (b) K_2CO_3, KI, 4-fluorobenzylchloride, acetone, reflux, 92%; (c) tert-butyl bromoacetate, K_2CO_3, DMF, 75°C, **5** only 96%; (d) tert-Butyl bromoacetate, DiPEA, DCM, reflux, mixture of **5** (7%), **6** (21%) and **7** (27%).

However, this yield was not reproducible as also published by Nagano *et al.* who showed only a 10% yield for the first step in their analog synthesis. The second route involves free *N1* on the pyrimidinone ring in the first 2 steps as shown on **Scheme 2**. Thiourea was condensed on methyl 2-oxocyclopentanecarboxylate to give in 65% yield thiouracile **3** which is reacted with 4-fluorobenzyl chloride in order to obtain the key intermediate **4** (92%). At this step, literature diverges regarding the conditions to perform the substitution on the *N1* position (**Figure 3**).

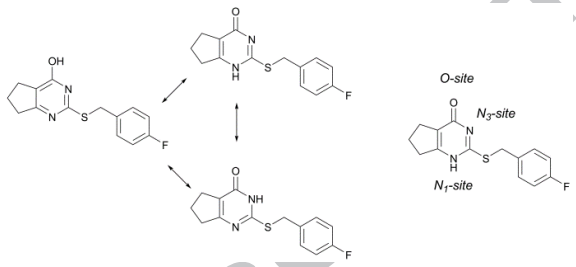
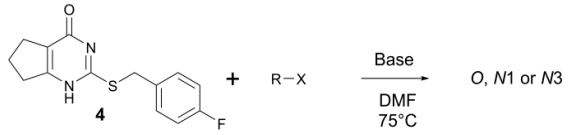


Figure 3. Mesomeric forms of 4 conferring three different potential alkylation sites.

Wang Y. *et al.* worked in DMF or MeCN using K_2CO_3 as a base and yielded a single regioisomer which they assigned to be *N1*-alkyated (≥ 90% yields for all analogs). Hickey *et al.* used less effective conditions, working in diluted DCM with DiPEA as the base and they assigned their major product as the *N1*-alkylated compound **6** in 37% yield. Both methods allowed acid **2** formation via hydrolysis in high yields.

In order to optimize our synthesis, we compared both Wang and Hickey's methods (**Scheme 2**). Following the exact procedure in DMF by Wang Y. *et al.*, we obtained a product supposed to be the ester **6** in 96% yield whereas using Hickey's protocol to obtain the same compound, we recovered another product with 10% yield. Both esters obtained behaved differently on SiO_2 TLC (0.95 and 0.25 in 40/60 Hex/EtOAc for Wang Y. and Hickey's methods respectively). Moreover, ^{13}C and ^{1}H NMR experiments supported the conclusion that both products were different (**Figure 4**). Indeed, in DMF at 75°C, we obtained the *O*-alkylated compound **5** whereas in DCM, the *N1*-alkylated desired product **6** was recovered. We then improved Hickey's conditions by working with refluxing DCM instead of room temperature (**Scheme 2**, condition d) and recovered **5**, **6** and **7** after purification (7%, 21% and 27%, respectively), allowing a better yield for compound **6**. The three possible mesomeric forms of compound **4** (**Figure 3**) allow 3 different alkylation sites thus forming 3 different regioisomers. In Hickey's conditions, the poor solubility of compound **4** in DCM led to very poor overall yields of **5**, **6** and **7**. Indeed, after purification, 35% of unreacted starting material were recovered. Changing the leaving group for a iodine instead of a bromine at either 40°C (DCM) or 80°C (DCE) did not improve yields (12 and 14% respectively). HMBC experiments allowed us to unambiguously assign the 3 isomers **5**, **6**, **7** obtained in Hickey's method. The α-carbon of the ester (C_{15}) was identified in the isomers to be 63 ppm (*O*-CH_2), 50 ppm (*N1*-CH_2) and 45 ppm (*N3*-CH_2) for the isomers **5**, **6**, and **7** respectively. The C_{15} was observed to couple in the HBMC spectra to C_1 in isomer **5**, C_1 and C_7 in isomer **6**, and C_6 and C_7 in isomer **7** (**Scheme 2**, also see supporting information). In DMF at 75°C (Wang's method), since we only obtained compound **5** (but not compound **6**) in 96% yield, we then tried to make changes on the base and alkylating agents in order to influence the regioselectivity of alkylation (see **Table 1**).

