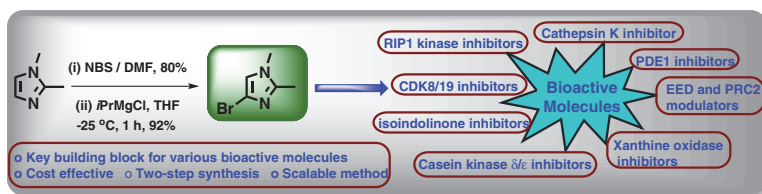


Cost-Effective and Scalable Synthesis of 4-Bromo-1,2-dimethyl-1H-imidazole: A Key Building Block for Bioactive Molecules

Muthalagu Vetrichelvan^{*a} Veeranjaneyulu Lanke^aBellam Chandu^aArvind Mathur^bAnuradha Gupta^b

^a Department of Discovery Synthesis, Biocon Bristol Myers Squibb R&D Centre, Syngene International Ltd., Biocon Park, Plot No. 2 & 3, Jigani Link Road, Bommasandra IV, Bangalore 560 099, India
muthalagu.vetrichelvan@syngeneintl.com

^b Small Molecule Drug Discovery, Bristol Myers Squibb Research and Early Development, P.O. Box 5400, Princeton, NJ 08543-4000, USA



Received: 02.08.2023

Accepted after revision: 08.09.2023

Published online: 14.09.2023 (Accepted Manuscript), 18.10.2023 (Version of Record)

DOI: 10.1055/a-2176-1585; Art ID: SO-2023-08-0056-OP

License terms:

© 2023. The Author(s). This is an open access article published by Thieme under the terms of the Creative Commons Attribution License, permitting unrestricted use, distribution and reproduction, so long as the original work is properly cited. (<https://creativecommons.org/licenses/by/4.0/>)

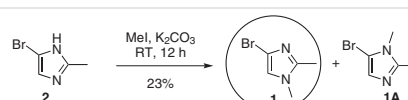
Abstract A cost-effective, scalable, high-yielding, and commercially viable synthesis of 4-bromo-1,2-dimethyl-1H-imidazole (**1**), an important building block to construct various bioactive molecules has been established. The main feature of this method includes the selection of appropriate starting material 1,2-dimethyl-1H-imidazole in which the existing issue of regioisomer formation is circumvented and the selective debromination is accomplished by using isopropyl magnesium chloride.

Key words bromination, debromination, imidazole derivative, cost-effective, scalable

4-Bromo-1,2-dimethyl-1H-imidazole (**1**) (Figure 1) has been identified as a promising key building block for the construction of various active pharmaceutical ingredients (APIs).¹ The structural motif of **1** has been utilized in several diversified bioactive compounds such as cathepsin K inhibitor,^{1a} xanthine oxidase inhibitors,^{1b} EED and PRC2 modulators,^{1c} PDE1 inhibitors,^{1d} casein kinase δ/ϵ inhibitors,^{1e} CDK8/19 inhibitors,^{1f} isoindolinone inhibitors,^{1g} RIP1 kinase inhibitors,^{1h} mGlu4 receptor positive allosteric modulators,¹ⁱ and TGF β inhibitors,^{1j} as illustrated in Figure 1.

As part of a medicinal chemistry effort focused on the identification of a casein kinase δ/ϵ inhibitor for anticancer therapy,^{1e} compound **V** was identified and progressed into development; this necessitated a robust and scalable synthesis to produce larger quantities for further clinical evaluation. The reported first-generation synthesis^{1e} to make **V** was revisited and it was found that the main issue would be

sourcing the large quantity of 4-bromo-1,2-dimethyl-1H-imidazole (**1**). As reliability on commercial sources for larger quantities remained challenging, an in-house effort to develop a robust route to synthesize **1** was critical. One of the options of synthesizing **1** was described by Efremov *et al.*^{1c} and Nichols *et al.*² involves methylating 5-bromo-2-methyl-1H-imidazole (**2**) (Scheme 1), resulting in a mixture of two regioisomers 4-bromo-1,2-dimethyl-1H-imidazole (**1**) and 5-bromo-1,2-dimethyl-1H-imidazole (**1A**), which were separated by preparative-TLC to afford the desired **1** in 23% yield. It was a big challenge to prepare larger quantities of **1** using this methodology; thus, an alternate approach was required.



