Tetrahedron Letters 55 (2014) 7229–7232

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Regioselective synthesis of multiply halogenated azaxanthones

Wenyuan Qian *, James Brown, Jian Jeffrey Chen, Yuan Cheng

Department of Medicinal Chemistry, Amgen Inc., One Amgen Center Drive, Thousand Oaks, CA 91320-1799, United States

ARTICLE INFO

Article history:
Received 23 October 2014
Revised 5 November 2014
Accepted 6 November 2014
Available online 13 November 2014

Keywords:
Azaxanthones
Multiple halogen substitution
Regiochemistry
Amide-directed metalation
Cyclization
Heterocycle synthesis

ABSTRACT

Four multiply halogenated azaxanthones **3**, **4b**, **5**, and **6** were synthesized as novel core building blocks of β-site amyloid precursor protein cleaving enzyme 1 (BACE1) inhibitors. Each of these heterocycles requires a specific synthetic strategy to control not only the aza-positions, but also the regiochemistry of the fully differentiated and highly reactive halogen substituents.

The tricyclic xanthone is a major scaffold for a range of natural and synthetic products that exhibit various interesting biological activities depending on the nature and pattern of the substituents.[1] Efficient assembly strategies that allow for accurate control of the substitution regiochemistry on this 'privileged structure' are therefore of great interest in medicinal chemistry. Many syntheses of the xanthone core are available, which typically require a biaryl ether or a benzophenone as the key intermediate.[2,3] Azaxanthones are also of interest as they modulate the physicochemical properties of xanthones. However, reports of azaxanthones are relatively sparse in the literature.[4]

Recently, we have developed a unique aminooxazoline xanthene series (**1**) as potent and CNS penetrant β-site amyloid precursor protein (APP) cleaving enzyme 1 (BACE1) inhibitors for the potential treatment of Alzheimer's disease (Fig. 1).[5] In this class, xanthone **2** served as the key intermediate in which the two differentiated halogen groups at the 2- and 7-positions offered flexibility in the structure–activity relationship (SAR) study to install a variety of R^1 and R^2 groups that can bind into the S_2' and S_3 pockets of the BACE 1 enzyme, respectively. Interestingly, through early core modifications, we found that a *single* N-insertion (azaxanthone) or fluorine-substitution at either 3- or 4-positions of the xanthene core **2** can improve in vitro potency, modulate CNS penetration, PKDM properties and/or cardiovascular safety profiles.[6] Based on these results, we reasoned that combinations of both the aza and fluorine modifications at the 3- and 4-positions (3-aza-4-F or 4-aza-3-F) on the xanthene skeleton would further optimize the overall properties as more efficacious BACE 1 inhibitors. In addition, we sought to explore the effect of nitrogen insertion at the 1-position. Consequently, rapid access to the four halogenated azaxanthones **3**, **4**, **5**, and **6** were highly desirable in our program.

These densely halogenated azaxanthones were unprecedented in the literature and presented unusual synthetic challenges. First of all, the annulation of a pyridine with four differentiated substituents was nontrivial in terms of the regiochemistry of not only the aza-positions but also the different halogens. Especially, the fluoride group on this subunit was expected to be highly activated due to the strong electron-withdrawing effect of the carbonyl group and the pyridine nitrogen. Moreover, multiply substituted fluoropyridines were not readily available as starting materials. Herein we describe several different synthetic strategies to address the unique issues in each of these novel targets.

