Tetrahedron Letters 53 (2012) 4161–4165

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

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

Rapid, microwave-assisted organic synthesis of selective ^{V600E}BRAF inhibitors for preclinical cancer research

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ARTICLE INFO

Article history:
Received 27 April 2012
Revised 25 May 2012
Accepted 29 May 2012
Available online 7 June 2012

Keywords:
PLX4720
PLX4032
BRAF
MAOS
Melanoma

ABSTRACT

We report dramatically improved total syntheses of two highly selective ^{V600E}BRAF inhibitors, PLX4720 and PLX4032, that leverages microwave-assisted organic synthesis (MAOS). Compared with previously reported approaches, our novel MAOS method significantly reduces overall reaction time without compromising yield. In addition to providing a gram-scale route to these compounds for preclinical oncology research, we anticipate this approach could accelerate the synthesis of azaindoles in high-throughput, library-based formats.

As mutations in vital genes accrue, normal programs of cell proliferation, differentiation, and death are recast, forming the basis of cancer. Of the known protein kinases, the BRAF paralog of the rapidly growing fibrosarcoma (raf) family of proteins is the most frequently mutated in human cancer.[1] Activating somatic mutations in BRAF occur in malignant melanomas (50%), ovarian cancer (30%), thyroid cancer (30%), colorectal cancer (CRC) (15%), and less frequently in other cancer types.[2,3] While several mutations in BRAF have been reported, the most common mutation substitutes valine for glutamic acid at codon 600 (^{V600E}BRAF) in the activation segment of the kinase. This particular mutation accounts for greater than 90% of BRAF mutations in cancer.[2] ^{V600E}BRAF is constitutively activated, as are its associated downstream effectors within the mitogen-activated protein kinase (MAPK) pathway.[4] Clinically, tumor expression of ^{V600E}BRAF correlates with elevated proliferation, aggressiveness, and poor prognosis.[5] Since growth and proliferation of tumors expressing ^{V600E}BRAF tend to rely upon MAPK pathway activity, pharmacological inhibition of ^{V600E}BRAF represents an attractive therapeutic approach in oncology.[6]

Small-molecule inhibition of BRAF in oncology has been historically approached using pan-kinase inhibitors,[7,8] such as sorafenib (Nexavar) (Fig. 1). However, for a variety of postulated reasons,[9] this approach has led to disappointing outcomes in ^{V600E}BRAF-dependent tumors such as melanoma.[10,11]

An encouraging alternative approach to pan-kinase inhibitors that have shown recent success has been the clinical development of ^{V600E}BRAF-selective small-molecule inhibitors. Currently, two of the most promising selective inhibitors include PLX4720[12] and its clinically used analogue, PLX4032 (vemurafinib).[13] Uniquely, these drugs selectively inhibit ^{V600E}BRAF kinase at low nanomolar concentrations and, accordingly, attenuate associated MAPK pathway activity in ^{V600E}BRAF tumors.[12–17] Recently, PLX4032 has been approved by the FDA for treatment of late-stage ^{V600E}BRAF-positive melanoma,[18] and continues to be evaluated in other single-agent and combination settings.[19–21]

Our laboratory's interest in developing and validating predictive imaging biomarkers to reflect tumor response to ^{V600E}BRAF inhibition required milligram- to gram-scale quantities of PLX4032 and PLX4720 suitable for preclinical in vivo studies. We found published production-scale syntheses of these compounds, yet these methods were inappropriate for typical academic research laboratories, as well as being time and labor intensive.[12,13] These compounds could also be purchased commercially, but only at great expense given the scale required for our research activities. To circumvent these limitations, we developed a rapid, in-house

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0040-4039/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2012.05.137

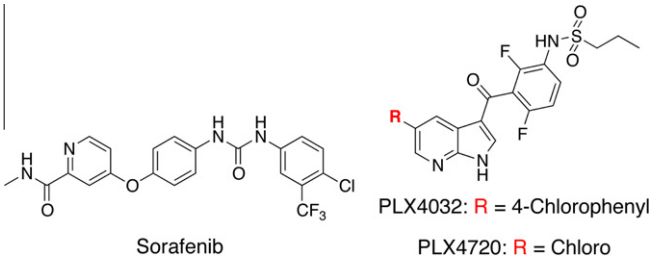


Figure 1. Chemical structures of select BRAF inhibitors.

approach to synthesize PLX4720 and PLX4032 that capitalized upon the advantages of microwave-assisted organic synthesis (MAOS). MAOS employs non-classical heating via microwaves in lieu of traditional thermal convection or conduction. Commonly, MAOS reaction times are dramatically reduced, reaction efficiencies are increased, and material and labor costs are reduced.[22,23]