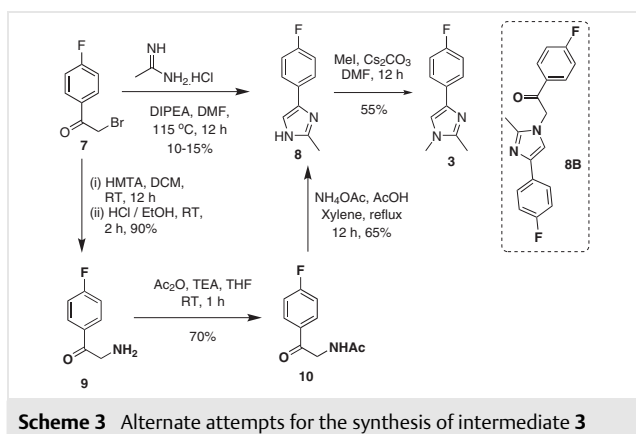
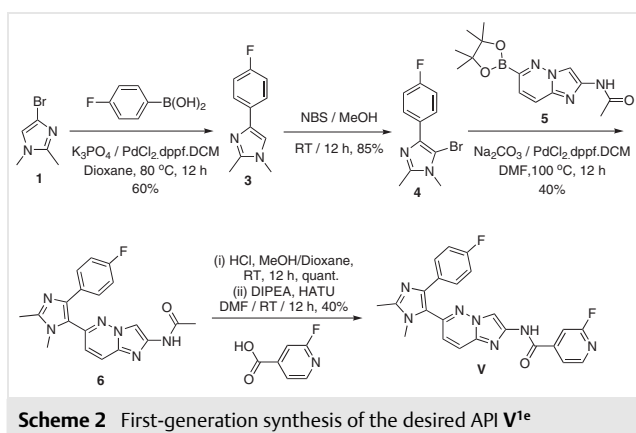
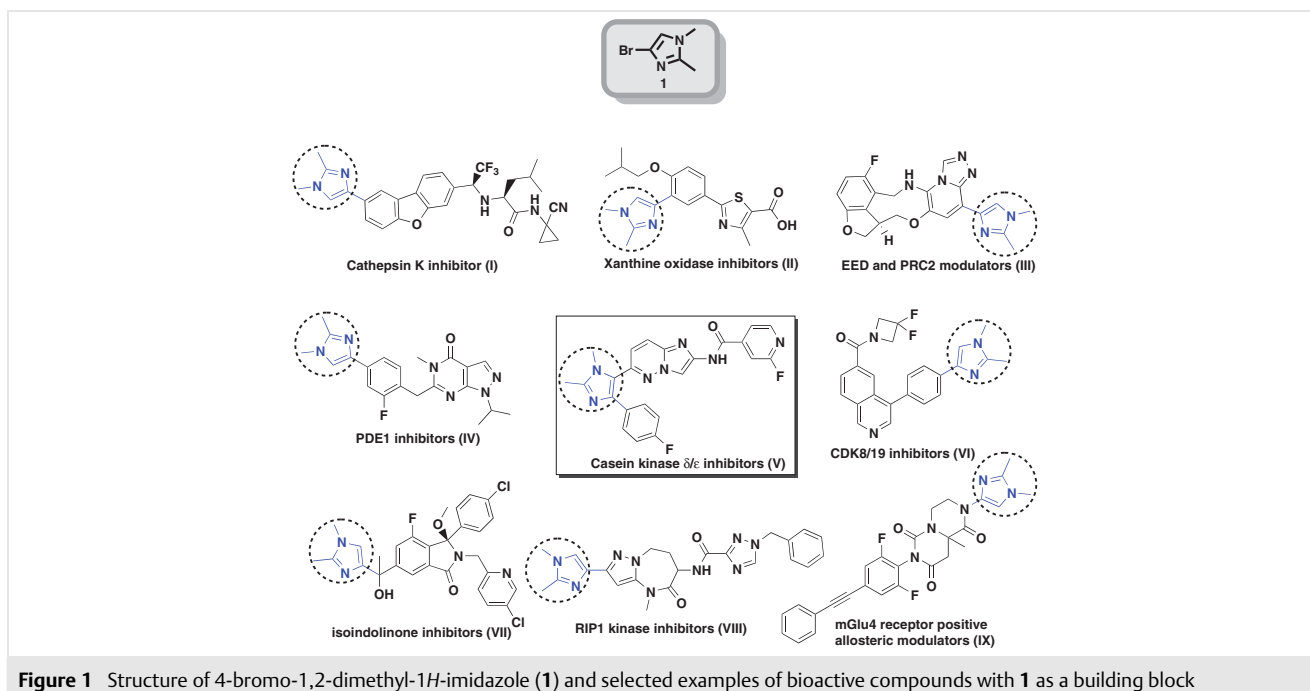
Scheme 1 Reported synthesis of **1**

