


An efficient synthesis of 8-substituted Odorantine derivatives by the Suzuki coupling reaction

P RAVI KUMAR^{a,b}, C BALAKRISHNA^a, B MURALI^a, RAMAKRISHNA GUDIPATI^a,
PRASANTA K HOTA^c, AVINASH B CHAUDHARY^a, A JAYA SHREE^b,
SATYANARAYANA YENNAM^a and MANORANJAN BEHERA^{a,*} 

^aDepartment of Medicinal Chemistry, GVK Biosciences Pvt. Ltd., Plot Nos 125(part) & 126, IDA, Mallapur, Hyderabad 500 076, Telangana, India

^bCentre for Chemical Sciences and Technology, Institute of Science and Technology, JNT University, Kukatpally, Hyderabad 500 085, Telangana, India

^cDepartment of Chemistry, School of Sciences, HNGB University, Srinagar (Garhwal), Uttarakhand 246 174, India

e-mail: Manoranjan.Behera@gvkbio.com

MS received 19 August 2015; revised 21 October 2015; accepted 8 January 2016

Abstract. An efficient method for the preparation of 8-substituted odorantine [(3-(3', 4'-methylenedioxyphenyl)-5,6,7-trimethoxyisoflavone] derivatives, structurally similar to glaziovianin A, a known cytotoxic substance, has been described. The key steps in the synthesis are site selective bromination reaction followed by Suzuki coupling reaction in very good yield. The structural assignment of the bromo derivative was determined utilizing 2D-HMBC and NOEs NMR techniques.

Keywords. Odorantine; suzuki coupling; isoflavones; fries rearrangement; bromination.

1. Introduction

The isoflavonoids are an important subgroup of flavonoids mainly present in the species of Leguminosae family.^{1,2} Glaziovianin A is a novel isoflavone derivative isolated from the leaves of the Brazilian tree *Asteelia glazioviana*.³ It exhibits a broad spectrum of cytotoxicity against a panel of 39 human cancer lines.⁴ Recently it has been reported that glaziovianin A and its derivatives are microtubule dynamics inhibitors by extending the time lag of tubulin polymerization without changing the net amount of polymerized tubulin *in vitro*.⁵ The seminal work has been done on glaziovianin A by Kigoshi *et al.*, which throws some light on the structure-cytotoxicity relationship.⁶ One position of ring A that was not studied is the 8-position of isoflavone; this may be due to synthetic difficulties or unavailability of the required starting material.^{7,8} Survey of literature shows that 8-aryl substitution has increased the potency of the molecule.^{9–14} For example, TP34 (figure 1) shows PTP1B-selective and IC₅₀ values were many fold lower than other formyl chromone derivative.¹⁵ In this context, we plan to derivatize odorantine, a naturally occurring isoflavone which is structurally similar to glaziovianin A by halogenation reaction and introduce

various aryl as well as alkyl group by Suzuki coupling reaction at the 8-position. Odorantine is a good starting point for halogenation as all the position of ring A is blocked except the 8th position.

Odorantine [(3-(3', 4'-methylenedioxyphenyl)-5,6,7-trimethoxyisoflavone] (**7**) was isolated from *Dipteryx odorata* Wild (Aubl.) (common name, *sarrapia* in Venezuela or *cumarú* in Brazil).^{16–18} It has also been isolated from the chloroform extract of the heartwood of *Cordyla Africana*.¹⁹ There is some ambiguity for the common name of this natural product *viz.*, 5,6,7-trimethoxy-3', 4'-methylenedioxyisoflavone. Some of the authors are using odoratin, odorantin and odorantine for the same compound **7**.^{20–23} We are using the name odorantine coined by Nakano, as the structure of the compound **7** was confirmed by him for the first time.²⁴ There are a few reports for the synthesis of Odorantine using the classical condensation reaction. Krishnamurti and Seshagiri²⁵ have prepared the Odorantine by Friedel-Crafts acylation followed by cyclization reaction. Chatterjea *et al.*,²⁶ have used two different approaches for the synthesis of Odorantine. First method involves a Wessely-Moser rearrangement and the second method involves the cyanohydrins approach. This reported six step synthesis suffers from several disadvantages such as, (a) it is very difficult to handle toxic reagent *viz.*,

*For correspondence

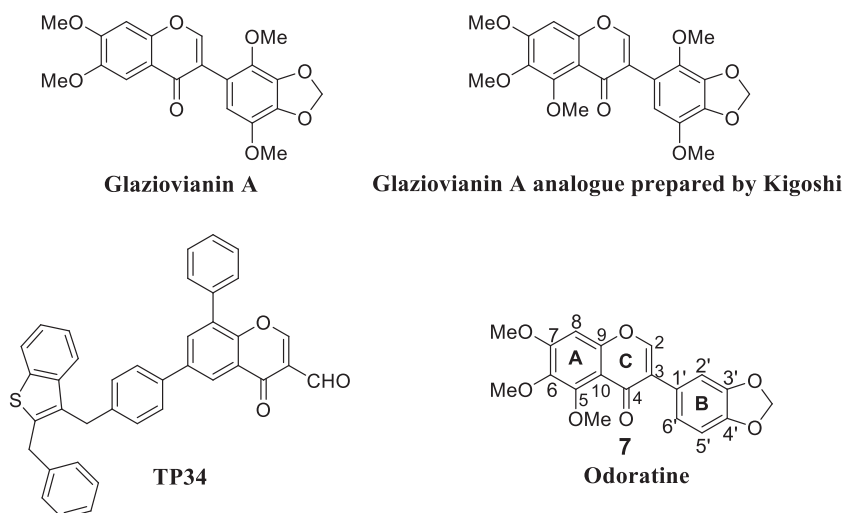
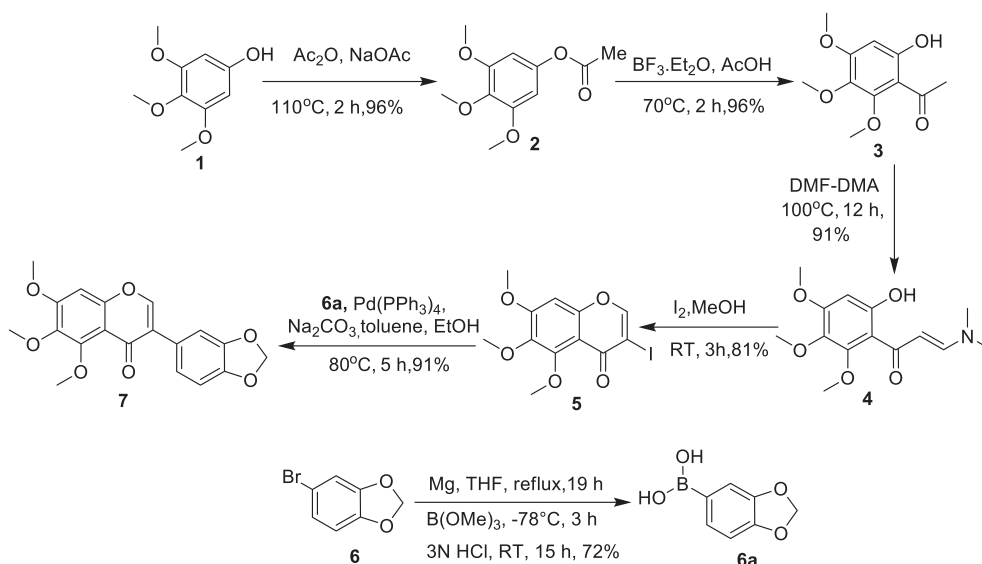


Figure 1. Structures of biologically active chromone derivatives.