The synthesis of 3-aza-4-F-xanthone **3** began with a copper catalyzed, regioselective Ullmann coupling between 2,5-dibromobenzoic acid (**7**) and 2-fluoro-3-hydroxypyridine (**8**) under conditions developed by Buchwald and co-workers (Scheme 1).[7] After workup, the resulting crude biaryl ether **9** was directly treated with diethylamine and TBTU to give amide **10** in 50% yield over two steps. Then, an amide-directed lithiation on the pyridine and the subsequent in situ cyclization provided the azaxanthone **11**.[4b,8] N-oxidation, which was necessary for the final installation of a chlorine atom, failed presumably due to the strong electron-withdrawing effects of the *para*-carbonyl and the *ortho*-F groups on the pyridine moiety in **11**. To circumvent this issue, N-oxidation

* Corresponding author. Tel.: +1 805 447 0078; fax: +1 805 480 1337.
E-mail address: wqian@amgen.com (W. Qian).

http://dx.doi.org/10.1016/j.tetlet.2014.11.032
0040-4039/

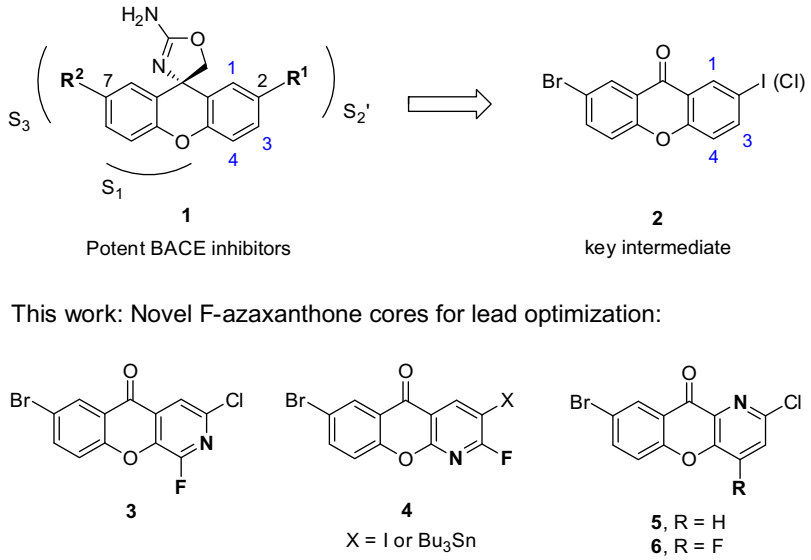
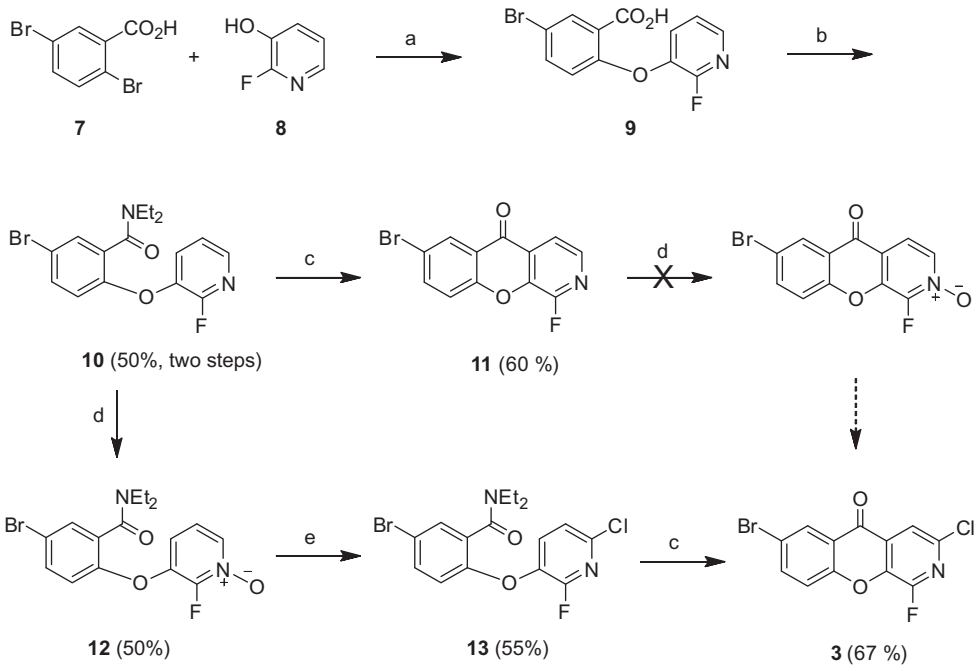


Figure 1. Multiply halogenated azaxanthones as key intermediates toward the development of novel BACE inhibitors.

