Synthesis of fluoro-functionalized diaryl-λ^3^-iodonium salts and their cytotoxicity against human lymphoma U937 cells

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Abstract
Conscious of the potential bioactivity of fluorine, an investigation was conducted using various fluorine-containing diaryliodonium salts in order to study and compare their biological activity against human lymphoma U937 cells. Most of the compounds tested are well-known reagents for fluoro-functionalized arylation reactions in synthetic organic chemistry, but their biological properties are not fully understood. Herein, after initially investigating 18 fluoro-functionalized reagents, we discovered that the ortho-fluoro-functionalized diaryliodonium salt reagents showed remarkable cytotoxicity in vitro. These results led us to synthesize more compounds, previously unknown sterically demanding diaryliodonium salts having a pentafluorosulfanyl (SF₅) functional group at the ortho-position, that is, unsymmetrical ortho-SF₅ phenylaryl-λ^3^-iodonium salts. Newly synthesized mesityl(2-(pentafluoro-λ^6^-sulfanyl)phenyl)iodonium exhibited the greatest potency in vitro against U937 cells. Evaluation of the cytotoxicity of selected phenylaryl-λ^3^-iodonium salts against AGLCL (a normal human B cell line) was also examined.

Introduction
There has been a surge in the number of reports about fluorine chemistry in recent decades. This is because fluorine is an extremely important element whose presence in a compound can completely change its original physical and chemical characteristics [1-3]. The chemical structures of various pharmaceuticals, agrochemicals and coatings contain fluorine or fluori-
nated functional groups [4-9]. Therefore, the development of efficient synthetic methodologies for organofluorine compounds has gained much attention [10-15]. Our research group has been actively working in this direction for decades [12,13,16-23]. Our primary goal has been to develop fluorinating and fluoro-functionalized reagents for fluorination [18,19], trifluoromethylation [13,18,19], trifluoromethylthiolation [12,21] and pentafluoroarylation [22,23]. Utilizing these reagents, we have successfully synthesized a wide variety of bioactive organofluorine compounds [24-30] including fluorinated thalidomide (antitumor) [24], fluorinated donepezil (cholinesterase inhibitor) [25], and fluorinated camptothecin (anticancer) [26]. During our research programs focused on the development of novel reagents for fluoro-functionalization [12,13,16-23], as well as the design and synthesis of biologically active fluorine-containing compounds [24-28], we noted that a series of fluoro-functionalization reagents could themselves be highly potential drug candidates. All of the reagents that we developed contain at least one fluorine atom in their structures, which may explain why they have potential biological activity [4-9]. In addition, examination of the successful records of heterocyclic compounds in the pharmaceutical history indicates that some of these reagents have a heterocyclic skeleton which makes them suitable as drug candidates [29-32]. Among these compounds, our group is interested in investigating the biological activity of hypervalent iodine-type reagents [33]. Hypervalent iodine compounds have been receiving a lot of attention lately due to their varied applications in organic synthesis [33-40]. A wide range of bioactive compounds make use of diaryliodonium reagents as a part of their synthesis [41-43]. On the other hand, there are only fragmented reports on the biological activity of diaryliodonium salts [44-49]. Goldstein et al. [45] and Doroshow et al. [46] reported that some diaryliodonium salts show effective antimicrobial and NOX inhibitor activity, respectively. Several aryliodonium salts, arylidonium ylides, and (diacyloxyiodo)arenes were also examined for their antibacterial activities against ice nucleation active Pseudomonas syringae, and arylidonium salts, especially those with electron-withdrawing groups, exhibit higher antibacterial activities [49]. Despite the long history of diaryliodonium salts, which exceeds 100 years, as Willgerodt's reagent [50], research on the biological effects of diaryliodonium salts is still undeveloped. Since there are iodine-containing pharmaceuticals such as a series of radiocontrast agents, levothyroxine, iodixaridine and amiodaron [51-54], we started to investigate a biological study of fluorine-containing hypervalent iodine compounds in vitro using U937 (a human histiocytic lymphoma cell line) [55-58]. The U937 cell line is maintained as replicative non-adherent cells having many of the biochemical and morphological characteristics of blood monocytes. This cell line was chosen due to the convenience with which it can be handled and its ease of growth [27]. Initially, 19 compounds [20-22,59-64] were examined for their potential cytotoxicity, and some of them showed potency, in particular ortho-fluoro-functionalized diaryliodonium salts. These findings led us to synthesize four more previously unknown diaryliodonium salts having a sterically demanding pentafluorosulfanyl (SF₅) functional group at the ortho-position, that is, unsymmetrical ortho-SF₅ phenylaryl-κ²-iodonium salts. Finally, one of the new compounds, namely mesityl(2-(pentafluoro-κ¹-sulfanyl)phenyl)iodonium salt, exhibited the greatest potency in vitro against U937 cells with an IC₅₀ value of 0.49 μM.