First-Generation Synthesis of **V**

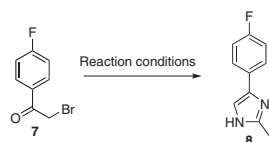
The first-generation synthesis of **V**, given in Scheme 2,^{1e} started with Suzuki–Miyaura coupling of 4-bromo-1,2-dimethyl-1H-imidazole (**1**) and 4-fluorophenylboronic acid to afford **3** in 60% yield. Bromination of **3** using NBS in MeOH gave **4** in 80% yield, and subsequent Suzuki–Miyaura coupling with the in-house synthesized boronate **5** resulted in **6** in 40% yield. Deacetylation of **6** using HCl afforded the amine in quantitative yield, which was taken for the amidation with 3-fluoro-pyridine-4-carboxylic acid to give the desired API **V** in 40% yield.

Alternate Approaches for Imidazole Intermediate **3**

Alternative approaches involved the construction of the imidazole ring of **3** from the corresponding bromoketone **7**, followed by methylation and bromination, as shown in



Scheme 3. Initial efforts to obtain **8** by reaction of 2-bromo-1-(4-fluorophenyl)ethan-1-one (**7**) with acetamide HCl salt in the presence of different bases and solvents resulted exclusively in the formation of either **8B** or a mixture of **8** and **8B**.³ Model reaction using 3 equivalents of DIPEA at 50 °C resulted in 12–25% yield of undesired **8B** instead of the desired product **8**. It was found that as soon as compound **8** was formed, it further reacted with **7** to afford *N*-alkylated undesired product **8B**. A similar observation of the formation of *N*-alkylated intermediate **8B** in a greater ratio was reported earlier.⁴ Increasing the temperature from 50 to 100 °C did not help to get the desired product (Table 1, entry 2). Further, changing the solvent from DMF to CH₃CN, and screening of other bases such as potassium carbonate or sodium hydroxide, did not give the desired product **8** (entries 3–5). As we could not obtain the desired product **8** in a single step, we followed the stepwise approach based on the earlier reports,^{5,1e} as shown in Scheme 3. 4-Fluorophenyl bromide **7** was converted into its corresponding amine **9** using hexamethylenetetramine in 90% yield, which was further acetylated using acetic anhydride and triethylamine to give **10**, with 70% yield. The acetylated compound **10** was reacted with NH₄OAc to give the desired imidazole intermediate **8** in 65% yield. The reaction of **8** with MeI in the presence of Cs₂CO₃ at room temperature for 12 h resulted in the desired 4-(4-fluorophenyl)-1,2-dimethyl-1H-imidazole (**3**) in 55% yield, along with minor quantities of its regioisomer. Though the approach was successful in making compound **3** and could afford the desired API **V** following the first-generation scheme, due to the longer sequence and challenges in separating the regioisomer at intermedi-

Table 1 Attempts to Synthesize Compound **8**

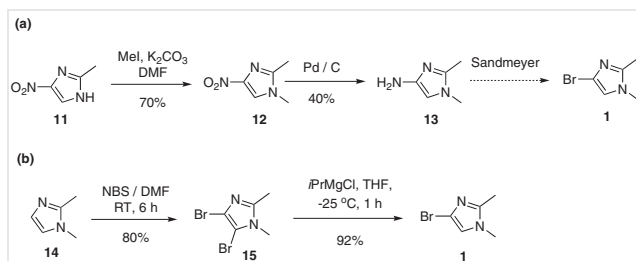
Entry	Reaction conditions ^a	8/8B (%) ^b
1	acetamidine (1.2 equiv), DIPEA (3 equiv), DMF, 50 °C, 12 h	0/12
2	acetamidine (1.2 equiv), DIPEA (3 equiv), DMF, 100 °C, 12 h	4/30
3	acetamidine (1.2 equiv), DIPEA (3 equiv), MeCN, 80 °C, 12 h	0/24
4	acetamidine (1.2 equiv), K ₂ CO ₃ (3 equiv), DMF, 100 °C, 12 h	10/32
5	acetamidine (1.2 equiv), NaOH (3 equiv), DMF, 100 °C, 12 h	0/18

^a All the reactions were carried out with a 2 mmol scale with solvent (2 mL).
^b ¹H NMR conversions.

ate **3**, we realized that it was not worth pursuing the approach shown Scheme 3 to make the required intermediate **3**.

