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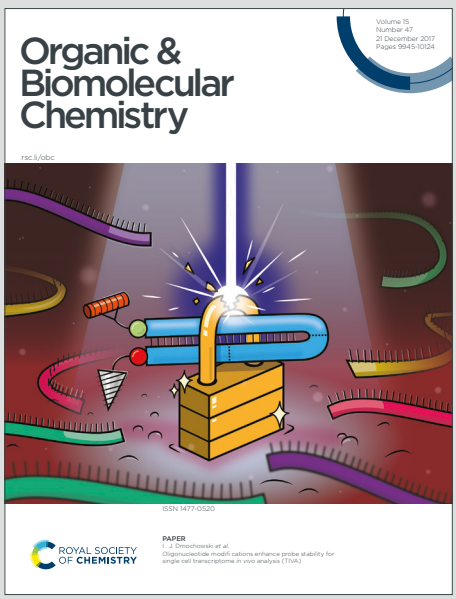

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DOI: 10.1039/C9OB01718F

ARTICLE

Rapid and efficient synthesis of a novel cholinergic muscarinic M_1 receptor positive allosteric modulator using flash chemistry

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

Shotaro Miura,[a,c] Koichiro Fukuda,[a,c] Shinichi Masada,[a] Hirotsugu Usutani, [b,d] Makoto Kanematsu,[b] David G. Cork,[b,e] and Tetsuji Kawamoto*[a,c]

Continuous flow-flash synthesis of a 2-bromobenzaldehyde derivative **18** as a key intermediate of a novel cholinergic muscarinic M_1 positive allosteric modulator **1** bearing an isoindolin-1-one ring system as a pharmacophore has been achieved using flow microreactors through selective I/Li exchange of 1-bromo-2-iodobenzene derivative **17** with BuLi and subsequent formylation at – 40 °C of the highly reactive 2-bromophenyllithium intermediate using DMF, which is difficult to achieve by a conventional batch process due to conversion of the highly reactive 2-bromophenyllithium intermediate into benzyne even at – 78 °C. Late-stage cyclization to the isoindolin-1-one ring system, through reductive amination of **18** followed by palladium-catalyzed carbonylation with carbon monoxide and intramolecular cyclization, efficiently afforded **1** for its further research and development.

Introduction

Positive allosteric modulators (PAMs) of the M_1 subtype of the muscarinic acetylcholine receptor[1] have attracted considerable attention as a new approach for the treatment of cognitive impairment, schizophrenia, and Alzheimer's disease.[2] Recently, a novel M_1 positive allosteric modulator (**TAK-071, 1**) bearing an isoindolin-1-one ring system as a pharmacophore has been developed by Takeda Pharmaceutical Company Limited with low cooperativity exhibiting improvement of cognitive function in rodents with few cholinergic side effects.[3,4]

The discovery synthetic route to **1**[4a] features a late-stage cyclization to give the isoindolin-1-one ring system through reductive amination of *o*-phthalaldehydic acid methyl ester derivative **11** with (3*S*,4*S*)-3-aminotetrahydro-2*H*-pyran-4-ol (**12**)[4a] followed by intramolecular condensation (Scheme 1). 2,3-Difluoro-4-methylbenzoic acid (**2**) was employed as a starting material to synthesize the 5-bromosalicylic acid methyl ester derivative **5** in 3 steps. Palladium-catalyzed borylation of **5** followed by Suzuki-coupling reaction of **6** with *para*-substituted benzyl halide **7** afforded diarylmethane **8**. Then, conversion of the hydroxyl group of **8** into formyl group was achieved in 3 steps to give **11** through triflation, palladium-catalyzed cross coupling reaction with tributyl(vinyl)tin, and oxidative cleavage of the vinyl group of **10** with OsO_4-$NaIO_4$.

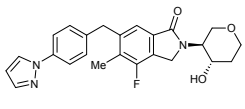
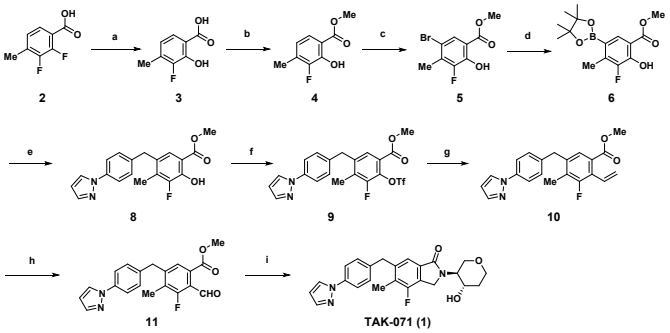


Fig. 1 Structure of **TAK-071** (**1**).



Scheme 1 Discovery synthetic route to **1**. Reagents and conditions: (a) NaOH, DMSO, 140 °C. (b) conc.H_2SO_4, MeOH, 60 °C. (c) Br_2, AcOH, 55% (3 steps). (d) bis(pinacolate)diboron, $(PPh_3)_2PdCl_2$, CH_3COOK, toluene, 110 °C, 81%. (e) 1-[4-(bromomethyl)phenyl]-1*H*-pyrazole (**7**), $Pd(PPh_3)_4$, Na_2CO_3, DME-water, 80 °C, 83%. (f) $PhNTf_2$, NaH, DMF, 74%; (g) tributyl(vinyl)tin, $(Ph_3P)_2PdCl_2$, LiCl, DMF, 90 °C, 91%. (h) OsO_4, $NaIO_4$, acetone-MeCN-water. (i) i) (3*S*,4*S*)-3-aminotetrahydro-2*H*-pyran-4-ol (**12**), $MgSO_4$, THF. ii) $NaBH(OAc)_3$, THF-MeOH, 51% (3 steps).