In this study, MAOS was successfully adapted to each of the traditional syntheses reported by Tsai et al.[12] and Bollag et al.[13] (Table 1), with MAOS offering significant advantages in all steps required to synthesize PLX4720 and four of the six steps required to synthesize PLX4032. We herein report dramatically reduced reaction times required for the synthesis of the drugs while achieving comparable, or in most cases, improved yields. The divergent synthesis developed for this study is shown in Scheme 1. In Table 1, we report conditions, reaction times, and yields described in the original literature (Refs. a,b) and the MAOS application. Assuming overnight to be 16 h, for PLX4720, MAOS resulted in a 91% reduction in overall reaction time (87–6 h). For PLX4032, four of the six steps were amenable to MAOS and resulted in a 33% reduction in reaction time (141–94 h). Successful gram-scale MAOS was carried out for select intermediates (**3**, **6b**) to ensure scalability of the developed method. Full synthetic methodology and characterization data can be found in Supplementary Data.

1. Synthesis of PLX4720 (8a)

1.1 MAOS of *N*-(3,5-difluorophenyl)propane-1-sulfonamide (3)

The divergent synthesis begins with formation of **3** by reaction of 2,4-difluoroaniline (**1**) and propane-1-sulfonyl chloride (**2**) in anhydrous methylene chloride, dimethyaminopyridine (DMAP), and pyridine. Previous studies carried out this reaction at room temperature overnight with a quantitative yield (Table 1, entry 1).[12] Microwave irradiation at 100 °C reduced the reaction time to 30 min. Subsequent flash chromatography on silica gel gave **3** in a comparable yield of 89% (Table 1, entry 2).

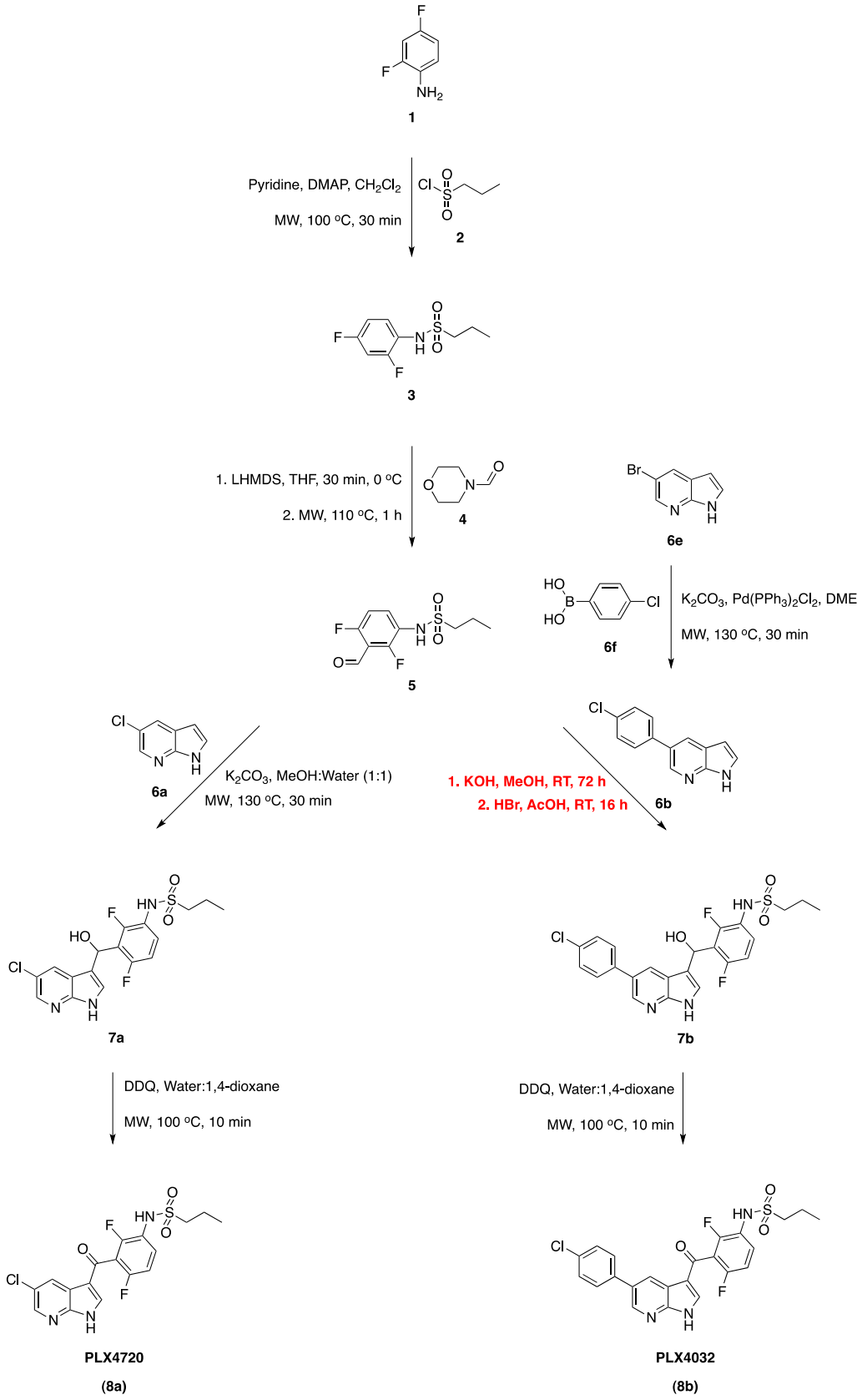
1.2 MAOS of *N*-(3-5-difluoro-4-formylphenyl)propane-1-sulfonamide (5)