Scalable Synthesis of 4-Bromo-1,2-dimethyl-1H-imidazole (**1**)

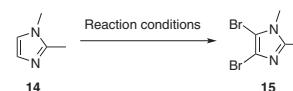
Based on literature precedence, the team came up with two different routes to synthesize compound **1** (Scheme 4). According to Scheme 4a, methylation of **11** followed by reduction of the nitro group to amine intermediate **13**, and Sandmeyer's deaminative bromination afforded **1**. The alternative route (Scheme 4b) commenced from commercially available 1,2-dimethyl-1H-imidazole **14**.



Scheme 4 (a) First alternate synthesis of **1** (b) Final optimized scheme for the synthesis of 4-bromo-1,2-dimethyl-1H-imidazole (**1**).

N-Methylation was performed on 2-methyl-4-nitro-1H-imidazole by following a reported protocol with methyl iodide and potassium carbonate (Scheme 4a) to give **12** in 70% yield.⁵ Reduction of nitro to amine by hydrogenation with Pd/C or iron powder yielded **13** in poor yields.⁶ Moreover, the conversion of amine **13** into the corresponding bromide *via* Sandmeyer reaction was not successful. For these reasons, Scheme 4a was abandoned. Based on our hy-

pothesis, we started exploring the synthesis of 4,5-dibromo-1,2-dimethyl-1H-imidazole (**15**) starting from commercially available 1,2-dimethyl-1H-imidazole (**14**). Bromination of **14** was performed with NBS by following a reported procedure,⁷ and optimization of the reported conditions gave better yields of **15** (Table 2). Here different solvents such as MeCN, DMF, and toluene were screened, and DMF was found to be a better solvent for this transformation (entries 1, 4, and 7). Interestingly, the time interval of the reaction also played a crucial role in achieving good yields (entries 4–6) of about 80%. Notably, the NBS-DMF system has associated safety concerns during scale up.⁸

Table 2 Optimization of Dibromination

Entry	Reaction conditions ^a	Yield (%) ^b
1	NBS (2 equiv), MeCN, r.t., 3 h	48
2	NBS (2.5 equiv), MeCN, 50 °C, 3 h	65
3	NBS (2.5 equiv), MeCN, 50 °C, 12 h	63
4 ^{7f}	NBS (2 equiv), DMF, r.t., 3 h	70
5	NBS (2.5 equiv), DMF, r.t., 6h	80
6	NBS (2 equiv), DMF, r.t., 12 h	75
7	NBS (2 equiv), toluene, r.t., 12 h	54

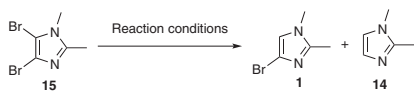
^a All the reactions were carried out with 2 mmol **14** and solvent (2 mL).
^b ¹H NMR conversion.

Optimization of Selective Debromination

Upon successful synthesis of 4,5-dibromo-1,2-dimethyl-1H-imidazole (**15**), we turned our attention towards the selective debromination of **15**. Based on the literature,⁹ an investigation was started to find suitable conditions for the selective debromination (Table 3). The reaction of **15** with tetramethylammonium fluoride (TMAF)^{9a} in DMSO at 100 °C resulted in the formation small amounts of the desired product (entry 1). In the same line, the reaction of **15** with 3 equivalents of NaI and 5 equivalents of TMSCl in acetonitrile as a solvent at 80 °C resulted in 33% yield of 4-bromo-1,2-dimethyl-1H-imidazole (**1**) and 66% yield of unreacted **15** (entry 2). The same reaction with NaI in the presence of Na₂SO₃ failed to give the desired product (entry 3).^{9c} Further, the reductive halogenation of **15** with sodium borohydride (NaBH₄)^{9d} at 80 °C did not produce the desired product (entry 4). Consequently, we focused on selective bromine exchange with organometallic reagent followed by quenching with the proton source.¹⁰ As planned, the reaction of **15** with 1.2 equivalents of *n*-butyl lithium in THF as solvent at –60 °C produced **1** in 78% yield (entry 5). When isopropyl magnesium chloride was used instead of *n*-BuLi, the formation of **1** improved to 83%, with 12% starting material (entry 6).¹¹ Increasing the number of equivalents of

isopropyl magnesium chloride from 1 to 1.2 resulted in complete consumption of starting material and 87% yield of the desired product **1** (entry 7).