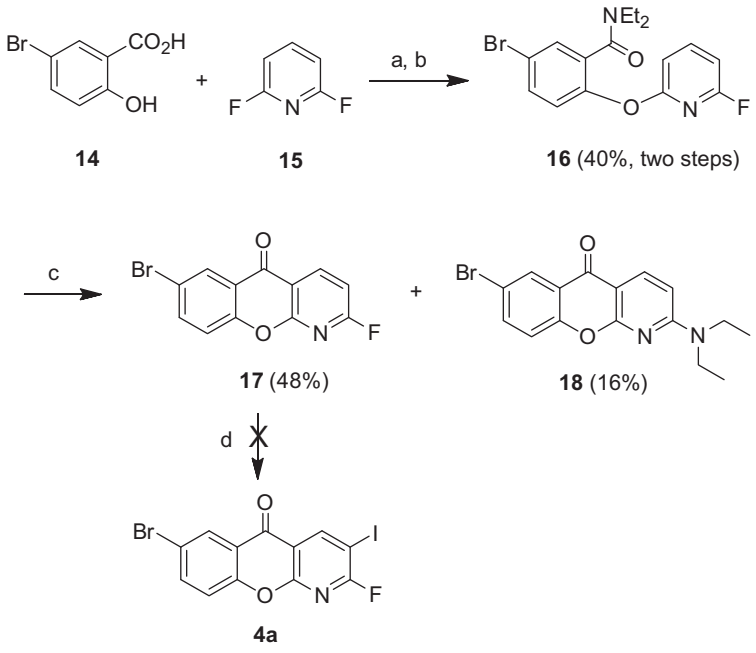


Scheme 1. Reagents and conditions: (a) $Cu(OTf)_2$, Cs_2CO_3, toluene, 110 °C; (b) Et_2NH, TBTU, DCM, rt; (c) LDA, THF, −78 °C; (d) UHP, TFAA, DCM, rt; (e) $POCl_3$, DCM, DMF, rt.

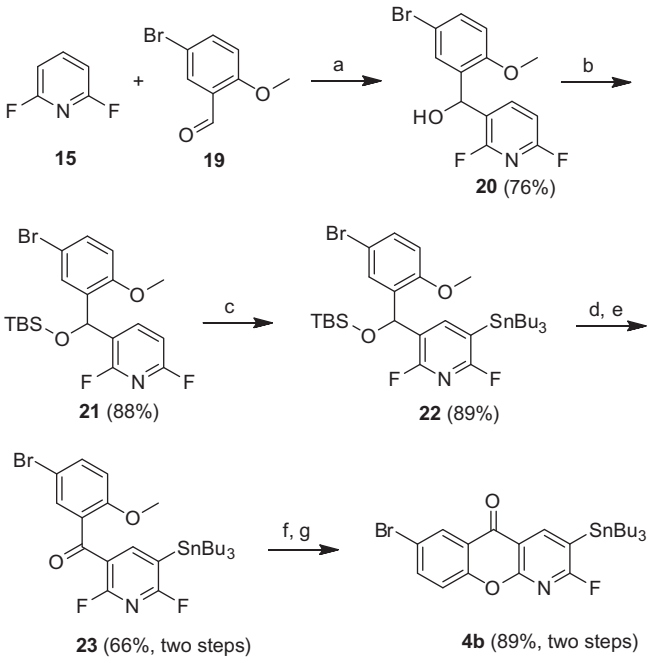
was performed successfully on the more electron-rich biaryl ether **10** to give **12**, which upon treatment of $POCl_3$ afforded chloride **13**. Finally, a tandem lithiation/cyclization yielded the desired tris-halogenated 3-azaxanthone **3**.