Results and Discussion

To begin our investigation related to bioactivity, we randomly selected some fluorinating reagents that we had already developed, including Shibata reagents I [20] and II [21] (trifluoromethylation reagent I and trifluoromethylthiolation reagent 2a, respectively), pentafluorophenylating reagent 2b and several hypervalent iodine reagents, i.e., diaryliodonium salts with a mesitylene ligand (3a-o) and a trisopropylphenyl ligand 4a [20-22,59-64] (Figure 1). We used the Muse™ Annexin V and Dead Cell Assay Kit (FITC), which is a common tool to detect the ability of compounds to induce cell death. U937, a human histiocytic lymphoma cell line (DS Pharma Biomedical EC85011440; Osaka, Japan) was used to examine the ability of our synthesized compounds to induce cell death.

The investigation was initially carried out using 20 μM of several of the compounds, all of which showed strong cytotoxicity (Figure S1 in Supporting Information File 1). We therefore opted to examine this potency using lower concentrations (1 μM and 5 μM) of these compounds. The data (treated cells and untreated controls) were plotted together to compare the results (Figure 2). Shibata reagents 1 and 2a were not very cytotoxic at 5 μM. Perfluorinated phenylthio reagent 2b and perfluorinated phenyl reagent 3a showed similar, but unimpressive, results at both concentrations. Pyridinyl reagent 3b, having a pyridine-SF₅ moiety, displayed high cytotoxicity (63.0% of annexin V-positive cells) at 5 μM, as did 3d with 58.6% cytotoxicity. However, another analogue of pyridine-SF₅ reagent 3c showed weak (10.8%) cytotoxicity. Next, we investigated the various SF₅-phenyl arylidonium salts 3e-h. They all displayed potent cytotoxicities at 5 μM (3e, 86.2%); 3f (78.6%); 3g (94.0%); 3h (94.1%) and 3i had the greatest result even at 1 μM (52.8%). Thereafter, we analysed SO₂CF₃-phenyl arylidonium salts 3i-k and CF₃-phenyl arylidonium salts 3l-m. We observed that ortho-substituted phenyl arylidonium salts 3k and 3m seemed to provide great potency at both concentrations (60.6% and 39.8% at 1 μM and 98.6% and 88.4% at 5 μM, respectively). The ortho-fluorophenyl arylidonium salt 3n was also analysed, and its potency at 5 μM was found to be
Figure 1: Compounds used for the biological study.

Figure 2: Compounds 1–4 induced cell death in U937 cells. Briefly, U937 cells (1 × 10⁴ cells/mL) were incubated with each test compound at 1 μM and 5 μM for 24 h. Cells were stained with annexin V and propidium iodide (PI). The data shown is the mean ± SD (n = 3).
Following this investigation, we found that the ortho-substituted diaryliodonium salts with an ortho-SO₂CF₃ group 3k and an ortho-CF₃ group 3m displayed impressive results. A common feature of ortho-substitution on the aromatic group is steric demand, which allowed us to analyse the cell death-inducing potency of phenyl aryliodonium salts with a more sterically demanding fluoro-functional group of SF₅ at the ortho-position. As we did not succeed in synthesizing ortho-SF₅-substituted aryliodonium salts previously [59], we decided to proceed with a further investigation of the synthesis of ortho-SF₅ phenyl aryliodonium salts.

Four ortho-SF₅-substituted diaryliodonium salts were designed with different arenes as auxiliary groups, namely, electron-rich with sterically demanding mesitylene type 4b and trisopropylphenyl type 5a, electron-rich anisole type 5a and simple phenyl type 6a, which altered their electronic and steric properties [37]. First, pentafluoro-(2-iodophenyl)-λ⁶-sulfane (7) was synthesized from commercially available 2-(pentafluoro-λ⁶-sulfanyl)aniline (8), by completing a Sandmeyer reaction (Scheme 1). Fluoroboric acid and sodium nitrite were used to generate the diazonium ion and then KI was used to introduce iodide, providing the desired product 7 in 87% yield.