[a] *Neuroscience Drug Discovery Unit, Research, Takeda Pharmaceutical Company Ltd., 26-1, Muraoka-Higashi 2-chome, Fujisawa, Kanagawa 251-8555, Japan.*
[b] *Process Chemistry, Pharmaceutical Sciences, Takeda Pharmaceutical Company Ltd., 26-1, Muraoka-Higashi 2-chome, Fujisawa, Kanagawa 251-8555, Japan.*
[c] *Present address: Chemistry Research Division, Axcelead Drug Discovery Partners, Inc. 26-1, Muraoka-Higashi 2-chome, Fujisawa, Kanagawa 251-0012, Japan.*
[d] *Present address: Kyoto University Original Co., Ltd., Kyoto University, Yoshida-Hommachi, Sakyo-ku, Kyoto 606-8501, Japan.*
[e] *Present address: 2-4-56 Ueno Higashi, Toyonaka, Osaka, 560-0013, Japan.*

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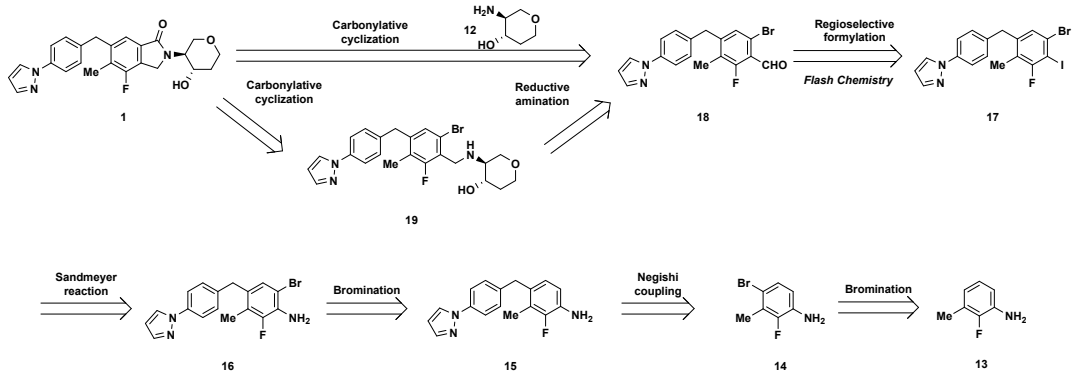


Scheme 2 Synthetic strategy for **1** involving late-stage carbonylative cyclization to isoindolin-1-one of **18** with **12** or **19**.

Although the original synthetic route was useful to provide **1** for initial drug discovery research, a more rapid and efficient approach to **1** suitable for its scale-up synthesis was necessary to be developed, from a less expensive starting material than **2** without using toxic reagents such as stannous and osmium reagents. The present paper describes development of an effcient and scalable synthetic route to an isoindolin-1-one drug candidate compound **1** involving flow-flash synthesis of its key intermediate for further research and development.

Results and discussion

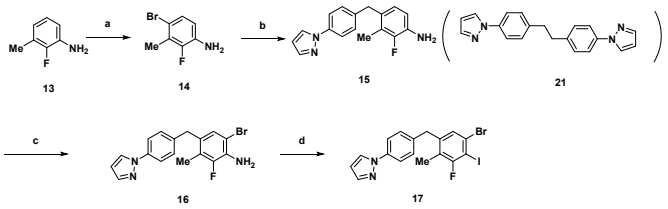
It is well known that palladium-catalyzed carbonylation with carbon monoxide followed by cyclization has popularly been used for syntheses of many heterocyclic compounds containing carbonyl groups, such as lactams, their related *N*-heterocycles, and lactones.[5] The carbonylative cyclizations of 2-bromobenzaldehydes with primary amines[6] or 2-bromobenzylamines[7] have been reported as convenient synthetic routes to isoindolin-1-one derivatives.[8] In addition, late-stage carbonylative cyclization to the isoindolin-1-one ring system of the drug candidate compounds would enable the convenient syntheses of those compounds labeled with ^{14}C using ^{14}CO gas, which are essential for drug research and development in nonclinical and clinical DMPK studies.[9] From these considerations, therefore, a new synthetic route to **1** was designed involving a late-stage carbonylative cyclization of the 2-bromobenzaldehyde derivative **18** with **12** or the 2-bromobenzylamine derivative **19**, which could be synthesized from the starting material **13** that is less expensive than **2** of the discovery route (Scheme 2). The key transformation in the new synthetic route to **1** is synthesis of a poly-substituted 2-bromobenzaldehyde derivative **18** from **17**.

Among the synthetic approaches to 2-bromobenzaldehyde derivatives,[10,11,12,13,14] selective iodine-metal exchange of the corresponding 1-bromo-2-iodobenzene derivatives with BuLi[13] or iPrMgBr[14] followed by formylation of the resulting 2-bromoaryllithium or 2-bromoarylmagnesium intermediate with DMF are known as convenient synthetic methods. Although organolithium compounds are widely utilized in organic syntheses because of their high reactivity towards electrophiles,[15,16] the 2-bromoaryllithium intermediate is known to undergo rapid elimination of bromide ion to generate benzyne,[17] giving various by-products even at - 78 °C. Therefore, in conventional batch process the halogen-lithium exchange reactions are generally carried out at temperatures lower than - 78 °C, which would not be suitable for their scale-up syntheses.[14e]

Yoshida *et al* have described how flash chemistry[18] using flow microreactors was used to rapidly generate a highly reactive 2-bromoaryllithium intermediate that could be reacted with electrophiles before it decomposed to benzyne.[19] Thus, flash chemistry would be anticipated to be applicable for the syntheses of 2-bromobenzaldehyde derivatives through selective I/Li exchange of 1-bromo-2-iodobenzene derivatives with BuLi and subsequent formylation of the highly reactive 2-bromoaryllithium intermediate with DMF.[20] Therefore, it was considered to be intriguing to investigate a scale-up synthesis of **18** from **17** using flash chemistry and flow microreactors.