KCN; (b) Use of diazomethane in large scale is not advisable due to explosive nature of diazomethane; (c) Long cyclization period using moisture sensitive ZnCl_2 and use of H_2SO_4 in the final step make this process less attractive in large scale synthesis. Bhardwaj and co-workers²⁷ also have synthesized Odoratine using two different routes using 2'-hydroxy-4',5',6'-trimethoxy-3,4-methylenedioxychalcone and 2,4,6-trihydroxy-3',4'-methylenedioxydesoxybenzoin as the required intermediates. All these synthesis involve a number of cumbersome steps, inconsistent results and the yields are also poor. The disadvantages of the Friedel-Crafts acylation are harsh reaction condition, regio-chemical uncertainties and instability of the requisite phenacetyl halides. Long cyclization period, use of expensive starting material and preparation of desoxybenzoin are other

disadvantages. Also, some of these methods involve acid catalyzed rearrangement reaction of epoxide and a nuclear hydroxylation reaction which are not general in nature. There are no reports in the literature for the synthesis of Odoratine and its derivatives using Pd-catalyzed cross-coupling reaction to the best of our knowledge.

During our research program on synthesis of natural products and derivatives for potential biological activity,²⁸ we choose odoratine as it can also be considered as derivative of glaziovianin A (figure 1) and can be used as potential inhibitor of tubulin polymerization. Herein we wish to report an efficient synthesis of odoratine and its derivatives using a simple protocol involving the Suzuki-Miyaura coupling reaction as the key step (scheme 1). Retro synthetic analysis shows that



Scheme 1. The synthesis of odoratine 7 using Suzuki Coupling.

3-iodo chromone can be prepared from the corresponding enaminone *via* iodo-cyclization reaction.^{29,30} We envisioned that the Suzuki coupling reaction^{31,32} could be used to synthesize odorant using the boronic acid **6a**, which can be prepared from the bromo compound **6** in the final step.

2. Experimental

2.1 Materials and characterization

Dry solvents were purchased from chemical suppliers and used without further purification. All melting points were taken in open capillaries and are uncorrected. Analytical thin-layer chromatography (TLC) was performed on commercially available Merck TLC Silica gel 60 F₂₅₄. Silica gel column chromatography was performed on silica gel 60 (spherical 100-200 μ m). FTIR spectra were recorded on Perkin-Elmer FT/IR-4000 spectrophotometer and only the characteristic peaks are reported. Mass spectra were scanned on a Shimadzu LCMS 2010 spectrometer. ¹H NMR spectra were recorded on Varian-400 (400 MHz) spectrometer. Chemical shifts of ¹H NMR spectra were reported relative to tetramethylsilane. ¹³C NMR spectra were recorded on Varian-400 (100 MHz) spectrometer. Chemical shifts of ¹³C NMR spectra were reported to relative to CDCl₃ (77.0). Splitting patterns were reported as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, double doublet; br, broad.

2.1a Experimental procedure for the preparation of 3,4,5-Trimethoxyphenyl acetate (2): A mixture of 3,4,5-trimethoxyphenol (5 g, 27 mmol) and sodium acetate (5 g, 60 mmol) in acetic anhydride (25 mL, 265 mmol) was heated at 110°C for 2 h. TLC analysis (30% ethyl acetate/ pet ether) showed completion of the reaction. Then the reaction mixture was concentrated under reduced pressure, diluted with water and extracted with dichloromethane thrice. The combined organic layer was washed with water and dried over anhydrous Na₂SO₄. The solvent was evaporated and the crude product was charged on silica gel column. Elution of the column with 20% ethyl acetate/ pet ether gave the compound **2** (5.91 g, 96%) as white solid. ¹H NMR (400 MHz, CDCl₃): δ 6.25 (s, 2H, Ar-H), 3.82 (s, 9H, 3-OCH₃), 2.25 (s, 3H, OCOCH₃); MS (EI) *m/z* 227 (M+1, 100).

2.1b Experimental procedure for the preparation of 1-(6-Hydroxy-2, 3, 4 trimethoxyphenyl) ethanone (3): BF₃OEt₂ (6 mL) was added drop wise to a solution of compound **2** (3 g, 13.3 mmol) in glacial acetic acid (10

mL). The reaction mixture was stirred at 70°C for 2 h. TLC analysis (30% ethyl acetate/ pet ether) showed completion of reaction. Then the reaction mixture was quenched with water and extracted with ethyl acetate. The organic phase was washed with water, brine and dried over anhydrous Na₂SO₄. The solvent was evaporated and the crude product was charged on silica gel column. Elution of the column with 10% ethyl acetate/ pet ether gave the compound **3** (2.90 g, 96%) as white solid. ¹H NMR (400 MHz, CDCl₃): δ 13.40 (s, 1H, Ar-OH), 6.22 (s, 1H, Ar-H), 4.00 (s, 3H, OCH₃), 3.59 (s, 3H, OCH₃), 3.58 (s, 3H, OCH₃), 2.40 (s, 3H, COCH₃); MS (EI) *m/z* 227 (M+1, 100).

2.1c Experimental procedure for the preparation of 3-(dimethylamino)-1-(6-hydroxy-2,3,4-trimethoxyphenyl) prop-2-en-1-one (4): DMF-DMA (8.87 mL, 66.37 mmol) was added drop wise to a solution of compound **3** (5 g, 22.12 mmol) in DMF (25 mL). The reaction mixture was stirred at 100°C for 16 h. TLC analysis (40% ethyl acetate/ pet ether) showed completion of reaction. The solvent was evaporated and the reaction mixture was quenched with ice during the process solids were precipitated out. The solids were filtered and dried under vacuum to give the compound **4** (5.2 g, 83%) as yellow crystals; M.p. 112-116°C; IR (KBr, ν , cm⁻¹): 3174, 2942, 2403, 1847, 1619, 1532, 1357, 1237, 1022; ¹H NMR (400 MHz, CDCl₃): δ 14.80 (s, 1H, Ar-OH), 7.96 (dd, *J* = 12.4 Hz, 1H, =CH), 6.33 (dd, *J* = 12.4 Hz, 1H, =CH), 6.24 (s, 1H, Ar-H), 3.92 (s, 3H, OCH₃), 3.78 (s, 3H, OCH₃), 3.76 (s, 3H, OCH₃), 3.19 (bs, 3H, NCH₃), 2.94 (bs, 3H, NCH₃); LC-MS *m/z* 282.06 (98.2%, M+H⁺).

2.1d Experimental procedure for the preparation of 3-iodo-5,6,7-trimethoxy-4H-chromen-4-one (5): To a stirred solution of compound **4** (4 g, 14.23 mmol) in MeOH (80 mL), iodine (4.3 g, 17.08 mmol) was added at 0°C under nitrogen atmosphere. Then the reaction mixture was stirred at room temperature for 3 h. TLC analysis (30% ethyl acetate/ pet ether) showed completion of reaction. Then, the resulting solids were filtered and washed with diethyl ether to give the compound **5** (4.2 g, 81% yield) as light brown solid; M.p. 183-185°C; IR (KBr, ν , cm⁻¹): 3434, 2943, 1629, 1614, 1414, 1285, 1127, 1094; ¹H NMR (400 MHz, DMSO-d₆): δ 8.68 (s, 1H, H-2), 7.04 (s, 1H, Ar-H), 4.12 (s, 3H, OCH₃), 3.98 (s, 3H, OCH₃), 3.95 (s, 3H, OCH₃); ¹³C NMR (100 MHz, CDCl₃): δ 171.1 (C-4), 158.1 (C-2), 155.7 (C-7), 154.4 (C-5), 152.4 (C-9), 140.8 (C-6), 111.2 (C-10), 95.9 (C-8), 88.7 (C-3), 62.1 (OCH₃-5), 61.4 (OCH₃-6), 56.3 (OCH₃-7); LC-MS *m/z* 362.97

(99.4%, $M+H^+$); ESI-HRMS calculated for $C_{12}H_{12}O_5I$ $[M+H]^+$: 362.9730, Found: 362.9763.