With 7 in hand, the synthesis of the ortho-SF₅ phenyl aryliodonium salts, we selected salts 3p and 5a having mesitylene and anisole dummy ligands, respectively, and analysed their potential to induce cell death in U937 cells (Figure 4). Anisole type salt 5a showed moderate cytotoxicity (45.2%) at 5 μM but the value decreased to 6.8% at 1 μM. Mesitylene type salt 3p, on the other hand, displayed high potencies (98.9% and 66.9%) at 5 μM and 1 μM, respectively. To ensure that the cytotoxicity of 3p was not due to its decomposed fragments, we analysed pentafluoro-(2-iodophenyl)-λ⁶-sulfane (7) and pentafluoro(phe-nyl)-λ⁶-sulfane (SF₅-C₆H₅, 9), which did not exhibit cytotoxicity.

From the above analysis, we selected a series of ortho-SF₅ phenyl aryliodonium salts, we selected salts 3p and 5a having mesitylene and anisole dummy ligands, respectively, and analysed their potential to induce cell death in U937 cells (Figure 4). Anisole type salt 5a showed moderate cytotoxicity (45.2%) at 5 μM but the value decreased to 6.8% at 1 μM. Mesitylene type salt 3p, on the other hand, displayed high potencies (98.9% and 66.9%) at 5 μM and 1 μM, respectively. To ensure that the cytotoxicity of 3p was not due to its decomposed fragments, we analysed pentafluoro-(2-iodophenyl)-λ⁶-sulfane (7) and pentafluoro(phe-nyl)-λ⁶-sulfane (SF₅-C₆H₅, 9), which did not exhibit cytotoxicity.

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From the above analysis, we selected a series of ortho-fluorinated diaryliodonium salts SO₂CF₃ type 3k, CF₃ type 3m and SF₅ type 3p and examined their IC₅₀ values based on an MTT assay (Table 1). While 3k was more potent than 3m at both...
concentrations, i.e., 1 μM and 5 μM (Figure 2), 3m has a lower IC\textsubscript{50} value of 0.68 μM than that of 3k (2.45 μM), as evaluated by the MTT assay. The best potency and IC\textsubscript{50} value (0.49 μM) was obtained for SF\textsubscript{5} type 3p, which is quite impressive when compared to the well-known antitumor drug cytosine arabinoside (ara-C), (0.16 μM) [27].

Since, 3k, 3m and 3p exhibited strong cytotoxicity against U937 cells, we finally evaluated their cytotoxicity against normal cells in vitro. AGLCL, a human normal B cell line (DS Pharma Biomedical EC9120566; Osaka, Japan) was chosen for the experiments and investigations were performed at 20 μM (Figure S2 in Supporting Information File 1) and 5 μM and 1 μM concentrations (Figure 5) of the compounds. Although 3k, 3m and 3p exhibited cytotoxicity even against AGLCL cells, a remarkable difference was observed. That is, moderate cytotoxicity at 5 μM (51.1%, 51.2% and 62.0%, respectively) and low cytotoxicity at 1 μM concentration (20.4%, 15.8% and 24.9%, respectively) against AGLCL cells were observed. It is noteworthy that the cytotoxicity displayed by 3k, 3m and 3p against U937 cells is much higher than those against AGLCL cells at both concentrations. These results strongly suggested that antitumor drug candidates could be designed by further structural modification of these compounds 3. Moreover, with 3p exhibiting the greatest potency against U937 cells with comparably lower toxicity against AGLCL cells, further biological studies using 3p including in vivo evaluation should be conducted. A mechanistic study that examines the structure–cytotoxicity relationships of a series of diaryliodonium salts 3 will also be conducted.