Treatment of 2-fluoro-3-methylaniline (**13**) with NBS in DMF gave **14**.[21] Then, the unsymmetrical diarylmethane **15** was efficiently synthesized by palladium-catalyzed cross coupling reaction of a benzylzinc reagent,[22] prepared from 1-[4-(chloromethyl)phenyl]-*1H*-pyrazole (**20**),[4a] with the aryl bromide **14**, concomitant with formation of the homo coupling product **21** (**15** : **21** = 8/1 - 16/1). Regioselective bromination of **15** and the following conversion of **16** into **17** by Sandmeyer reaction were achieved in moderate yield.

Thus, scale-up synthesis of **17** was successfully achieved according to the synthetic routes to obtain **17** in 1.42 kg (total 44% in 5 steps from **13,** Scheme 3).



Scheme 3. Synthesis of key intermediate **17**. Reagents and conditions: (a) NBS, DMF, rt, 89 and 82%. (b) (1) 1-[4-(chloromethyl)phenyl]-*1H*-pyrazole (**20**), Zn, LiCl, $BrCH_2CH_2Br$, TMSCl. (2) **14**, $Pd(dppf)Cl_2$, Na_2CO_3, 72 and 87%. (c) NBS, DMF, 95 and 95%. (d) KI, $NaNO_2$, 6 N $HCl_{aq.}$, 70 and 59%.

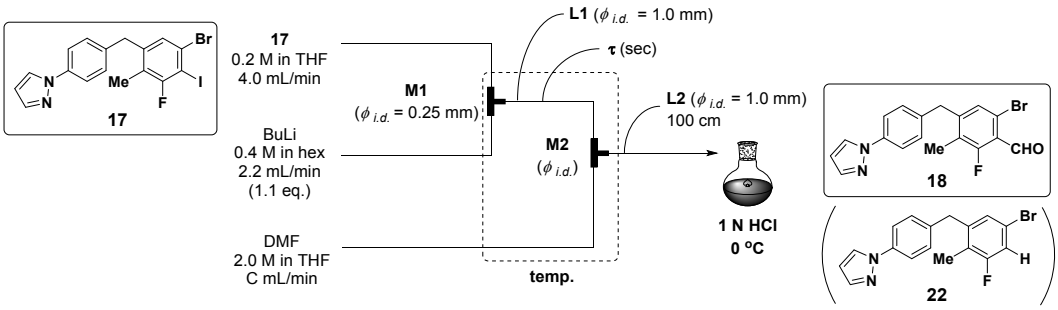
Synthesis of compound **18** from **17** was investigated using a flash chemistry reaction system[18] made up of two T-shaped mixers (M1 and M2) and two microtube reactors (L1 and L2) (Table 1). The solution streams of **17** and BuLi (0.2 M in THF and 0.4 M in hexane, respectively) were delivered into a T-shaped mixer (M1, $\phi_{i.d.}$ = 0.25 mm) at flow rates of 4.0 and 2.2 mL/min, respectively, using syringe pumps and the 2-bromophenyllithium intermediate that was formed was then delivered to M2 for formylation with a solution stream of DMF in THF (2.0 M in THF), supplied by another syringe pump under varying reaction conditions (residence time (τ), reaction temperature, flow rate of the solution of DMF in THF, and T-shaped mixer (M2)). Treatment of the reaction solution with aqueous 1 N HCl solution was followed by HPLC measurement of the ratios of **17**, **18**, an identified by-product **22**, and the major unidentified product (Table 1).

The flow-flash chemistry reaction at - 78 °C was found to give rise to **18** in low yield, concomitant with **17** and **22**, suggesting that the I/Li exchange reaction of **17** did not go to completion and a portion of the resulting 2-bromophenyllithium intermediate was converted to **22** upon HCl quench (entry 1). Although compound **17** was fully consumed at 0 °C to afford **18** and **22** in similar yields to those in entry 1, significant formation of the major unidentified by-product was observed, probably due to decomposition of the 2-bromophenyllithium intermediate to benzyne (entry 2). At - 40 °C, full conversion of **17** to the 2-bromophenyllithium intermediate was found, without significant formation of the unidentified by-products, to give **18** in slightly higher yield (entry 3) than those in entry 2, concomitant with formation of **22** in similar yield.

Next, a T-shaped mixer (M2) with a smaller inner diameter ($\phi_{i.d.}$ = 0.25 mm) was employed and an increase in **18** and a decrease in **22** was observed (entries 4 and 5), suggesting that formylation of the 2-bromophenyllithium intermediate with DMF was enhanced by more efficient mixing of the solutions. Finally, a shorter residence time for the I/Li exchange reaction (τ) of **17** with BuLi gave **18** in slightly higher yield (entry 5) than that for entry 4,without a significant increase in **17** and **22**, and the productivity of **18** was estimated to be 12.4 g/h.

Encouraged by the results of the feasibility studies in Table 1, reaction conditions for a scale-up synthesis of **18** were investigated by modifying the flow-flash reaction system to achieve a higher productivity of **18**. Thus, continuous solution streams of **17**, BuLi, and DMF with higher concentrations (0.4 M in THF, 1.6 M in hexane, and 4.0 M in THF, respectively) were provided at similar or higher flow rates (A, B, and C mL/min, respectively) to the flow-

Table 1 Set-up of the lithiation-formylation flow-flash reaction system and feasibility study of synthesis of **18** from **17** by flow-flash chemistry using flow microreactors.[a]



entry	Temp (°C)[b]	DMF Flow rate (mL/min)	DMF eq.[c]	L1 (cm)	τ[d] (sec)	M2 $\phi_{i.d.}$[e] (mm)	HPLC area (%) 17	18	22[f]	Major unidentified by-product[g]
1	- 78	2.0	2	10	0.76	0.5	33	43	8	0
2	0	4.0	10	10	0.76	0.5	0	51	7	14
3	- 40	4.0	10	10	0.76	0.5	0	62	11	0
4	- 40	4.0	10	10	0.76	0.25	0	65	4	0
5	- 40	4.0	10	5	0.38	0.25	0	69	5	0

[a] [**17**] = 0.2 M in THF, 4.0 mL/min; [BuLi] = 0.4 M in hexane, 2.2 mL/min; [DMF] = 2.0 M in THF. [b] Bath temperature. [c] Equivalency to **17**. [d] Residence time. [e] Inner diameter of microreactor (M2). [f] A by-product identified by its HPLC retention time. [g] Mainly butylated by-products. Other than the major unidentified by-product various amounts of other unidentified by-products were observed.