Table 1. Change in alkylating agent and base on substitution yields (via Wang's method).



Entry	Base	R-X	*O*	*N1*	*N3*
1	K_2CO_3		96(**5**)	0	0
2	DiPEA		95(**5**)	0	0
3	NMM		97(**5**)	0	0
4	K_2CO_3		21(**9**)	0	0
5	K_2CO_3		58(**9**)	0	0

[a]Yields were calculated after chromatographic purification on silica gel.

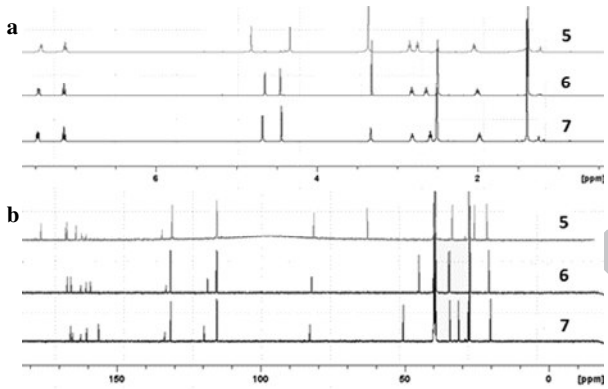
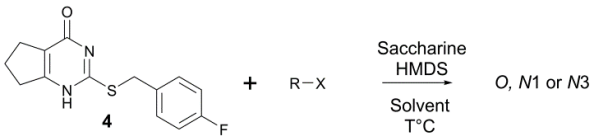


Figure 4. ^1H and ^{13}C spectra in DMSO-d_6 of **5**, **6** and **7**. **a**: ^1H NMR spectra; **b**: ^{13}C NMR spectra.

However, no displacement of selectivity was observed and only *O*-alkylated compounds **5** and **9** were recovered (see supporting information). When moving from halogens to a tosylate (**10**) or a triflate (**11**), we also observed decreasing yields (entries **4** and **5**). Surprisingly, these results do not follow the general reactivity of leaving groups.[21] The thiouracile ring from compound **4** comprises a keto-enol tautomerism providing three potential alkylation sites. Low polar aprotic solvent (such as DCM) may favor *N*-alkylation whereas polar aprotic (such as DMF) gave exclusively the *O*-alkylated isomer. In 2004, Mulholland *et al.* patented an innovative method leading to selective *N1*-alkylation of the thiouracile ring.[22] The 2 first steps used in our synthesis are depicted in **Scheme 3**.

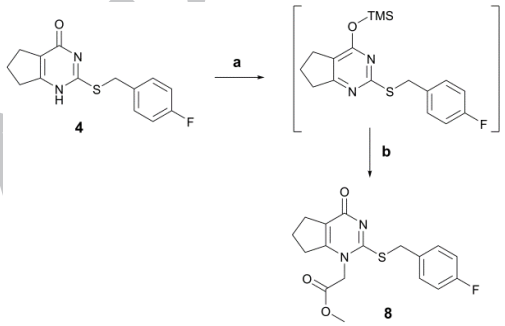
This method allows the formation of the silyl ether which protects the *O* and *N3*-alkylation sites. Using these experimental conditions, we obtained the desired compound **8** in 93% yield. However, this approach requires a triflate as a leaving group, which makes the synthesis more tedious since they are unstable. **Table 2** shows our attempts to change the leaving group or the solvent in Mulholland's conditions. When the silyl ether is formed, if the leaving group was a tosylated alcohol (**11**) or an alkyl halide (entries **1**, **2** and **3**), the *N1*-alkylation product was not formed and only starting material was recovered.