**Conclusion**

In conclusion, we have analysed a series of fluorinating reagents and diaryliodonium salts for their applicability in
producing cell death based on U937 (a human histiocytic lymphoma cell line). We have also successfully synthesized novel ortho-SF₅ phenylaryl-κ² iodonium salts. As expected, several fluorinated diaryliodonium salts exhibited cytotoxicity. Among the series, the newly synthesized ortho-SF₅ salt 3p displayed the greatest potency. The ortho-fluorinated diaryliodonium salts 3k, 3m and 3p were also examined for comparison studies with AGLCL (a normal human B cell line). Although the values were rather low, selectivity was indeed observed against U937 cells. Also, even though the results are in a preliminary stage of biological evaluation, this is the first report to highlight the cytotoxicity of diaryliodonium salts against U937 cells. Since diaryliodonium salts are fundamentally oxidizing agents, there might be a stronger correlation between cytotoxicity and the oxidation potential of these salts. We will continue the biological investigation of these salts in this direction. From the viewpoint of organic synthesis, the newly synthesized ortho-SF₅-substituted unsymmetrical iodonium salts 3p, 4b, 5a and 6a have potential use as electrophilic SF₅-phenylation reagents for a range of nucleophiles such as alcohols, amines, thios, and active methylene nucleophiles [59-61]. The application of these ortho-SF₅-substituted diaryliodonium salts in organic synthesis, as well as their detailed bioactive behaviour, will be reported in due course.

Experimental

Biological assay

Quantification of cytotoxicity by annexin V and propidium iodide (PI): Cytotoxicity was detected with the Muse™ Annexin V and Dead Cell Assay Kit (Merck Millipore Corp., Darmstadt, Germany) and Muse Cell Analyzer (Merck Millipore Corp.) according to the manufacturer’s protocols. Cells incubated in the presence or absence of the fluorinated compounds for 24 h were collected by centrifugation (2,000 rpm at 4 °C for 5 min). Cells were suspended in 100 μL of RPMI 1640 medium (Sigma-Aldrich, Steinheim, Germany), and incubated with 100 μL of annexin V reagent (in the kit) at room temperature for 20 min. These cells were measured by the Muse Cell Analyzer.

Statistical analysis: Data were analyzed using Excel software. Results are expressed as the mean ± SD of three independent replicates.

MTT assay: The 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay was performed to evaluate cell viability by diaryliodonium salt compounds using the MTT cell proliferation assay kit (Cayman Chemical Company, Ann Arbor, USA). U937 cells were incubated in solutions containing the diaryliodonium salts (3k, 3m or 3p). After this treatment, the U937 cells were seeded in culture medium (100 μL) in a 96-well plate (Becton and Dickinson, at a density of 2 × 10⁵ cells/well) and incubated at 37 °C for 24 h. MTT reagent (10 μL) was added to each well. After mixing gently, the cells were incubated for 3 h at 37 °C in a CO₂ incubator. The culture medium was aspirated and the crystal-dissolving solution (100 μL) was added to each well and mixed. Finally, the optical density was measured (550 nm) using a microplate reader (BIO-RAD, Benchmark, Hercules, USA).

General information

All reactions were performed in oven-dried glassware under positive pressure of nitrogen or argon unless mentioned otherwise. Solvents were transferred via a syringe and were introduced into reaction vessels through a rubber septum. All reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm Merck silica gel (60-F254). The TLC plates were visualized with UV light (254 nm). Column chromatography was carried out on columns packed with silica gel (60N spherical neutral size 63–210 μm). The ¹H NMR (300 MHz), ¹⁹F NMR (282 MHz), and ¹³C NMR (125 MHz) spectra for solution in CDCl₃ or (CD₃)₂CO were recorded on Varian Mercury 300 and Bruker Avance 500 spectrometers. Chemical shifts (δ) are expressed in ppm downfield from TMS (δ = 0.00) or CsF₆ [δ = −162.2 (CDCl₃) or −163.5 ((CD₃)₂CO)] as an internal standard. Mass spectra were recorded on a Shimadzu GCMS-QP5050A (EI/MS) and Shimazu LCMS-2020 (ESIMS) spectrometer. The solvent CH₂Cl₂ was dried and distilled before use.