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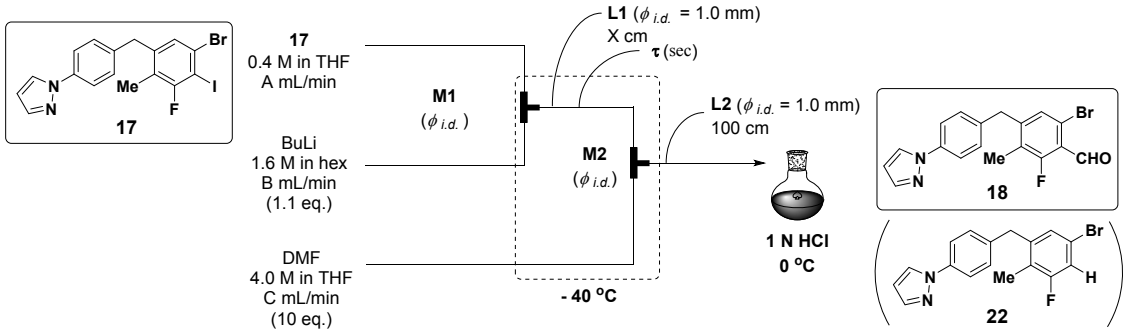
Table 2 Optimization of the flow-flash chemistry reaction condition using flow microreactors.[a]



entry	Flow rate (mL/min)			L1 (cm)	τ^b (sec)	Microreactor $\phi_{i.d.}{}^c$ (mm)		HPLC area (%)			Productivity **18** (g/h)[e]
	A	B	C	X		M1	M2	**17**	**18**	**22**[d]	
1	8	2.2	8	10	0.46	1.0	1.0	39	48	3.4	34.4
2	20	5.5	20	25	0.46	1.0	1.0	14	69	3.1	123.6
3	20	5.5	20	25	0.46	0.5	1.0	0.5	85	2.8	152.3

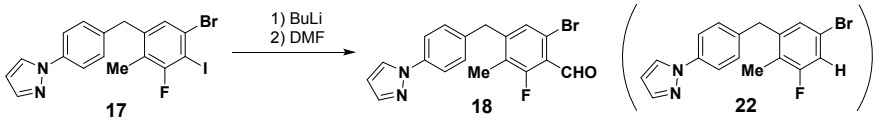
[a] at - 40 °C (bath temperature), [**17**] = 0.4 M in THF, [BuLi] = 1.6 M in hexane, [DMF] = 4.0 M in THF. [b] Residence time. [c] Inner diameter of microreactor. [d] A by-product identified by its HPLC retention time. Varying amounts of unidentified by-products were also observed.
[e] Estimated productivity.

flash reaction system with T-shaped mixers (M1 and M2) at - 40 °C of larger inner diameter than those employed for the reactions in Table 1. The ratio of **17**, **18**, and **22** were measured by means of an HPLC and the results are shown in Table 2.

Solution streams of **17** and BuLi were provided into a T-shaped mixer (M1, $\phi_{i.d.}$ = 1.0 mm) at 8.0 and 2.2 mL/min, respectively, to result in formation of **18** in moderate yield concomitant with a small amount of **22** and recovery of a significant amount of **17** (entry 1). The result suggests that insufficient mixing of the solutions **17** and BuLi took place in M1 at the flow rates of the solutions employed. Thus, the solution streams of **17** and BuLi were provided into M1 at higher flow rates (20 and 5.5 mL/min, respectively) and an increased conversion of **17** into **18** was found without significant change in formation of **22** (entry 2). To generate the 2-bromophenyllithium intermediate from **17** and BuLi more efficiently a T-shaped mixer (M1) with a smaller inner diameter ($\phi_{i.d.}$ = 0.5 mm) was employed for the same flow rates of the solutions and it was found that **17** was almost fully consumed to yield **18** in higher yield, concomitant with a smaller amount of **22** (entry 3). Then, the estimated productivity of **18** was calculated to be 152.3 g/h, which is about 12 times more than that in Table 1 for entry 5.

A scale-up synthesis of **18** was investigated further by continuous flow-flash synthesis according to the method in Table 2 entry 3, using gear pumps to provide solution streams of **17**, BuLi, and DMF (Table 3). Although a small amount of unreacted **17** was observed, compound **18** was obtained concomitant with a fairly consistent amount of **22**, in separate experiments (entries 1 and 2) of similar operation time (*ca.* 30 min). The obtained solution of crude product was concentrated to dryness and then slurried with MTBE to afford **18** (67.7 g (78%) and 64.0 g (66%), respectively) with enough purity for use in the subsequent step.

Table 3 Scale-up synthesis of **18** from **17**.[a]



entry	Reaction System	**17** (g)	Temp (°C)[b]	Operation Time (min)	HPLC area (%)			Yield **18** (g, (%))[d]
					17	**18**	**22**[c]	
1	Flow	109.5	- 40	29	5.0	78.9	2.9	67.7, (78)

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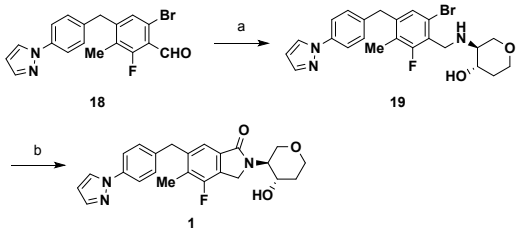
2	Flow	122.6	- 40	32	2.5	73.7	4.0	64.0, (66)
3	Flow	927.0	- 40	246	10.9	68.8	3.2	455, (62)
4	Batch	0.5	- 78	30	0	75.6	3.9	0.24, (60)
5	Batch	1.52	- 78	30	0	71.3	8.9	0.74, (62)

[a] Flow: The same reaction condition was employed as that in Table 2 entry 3, using gear pumps to provide solutions. Batch: In THF, [**17**] = 1.66 x 10^{-1} M, [BuLi] = 1.66 x 10^{-1} M, [DMF] = 1.65 M. [b] Bath temperature. [c] A by-product identified by its HPLC retention time. Varying amounts of unidentified by-products were also observed. [d] Isolated yield.