Table 2. Change in alkylating agent and solvent on substitution yields (via Mulholland's method).



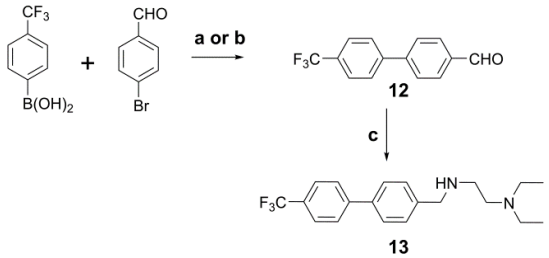
Entry	Solvent	R-X	O^a	$N1^a$	$N3^a$
1	DCM/40°C		0	0	0
2	DCM/40°C		0	0	0
3	DCM/40°C		0	0	0
4	DCM/40°C		0	93(**8**)	0
5	DMF/75°C		26(**7**)	0	26(**5**)

[a]Yields were calculated after chromatographic purification on silica gel.



Scheme 3. Selective *N1*-alkylation of the thiouracile ring (adapted from Mulholland's method). Reagents and conditions: (a) saccharin, HMDS, DCM, reflux; (b) (trifluoromethanesulfonyloxy)-acetic acid methyl ester, DCM, reflux;

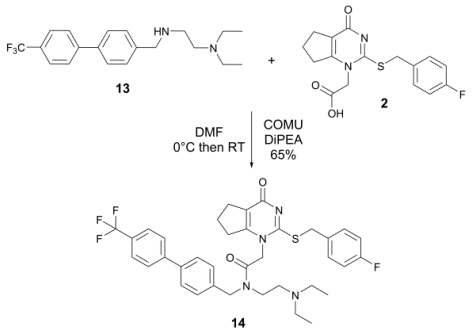
In order to obtain groups 3 and 4 of **14**, we synthesized **12** via Suzuki coupling in 89% yield (**Scheme 4**). We then optimized this step in water[23] which allowed us to increase our yield up to 98% without chromatographic purification.



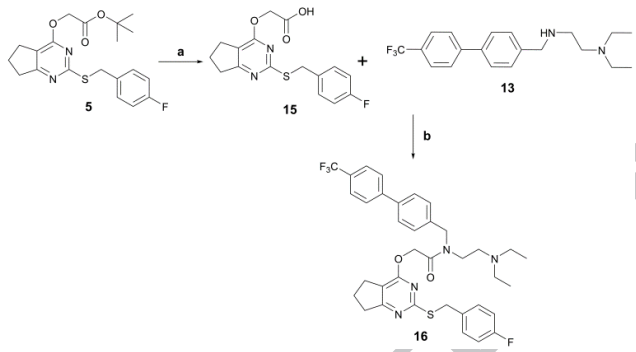
Scheme 4. Optimization of the synthesis of groups 3 and 4. Reagents and conditions: (a) $Pd(OAc)_2$, TBAB, K_2CO_3, dioxane/water, 70°C, 89%; (b) $Pd(OAc)_2$, TBAB, Na_2CO_3, water, 150°C, 98% ; (c) $NaBH(OAc)_3$, *N,N*-diethylethylenediamine, DCM, 0°C then RT, 80% ;

The subsequent reductive amination led to **13** which was obtained in 70% yield over 3 steps. We were then able to react **2** and **13** in a peptide coupling reaction[24] forming **14** in 65% yield after complete purification (**Scheme 5**). As shown in **Scheme 6**, we also synthesized the *O*-alkylated Darapladib (**16**) in order to

test its Lp-PLA$_2$ inhibitory activity. We were able to hydrolyze efficiently **5** in 76% yield. The peptide coupling allowed **16** isolation in 80% yield. Both Woolford *et al* and Liu *et al* showed that the thiouracile moiety and particularly the carbonyl oxygen forms hydrogen bonding with Leu153, Phe274 and Gln352 while the fluorophenyl moiety interacts with Leu107, Leu159, Ala355 and Phe357 in the active site of Lp-PLA$_2$.[25,26] Group 4 brings lipophilic interactions with Phe125 along with π-π interactions that improve the already strong affinity towards Lp-PLA$_2$. However, in the case of *O*-alkylated products, the carbonyl oxygen may not be available to interact within the active site of the enzyme.