To prepare the 3-F-4-azaxanthone **4**, a 'reversed' first step coupling was conveniently conducted between 5-bromo-2-hydroxybenzoic acid (**14**) and the symmetric 2,6-difluoropyridine (**15**) under catalyst-free conditions (Scheme 2). Following the amide formation (**16**), the tandem lithiation/cyclization process provided the azaxanthone core **17**. Interestingly, compared to the regioisomer **11** in Scheme 1, the fluoride on **17** is much more reactive because of the double activation by the *para*-carbonyl group and the *ortho*-nitrogen atom. As a result, a diethylamine substitution byproduct **18** was also isolated. To our disappointment, efforts of fluorine-directed *ortho*-metalation and electrophile quenching failed to install the desired iodine onto this heterocycle.

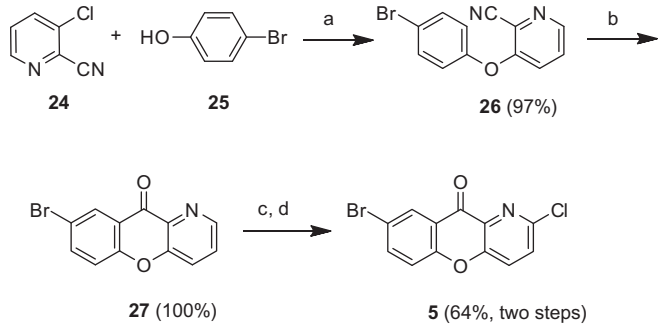
After many unsuccessful trials, a totally different route was developed (Scheme 3). Mono-lithiation of **15**, followed by trapping with aldehyde **19** provided the benzhydryl alcohol **20** which was then protected as TBS ether **21**. Next, instead of the highly reactive iodide, we chose to install a more stable Bu_3Sn group after the second fluorine-directed *ortho*-lithiation of the pyridine. This group can also serve as a handle for further functionalizations. Removal of the TBS group, followed by oxidation yielded the biaryl ketone **23**. Finally, cleavage of the methyl group under mild conditions unveiled the hydroxyl group, which cyclized in an intramolecular S_NAr fashion with the highly activated difluoropyridine moiety to furnish the trisubstituted 4-azaxanthone **4b**.



Scheme 2. Reagents and conditions: (a) Cs_2CO_3, DMSO, 110 °C; (b) Et_2NH, TBTU, DCM, rt; (c) LDA, THF, −78 °C; (d) LDA, then I_2, THF, −78 °C.



Scheme 3. Reagents and conditions: (a) LDA, THF, −78 °C; (b) TBSCl, Imidazole, DMF, 50 °C; (c) LDA, then Bu_3SnCl, THF, −78 °C; (d) TBAF, THF, rt; (e) TPAP, NMO, DCM, rt; (f) 9-Br-BBN, DCM, rt; (g) K_2CO_3, MeCN, rt.