2.1e Experimental procedure for the preparation of [(3-(3', 4'-methylenedioxyphenyl)-5,6,7-trimethoxyiso-flavone) (7): To a solution of compound **5** (1 g, 2.76 mmol) in degassed toluene (10 mL) and ethanol (5 mL), compound **6a** (0.687 g, 4.14 mmol), 2M Na_2CO_3 (4.14 mL, 8.28 mmol) and $Pd(PPh_3)_4$ (0.466 g, 0.41 mmol) was added under argon atmosphere. Then, the reaction mixture was refluxed for 5 h. TLC analysis (10% ethyl acetate/ chloroform) showed completion of reaction. Then reaction mixture was diluted with ethyl acetate and washed with water, brine and dried over Na_2SO_4 . The solvent was evaporated and the crude product was charged on silica gel column. Elution of the column with 5% ethyl acetate/ chloroform gave the compound **7** (900 mg, 91%) as white solid; M.p. 176-180°C; IR (KBr, ν , cm^{-1}): 2938, 1643, 1618, 1600, 1453, 1247, 1131; 1H NMR (400 MHz, $CDCl_3$): δ 7.80 (s, 1H, H-2), 7.08 (d, $J = 1.6$ Hz, 1H, Ar-H), 6.92 (dd, $J = 2.0$ Hz, 1H, Ar-H), 6.82 (d, $J = 8.0$ Hz, 1H, Ar-H), 6.58 (s, 1H, Ar-H), 5.96 (s, 2H, OCH_2O), 3.95 (s, 6H, 2- OCH_3), 3.90 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.9 (C-4), 157.7 (C-7), 154.5 (C-5), 152.9 (C-2), 150.5 (C-9), 147.5 (C-3'), 147.5 (C-4'), 140.5 (C-6), 125.6 (C-1'), 125.4 (C-3), 122.4 (C-6'), 113.5 (C-10), 109.9 (C-2'), 108.2 (C-5'), 101.0 (OCH_2O -3',4'), 96.0 (C-8), 62.0 (OCH_3 -5), 61.4 (OCH_3 -6), 56.2 (OCH_3 -7); LC-MS m/z 357.09 (99.5%, $M+H^+$); ESI-HRMS calculated for $C_{19}H_{17}O_7$ $[M+H]^+$: 357.0974, Found: 357.0965.

2.1f Experimental procedure for the preparation of 3-(6-bromobenzo[d][1,3]dioxol-5-yl)-5,6,7-trimethoxy-4H-chromen-4-one (8): To a stirred solution of compound **7** (0.2 g, 0.56 mmol) in chloroform (10 mL), bromine (0.089 g, 0.56 mmol) was added at 0°C and stirred at RT for 24 h. TLC analysis (20% ethyl acetate/pet ether) showed completion of the reaction. Then reaction mixture was concentrated under vacuum, diluted with water and extracted with ethyl acetate. The organic phase was washed with water and dried over anhydrous Na_2SO_4 . The solvent was evaporated and the crude product was charged on silica gel column. Elution of the column with 5% ethyl acetate/pet ether gave the compound **8** (0.12 g, 50%) as white solid; M.p. 214-217°C; IR (KBr, ν , cm^{-1}): 2944, 1644, 1602, 1475, 1294, 1233, 1131; 1H NMR (400 MHz, $CDCl_3$): δ 7.74 (s, 1H, H-2), 7.11 (s, 1H, Ar-H), 6.82 (s, 1H, Ar-H), 6.72 (s, 1H, Ar-H), 6.00 (s, 2H, OCH_2O), 4.06 (s, 6H, 2 OCH_3), 3.98 (s, 3H,

OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.2 (C-4), 157.8 (C-7), 154.7 (C-9), 153.0 (C-5), 152.6 (C-2), 148.5 (C-3'), 147.3 (C-4'), 140.7 (C-6), 125.89 (C-1'), 125.83 (C-3), 115.6 (C-6'), 113.6 (C-10), 112.9 (C-5'), 111.9 (C-2'), 101.9 (OCH_2O -3', 4'), 96.1 (C-8), 62.1 (OCH_3 -5), 61.5 (OCH_3 -6), 56.2 (OCH_3 -7); LC-MS m/z 435.00 (97.5%, $M+H^+$); ESI-HRMS calculated for $C_{19}H_{16}O_7Br$ $[M+H]^+$: 435.0079, Found: 435.0252.

2.1g Experimental procedure for the preparation of 8-bromo-3-(6-bromobenzo[d][1,3]dioxol-5-yl)-5,6,7-trimethoxy-4H-chromen-4-one (8a): To a stirred solution of compound **7** (0.1 g, 0.28 mmol) in acetonitrile (5 mL), NBS (0.075 g, 0.42 mmol) was added at 0°C and stirred at RT for 24 h. TLC analysis (20% ethyl acetate/pet ether) showed completion of the reaction. Then, reaction mixture was concentrated under vacuum, diluted with water and extracted with ethyl acetate. The organic phase was washed with water and dried over anhydrous Na_2SO_4 . The solvent was evaporated and the crude product was charged on silica gel column. Elution of the column with 5% ethyl acetate/pet ether gave the compound **8a** (0.128 g, 91%) as white solid; M.p. 200-205°C; IR (KBr, ν , cm^{-1}): 2944, 1639, 1584, 1480, 1397, 1292, 1236, 1030; 1H NMR (400 MHz, $CDCl_3$): δ 7.86 (s, 1H, H-2), 7.11 (s, 1H, Ar-H), 6.79 (s, 1H, Ar-H), 6.01 (s, 2H, OCH_2O), 4.07 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.2 (C-4), 156.0 (C-7), 153.1 (C-2), 153.0 (C-5), 150.7 (C-9), 148.7 (C-3'), 147.3 (C-4'), 144.8 (C-6), 125.9 (C-1'), 125.2 (C-3), 116.5 (C-5'), 115.6 (C-2'), 113.0 (C-6'), 111.7 (C-10), 102.0 (OCH_2O -3', 4'), 101.2 (C-8), 62.3 (OCH_3 -5), 61.8 (OCH_3 -6), 61.5 (OCH_3 -7); LC-MS m/z 512.91 (97.5%, $M+H^+$); ESI-HRMS calculated for $C_{19}H_{15}O_7Br_2$ $[M+H]^+$: 512.9185, Found: 512.9421.

2.1h Experimental procedure for the preparation of 8-bromo-3-iodo-5,6,7-trimethoxy-4H-chromen-4-one (9): To a stirred solution of compound **5** (3.5 g, 9.66 mmol) in carbon tetrachloride (40 mL), benzoyl peroxide (0.701 g, 2.90 mmol) and N-bromosuccinimide (3.44 g, 19.33 mmol) was added under nitrogen atmosphere. Then, the reaction mixture was refluxed for 14 h. TLC analysis (30% ethyl acetate/ pet ether) showed completion of the reaction. Then, reaction mixture was concentrated under vacuum, diluted with water and extracted with ethyl acetate. The organic phase was washed with water and dried over anhydrous Na_2SO_4 . The solvent was evaporated and the crude product was charged on silica gel column. Elution of the column with 8%

ethyl acetate/ pet ether gave the compound **9** (3.90 g, 91.6%) as white solid; M.p. 155-158°C; IR (KBr, ν , cm^{-1}): 2947, 1651, 1599, 1464, 1401, 1277, 1093; ^1H NMR (400 MHz, CDCl_3): δ 8.24 (s, 1H, H-2), 4.06 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, CDCl_3): δ 171.1 (C-4), 156.3 (C-2), 156.1 (C-7), 152.6 (C-5), 150.5 (C-9), 145.0 (C-6), 114.0 (C-10), 100.9 (C-8), 88.2 (C-3), 62.2 (OCH_3 -5), 61.7 (OCH_3 -6), 61.5 (OCH_3 -7); LC-MS m/z 440.88 (97.5%, $\text{M}+\text{H}^+$); ESI-HRMS calculated for $\text{C}_{12}\text{H}_{11}\text{O}_5\text{BrI}$ $[\text{M}+\text{H}]^+$: 440.8835, Found: 440.8881.