Synthesis of **5** features a two-step formylation of **3** with morpholine-4-carbaldehyde (**4**). Previously,[12] in situ generation of lithium diisopropylamide (LDA) using *n*-butyllithium in THF and diisoproplyamine was carried out at 0 °C for one hour. This was followed by deprotonation of **3** with this LDA solution for 4 h. Subsequent formylation with morpholine-4-carbaldehyde (**4**) at −78 °C for 4 h, and a further 16 h at room temperature gave **5** in 51% yield (Table 1, entry 3). In this study, given the temperature requirements of the deprotonation, we chose not to pursue MAOS. Moreover, we attained comparable yields using commercially available lithium bis(trimethylsilyl)amide (LHMDS) in place of LDA. The subsequent formylation, however, was adaptable to MAOS *via* microwave irradiation at 100 °C for 1 h, with a comparable yield of 56% (Table 1, entry 4).

Table 1
Summary of Compounds and Conditions.

Entry	MAOS	Reaction conditions	Temperature	Time	Yield
*MAOS of N-(3,5-difluorophenyl)propane-1-sulfonamide (**3**)*					
1	No	Pyridine, DMAP, CH_2Cl_2	Reflux	16 h	Quant.[a]
2	Yes	Pyridine, DMAP, CH_2Cl_2	100 °C	30 min	89%
*MAOS of N-(3-5-difluoro-4-formylphenyl)propane-1-sulfonamide (**5**)*					
3	No	LDA, THF	−78 °C/RT	5/16 h	51[a]
4	Yes	LHMDS, THF	0/110 °C	30 min/1 h	56
*MAOS of 5-(4-chlorophenyl)-1H-pyrrolo[2,3-b]pyridine (**6b**)*					
5	No	K_2CO_3, $Pd(PPh_3)_2Cl_2$, DME	Reflux	16 h	81[b]
6	Yes	K_2CO_3, $Pd(PPh_3)_2Cl_2$, DME	130 °C	30 min	76
*MAOS of N-(3-((5-chloro-1H-pyrrolo[2,3-b]pyridine-3-yl)(hydroxyl)methyl)2,4-difluorophenyl)propane-1-sulfonamide (**7a**)*					
7	No	K_2CO_3, MeOH:water	RT	48 h	88[a]
8	Yes	K_2CO_3, MeOH:water	130 °C	30 min	88
*Synthesis of N-(3-((5-(4-chlorophenyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)(hydroxy)methyl)-2,4-difluorophenyl)propane-1-sulfonamide (**7b**)*					
9	No	KOH, MeOH	RT	72 h	NA[c]
10	No	HBr (aq), AcOH	RT	16 h	NA[c]
11	No	KOH, MeOH	RT	72 h	NA[d]
12	No	HBr (aq), AcOH	RT	16 h	44%[e]
*MAOS of N-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluorophenyl)propane-1-sulfonoamide (**8a**, PLX4720)*					
13	No	DDQ, H_2O:1,4-dioxane	RT	2 h	90[a]
14	Yes	DDQ, H_2O:1,4-dioxane	100 °C	10 min	87
*MAOS of N-(3-(5-(4-chlorophenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluorophenyl)propane-1-sulfonamide (**8b**, PLX4032)*					
15	No	DDQ, H_2O:1,4-dioxane	RT	2 h	45[f]
16	Yes	DDQ, H_2O:1,4-dioxane	100 °C	10 min	92

[a] See Tsai et al. 2008.
[b] See Bollag et al. 2010.
[c] See Bollag et al. 2010, combined yield with entry 15.
[d] Combined yield with entry 12.
[e] Combined yield with entry 11.
[f] See Bollag et al. 2010, combined yield with entries 9 and 10.



Scheme 1. MAOS of PLX4720 and PLX4032 (MW = microwaves).