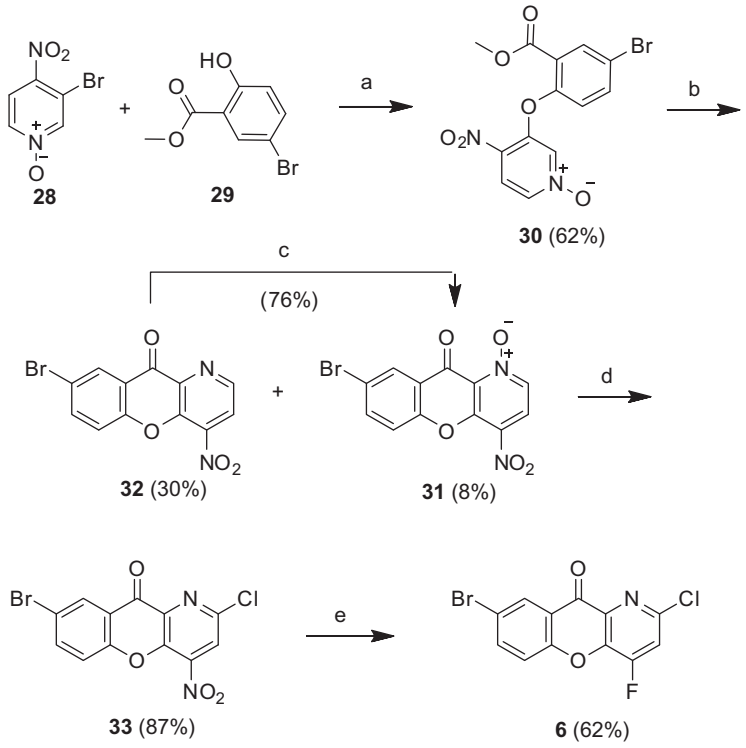


Scheme 4. Reagents and conditions: (a) Cs_2CO_3, DMSO, 85 °C; (b) PPA, 180 °C; (c) UHP, TFAA, DCM, rt; (d) $POCl_3$, DCM, DMF, rt.

The preparation of the disubstituted 1-azaxanthone **5** was straightforward (Scheme 4). S_NAr reaction between an activated chloride **24** and phenol **25** resulted in the biaryl ether **26** in nearly quantitative yield after simple aqueous workup and filtration. Then, an intramolecular Friedel–Crafts reaction in PPA, followed by in situ hydrolysis provided the 1-azaxanthone core **27**. N-oxidation and subsequent treatment with $POCl_3$ produced the desired chloride **5**. This four-step procedure does not need any column purification and achieved high overall yield at 100 g scale.

Compared to the robust synthesis of **5**, introducing an extra fluorine at the 4-position of the 1-azaxanthone core presented a much more difficult task (**6**, Fig. 1). The four different strategies to access **3**, **17**, **4b**, and **5** cannot be simply applied to this target because the corresponding multiply functionalized 4-F-pyridine starting materials are not easily available and/or could cause selectivity issues in the intermediate steps. In addition, the 4-F on pyridine is highly reactive. Based on these considerations, we chose 3-bromo-4-nitropyridine 1-oxide (**28**) as a surrogate to couple with the sodium salt of methyl 5-bromo-2-hydroxybenzoate (**29**, Scheme 5). Both the *N*-oxide and the nitro group on **28** directed the substitution to the bromide and no nitro group displacement was detected in this regioselective S_NAr reaction.[9] Treatment of the resulting biaryl ether **30** with LDA gave a mixture of the desired azaxanthone **31** and the deoxygenated product **32**, together with 40% of recovered starting material. The *N*-oxide **31** served as the direct precursor to chloride **33**. Gratifyingly, the pyridine-activated nitro group was selectively displaced in the presence of the chloride to give fluoride **6** at the final stage.[10]

In summary, we have showcased the rapid construction of several isomeric azaxanthones with fully differentiated halogen substitutions as novel and flexible core structures for drug discovery. In some cases, a well-established assembly strategy for one azaxanthone is of limited value for a very similar structure bearing just one extra halogen due to the new chemo- and regioselectivity



Scheme 5. Reagents and conditions: (a) NaH, DMF, 50 °C; (b) LDA, THF, −78 °C; 40% of starting material recovered; (c) UHP, TFAA, DCM, rt; (d) $POCl_3$, DMF, DCM, rt; (e) TBAF, THF/DMF, 0 °C.

issues associated with this 'small' change. Consequently, alternative approaches needed to be developed, as highlighted by the comparison of the syntheses between **17** and **4b**, as well as **5** and **6**, respectively. The SAR study and identification of high-quality BACE inhibitors based on these new scaffolds will be disclosed in due course.

Acknowledgements

The authors thank Dr. Jennifer Allen and Dr. Margaret Chu-Moyer for discussion.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.11.032.