2.1i Experimental procedure for the preparation of 3-(benzo[1,3]dioxol-5-yl)-8-bromo-3-iodo-5,6,7-trimethoxy-4H-chromen-4-one (10): To a solution of compound **9** (1 g, 2.27 mmol) in degassed toluene (10 mL) and ethanol (5 mL), compound **6a** (0.452 g, 2.72 mmol), 2M Na_2CO_3 (3.40 mL, 6.81 mmol) and $\text{Pd}(\text{PPh}_3)_4$ (0.250 g, 0.22 mmol) were added under argon atmosphere. Then, the reaction mixture was refluxed for 5 h. TLC analysis (30% ethyl acetate/ pet ether) showed completion of the reaction. Then, the reaction mixture was diluted with ethyl acetate and washed with water, brine and dried over Na_2SO_4 . The solvent was evaporated and the crude product was charged on silica gel column. Elution of the column with 20% ethyl acetate/ pet ether gave the compound **10** (840 mg, 85%) as white solid; M.p. 163-165°C; IR (KBr, ν , cm^{-1}): 3433, 2946, 1648, 1462, 1407, 1251, 1012; ^1H NMR (400 MHz, CDCl_3): δ 7.92 (s, 1H, H-2), 7.06 (s, 1H, Ar-H), 6.94 (d, $J = 8.0$ Hz, 1H, Ar-H), 6.86 (d, $J = 8.0$ Hz, 1H, Ar-H), 6.00 (s, 2H, OCH_2O), 4.05 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$): δ 173.6 (C-4), 155.2 (C-7), 152.4 (C-2), 152.3 (C-5), 149.9 (C-3'), 147.0 (C-4'), 146.9 (C-9), 144.1 (C-6), 125.0 (C-1'), 123.9 (C-3), 122.6 (C-6'), 115.9 (C-2'), 109.5 (C-5'), 108.0 (C-10), 101.0 (OCH_2O -3',4'), 100.4 (C-8), 61.8 (OCH_3 -5), 61.6 (OCH_3 -6), 61.3 (OCH_3 -7); LC-MS m/z 435.00 (99%, $\text{M}+\text{H}^+$); ESI-HRMS calculated for $\text{C}_{19}\text{H}_{16}\text{O}_7\text{Br}$ $[\text{M}+\text{H}]^+$: 435.0079, Found: 435.0077.

2.2 General procedure for the preparation of compounds 11a-j

To a solution of compound **10** (0.23 mmol) in degassed toluene (5 mL), boronic acid (0.46 mmol), 2M K_3PO_4 (0.69 mmol) and $\text{Pd}(\text{PPh}_3)_4$ (0.011 mmol) were added under argon atmosphere. Then, the reaction mixture was refluxed for 14 h. Then, the reaction mixture was diluted with ethyl acetate and washed with water, brine and dried over Na_2SO_4 . The solvent was evaporated and

the crude product was charged on silica gel column. Elution of the column with 20-30% ethyl acetate/ pet ether gave the compounds **11a-j**.

2.2a 3-(benzo[d][1,3]dioxol-5-yl)-5,6,7-trimethoxy-8-p-tolyl-4H-chromen-4-one (11a): White solid; M.p. 171-175°C; IR (KBr, ν , cm^{-1}): 3434, 2934, 1646, 1457, 1396, 1239, 1034, 816, 517; ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 8.20 (s, 1H, H-2), 7.25-7.30 (m, 4H, Ar-H), 7.08 (d, $J = 1.2$ Hz, 1H, Ar-H), 6.90-7.00 (m, 2H, Ar-H), 6.02 (s, 2H, OCH_2O), 3.85-3.90 (d, $J = 6.4$ Hz, 6H, 2- OCH_3), 3.70 (s, 3H, OCH_3), 2.38 (s, 3H, CH_3); ^{13}C NMR (100 MHz, CDCl_3): δ 175.5 (C-4), 155.8 (C-7), 152.7 (C-2), 151.1 (C-5), 151.1 (C-3'), 147.6 (C-4'), 147.6 (C-9), 144.4 (C-6), 137.6 (C-4''), 130.3 (C-3'',5''), 128.9 (C-1''), 128.6 (C-2'',6''), 125.6 (C-1'), 125.0 (C-3), 122.4 (C-6'), 120.8 (C-2'), 116.0 (C-5'), 109.9 (C-8), 108.3 (C-10), 101.1 (OCH_2O -3',4'), 62.1 (OCH_3 -5), 61.5 (OCH_3 -6), 61.4 (OCH_3 -7), 21.3 (CH_3 -4''); LC-MS m/z 447.14 (98.2%, $\text{M}+\text{H}^+$); ESI-HRMS calculated for $\text{C}_{26}\text{H}_{23}\text{O}_7$ $[\text{M}+\text{H}]^+$: 447.1437, Found: 447.1444.

2.2b 3-(benzo[d][1,3]dioxol-5-yl)-5,6,7-trimethoxy-8-(4-methoxyphenyl)-4H-chromen-4-one (11b): White solid; M.p. 160-164°C; IR (KBr, ν , cm^{-1}): 3436, 2937, 1644, 1244, 1034, 816; ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 8.20 (s, 1H, H-2), 7.32 (d, $J = 8.8$ Hz, 2H, Ar-H), 6.91-7.10 (m, 5H, Ar-H), 6.02 (s, 2H, OCH_2O), 3.85-3.91 (d, $J = 7.2$ Hz, 6H, 2- OCH_3), 3.80 (s, 3H, OCH_3), 3.62 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, CDCl_3): δ 175.5 (C-4), 159.2 (C-4''), 155.9 (C-7), 152.6 (C-2), 151.2 (C-5), 151.0 (C-3'), 147.6 (C-4'), 147.6 (C-9), 144.4 (C-6), 131.6 (C-2'', 6''), 125.6 (C-1'), 125.0 (C-1''), 123.7 (C-3), 122.4 (C-6'), 120.5 (C-3'', 5''), 116.0 (C-2'), 113.7 (C-5'), 109.9 (C-8), 108.3 (C-10), 101.1 (OCH_2O -3', 4'), 62.1 (OCH_3 -5), 61.5 (OCH_3 -6), 61.3 (OCH_3 -7), 55.2 (OCH_3 -4''); LC-MS m/z 463.13 (99%, $\text{M}+\text{H}^+$); ESI-HRMS calculated for $\text{C}_{26}\text{H}_{23}\text{O}_8$ $[\text{M}+\text{H}]^+$: 463.1353, Found: 463.1393.