Scheme 5. Peptide coupling in the divergent synthesis of **14**.



Scheme 6. Synthesis of **16**. Reagents and conditions: (a) TFA, DCM, RT, 76%; (b) COMU, DiPEA, DMF, 0°C then RT, 80%.

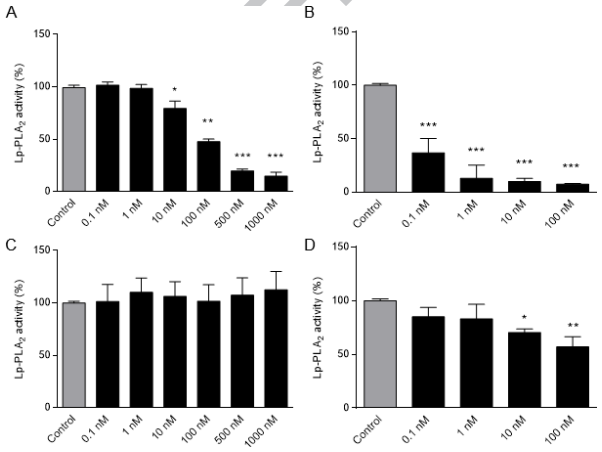


Figure 5. Lp-PLA$_2$ activity test of **14** compared to 3 synthesized analogs. A: (**6**), B: (**14**), C: (**5**), D: (**16**). Data are expressed as means ± SEM of three independent experiments performed in triplicate. Statistical evaluation was performed by using one-way ANOVA and Tukey test (PRISM software). Significant differences were considered for p values inferior to 0.05. *p<0.05, **p<0.01, ***p<0.001 as compared to control.

To test this hypothesis, we decided to compare the ability of **14**, **16**, and esters **5**, **6** to inhibit Lp-PLA$_2$ (**Figure 5**) according to the protocol described in the experimental section. **5** did not inhibit Lp-PLA$_2$ activity whereas **6** showed a dose-dependent inhibitory effect. This underlines the importance of the regioisomer since *O*-alkylated chains block the crucial interaction within the enzyme recognition site. The same effect can be observed with **14** and **16**.

Our work summarizes different methods to synthesize **14** and points out ambiguities in the literature during the alkylation of the thiouracile intermediate. We have shown that, based on our results, alkylation in DMF yield most likely the *O*-alkylated analogs instead of the *N1*-alkylated isomers as claimed by the literature. We showed that the method developed by GSK (Mulholland's method) is highly substrate-dependent and cannot be used without triflated alcohols. **14**, **6** as well as **16** and **5** were tested for their ability to inhibit Lp-PLA$_2$. *In vitro* experiments demonstrated that the *O*-alkylated molecules did not modify Lp-PLA$_2$ activity compared to *N1*-alkylated compounds. In conclusion, caution should be exerted when modifying experimental conditions (temperature, solvent, etc.) that may lead to the production of unexpected regioisomers. A more advanced characterization analysis such as 2D NMR should be performed to ascertain the exact structure of the desired compounds.