Finally, the continuous flow-flash synthesis was successfully demonstrated for as long as 246 min to give **18** in 455 g (62%, entry 3). In contrast to the results of continuous flow-flash synthesis of **18**, the corresponding reaction by conventional batch process at - 78 °C brought about a significant increase in **22** and decrease in **18** as the reaction was scaled-up (entries 4 and 5).

These results strongly support the idea that continuous flow-flash synthesis of **18** from **17** would be suitable for scale-up synthesis. Subsequently, a scale-up synthesis of **18** (587 g) has been successfully achieved from **17** (1.16 kg) in 5.1 h with the continuous flow-flash reaction system using microreactors.

The above obtained **18** was condensed with (3*S*,4*S*)-3-aminotetrahydro-2*H*-pyran-4-ol (**12**) in refluxing toluene followed by treatment with $NaBH(OAc)_3$ in DMA to afford **19** in good yield. Next, palladium-catalyzed carbonylation[7] of **19** with carbon monoxide followed by cyclization to isoindolin-1-one ring system was carried out in DMF/MeOH at 100 °C for 4 h. After treatment of the reaction mixture with aqueous 5% NH_3 solution and 3-amino-propyl silica gel for Pd-scavenging, the crude product was recrystallized from EtOH/heptane (1:1) to afford **1** with residual palladium levels of 5.2 ppm. Thus, scale-up synthesis of **1** in 435 g has been achieved with excellent quality, as required for its further research and development (Scheme 4).



Scheme 4 Synthesis of **1** from **18.** Reagents and conditions: (a) (i) (3*S*,4*S*)-3-aminotetrahydro-2*H*-pyran-4-ol (**12**), toluene, reflux, 1 h. (ii) $NaBH(OAc)_3$, DMA, 0 °C, 1 h, 70 and 79%. (b) CO (0.5 MPa), $Pd(dppf)Cl_2$, $^iPr_2NEt$, DMF, MeOH, 100 °C, 4 h, and then treatment for Pd-scavenging, 78 and 81%.

Conclusions

Rapid and efficient scale-up synthesis of a novel M_1 positive allosteric modulator (**TAK-071, 1**) has successfully been achieved for its further research and development according to a new synthetic route from 2-bromobenzaldehyde derivative **18** as a synthetic key intermediate, which was synthesized using flow-flash chemistry in a flow microreactor system. Reaction optimization for the flash chemistry at - 40 °C and then modification for selective I/Li exchange of the 1-bromo-2-iodobenzene derivative **17** with BuLi, followed by subsequent treatment with DMF to formylate the transiently generated 2-bromoaryllithium intermediate, brought about production of **18** in a total of 587 g from 1.16 kg of **17** in 5.1 h, which was a more efficient process than the corresponding conventional batch process using iPrMgBr or BuLi at - 78 °C. Late-stage cyclization to give the isoindolin-1-one ring system, through reductive amination of **18** with (3*S*,4*S*)-3-aminotetrahydro-2*H*-pyran-4-ol (**12**) followed by palladium-catalyzed carbonylation with carbon monoxide and intramolecular cyclization, efficiently afforded **1** in hundred-gram scale with excellent quality as required for its further research and development. Furthermore, the new synthetic route to **1** would enable a convenient synthesis of the same compound labeled with ^{14}C using ^{14}CO gas, which is essential for drug research and development in DMPK studies.

In conclusion, the present study suggests that flash chemistry enables rapid and efficient scale-up syntheses of 2-bromobenzaldehyde derivatives from the corresponding 1-bromo-2-iodobenzene derivatives, to give key intermediates of the drug candidate compounds bearing isoindolin-1-one ring system and its related heterocyclic pharmacophores that are required for drug research and development.

Experimental section

General

Melting points were determined on an OptiMelt melting point apparatus MPA100 and were not corrected. NMR spectra were recorded on a Bruker AVANCE III (300 MHz). All the solvents and reagents were purchased from commercial suppliers and used without purification. LC-MS analyses were performed at 220 or 254 nm on a Shimadzu UFLC-Mass Spectrometer System, operating in ESI (+ or −) ionization mode using a linear gradient of water/MeCN containing TFA (0.05 or 0.1%) or NH_4OAc (5 mM) as mobile phase. HPLC analyses were carried out using Agilent 1200 series at 40 °C with a column (ZORBAX, SB-C18, Ø4.6× 50 mm, 1.8 μm), flow rate = 1.0 mL/min, and mobile phase = TFA (0.05%) in MeCN or water. The flow-flash reaction system[17,18, 20b] composed of microreactors M1 and M2 (stainless tee pieces, ($\phi_{i.d.}$ = 0.25 mm (Sannkouseikikougyou), $\phi_{i.d.}$ = 0.5 mm (Shimadzu-GLC tee piece, part no. 6010-72357), or $\phi_{i.d.}$ = 1.0 mm (Shimadzu-GLC tee piece, custom-made item)), stainless precooling loop-tubes and microtube reactors (ϕ_{id} = 1.0 mm, L (50 cm), L1 (25 cm), and L2 (100 cm)) was placed in a cooling bath (PSL-2000, EYELA) where stream solutions of **17**, BuLi, and DMF were delivered using syringe pumps (ISIS Ltd., Osaka Japan, Fusion 100).