2.2c 4-(3-(benzo[d][1,3]dioxol-5-yl)-5,6,7-trimethoxy-4-oxo-4H-chromen-8-yl)benzonitrile (11c): White solid; M.p. 173-177°C; IR (KBr, ν , cm^{-1}): 3429, 2936, 2226, 1647, 1459, 1395, 1239, 1059, 1009, 816, 559; ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 8.02 (s, 1H, H-2), 7.95 (d, $J = 8.4$ Hz, 2H, Ar-H), 7.63 (d, $J = 8.0$ Hz, 2H, Ar-H), 7.08 (s, 1H, Ar-H), 6.96 (m, 2H, Ar-H), 6.02 (s, 2H, Ar-H), 3.85-3.90 (d, $J = 2.8$ Hz, 6H, 2- OCH_3), 3.80 (s, 3H, OCH_3); ^{13}C NMR (100 MHz,

CDCl_3): δ 173.8 (C-4), 154.8 (C-7), 152.9 (C-2), 152.1 (C-5), 150.0 (C-3', 4'), 145.8 (C-9, 1''), 143.6 (C-6), 136.7 (C-3'', 5''), 131.9 (C-2'', 6''), 131.6 (C-1'), 125.3 (C-3), 123.7 (C-6'), 122.4 (CN-4''), 118.6 (C-4''), 115.3 (C-2'), 110.6 (C-5'), 109.4 (C-8), 107.9 (C-10), 100.9 (OCH_2O -3', 4'), 61.7 (OCH_3 -5), 61.3 (OCH_3 -6), 61.3 (OCH_3 -7); LC-MS m/z 458.12 (98%, $\text{M}+\text{H}^+$); ESI-HRMS calculated for $\text{C}_{26}\text{H}_{20}\text{O}_7\text{N}$ [$\text{M}+\text{H}$] $^+$: 458.1206, Found: 458.1240.

2.2d Methyl 3-(3-(benzo[d][1,3]dioxol-5-yl)-5,6,7-trimethoxy-4-oxo-4H-chromen-8-yl)benzoate (11d): White solid; M.p. 174-179°C; IR (KBr, ν , cm^{-1}): 3414, 2944, 1716, 1646, 1456, 1237, 1063, 759, 513; ^1H NMR (400 MHz, CDCl_3): δ 8.10 (m, 2H, Ar-H), 7.70 (s, 1H, Ar-H), 7.52-7.60 (m, 2H, Ar-H), 7.05 (s, 1H, Ar-H), 6.90 (d, J = 8.0 Hz, 1H, Ar-H), 6.80 (d, J = 7.6 Hz, 1H, Ar-H), 5.95 (s, 2H, OCH_2O), 4.01 (s, 3H, OCOCH_3), 3.97 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, CDCl_3): δ 175.3 (C-4), 166.8 (C=O-3''), 155.7 (C-7), 153.3 (C-2), 151.0 (C-5), 150.9 (C-3'), 147.6 (C-4'), 144.3 (C-9), 135.0 (C-1''), 132.1 (C-6), 131.8 (C-6''), 130.3 (C-3''), 129.0 (C-2'', 4''), 128.2 (C-5''), 125.4 (C-1'), 125.2 (C-3), 122.5 (C-6'), 119.7 (C-2'), 116.0 (C-5'), 109.9 (C-8), 108.3 (C-10), 101.12 (OCH_2O -3', 4'), 62.1 (OCH_3 -5), 61.5 (OCH_3 -6), 61.5 (OCH_3 -7), 52.1 (OCH_3 -3''); LC-MS m/z 491.13 (96%, $\text{M}+\text{H}^+$); ESI-HRMS calculated for $\text{C}_{27}\text{H}_{23}\text{O}_9$ [$\text{M}+\text{H}$] $^+$: 491.1342, Found: 491.1354.

2.2e (E)-3-(benzo[d][1,3]dioxol-5-yl)-5,6,7-trimethoxy-8-styryl-4H-chromen-4-one (11e): White solid; M.p. 119-124°C; IR (KBr, ν , cm^{-1}): 3636, 2936, 1640, 1459, 1402, 1253, 1109, 1033, 817, 690, 526; ^1H NMR (400 MHz, CDCl_3): δ 7.93 (s, 1H, H-2), 7.52-7.61 (m, 3H, Ar-H), 7.28-7.42 (m, 4H, Ar-H), 7.1 (d, J = 1.6 Hz, 1H, =CH), 6.95-6.98 (dd, J = 1.6 Hz, 1H, Ar-H), 6.86 (d, J = 8.0 Hz, 1H, =CH), 6.0 (s, 2H, OCH_2O), 4.01 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, CDCl_3): δ 175.4 (C-4), 156.2 (C-2), 153.2 (C-5), 152.5 (C-7), 151.6 (C-3'), 150.7 (C-4'), 147.6 (C-9), 144.5 (C-6), 138.0 (C-1''), 134.6 (=CH-8), 128.7 (=CH-1''), 127.9 (C-3'', 5''), 126.5 (C-2'', 6''), 125.4 (C-4''), 125.3 (C-1'), 122.5 (C-3), 117.4 (C-6'), 116.4 (C-10), 116.2 (C-2'), 109.9 (C-5'), 108.3 (C-8), 101.1 (OCH_2O -3', 4'), 62.1 (OCH_3 -5), 61.5 (OCH_3 -6), 61.1 (OCH_3 -7); LC-MS m/z 459.14 (98.5%, $\text{M}+\text{H}^+$); ESI-HRMS calculated for $\text{C}_{27}\text{H}_{23}\text{O}_7$ [$\text{M}+\text{H}$] $^+$: 459.1444, Found: 459.1486.

2.2f 3-(benzo[d][1,3]dioxol-5-yl)-8-(3,4-difluorophenyl)-5,6,7-trimethoxy-4H-chromen-4-one (11f): White solid; M.p. 113-117°C; IR (KBr, ν , cm^{-1}): 3449, 2937, 1643, 1392, 1246, 1038, 765, 576; ^1H NMR (400 MHz, CDCl_3): δ 7.72 (s, 1H, H-2), 7.2-7.34 (m, 2H, Ar-H), 7.12 (s, 1H, Ar-H), 7.04 (s, 1H, Ar-H), 6.91 (d, J = 8.0 Hz, 1H, Ar-H), 6.84 (d, J = 8.0 Hz, 1H, Ar-H), 5.97 (s, 2H, OCH_2O), 4.01 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, CDCl_3): δ 175.2 (C-4), 155.6 (C-7) (J C-F 213.3), 153.5 (C-2), 151.3 (C-5), 150.8 (C-3''), 148.8 (C-3') (J C-F 247.4), 147.7 (C-4''), 147.6 (C-4'), 144.3 (C-9), 128.4 (C-6), 126.9 (C-1''), 125.3 (C-6''), 122.4 (C-1'), 119.8 (C-3), 119.6 (C-6'), 118.6 (C-2''), 117.1 (C-5''), 116.9 (C-2'), 116.0 (C-5'), 109.8 (C-8), 108.3 (C-10), 101.1 (OCH_2O -3', 4'), 62.1 (OCH_3 -5), 61.8 (OCH_3 -6), 61.4 (OCH_3 -7); LC-MS m/z 469.10 (96.8%, $\text{M}+\text{H}^+$); ESI-HRMS calculated for $\text{C}_{25}\text{H}_{19}\text{O}_7\text{F}_2$ [$\text{M}+\text{H}$] $^+$: 469.1099, Found: 469.1121.

2.2g 3-(benzo[d][1,3]dioxol-5-yl)-5,6,7-trimethoxy-8-(thiophen-3-yl)-4H-chromen-4-one (11g): White crystals; M.p. 120-124°C; IR (KBr, ν , cm^{-1}): 3432, 3102, 2937, 1643, 1400, 1239, 1016, 793, 505; ^1H NMR (400 MHz, CDCl_3): δ 7.82 (s, 1H, H-2), 7.42-7.48 (m, 2H, Ar-H), 7.23 (s, 1H, Ar-H), 7.12 (s, 1H, Ar-H), 6.92 (dd, J = 1.4 Hz, 1H, Ar-H), 6.84 (d, J = 7.6 Hz, 1H, Ar-H), 5.97 (s, 2H, OCH_2O), 4.01 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, CDCl_3): δ 175.4 (C-4), 156.0 (C-7), 152.8 (C-5), 151.1 (C-2), 150.9 (C-3'), 147.6 (C-4'), 144.5 (C-9), 130.4 (C-1''), 129.5 (C-6), 125.5 (C-2'', 3''), 125.4 (C-1'), 125.1 (C-5''), 124.5 (C-3), 122.4 (C-6'), 116.1 (C-2'), 115.8 (C-5'), 109.9 (C-8), 108.3 (C-10), 101.1 (OCH_2O -3', 4'), 62.1 (OCH_3 -5), 61.5 (OCH_3 -6), 61.3 (OCH_3 -7); LC-MS m/z 439.04 (96.5%, $\text{M}+\text{H}^+$); ESI-HRMS calculated for $\text{C}_{23}\text{H}_{19}\text{O}_7\text{S}$ [$\text{M}+\text{H}$] $^+$: 439.0449, Found: 439.0452.