Table 3 Optimization of the Debromination



Entry	Reaction conditions ^a	1/14 (%) ^b
1	15 , TMAF (2 equiv), DMSO (0.1 M), 100 °C	5/84
2	15 , NaI (3 equiv), TMSCl (5 equiv), MeCN (0.1 M), 80 °C	33/66
3	15 , NaI (0.1 equiv), Na ₂ SO ₃ (2 equiv), MeCN (0.1 M), 25 °C	NR
4	15 , NaBH ₄ (2 equiv), MeCN (0.1 M), 80 °C	NR
5	15 , <i>n</i> -BuLi (1.2 equiv), THF (0.1 M), -60 °C	78/0
6	15 , <i>i</i> PrMgCl (1 equiv), THF (0.1 M), 25 °C	83/12
7	15 , <i>i</i> PrMgCl (1.2 equiv), THF (0.1 M), 25 °C	87/0
8	15 , <i>i</i> PrMgCl (1.2 equiv), THF (0.1 M), 0 °C	90/0
9	15 , <i>i</i> PrMgCl (1.2 equiv), THF (0.1M), -25 °C	95 (92) ^c /0
10	15 , <i>i</i> PrMgCl (1.2 equiv), THF (0.1 M), -78 °C	94/0
11	15 , <i>i</i> PrMgCl (1.2 equiv), toluene (0.1 M), r.t.	85/0
12	15 , <i>i</i> PrMgCl (1.2 equiv), Et ₂ O (0.1 M), r.t.	87/0

^a All the reactions were carried out with 2 mmol of **15** and solvent (2 mL)

^b Based on ¹H NMR conversion. NR – no reaction.

^c Isolated yield in parentheses.

When a series of control experiments were conducted to examine the effect of reaction temperature, the reaction at 0 °C under standard conditions produced 90% yield of the desired product (entry 8). Additionally, decreasing the temperature from 0 to -25 °C, improved the yield from 90 to 95%; however, a further decrease in temperature to -78 °C showed no significant improvement in the yield of **1** (Table 3, entries 8–10). Solvent screening studies revealed that both toluene and Et₂O are efficient solvents for the reaction but gave slightly lower yields (entries 11 and 12). Under these optimized conditions, a scaled-up reaction was performed on a 100 g to 1 Kg scale and the isolated yield was ca. 92%.

In conclusion, we developed a cost-effective, two-step, scalable synthesis of 4-bromo-1,2-dimethyl-1H-imidazole (**1**), which is an important building block for synthesizing various APIs of biological interest. Following the new route, ca. 1 kg of **1** was synthesized consistently. The developed synthetic route uses the less expensive raw material 1,2-dimethyl-1H-imidazole and provided **1** with an overall yield of 74%.

All starting materials, reagents, and solvents were purchased from commercial suppliers and used without further purification. All reactions were performed under a nitrogen atmosphere unless otherwise

specified. Reactions were monitored by thin-layer chromatography (TLC) using Merck silica gel 60 F₂₅₄ pre-coated plates and visualized with a UV lamp. All ¹H NMR (400 MHz), ¹³C NMR (100 MHz), and ¹⁹F NMR spectra were recorded with a Bruker 400 MHz spectrometer, and chemical shifts are reported in ppm using TMS or the residual solvent peak as reference. High-resolution mass spectra (HRMS) were recorded with a Thermo Scientific LTQ XL Orbitrap velos using direct infusion modes. LC-MS analyses were conducted with an Agilent 6140 quadrupole LCMS instrument using C18 columns.

Synthesis of 4,5-Dibromo-1,2-dimethyl-1H-imidazole (**15**)

To a stirred solution of 1,2-dimethyl-1H-imidazole (500 g, 5.2 mol, 1 equiv) in DMF (5 L) in a 30 L reactor, *N*-bromosuccinimide (2.314 Kg, 13 mol, 2.5 equiv) was added slowly at room temperature and the reaction mixture was stirred at room temperature for another 6 h. Upon completion of the reaction (monitored by LCMS and TLC), the reaction was quenched with sodium thiosulfate solution and the mixture was extracted with EtOAc (3 × 1 L). The organic layers were combined and dried over sodium sulfate, followed by concentration to obtain the crude product. The desired product was purified by ISCO column chromatography to afford **15**.