1.3 MAOS of *N*-(3-((5-chloro-1H-pyrrolo[2,3-*b*]pyridine-3-yl)(hydroxyl)methyl)2,4-difluorophenyl)propane-1-sulfonamide (7a)

The PLX4720 intermediate **7a** was originally synthesized in 88% yield from the reaction of **5** with the azaindole core 5-chloro-1*H*-pyrrolo[2,3-*b*]pyridine (**6a**) in methanol:water (1:1) for 48 h at room temperature (Table 1, entry 7).[12] Optimization with microwave irradiation resulted in final reaction conditions of 130 °C in the same solvent system for only a fraction of the original time (30 min). Purification by flash chromatography on silica gel gave **7a** in a matching yield of 88% (Table 1, entry 8).

1.4 MAOS of *N*-(5-chloro-1H-pyrrolo[2,3-*b*]pyridine-3-carbonyl)-2,4-difluorophenyl)propane-1-sulfonoamide (8a, PLX4720)

From compound **7a**, reported oxidation to PLX4720 (**8a**) utilized 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in a mixture of water and 1,4-dioxane at room temperature for 2 h, with a yield of 90% (Table 1, entry 13).[12] Under MAOS, an optimized reaction temperature of 100 °C was achieved with a reduction in reaction time to 10 min, a factor of 12, while still achieving a comparable yield of 87% (Table 1, entry 14).

2. Synthesis of PLX4320 (8b)

2.1 MAOS of 5-(4-chlorophenyl)-1H-pyrrolo[2,3-*b*]pyridine (6b)

Suzuki coupling of 5-bromo-1*H*-pyrrolo[2,3-*b*]pyridine (**6e**) with 4-(chlorophenyl)boronic acid (**6f**) in the presence of K_2CO_3 and $Pd(PPh_3)_2Cl_2$ in 1,2-dimethoxyethane (DME) for 30 min at 130 °C secured the necessary PLX4032 azaindole core (**6b**) (Table 1, entry 6). Previous synthesis of this intermediate required overnight reflux, with a yield of 81% (Table 1, entry 5),[13] thus underscoring the effectiveness of MAOS in reducing overall reaction time.

2.2 Synthesis of *N*-(3-((5-(4-chlorophenyl)-1H-pyrrolo[2,3-*b*]pyridin-3-yl)(hydroxy)methyl)-2,4-difluorophenyl)propane-1-sulfonamide (7b)

Coupling of the respective azaindole cores of PLX4032 (**6b**) and PLX4720 (**6a**) with intermediate (**5**) is where the synthesis diverges. For PLX4032, unlike PLX4720, application of MAOS of **6b** with **5** in the presence of KOH and methanol proved less advantageous (Table 1, entry 11), frequently yielding mixed by-products. Moreover, deprotection of the methyl ether intermediate (structure not shown) with aqueous hydrogen bromide and acetic acid to the final product (**7b**) (Table 1, entry 12) was also problematic under microwave irradiation, primarily yielding by-products. Modification of both reaction conditions marginally affected applicability of microwave irradiation. Accordingly, MAOS was not pursued further, in favor of the published methodology of Bollag et al.[13] Nevertheless, the combined yield of these two steps in our hands was 44%, compared to Bollag's 45%, which also included the final synthetic step (Table 1, entry 15).

2.3 MAOS of *N*-(3-(5-(4-chlorophenyl)-1H-pyrrolo[2,3-*b*]pyridine-3-carbonyl)-2,4-difluorophenyl)propane-1-sulfonamide (8b, PLX4032)

Bollag et al.[13] reported a final oxidation of precursor **7b** to PLX4032 (**8b**) analogous to Tsai et al.[12] The exact yield of this step is unknown as it was reported in combination with the two preceding reactions (Table 1, entry 15). Nonetheless, the MAOS conditions developed for the final-step oxidation of PLX4720 (**8a**) were also employed toward PLX4032 (**8b**). Irradiation of **7b** at 100 °C for 10 min gave a 92% yield of the final PLX4032 (**8b**) (Table 1, entry 16).

In summary, we report optimized, gram-scale syntheses of PLX4720 and PLX4032 that leverage MAOS. Where, applicable, the MAOS protocol reported herein significantly improves overall reaction times while maintaining or even improving synthetic yields. We envision this methodology could potentially be extended not only to the synthesis of PLX4032 and PLX4720, but to other novel azaindoles as well.

Acknowledgments

The authors wish to gratefully acknowledge funding from the National Cancer Institute (NCI): 1R01 CA140628, 1RC1 CA145138-01, K25 CA127349, 1P50 CA128323 (Vanderbilt ICMIC Program), 2P50 CA095103 (Vanderbilt SPORE in GI Cancer), 5P30 DK058404, and the Kleberg Foundation. The authors wish to thank Dr. Yiu-Yin Cheung for helpful discussions.

Supplementary data

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.tetlet.2012.05.137.

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