4-Bromo-2-fluoro-3-methylaniline (**14**)**.** To a solution of 2-fluoro-3-methylaniline (**13**, 50.0 g, 399.6 mmol) in DMF (150 mL), was added a solution of NBS (71.1 g, 399.6 mmol) in DMF (170 mL) dropwise over 1 h at room temperature (water bath, < 20 °C). The mixture was stirred for 30 min. The mixture was poured into ice-water (650 mL) and was extracted with EtOAc (150 mL x 3). The organic layer was washed with saturated aqueous $NaHCO_3$ solution (150 mL), water (100 mL x 3), and brine (100 mL), and

dried over Na_2SO_4. The solution was concentrated *in vacuo* to give 4-bromo-2-fluoro-3-methylaniline (**14**, 72.3 g, 355.6 mmol, 89 %) as pale pink crystals. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.19 (3H, d, J = 3.0 Hz), 5.23 (2H, s), 6.56 (1H, t, J = 8.9 Hz), 7.06 (1H, dd, J = 8.7, 1.5 Hz). ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.9, 109.1, 115.1, 124.2, 127.7, 136.5, 149.4. LCMS m/z calcd for C_7H_7BrFN: 204.04, found 205.0 [M + H]; Anal Calcd for C_7H_7BrFN: C, 41.21; H, 3.46; N, 6.86. Found: C, 41.28; H, 3.57; N, 7.11. mp 47.0 – 50.5 °C.

4-[4-(1*H*-Pyrazol-1-yl)benzyl)]-2-fluoro-3-methylaniline (15). A flask equipped with a magnetic stirring bar was flushed with N_2 gas before it was charged with LiCl (0.935 g, 22.054 mmol) and zinc powder (1.442 g, 22.054 mmol) and was heated at 180 °C for 30 min under vacuum. After cooling the flask to room temperature, a solution of 1,2-dibromoethane (0.026 mL, 0.30 mmol) in THF (dry) (9 mL) was placed in the flask flushed with N_2 gas and the mixture was heated to reflux. To the refluxing mixture was added TMSCl (0.038 mL, 0.30 mmol) and the mixture was stirred at 65 - 70 °C for 15 min. To the mixture was added a solution of 1-[4-(chloromethyl)phenyl]-1*H*-pyrazole (**20**, 3.0 g, 15.573 mmol) in THF (dry) (9 mL) at room temperature and the resulting mixture was stirred at 60 - 65 °C for 3 h. After cooling the mixture to room temperature, the supernatant solution of the resulting benzylzinc reagent was added to a solution of 4-bromo-2-fluoro-3-methylaniline (**14**, 3.2 g, 15.573 mmol) and PEPPSI-IPr (100 mg, 0.148 mmol) in THF (dry) (12 mL). The mixture was stirred at room temperature under N_2 for 16 h. The reaction mixture was poured into aqueous saturated NH_4Cl solution (30 mL) and was extracted with EtOAc (20 mL x 2). The organic layer was washed with brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by a pad of silica gel (silica gel (1200 g), eluted with 2:1 - 1:1 EtOAc in hexane) to give crude product (230.0 g) as a light orange solid, which was rinsed with hexane (690 mL) to give 4-[4-(1*H*-pyrazol-1-yl)benzyl]-2-fluoro-3-methylaniline (**15**, 173.6 g, 72.4%) as a pale yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32 (12H, s), 2.24 (1H, d, J = 2.27 Hz), 2.43 (3H, d, J = 2.64 Hz), 3.85 (2H, brs), 6.46 - 6.66 (1H, m), 7.36 (1H, d, J = 7.93 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 11.1, 37.7, 108.1, 113.7, 118.9, 122.9, 125.7, 127.6, 128.0, 129.7, 134.9, 138.2, 139.6, 141.1, 150.0. LCMS m/z calcd for $C_{17}H_{16}FN_3$: 281.33, found 282.1 [M + H]. Anal. Calcd for $C_{17}H_{16}FN_3$: C, 72.58; H, 5.73; N, 14.94. Found: C, 72.30; H, 5.80; N, 14.78. mp 102-104 °C.

4-[4-(1*H*-Pyrazol-1-yl)benzyl]-6-bromo-2-fluoro-3-methylaniline (16). A solution of NBS (87 g, 490.42 mmol) in DMF (400 mL) was added dropwise to a solution of 4-[4-(1*H*-pyrazol-1-yl)benzyl]-2-fluoro-3-methylaniline (**15**, 153.3 g, 544.92 mmol) in DMF (800 mL) at room temperature. The mixture was stirred at room temperature for 30 min. To the reaction mixture was added dropwise water (1.41 L) and stirred at room temperature for 16 h. The resulting precipitate was collected by filtration and was washed with water and hexane to give 4-[4-(1*H*-pyrazol-1-yl)benzyl]-6-bromo-2-fluoro-3-methylaniline (**16**, 187 g, 95 %) as a light brown powder. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.07 (3H, d, J = 2.64 Hz), 3.90 (2H, s), 3.95 - 4.12 (2H, m), 6.41 - 6.48 (1H, m), 6.99 (1H, d, J = 1.51 Hz), 7.17 (2H, d, J = 8.69 Hz), 7.56 - 7.64 (2H, m), 7.71 (1H, d, J = 1.51 Hz), 7.89 (1H, d, J = 1.89 Hz). ^{13}C NMR (75 MHz, DMSO-d_6) δ 11.2, 37.1, 105.4, 108.1, 119.0, 122.8, 128.0, 128.4, 128.8, 129.8, 133.3, 138.4, 138.9, 141.2, 149.6, LCMS m/z calcd for $C_{17}H_{15}BrFN_3$: 360.22, found 361.9 [M + H]; Anal Calcd for $C_{17}H_{15}BrFN_3$: C, 56.68; H, 4.20; N, 11.67. Found: C, 56.85; H, 4.29; N, 11.94. mp 145-150 °C.