References and notes

1. For selected recent reviews on xanthones with biological activities, see (a) Pinto, M. M. M.; Sousa, M. E.; Nascimento, M. S. J. *Curr. Med. Chem.* **2005**, *12*, 2517–2583; (b) El-Seedi, H. R.; El-Barbary, M. A.; El-Ghorab, D. M. H.; Bohlin, L.; Borg-Karlson, A.-K.; Goeransson, U.; Verpoorte, R. *Curr. Med. Chem.* **2010**, *17*, 854–901; (c) Winter, D. K.; Sloman, D. L.; Porco, J. A., Jr. *Nat. Prod. Rep.* **2013**, *30*, 382–391.
2. For selected reviews on the synthesis of xanthones, see (a) Sousa, M. E.; Pinto, M. M. M. *Curr. Med. Chem.* **2005**, *12*, 2447–2479; (b) Azevedo, C. M. G.; Afonso, C. M. M.; Pinto, M. M. M. *Curr. Org. Chem.* **2012**, *16*, 2818–2867; (c) Masters, K.-S.; Brase, S. *Chem. Rev.* **2012**, *112*, 3717–3776.
3. For recent examples of non-classical syntheses of xanthones, see: (a) Menendez, C. A.; Nador, F.; Radivoy, G.; Gerbino, D. C. *Org. Lett.* **2014**, *16*, 2846–2849; (b) Wang, P.; Rao, H.; Hua, R.; Li, C.-J. *Org. Lett.* **2012**, *14*, 902–905; (c) Zhang, H.; Shi, R.; Gan, P.; Liu, C.; Ding, A.; Wang, Q.; Lei, A. *Angew. Chem., Int. Ed.* **2012**, *51*, 5204–5207; (d) Zhao, J.; Larock, R. C. *Org. Lett.* **2005**, *7*, 4273–4275.
4. (a) Zhang, X.; Yang, L.; Wu, Y.; Du, J.; Mao, Y.; Wang, X.; Luan, S.; Lei, Y.; Li, X.; Sun, H.; You, Q. *Tetrahedron Lett.* **2014**, *55*, 4883–4887; (b) Familoni, O. B.; Ionica, I.; Bower, J. F.; Snieckus, V. *Synlett* **1997**, 1081–1083; (c) Trecourt, F.; Queguiner, G. *J. Chem. Res.* **1982**, 76–77.
5. Huang, H.; La, D. S.; Cheng, A. C.; Whittington, D. A.; Patel, V. F.; Chen, K.; Dineen, T. A.; Epstein, O.; Graceffa, R.; Hickman, D.; Kiang, Y.-H.; Louie, S.; Luo, Y.; Wahl, R. C.; Wen, P. H.; Wood, S.; Fremeau, R. T., Jr. *J. Med. Chem.* **2012**, *55*, 9156–9169.
6. (a) Epstein, O.; Bryan, M. C.; Cheng, A. C.; Derakhchan, K.; Dineen, T. A.; Hickman, D.; Hua, Z.; Human, J. B.; Kreiman, C. E.; Marx, I.; Weiss, M. M.; Qu, Y.; Wahl, R. C.; Wen, P. H.; Whittington, D. A.; Wood, S.; Zheng, X.; Fremeau, R. T., Jr.; White, R. D.; Patel, V. F. *J. Med. Chem.* submitted for publication, http://dx.doi.org/10.1021/jm501266w.; (b) Dineen, T. A.; Chen, K.; Cheng, A. C.; Epstein, O.; Esmay, J.; Hickman, D.; Kreiman, C. E.; Marx, I. E.; Wahl, R. C.; Wen, P. H.; Weiss, M. M.; Whittington, D. A.; Wood, S.; Fremeau, R. T., Jr.; White, R. D.; Patel, V. F. *J. Med. Chem.* submitted for publication, http://dx.doi.org/10.1021/jm5012676.
7. Marcoux, J.-F.; Doye, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 10539–10540.
8. Snieckus, V. *Chem. Rev.* **1990**, *90*, 879–933.
9. Eggers, L.; Grahn, W. *Synthesis* **1996**, 763–766.
10. Kuduk, S. D.; DiPardo, R. M.; Bock, M. G. *Org. Lett.* **2005**, *7*, 577–579.