2.2h 3-(benzo[d][1,3]dioxol-5-yl)-5,6,7-trimethoxy-8-methyl-4H-chromen-4-one (11h): Off-white solid; M.p. 101-105°C; IR (KBr, ν , cm^{-1}): 3431, 2924, 2179, 1643, 1401, 1237, 1033, 812, 615, 493; ^1H NMR (400 MHz, CDCl_3): δ 7.9 (s, 1H, H-2), 7.1 (d, J = 1.6 Hz, 1H, Ar-H), 6.98 (dd, J = 1.4 Hz, 1H, Ar-H), 6.85 (d, J = 8.4 Hz, 1H, Ar-H), 5.97 (s, 2H, OCH_2O), 4.01 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 2.3 (s, 3H, CH_3); ^{13}C NMR (100 MHz, CDCl_3): δ 175.6 (C-4), 166.0 (C-9), 152.0 (C-2), 151.1 (C-5), 151.0 (C-7), 147.6 (C-3'), 147.5 (C-4'), 144.1 (C-6), 125.7 (C-1'), 125.0 (C-3), 122.5 (C-6'), 115.9 (C-2'), 115.8 (C-8), 109.9 (C-5'), 108.3 (C-10), 101.1 (OCH_2O -3', 4'),

62.0 (OCH₃-5), 61.4 (OCH₃-6), 61.1 (OCH₃-7), 8.6 (CH₃-8); LC-MS *m/z* 371.11 (95.5%, M+H⁺); ESI-HRMS calculated for C₂₀H₁₉O₇ [M+H]⁺: 371.1131, Found: 371.1160.

2.2i 3,8-di(benzo[d][1,3]dioxol-5-yl)-5,6,7-trimethoxy-4H-chromen-4-one (**11i**): White crystals; M.p. 131–136°C; IR (KBr, ν , cm⁻¹): 3434, 2893, 1650, 1464, 1233, 1039, 796, 554; ¹H NMR (400 MHz, CDCl₃): δ 7.74 (s, 1H, H-2), 7.06 (d, *J* = 0.8 Hz, 1H, Ar-H), 6.83–6.94 (m, 5H, Ar-H), 6.02 (s, 2H, OCH₂O), 5.94 (s, 2H, OCH₂O), 4.01 (s, 3H, OCH₃), 3.97 (s, 3H, OCH₃), 3.80 (s, 3H, OCH₃); ¹³C NMR (100 MHz, CDCl₃): δ 175.4 (C-4), 155.9 (C-7), 152.8 (C-2), 151.2 (C-5), 151.0 (C-3''), 147.6 (C-3'), 147.5 (C-4'), 147.2 (C-9), 144.3 (C-4''), 125.5 (C-6), 125.1 (C-1''), 125.0 (C-1'), 124.0 (C-3), 122.4 (C-6''), 120.4 (C-2''), 116.0 (C-2'), 110.0 (C-5''), 109.9 (C-5'), 108.3 (C-8), 108.2 (C-10), 101.2 (OCH₂O-3'', 4''), 101.1 (OCH₂O-3', 4'), 62.1 (OCH₃-5), 61.5 (OCH₃-6), 61.4 (OCH₃-7); LC-MS *m/z* 477.11 (98.6%, M+H⁺); ESI-HRMS calculated for C₂₆H₂₁O₉ [M+H]⁺: 477.1190, Found: 477.1186.

2.2j 3-(benzo[d][1,3]dioxol-5-yl)-5,6,7-trimethoxy-8-(quinolin-3-yl)-4H-chromen-4-one (**11j**): White solid; M.p. 103–107°C; IR (KBr, ν , cm⁻¹): 3435, 2927, 1645, 1458, 1236, 1018, 786, 637, 549; ¹H NMR (400 MHz, CDCl₃): δ 8.94 (s, 1H, H-2), 8.24 (s, 1H, Ar-H), 8.20 (d, *J* = 8.4 Hz, 1H, Ar-H), 7.9 (d, *J* = 7.6 Hz, 1H, Ar-H), 7.8 (m, 1H, Ar-H), 7.7 (s, 1H, Ar-H), 7.6 (t, *J* = 7.4 Hz, 1H, Ar-H), 7.05 (s, 1H, Ar-H), 6.92 (d, *J* = 8.4 Hz, 1H, Ar-H), 6.84 (d, *J* = 8.0 Hz, 1H, Ar-H), 5.94 (s, 2H, OCH₂O), 4.01 (s, 3H, OCH₃), 3.97 (s, 3H, OCH₃), 3.85 (s, 3H, OCH₃); ¹³C NMR (100 MHz, CDCl₃): δ 175.2 (C-4), 156.0 (C-7), 153.9 (C-5), 152.0 (C-2), 151.2 (C-2''), 150.9 (C-3'), 147.7 (C-4'), 147.6 (C-9), 147.2 (C-9''), 144.4 (C-8''), 137.6 (C-6), 129.8 (C-10''), 129.2 (C-1''), 127.9 (C-7''), 127.7 (C-5''), 126.6 (C-4''), 125.45 (C-6''), 125.2 (C-1'), 125.1 (C-3), 122.5 (C-6'), 117.0 (C-2'), 116.1 (C-5'), 109.9 (C-8), 108.3 (C-10), 101.1 (OCH₂O-3', 4'), 62.2 ((OCH₃-5), 61.6 (OCH₃-6), 61.61 (OCH₃-7); LC-MS *m/z* 484.13 (98.7%, M+H⁺); ESI-HRMS calculated for C₂₈H₂₂O₇N [M+H]⁺: 484.1368, Found: 484.1396.

3. Results and Discussion

The synthesis of odorantine commenced with commercially available 3,4,5-trimethoxy-phenol **1** (scheme 1). The phenol **1** was acetylated with acetic anhydride in the presence of NaOAc to produce *o*-acetylated derivative **2**. Compound **2** was subjected to the Fries

rearrangement in the presence of BF₃·Et₂O/AcOH to give the required *o*-hydroxyacetophenone derivative **3**. Enaminone **4** was prepared by reaction of the acetophenone **3** with DMF-DMA. The enaminone was characterized by ¹H-NMR and LC-MS data. An initial attempt to cyclize the enaminone using I₂ in DMF was not successful. This may be due to poor solubility of enaminone in DMF and we have observed some undesired products by LC-MS (Liquid Chromatography Mass Spectra) analysis. But by changing the solvent from DMF to MeOH the enaminone **4** was smoothly converted into iodo-chromone **5**, ready for the Suzuki coupling reaction. Compound **5** was characterized by ¹H-NMR, ¹³C-NMR and LC-MS data. The characteristic chromone ring C proton at δ 8.6 in ¹H-NMR confirms the formation of compound **5**. The IR spectrum of compound **5** shows the carbonyl peak at 1630 cm⁻¹. Since the boronic acid **6a** was expensive, we prepared the boronic acid **6a** from corresponding bromo derivative **6**. The iodo-chromone reacted with boronic acid **6a** under the Suzuki reaction condition to give odorantine **7** in very good yield. The odorantine was characterized by ¹H-NMR, ¹³C-NMR and LC-MS data consistent with the reported value.¹⁹

After synthesizing the natural product odorantine, we planned to quickly make a few derivatives. In this context, bromination of the compound **7** was screened using various reaction conditions (table 1). Among the conditions screened, NBS in both the solvents CH₃CN and CCl₄ gave dibrominated compound **8a**. The compound **8a** was characterized by ¹H-NMR, ¹³C-NMR, NOESY and LC-MS data. The disappearance of peak at δ 6.6 confirm the introduction of one bromine on ring A. In the NOESY (Nuclear Overhauser Effect Spectroscopy) spectra of **8a** correlation were found between the protons of Ha of ring C and Hb of ring B (scheme 2).