1-[4-(5-Bromo-3-fluoro-4-iodo-2-methylbenzyl)phenyl]-1*H*-pyrazole (17). The solution of $NaNO_2$ (2.87 g, 41.64 mmol) in water (20 mL) was added dropwise to a slurry of 4-[4-(1*H*-pyrazol-1-yl)benzyl]-6-bromo-2-fluoro-3-methylaniline (**16**, 10 g, 27.76 mmol) in aqueous 36% HCl solution (45 mL, 540.0 mmol) at 0 °C. After the mixture was stirred at 0 °C for 30 min, the resulting solution of diazonium salt was slowly transferred *via* cannula into a solution of potassium iodide (16.13 g, 97.16 mmol) in water (30 mL) and acetonitrile (30 mL) at room temperature. The resulting mixture was stirred for 1 h. The reaction mixture was diluted with EtOAc (300 mL) and THF (100 mL), and the aqueous layer was extracted with EtOAc (200 mL). The combined organic extracts were washed with water (100 mL), aqueous 2 M sodium hydroxide solution (100 mL), aqueous saturated sodium thiosulfate solution (100 mL x 2), water (100 mL) and brine (100 mL), and then dried over $MgSO_4$. The solution was concentrated *in vacuo* and the residue was purified by column chromatography (silica gel (450 g), eluted with 20% EtOAc in hexane). The obtained solid was washed with hexane (45 mL) to give 1-[4-(5-bromo-3-fluoro-4-iodo-2-methylbenzyl)phenyl]-1*H*- pyrazole (**17**, 9.2 g, 19.5 mmol, 70 %) as a tan powder. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.15 (3H, d, J = 2.27 Hz), 3.97 (2H, s), 6.44 - 6.49 (1H, m), 7.14 – 7.19 (2H, m), 7.24 (1H, s), 7.58 - 7.65 (2H, m), 7.72 (1H, d, J = 1.51 Hz), 7.90 (1H, d, J = 3.02 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.5, 38.3, 87.7, 107.6, 119.5, 123.2, 126.7, 127.2, 129.2, 129.6, 136.7, 138.9, 141.1, 142.5, 160.9. LCMS m/z calcd for $C_{17}H_{13}BrFIN_2$: 471.11, found 472.8 [M + H]; Anal Calcd for $C_{17}H_{13}BrFIN_2$: C, 43.34; H, 2.78; N, 5.95. Found: C, 43.58; H, 2.85; N, 6.04. mp 150 - 151.5 °C.

4-[4-(1*H*-Pyrazol-1-yl)benzyl]-6-bromo-2-fluoro-3-methylbenzaldehyde (18).

Representative protocol for feasibility studies on synthesis of 18 from 17 by conventional batch process (Table 3. entry 5). To a solution of 1-[4-(5-bromo-3-fluoro-4-iodo-2-methylbenzyl)phenyl]-1*H*-pyrazole (**17**, 1.52 g, 3.23 mmol) in THF (15 mL) was added a solution of BuLi in hexane (1.6 M, 2.017 mL, 3.23 mmol) at - 78 °C under nitrogen. After being stirred for 10 min, DMF (2.498 mL, 32.26 mmol) was added and stirred for 30 min. The reaction mixture was treated with aqueous 1 N HCl solution at -78 °C and was extracted with EtOAc. The organic layer was separated, washed with water and brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silicagel column chromatography and washed with EtOAc-heptane to give 4-[4-(1*H*-pyrazol-1-yl)benzyl]-6-bromo-2-fluoro-3-methylbenzaldehyde (**18**, 0.43g, 1.152 mmol, 35.7 %). The crystals that appeared from the mother liquor were collected and washed with heptane to give **18** (0.31 g, 0.84 mmol, 26.1%).

Representative protocol for optimization of reaction condition of the flow-flash synthesis of 18 using flow microreactors (Table 2. entry 3): To the microreactor (M1) of the flow-flash reaction

system described above, were provided continuous streams of solutions of **17** (0.4 M in THF) and BuLi (1.6 M in hexane) at flow rates of 20 and 5.5 mL/min respectively at - 40 °C. The resulting solution of 2-bromophenyllithium intermediate was provided into the next microreactor (M2) to be formylated with a continuous stream of a solution of DMF (4.0 M in THF) delivered by the syringe pump at a flow rate of 20 mL/min, at - 40 °C. The reaction solution obtained from L2 was poured into aqueous 1 N HCl solution at 0 °C and was extracted with EtOAc. The organic layer was concentrated and was subjected to an HPLC analysis to determine the ratio of **17**, **18**, **22**, and by-products. After operation of the flow-flash synthesis of **18** from **17** for 60 min, the collected reaction mixture was purified by column chromatography (silica gel (450 g), eluted with 20% EtOAc in hexane) to afford the crude product, which was recrystallized from EtOH-heptane to give **18** as off-white crystals. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.56 (4H, s), 2.14 - 2.20 (3H, m), 4.00 - 4.06 (2H, m), 6.43 - 6.49 (1H, m), 7.18 (2H, d, *J* = 8.69 Hz), 7.24 (1H, d, *J* = 1.13 Hz), 7.62 - 7.68 (2H, m), 7.69 - 7.74 (1H, m), 7.85 - 7.94 (1H, m), 10.29 - 10.36 (1H, m). ^{13}C NMR (75 MHz, CDCl3) δ 10.6, 38.8, 107.7, 119.6, 120.8, 122.1, 125.0, 126.7, 129.7, 130.7, 135.9, 139.1, 141.2, 148.1, 161.7, 188.6. LCMS m/z calcd for $C_{18}H_{14}BrFN_2O$: 373.22, found 374.00 [M + H]. Anal Calcd for $C_{18}H_{14}BrFN_2O$: C, 57.93; H, 3.78; N, 7.51. Found: C, 57.87; H, 3.86; N, 7.55. mp 117 - 119.5 °C.