Preparation of pentafluoro(2-iodophenyl)-κ⁶-sulfane (7): The preparation of 7 was based on a modified procedure in the literature [67]. To 4 mL of HBF₄ in a round bottomed flask, 1.1 g of 2-(pentafluoro-κ⁶-sulfanylaniline was added and...
heated until a clear solution formed. The solution was cooled to 0 °C and a cold solution of NaN₃ (380 mg in 2.5 mL distilled water) was added dropwise. The reaction was allowed to stir at 0 °C for 15 min after which it was added dropwise to a cold stirred solution of KI (1.33 g in 10 mL distilled water) at 0 °C. The reaction was allowed to warm to room temperature then stirred for 20 min. The reaction mixture was extracted with diethyl ether (3 × 20 mL). The combined organic extract was washed with NaHCO₃ solution and Na₂SO₄ solution and dried over Na₂SO₄. The solvent was concentrated under reduced pressure to give a crude product which was purified using silica gel column chromatography (9:1, hexane/ethyl acetate) to give 1.4 g of 7 as a yellow oil in 87% yield. HRMS (EI–TOF) m/z [M+]: calcd for C₆H₄F₂S₃I, 329.8999; found, 329.9010; ¹H NMR (CDCl₃, 300 MHz) δ 7.10 (t, J = 9 Hz, 1H), 7.41–7.47 (m, 1H), 7.80 (dd, J = 9 Hz, 3 Hz, 1H), 8.14 (d, J = 9 Hz, 1H); ¹³F NMR (CDCl₃, 282 MHz) δ 63.55 (d, J = 3 Hz, 1F), 83.56 (q, J = 155.1 Hz, 4F), 133.4 (1H) NMR (CDCl₃, 126 MHz) δ 88.4, 128.1, 130.3 (t, J = 3.75 Hz), 132.4, 144.1, 158.57 (q, J = 15 Hz).

General procedure A: preparation of diaryliodonium salts

These salts were prepared according to a modified procedure in the literature [64,65]. m-CPBA (assume 70 wt %, 1.1 equiv) was dried in vacuo at room temperature for 1 h before the addition of 7 (1.0 equiv) and CH₂Cl₂ (6.0 mL/mmol ArI) in a round-bottomed flask. The solution was cooled to 0 °C followed by the dropwise addition of TF0H (1.7 equiv). The resulting mixture was stirred at room temperature for 2 h. It was then cooled to 0 °C and the arene (1.1 equiv) was added dropwise. The mixture was warmed to room temperature and stirred for 18 h. The solvent was then removed under reduced pressure. The resulting crude product was precipitated by the addition of Et₂O. The precipitate was filtered and dried in vacuo to give 3–6 as an off-white to white solid.

### (4-Methoxyphenyl)(2-(pentfluoro-1H-sulfanyl)phenyl)iodonium trifluoromethanesulfonate (5a):
Following general procedure A, 7 (416 mg, 1.26 mmol), m-CPBA (340 mg, 1.38 mmol), TF0H (0.24 mL, 2.14 mmol) and anisole (0.15 mL, 1.38 mmol) in CH₂Cl₂ (6 mL) were used from 0 °C to room temperature for 18 h to give 5a as a white solid (600 mg) in 81% yield. mp: 108.7–110.4 °C; HRMS (ESI–TOF) m/z [M + OTf]⁺: calcd for C₁₅H₁₁OF₃S₁, 436.9495; found, 436.9499; ¹H NMR ((CD₃)₂CO, 300 MHz) δ 3.90 (s, 3H), 7.16 (d, J = 9 Hz, 2H), 7.86 (t, J = 9 Hz, 1H), 8.03 (t, J = 9 Hz, 1H), 8.29 (d, J = 9 Hz, 3H), 8.92 (d, J = 6 Hz, 1H); ¹³F NMR ((CD₃)₂CO, 282 MHz) δ 79.75 (s, 3F), 65.79 (d, J = 149.5 Hz, 4F), 81.73 (q, J = 152.3 Hz, 1F); ¹³C[¹H] NMR ((CD₃)₂CO, 126 MHz) δ 56.4, 104.8, 109.8, 118.9, 131.7, 134.6, 136.9, 138.8, 142.2, 154.1–154.4 (m), 164.5.