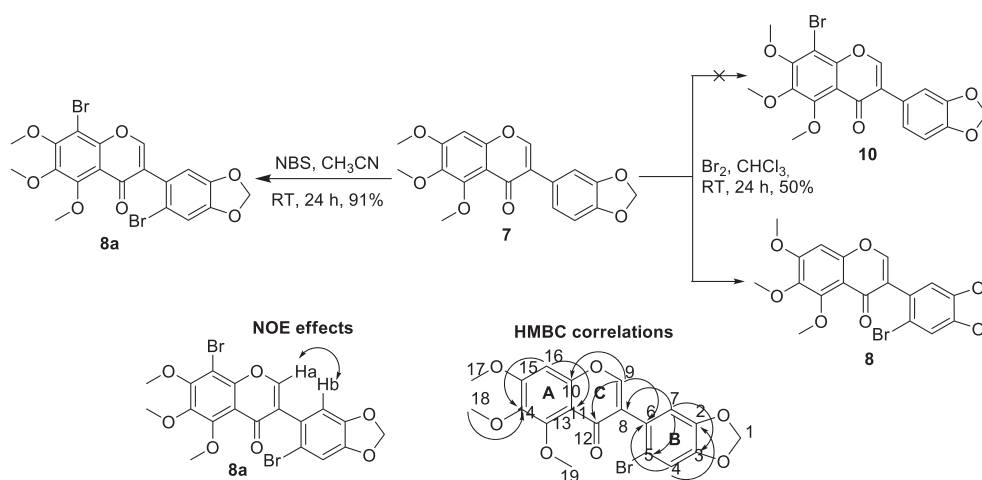
Table 1. Bromination of odorantine.

Entry	Conditions	Time	Yield (%) ^a
1	KBrO ₃ , oxone, MeOH	24 h	42
2	DDB, dioxane, diethyl ether	24 h	20
3	NBS, CH ₃ CN	24 h	91 ^b
4	NBS, CCl ₄	24 h	65 ^b
5	Br ₂ , CHCl ₃	24 h	45
6	NBS, H ₂ SO ₄ , THF	24 h	78
7	NBS, Bz ₂ O, CCl ₄	24 h	38
8	NBS, CH ₃ CN, h ν ^c	9 h	58
9	KBr, HNO ₃ , Ac ₂ O	9 h	0

^aDetermined by analysis of the crude reaction mixture by analytical LC/MS.

^bDibrominated product formed.

^cThe reaction was performed under 100W electricity bulb.



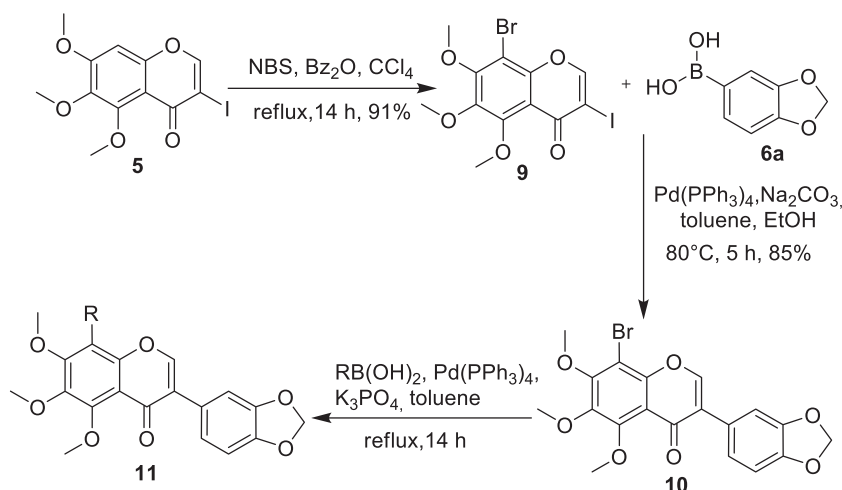
Scheme 2. Bromination of odoratine and NOE and HMBC correlation study.

Although by using NBS/H₂SO₄/THF condition the conversion was good, it was very difficult to extract the crude reaction mixture during work up procedure using water. Using Br₂ in CHCl₃ condition, we could isolate mono-brominated compound **8** in milligram quantities. Initially we thought the mono-brominated product to be compound **10** not the compound **8**. To confirm the position of bromine, ¹H NMR studies was conducted. The presence of characteristic proton at δ 6.8 and disappearance of peak at δ 6.9 in ¹H-NMR indicates the formation of the compound **8**. The structure of the compound **8** was further confirmed by NOESY and HMBC (Heteronuclear Multiple-Bond Correlation) studies (scheme 2). H-9 of ring **C** is giving HMBC correlation with C-12, C-10 and C-6. Similarly, H-16 of ring **A** is giving correlation with C-14 and C-13 of the same ring **A** and C-7 of ring **B** is giving HMBC correlation with C-8, C-3 and C-5, which shows that Br is attached to C-5 of ring **B**. May be the presence of

dioxolane ring is helping the electrophilic bromination reaction to occur in ring **B**.

Then, we diverted our attention to bromination of the 3-iodo-chromone **5** to get 8-bromo-chromone derivative (scheme 3). We believe that there will be difference in reactivities of iodo compounds vs bromo compounds in Suzuki coupling reaction condition.

Initially, bromination of the compound **5** was performed in NBS/CH₃CN condition which gave poor yield of the compound **9**. Screening of optimal condition was performed again using various solvents, reagents and temperature. Among the conditions screened, we found that NBS/Bz₂O/CCl₄ gave better yield compared to all other conditions. The compound **9** was characterized by ¹H-NMR, ¹³C-NMR and LC-MS data. An IR spectrum of the compound **9** shows the carbonyl peaks at 1651cm⁻¹. The characteristic chromone ring **C** proton at δ 8.2 and disappearance of proton at δ 7.0 in ¹H-NMR confirms formation of compound **9**.