(3*S*,4*S*)-3-[[4-[4-(1*H*-Pyrazol-1-yl)benzyl]-6-bromo-2-fluoro-3-methylbenzyl]-amino]-tetrahydro-*2H*-pyran-4-ol (19). A mixture of 4-[4-(1*H*-pyrazol-1-yl)benzyl]-6-bromo-2-fluoro-3-methyl-benzaldehyde (**18**, 10 g, 26.79 mmol), (3*S*,4*S*)-3-aminotetrahydro-2*H*-pyran-4-ol (**12**, 3.20 g, 27.33 mmol) in toluene (150 mL) was heated to refluxed for 1 h. The mixture was concentrated *in vacuo* and the residue was dissolved in DMA (60 mL). To the solution, was added a solution of sodium triacetoxyborohydride in DMA at 0 °C (prepared by an addition of acetic acid (6.14 mL, 107.18 mmol) dropwise to a suspension of sodium borohydride (1.32 g, 34.83 mmol) in DMA (100 mL) at 0 °C and stirring at 0 °C for 1 h). The mixture was stirred at 0 °C for 1 h before aqueous 2 N NaOH solution (55 mL) was added at the same temperature. The mixture was stirred at room temperature for 30 min and was extracted with toluene and iPrOAc (1:1, 200 mL). The aqueous layer was extracted with a mixture of toluene and iPrOAc (1:1, 100 mL). The combined organic layer was washed with water (100 mL) and then extracted with aqueous 1 N HCl solution (300 mL). The aqueous layer was diluted with water (50 mL) and basified with aqueous 15% K_2CO_3 solution (125 mL) at 0 °C before it was extracted back with toluene and iPrOAc (1:1, 300 mL). The organic layer was diluted with EtOAc (100 mL) and washed with water (100 mL), brine (50 mL) and dried over $MgSO_4$. The solution was concentrated *in vacuo* and the crude product was dissolved in EtOAc (100 mL) at 60 °C and cooled to room temperature. To the solution, was added heptane (100 mL) and the resulting mixture was stirred for 30 min. The crystals that appeared were collected by filtration, washed with heptane (50 mL) and dried under reduced pressure to give (3*S*,4*S*)-3-[[4-[4-(1*H*-pyrazol-1-yl)benzyl]-6-bromo-2-fluoro-3-methyl-benzyl]-amino]tetrahydro-2*H*-pyran-4-ol (**19**, 8.84 g, 69.6 %) as colorless crystals. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.60-1.75 (1H, m), 1.91-2.01 (1H, m), 2.11 (3H, d, *J* = 2.3 Hz), 2.56 (1H, td, *J* = 9.6, 4.5 Hz), 2.74 (1H, brs), 2.93-3.08 (1H, m), 3.30-3.48 (2H, m), 3.85-4.00 (4H, m), 4.00-4.18 (2H, m), 6.41-6.49 (1H, m), 7.07-7.23 (3H, m), 7.56-7.68 (2H, m), 7.71 (1H, d, *J* = 1.9 Hz), 7.90 (1H, d, *J* = 2.6 Hz). (1H for NH was not observed in ^{1}H NMR). ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.0, 33.7, 38.4, 44.9, 61.1, 66.5, 69.9, 71.7, 107.6, 119.5, 121.8, 123.5, 125.2, 126.7, 129.3, 129.6, 137.1, 138.8, 141.1, 141.5, 159.9. LCMS m/z calcd for $C_{23}H_{25}BrFN_3O_2$: 474.73, found 476.0 [M + H]. Anal Calcd for $C_{23}H_{25}BrFN_3O_2$: C, 58.23; H, 5.31; N, 8.86. Found: C, 58.24; H, 5.32; N, 8.99. mp 140.1-140.9 °C;

6-[4-(1*H*-Pyrazol-1-yl)benzyl]-4-fluoro-2-[(3*S*,4*S*)-4-hydroxytetrahydro-2*H*-pyran-3-yl]-5-methylisoindolin-1-one (1, TAK-071). To a solution of (3*S*,4*S*)-3-[[4-[4-(1*H*-pyrazol-1-yl)benzyl]-6-bromo-2-fluoro-3- methyl-benzyl]amino]tetrahydro-2*H*-pyran-4-ol (**19**, 8.0 g, 16.86 mmol) and DIEA (8.66 mL, 50.59 mmol) in DMF (40 mL) and MeOH (10 mL), was added $Pd(dppf)Cl_2$ (0.37 g, 0.51 mmol) at room temperature. The mixture was stirred at 100 °C under carbon monoxide atmosphere at 0.5 MPa for 3.5 h. The mixture was concentrated *in vacuo* and the residue was diluted with EtOAc (160 mL) and water (80 mL). Activated charcoal (0.8 g) was added to the mixture and stirred at room temperature for 30 min. The insoluble material was removed by filtration and the filter cake was washed with EtOAc. The organic layer was washed with aqueous 1 N HCl solution (100 mL), water (120 mL x 2), aqueous 5% NH_3 solution (120 mL), water (120 mL x 3) and brine (60 mL) and was dried over $MgSO_4$. The solution was concentrated *in vacuo* and the residue was dissolved in THF (120 mL) and EtOAc (160 mL), and the resulting solution was treated with silica gel coated with amine (40 g) at room temperature for 14 h. The mixture was filtered and the filter cake was washed with EtOAc (1200 mL). The combined filtrate was concentrated *in vacuo* to give crude product, which was recrystallized from ethanol-heptane (1:1, 200 mL) to give (**1**, 5.51 g, 78 %), identical with that reported in the literature.[4a]

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We are grateful to Dr. Makoto Kamata, Dr. Masami Yamada, Mr. Minoru Nakamura, Dr. Masataka Murakami and Dr. Hiroki Sakamoto for their helpful discussion regarding development of a new synthetic route to compound **1** and preparation of the manuscript.

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DOI: 10.1039/C9OB01718F

Continuous flash synthesis of a 2-bromobenzaldehyde derivative from the corresponding 1-bromo-2-iodobenzene derivative is described for rapid and efficient synthesis of a novel cholinergic muscarinic M_1 receptor positive allosteric modulator.