### (2-(Pentafluoro-1H-sulfanyl)phenyl)(2,4,6-trisopropylphenyl)iodonium trifluoromethanesulfonate (4b):
Following general procedure A, 7 (330 mg, 1 mmol), m-CPBA (271 mg, 1.1 mmol), TF0H (0.2 mL, 1.7 mmol) and triisopropylbenzene (0.26 mL, 1.1 mmol) in CH₂Cl₂ (6 mL) were used from 0 °C to room temperature for 18 h to give 4b as a white solid (604 mg) in 86% yield. mp: 106.6–107.9 °C; HRMS (ESI–TOF) m/z [M – OTf]⁺: calcd for C₂₁H₂₇F₃S₁, 533.0798; found, 533.0798; ¹H NMR ((CD₃)₂CO, 300 MHz) δ 1.31 (t, J = 9 Hz, 18H), 3.14 (q, J = 9 Hz, 1H), 3.30 (q, J = 6 Hz, 2H), 7.45 (d, J = 9 Hz, 1H), 7.58 (s, 2H), 7.76 (t, J = 6 Hz, 1H), 7.96 (d, J = 9 Hz, 1H), 8.37 (dd, J = 9 Hz, 1.5 Hz, 1H); ¹³F NMR ((CD₃)₂CO, 282 MHz) δ 79.91 (s, 3F), 64.02 (d, J = 6 Hz, 1H); ¹³C[¹H] NMR ((CD₃)₂CO, 126 MHz) δ 37.0, 44.3, 79.9, 132.4, 144.1, 158.57 (q, J = 15 Hz).
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References
1. Müller, K.; Faeh, C.; Diederich, F. Science 2007, 317, 1881–1886. doi:10.1126/science.1131943
2. Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. Chem. Soc. Rev. 2008, 37, 320–330. doi:10.1039/B610213C
3. Smart, B. E. J. Fluorine Chem. 2001, 109, 3–11. doi:10.1016/S0022-1139(01)00375-X
4. Wang, J.; Sánchez-Roselló, M.; Acería, J. L.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. Chem. Rev. 2014, 114, 2432–2506. doi:10.1021/cr5002879
5. Kirsch, P. Modern Fluororganic Chemistry: Wiley-VCH: Weinheim, 2013. doi:10.1002/9783527651351
6. Zhou, Y.; Wang, J.; Gu, Z.; Wang, S.; Zhu, W.; Acería, J. L.; Soloshonok, V. A.; Izawa, K.; Liu, H. Chem. Rev. 2016, 116, 422–518. doi:10.1021/acs.chemrev.5b00392
7. Jeschke, P. ChemBioChem 2004, 5, 570–589. doi:10.1002/cbic.200300833
8. Gillis, E. P.; Eastman, K. J.; Hill, M. D.; Donnelly, D. J.; Meanwell, N. A. J. Med. Chem. 2015, 58, 8315–8359. doi:10.1021/acs.jmedchem.5b00258
9. Ojima, I. Fluorine in Medicinal Chemistry and Biological Chemistry: Wiley-Blackwell, 2009.
10. Liang, T.; Neumann, C. N.; Ritter, T. Angew. Chem., Int. Ed. 2013, 52, 8214–8264. doi:10.1002/anie.201206566
11. Ni, C.; Hu, M.; Hu, J. Chem. Rev. 2015, 115, 765–825. doi:10.1021/acs.jmedchem.5b00336
12. Xu, X.-H.; Matsuzaki, K.; Shibata, N. Chem. Rev. 2015, 115, 731–764. doi:10.1021/acs.chemrev.5b00193b
13. Shibata, N.; Matasev, A.; Cahard, D. Beilstein J. Org. Chem. 2010, 6, No. 65. doi:10.3762/bjoc.6.65
14. Ami, H.; Uneyama, K. Chem. Rev. 2009, 109, 2119–2183. doi:10.1021/cr800388c
15. Ni, C.; Hu, J. Chem. Soc. Rev. 2016, 45, 5441–5454. doi:10.1039/C6CS00351F
16. Kawai, H.; Shibata, N. Chem. Rec. 2014, 14, 1024–1040. doi:10.1002/hcr.201402023
17. Shibata, N.; Ishimaru, T.; Nakamura, S.; Toru, T. J. Fluorine Chem. 2007, 128, 469–483. doi:10.1016/j.jfluchem.2006.12.014
18. Shibata, N.; Mizuta, S.; Kawai, H. Tetrahedron: Asymmetry 2008, 19, 2633–2644. doi:10.1016/j.tetasy.2008.11.011