Yield: 1.055 Kg (80%); pale-yellow solid.

¹H NMR (400 MHz, CDCl₃): δ = 2.40 (s, 3 H), 3.54 (s, 3 H).

The physical and spectral properties of this compound were consistent with those reported.^{7f}

Synthesis of 4-Bromo-1,2-dimethyl-1H-imidazole (**1**)

To a stirred solution of 4,5-dibromo-1,2-dimethyl-1H-imidazole (**15**) (1.0 Kg, 3.94 mol, 1 equiv) in THF (0.1 M, 10 L) in a 30 L reactor, a solution of isopropyl magnesium chloride in THF (2 M, 2.16 L, 4.33 mol, 1.1 equiv) was added slowly dropwise at -25 °C over a period of 1 hour. The reaction mixture was then stirred at -25 °C for an additional 1 h. Upon completion of the reaction, as monitored by LCMS, the reaction was quenched with saturated ammonium chloride solution and the mixture was extracted with EtOAc (3 × 2 L). The organic layers were combined and concentrated to obtain the crude product, which was triturated with a mixture of CH₂Cl₂ and petroleum ether (1:10) to give **1**.

Yield: 635 g (92%); off-white solid.

¹H NMR (400 MHz, DMSO-*d*₆): δ = 2.24 (s, 3 H), 3.51 (s, 3 H), 7.13 (s, 1 H).

¹³C NMR (400 MHz, DMSO-*d*₆): δ = 12.2, 32.5, 111.2, 119.6, 144.9.

The physical and spectral properties of this compound were consistent with those reported.^{1c,2} The structure was further confirmed by 2D-NOESY NMR analysis; see the Supporting Information for full spectral details.

Conflict of Interest

The authors declare no conflict of interest.

Acknowledgment

We thank Dr Li Jianqing and Dr James Kempson for their helpful suggestions and proofreading. Analytical support from the Discovery Analytical Department, Biocon Bristol Myers Squibb Research Centre (BBRC), Bangalore (India) is gratefully acknowledged.

Supporting Information

Supporting information for this article is available online at <https://doi.org/10.1055/a-2176-1585>.