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References and notes

There are no conflicts to declare. The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript

1. Lusis, A. J. *Nature* **2000**, *407*, 233.
2. Zalewski, A.; Macphee, C. *Arterioscler. Thromb. Vasc. Biol.* **2005**, *25*, 923.
3. Madjid, M.; Ali, M.; Willerson, J. T. *Tex. Heart Inst. J.* **2010**, *37*, 25.
4. Cai, A.; Zheng, D.; Qiu, R.; Mai, W.; Zhou, Y. *Dis. Markers* **2013**, *34*, 323.
5. Tew, D. G.; Boyd, H. F.; Ashman, S.; Theobald, C.; Leach, C. A. *Biochemistry* **1998**, *37*, 10087.
6. Blackie, J. A.; Bloomer, J. C.; Brown, M. J. B.; Cheng, H.-Y.; Hammond, B.; Hickey, D. M. B.; Ife, R. J.; Leach, C. A.; Lewis, V. A.; Macphee, C. H.; Milliner, K. J.; Moores, K. E.; Pinto, I. L.; Smith, S. A.; Stansfield, I. G.; Stanway, S. J.; Taylor, M. A.; Theobald, C. J. *Bioorg. Med. Chem. Lett*. **2003**, *13*, 1067.
7. Nagano, J. M.; Hsu, K. L.; Whitby, L. R.; Niphakis, M. J.; Speers, A. E.; Brown, S. J.; Spicer, T.; Fernandez-Vega, V.; Ferguson, J.; Hodder, P.; Srinivasan, P.; Gonzalez, T. D.; Rosen, H.; Bahnson, B. J.; Cravatt, B. F. *Bioorg. Med. Chem. Lett*. **2013**, *23*, 839.
8. Wang, K.; Xu, W.; Liu, Y.; Zhang, W.; Wang, W.; Shen, J.; Wang, Y. *Bioorg. Med. Chem. Lett*. **2013**, *23*, 1187.
9. White, H. D.; Held, C.; Stewart, R.; Tarka, E.; Brown, R.; Davies, R. Y.; Budaj, A.; Harrington, R. A.; Steg, P. G.; Ardissino, D.; Armstrong, P. W.; Avezum, A.; Aylward, P. E.; Bryce, A.; Chen, H.; Chen, M. F.; Corbalan, R.; Dalby, A. J.; Danchin, N.; De

Winter, R. J.; Denchev, S.; Diaz, R.; Elisaf, M.; Flather, M. D.; Goudev, A. R.; Granger, C. B.; Grinfeld, L.; Hochman, J. S.; Husted, S.; Kim, H. S.; Koenig, W.; Linhart, A.; Lonn, E.; López-Sendón, J.; Manolis, A. J.; Mohler, E. R. 3rd; Nicolau, J. C.; Pais, P.; Parkhomenko, A.; Pedersen, T. R.; Pella, D.; Ramos-Corrales, M. A.; Ruda, M.; Sereg, M.; Siddique, S.; Sinnaeve, P.; Smith, P.; Sritara, P.; Swart, H. P.; Sy, R. G.; Teramoto, T.; Tse, H. F.; Watson, D.; Weaver, W. D.; Weiss, R.; Viigimaa, M.; Vinereanu, D.; Zhu, J.; Cannon, C. P.; Wallentin, L. *N. Engl. J. Med.* **2014**, *370*, 1702.