19. Shibata, N.; Suzuki, E.; Asahi, T.; Shiro, M. J. Am. Chem. Soc. 2001, 123, 7001–7009. doi:10.1021/ja010789l
20. Matsune, A.; Nortlase, S.; Nomura, Y.; Tokunaga, E.; Nakamura, S.; Shibata, N. Angew. Chem., Int. Ed. 2010, 49, 572–576. doi:10.1002/anie.200905225
21. Yang, Y.-G.; Azuma, A.; Tokunaga, E.; Yamasaki, M.; Shiro, M.; Shibata, N. J. Am. Chem. Soc. 2013, 135, 8782–8785. doi:10.1021/ja402455f
22. Matsuzaki, K.; Okuyama, K.; Tokunaga, E.; Shiro, M.; Shibata, N. Chem. Commun. 2014, 3, 233–237. doi:10.1020/jp402045
23. Saidalim, I.; Suzuki, S.; Tokunaga, E.; Shibata, N. Chem. Soc. 2016, 7, 2106–2110. doi:10.1039/C5CS04208A
24. Tokunaga, E.; Akiyama, H.; Soloshonok, V. A.; Inoue, Y.; Hara, H.; Shibata, N. Polyhedron 2017, 12, e0182152. doi:10.1371/journal.pone.0182152
25. Maeno, M.; Kondo, H.; Tokunaga, E.; Shibata, N. RSC Adv. 2016, 6, 8558–8562. doi:10.1039/C5RA21253K
26. Shibata, N.; Ishimaru, T.; Nakamura, M.; Toru, T. Synlett 2004, 2509–2512. doi:10.1055/s-2004-834810
27. Yang, Y.-D.; Tokunaga, E.; Akiyama, H.; Saito, N.; Shibata, N. Chem. Med. Chem. 2014, 9, 913–917. doi:10.1002/cmdc.201400059
28. Nishimine, T.; Taira, H.; Mori, S.; Mutsuba, O.; Tokunaga, E.; Akiyama, H.; Soloshonok, V. A.; Shibata, N. Chem. Commun. 2017, 53, 1128–1131. doi:10.1039/C6CC08830A
29. Dinges, J.; Lambeth, C. Bioactive Heterocyclic Compound Classes: Pharmaceuticals; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2012.
30. Gomtsyan, A. Chem. Heterocycl. Compd. 2012, 48, 7–10. doi:10.1007/s10593-012-0960-z
31. Kosjek, T.; Heath, E. Halogenated heterocycles as pharmaceuticals. In Halogenated Heterocycles; Iskra, J., Ed.; Springer-Verlag: Berlin, Heidelberg, 2011; Vol. 27, pp 219–248. doi:10.1007/978-3-642_2011_61
32. Taylor, A. P.; Robinson, R. P.; Fobian, Y. M.; Blakemore, D. C.; Jones, L. H.; Fadley, O. J. Biomol. Chem. 2016, 14, 6611–6637. doi:10.1039/C6OB00939K
33. Merritt, E. A.; Olofsson, B. Angew. Chem., Int. Ed. 2009, 48, 9052–9070. doi:10.1002/anie.200904689
34. Grushin, V. V. Chem. Soc. Rev. 2000, 29, 315–324. doi:10.1039/a909004t
35. Arad, K.; Töth, B. L.; Tolnai, G. L.; Novák, Z. Synlett 2016, 27, 1456–1485. doi:10.1055/s-0035-1561369
36. Chatterjee, N.; Goswami, A. Eur. J. Org. Chem. 2017, 3023–3032. doi:10.1002/ange.201601651
37. Malmgren, J.; Santoro, S.; Jallalian, N.; Himo, F.; Olofsson, B. Chem. – Eur. J. 2013, 19, 10334–10342. doi:10.1002/chem.201300860
38. Ito, M.; Itani, I.; Toyoda, Y.; Morimoto, K.; Doi, T.; Kita, Y. Angew. Chem., Int. Ed. 2012, 51, 12555–12558. doi:10.1002/anie.201206917
39. Sokolovs, I.; Lubriks, D.; Suna, E. J. Am. Chem. Soc. 2014, 136, 6920–6928. doi:10.1021/ja502174d
40. Phipps, R. J.; McMurray, L.; Ritter, S.; Dung, H. A.; Gaunt, M. J. J. Am. Chem. Soc. 2012, 134, 10773–10776. doi:10.1021/ja3039807