References

- (1) (a) Wu, J.; Zhou, S.; Xiao, Y.; Huang, Y.; Duan, Z.; Huang, Y.; Lu, Y. *WO* 2021147882 Al, **2021**. (b) Kawana, A.; Kanazawa, C.; Tera, M.; Takahashi, Y. *WO* 2016017699 Al, **2016**. (c) Efremov, I. V.; Kazmirski, S.; Li, Q.; Thompson, I. L. A.; Wallace, O. B.; Johnstone, S. D.; Zhou, F.; Rahl, P. *WO* 2020190754 Al, **2020**. (d) Bookser, B.; Botrous, I.; Branstetter, B.; Dyck, B.; Weinhouse, M. *US* 20190177327 Al, **2019**. (e) Velaparthy, U.; Darne, C. P.; Dodd, D. S.; Sampognaro, A. J.; Wittman, M. D.; Kumaravel, S.; Mullick, D.; Reddy, C. R.; Liu, P. *WO* 2014100533 Al, **2014**. (f) Schiemann, K.; Blagg, J.; Mallinger, A.; Rink, C.; Sejberg, J.; Honey, M. *WO* 2016009076 Al, **2016**. (g) Chessari, G.; Howard, S.; Buck, I. M.; Cons, B. D.; Johnson, C. N.; Holvey, R. S.; Rees, D. C.; St. Denis, J. D.; Tamanini, E.; Golding, B. T.; Hardcastle, I. R.; Cano, C. F.; Miller, D. C.; Noble, M. E. M.; Griffin, R. J.; Osborne, J. D.; Peach, J.; Lewis, A.; Hirst, K. L.; Whittaker, B. P.; Watson, D. W.; Mitchell, D. R. *WO* 2017055859 Al, **2017**. (h) Patel, S.; Hamilton, G.; Stivala, C.; Chen, H.; Zhao, G. *WO* 2017004500 Al, **2017**. (i) Jaeschke, G.; O'Hara, F.; Plancher, J.-M.; Ricci, A.; Rueher, D.; Vieira, E. *WO* 2017021384 Al, **2017**. (j) Kinsella, T.; Gelman, M.; Hong, H.; Darwish, I. S.; Singh, R.; Yu, J.; Borzilleri, R. M.; Velaparthy, U.; Liu, P.; Darne, C.; Rahaman, H.; Warriier, J. S. *WO* 2016140884 Al, **2016**.
- (2) Nichols, P. L.; Skidmore, J.; Ward, R. W.; Wilson, D. M. *WO* 2009000819 Al, **2009**.
- (3) Ren, Q.; Liu, X.; Huang, J.; Zhang, Y.; Goldmann, S. *WO* 2019001396 A, **2019**.
- (4) Elejalde, N.-R.; Macías, M.; Castillo, J.-C.; Sortino, M.; Svetaz, L.; Zacchino, S.; Portilla, J. *ChemistrySelect* **2018**, 3, 5220.
- (5) Lu, G. L.; Ashoorzadeh, A.; Anderson, R. F.; Patterson, A. V.; Smaill, J. B. *Tetrahedron Lett.* **2013**, 69, 9130.
- (6) Crawford, J. J.; Ortwine, D. F.; Wei, B. Q.; Young, W. B. *WO* 2013067274 A1, **2013**.
- (7) (a) McLoughlin, P. T. F.; Clyne, M. A.; Aldabbagh, F. *Tetrahedron* **2004**, 60, 8065. (b) Bahnous, M.; Mouats, C.; Fort, Y.; Gros, P. C. *Tetrahedron Lett.* **2006**, 47, 1949. (c) Frutos, R. P.; Krishnamurthy, D.; Patel, N. D.; Rodriguez, S.; Senanayake, C. H. *WO* 2007121390 A1, **2007**. (d) Guiry, P.; Godson, C. *WO* 2018033642 Al, **2018**. (e) De Gaetano, M.; Butler, E.; Gahan, K.; Zanetti, A.; Marai, M.; Chen, J.; Cacace, A.; Hams, E.; Maingot, C.; McLoughlin, A.; Brennan, E.; Leroy, X.; Loscher, C. E.; Fallon, P.; Perretti, M.; Godson, C.; Guiry, P. J. *Eur. J. Med. Chem.* **2019**, 162, 80. (f) Lessia, M.; Panattonib, A.; Guglielmeroa, C. L.; Mineia, P.; Bellina, F. *Synthesis* **2019**, 51, 933.
- (8) Shimizu, S.; Imamura, Y.; Ueki, T. *Org. Process Res. Dev.* **2014**, 18, 354.
- (9) (a) Bastosa, M. M.; Barbosaa, P. J.; Pinto, C. A.; Kover, B. W.; Takeuchi, Y.; Boechata, N. *J. Braz. Chem. Soc.* **2001**, 12, 417. (b) Sako, M.; Kihara, T.; Okada, K.; Ohtani, Y.; Kawamoto, H. *J. Org. Chem.* **2001**, 66, 3610. (c) Lee, H. S.; Chang, M. Y.; Yoon, M. C. *Bull. Korean Chem. Soc.* **2004**, 25, 1723. (d) Uzelac, E. J.; Rasmussen, S. C. *J. Org. Chem.* **2017**, 82, 5947.
- (10) (a) Conboy, G.; Taylor, R. G. D.; Findlay, N. J.; Kanibolotsky, A. L.; Inigo, A. R.; Ghosh, S. S.; Ebenhoch, B.; Jagadamma, L. K.; Thalluri, G. V. V.; Sajjad, M. T.; Samuel, I. D. W.; Skabara, P. J. *J. Mater. Chem. C* **2017**, 5, 11927. (b) Tsutsumi, S.; Okonogi, T.; Shibahara, S.; Ohuchi, S.; Hatshusiba, E.; Patchett, A. A.; Christensen, B. G. *J. Med. Chem.* **1994**, 37, 3492. (c) Blom, P. M.; Housseman, C. G.; Daugan, A.; Dumoulin, A.; Laugeois, M.; Denis, A.; Faucher, N.; Botez, I.; Le Tiran, A.; Christensen, K.; Lamotte, Y. *WO* 2021224320 Al, **2021**.
- (11) Frutos, P. R.; Rodriguez, S.; Patel, D. N.; Reeves, D.; Tampone, T.; Senanayake, H. C. *Asian J. Org. Chem.* **2014**, 3, 769.