10. Maher-Edwards, G.; De'Ath, J.; Barnett, C.; Lavrov, A.; Lockhart, A. *Alzheimer's Dementia: Transl. Res. Clin. Interventions*. **2015**, *1*, 131.
11. Chen, X.; Wang, K.; Xu, W.; Ma, Q.; Chen, M.; Du, L.; Mo, M.; Wang, Y.; Shen, J. *J. Med. Chem.* **2016**, *59*, 2674.
12. Therkelsen, F. D.; Hansen, A. L.; Pedersen, E. B.; Nielsen, C. *Org. Biomol. Chem.* **2003**, *1*, 2908.
13. Wang, K.; Xu, W.; Zhang, W.; Mo, M.; Wang, Y.; Shen, J. *Bioorg. Med. Chem. Lett*. **2013**, *23*, 2897.
14. Cardwell, K. S.; Crawford, C. F.; Davies, S. H.; Wade, C. E. Novel processes. *WO Patent* 146,494, **2011**.
15. Hickey, D. M. B. H.; Robert J.; Leach, C. A.; Pinto, I. L.; Smith, S. A.; Stanway, S. J. Pyrimidine compounds. *US Patent* 7,638,520, **2009**.
16. Shen, J. S.; Wang, Y.; Wang, K. Azole heterocyclic compound, preparation method, pharmaceutical composition and use. *US Patent* 0,171,431, **2014**.
17. Azad, M. A. K.; Jain, A. K.; Pandey, G.; Singh, K.; Prasad, M. Processes for the preparation of darapladib and its intermediates. *WO Patent* 087,239, **2015**.
18. Wang, Y.; Xu, W. R.; Shao, H.; Xie, Y. F.; Wang, J. W. *Chin. J. Chem.* **2011**, *29*, 2039.
19. Praveen, C.; Parthasarathy, K.; Kumar, P. S.; Perumal, P. T. *Indian J. Chem.* **2015**, *54B*, 373.
20. Aruna, G.; Jyostna T. S.; Achaiah G. *Int. J. Pharm. Sci. Nanotech.* **2010**, *3*, 877.
21. Singh, M. S. *Advanced Organic Chemistry: Reactions And Mechanisms*. Dorling Kindersley (RS) Prentice Hall, **2004**, p 87.
22. Mulholland, K. R.; Ross, A. R.; Slater, G. R.; Smith, G. E. Process to prepare (1-carboxymethyl)-pyrimidinone compounds. *US Patent* 7,232,902, **2007**
23. Leadbeater, N. E.; Marco, M. *J. Org. Chem.* **2003**, *68*, 888.
24. El-Faham, A.; Albericio, F. *J. Pept. Sci*. **2010**, *16*, 6.
25. Woolford A, J.-A.; Pero J. E.; Aravapalli S.; Berdini V.; Coyle J. E.; Day P. J.; Dodson A. M.; Grondin P.; Holding F. P.; Lee L. Y. W.; Li P.; Manas E. S.; Marino J. P.; Martin A. C. L.; McCleland B. W.; McMenamin R. L.; Murray C. W.; Neipp C. E.; Page L. W.; Patel V. K.; Potvain F.; Rich S. J.; Rivero R. A.; Smith K.; Somers D. O.; Trottet L.; Velagaleti R.; Williams G.; Xie R. *J. Med. Chem.* **2016**, *59*, 5356.
26. Liu, Q. F.; Chen, X. D.; Chen, W. Y.; Yuan, X. J.; Su, H. X.; Shen, J. H.; Xu, Y. C. *J. Med. Chem.* **2016**, *59*, 5115.

Supplementary Material

Supporting Information Available: NMR spectra including 1D (^{1}H and ^{13}C) and 2D (HMBC), NMR attributions. Structure of compound **9**.

Graphical Abstract

Regioselectivity of Thiouracile Alkylation: Application to Optimization of Darapladib Synthesis

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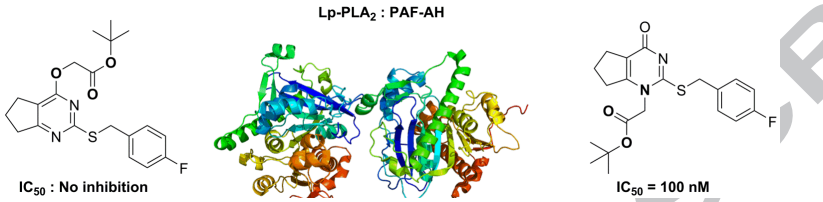

Highlights

- Thiouracile bears a keto-enol tautomerism allowing three different alkylation sites
- Inconsistent alkylation conditions led to the publication of wrong regioisomers
- Alkylation position is linked to the interaction between the inhibitor and Lp-PLA_2
- A new potent inhibitor of Lp-PLA_2 (52 nM) is described and should be tested in vivo