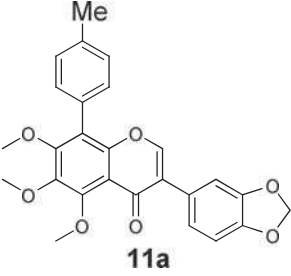
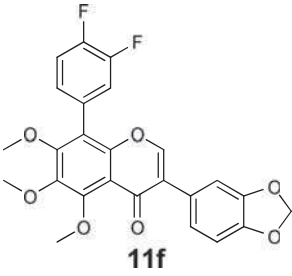
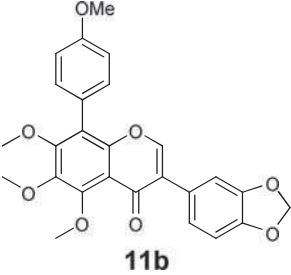
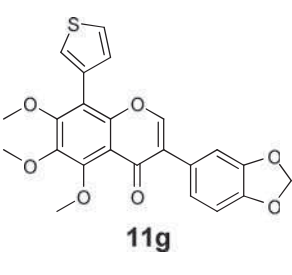
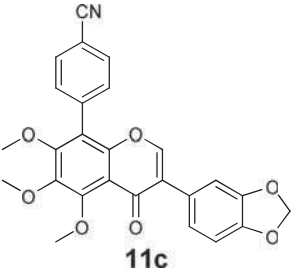
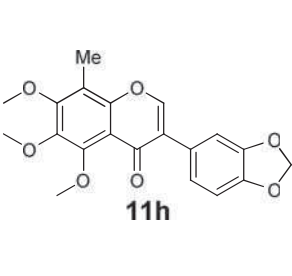
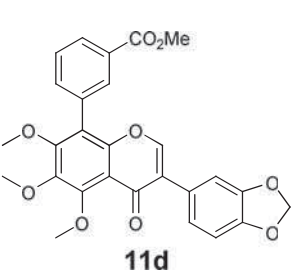
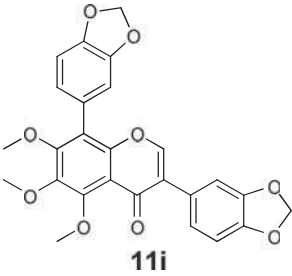
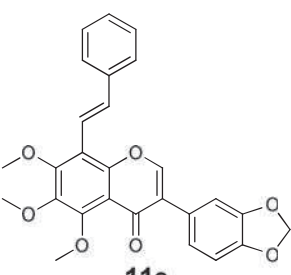
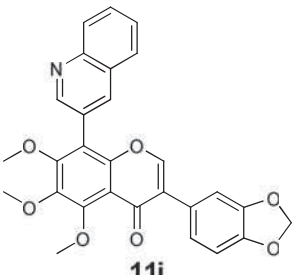


Scheme 3. Derivatization of odoratine at 8-position by Suzuki coupling.

After synthesizing the key building block **9**, it was subjected to the Suzuki reaction with boronic acid **6a** using $\text{Pd}(\text{PPh}_3)_4/\text{Na}_2\text{CO}_3/\text{toluene}/\text{EtOH}/\text{H}_2\text{O}$ condition to give compound **10** in good yield. As expected (iodo vs bromo), we have isolated only mono-aryl product **10** using 1.2 equivalent of the boronic acid **6a** in the Suzuki reaction condition.

But unfortunately using the same reaction condition ($\text{Pd}(\text{PPh}_3)_4/\text{Na}_2\text{CO}_3/\text{toluene}/\text{EtOH}/\text{H}_2\text{O}$), the compound **10** did not yield any Suzuki product **11a** even after prolonged reaction time and use of excess reagents. Then, the Suzuki reaction condition of the compound **10** with 4-methyl-phenyl boronic acid was tried using $\text{K}_3\text{PO}_4/\text{Pd}(\text{PPh}_3)_4/\text{toluene}$ condition and

Table 2. List of 8-substituted odorant derivatives.

Entry	Product	Yield (%)	Entry	Product	Yield
1		97	6		92
2		81	7		79
3		98	8		62
4		70	9		95
5		82	10		94

gratifyingly, we could isolate the compound **11a** in good yield.

Once the Suzuki reaction condition was standardized, various boronic acids were subjected to cross-coupling reaction to give the compounds **11a-11j** (table 2). All compounds, **11a-11j** were well characterized by $^1\text{H-NMR}$, LC-MS and $^{13}\text{C-NMR}$ (for unknown compounds). As indicated in table 2, both the electron withdrawing (entry 3) as well as electron donating group (entry 2) on aryl boronic acid gave similar yield of the cross-coupling product. The alkyl (entry 5) as well heteroaryl (entry 7) boronic acid also gave good yield of the coupling product.

It is noteworthy to mention here that previously inaccessible methyl (entry 8) and 5-benzo-dioxole derivatives (entry 9) were synthesized using this method.

4. Conclusions

We have developed an efficient and versatile synthetic protocol to synthesize the 8-substituted odoratine derivatives in very good yield for the first time. Site-selective bromination of odoratine has been demonstrated using two different routes. 2D (^1H - ^{13}C) HMBC measurements can be readily utilized for the unambiguous structural characterization of the site-selective brominated product.

Supplementary Information (SI)

The spectroscopic data ($^1\text{H-NMR}$, $^{13}\text{C-NMR}$, IR and HRMS) of synthesized compounds are presented in the Supplementary Information, available at www.ias.ac.in/chemsci.

Acknowledgements

Authors are grateful to GVK Biosciences management for the financial support. We thank Dr. Sudhir Kumar Singh for encouragement and motivation. Help from the analytical department for the analytical data is appreciated. PKH gratefully acknowledges UGC, New Delhi for providing UGC-FRPS research start-up grant.

References

- Kinoshita T, Ichinose K and Sankawa U 1990 *Tetrahedron Lett.* **31** 7355
- Singh O V and Muthukrishnan M 2005 *Ind. J. Chem.* **44B** 2575
- Yokosuka A, Haraguchi M, Usui T, Kazami S, Osada H, Yamori T and Mimaki Y 2007 *Bioorg. Med. Chem. Lett.* **17** 3091
- Hayakawa I, Shioda S, Ikedo A and Kogishi H 2014 *Bull. Chem. Soc. Jpn.* **87** 544
- Chinen T, Kazami S, Nagumo Y, Hayakawa I, Ikedo A, Takagi M, Yokosuka A, Imamoto N, Mimaki Y, Kigoshi H, Osada H and Usui T 2013 *ACS Chem. Bio.* **8** 884
- Ikedo A, Hayakawa I, Usui T, Kazami S, Osada H and Kigoshi H 2010 *Bioorg. Med. Chem. Lett.* **20** 5402
- Hayakawa I, Ikedo A and Kigoshi H 2007 *Chem. Lett.* **36** 1382
- Hayakawa I, Ikedo A, Chinen T, Usui T and Kigoshi H 2012 *Bioorg. Med. Chem.* **20** 5745
- Boland G M and Donnelly D M 1998 *Nat. Prod. Rep.* **24** 1
- Li Y H, Fu H G, Su F, Gao L M, Tang S, Bi C W, Li Y H, Wang Y X and Song D Q 2013 *Chemistry Central J.* **7** 117
- Mukne A P, Viswanathan V and Phadatare A G 2011 *Pharmacogn. Rev.* **5** 13
- Malla P, Kumar R and Kumar M 2013 *Chem. Biol. Drug Des.* **82** 71
- Shim Y S, Kim K C, Chi D Y, Lee K H and Cho H 2003 *Bioorg. Med. Chem.* **13** 2561
- Kim J, Seunghee Hong and Sungwoo Hong 2011 *Bioorg. Med. Chem. Lett.* **21** 6977
- Shim Y S, Kim K C, Lee K A, Shrestha S, Lee K H, Kim C K and Cho H 2005 *Bioorg. Med. Chem.* **13** 1325
- Griffiths L A 1962 *J. Expt. Bot.* **13** 169
- Haskins F A and Gorz H 1963 *J. Science* **139** 496
- Lehn J M and Ourisson G 1962 *Bull. Soc. Chim. France* 1133
- Campbell R V M and Tannock J 1973 *J. Chem. Soc. Perkin Trans. I* 2222
- Ngamga D, Yankep E, Tane P, Bezabih M, Ngadjui B T, Fomum Z T and Abegaz B M 2005 *Z. Naturforsch., B: Chem. Sci.* **60b** 973
- Combes S, Finet J P and Siri D 2002 *J. Chem. Soc. Perkin Trans. I* 38
- Yankep E, Njamen D, Fotsing M T, Fomum Z T, Mbanya J C, Giner R M, Recio M C, Manez S and Rios J L 2003 *J. Nat. Prod.* **66** 1288
- Antus S, Farkas L, Kardos-Balogh Z and Nogradi M 1975 *Chem. Ber.* **108** 3883
- Nakano T, Alonso J, Grillet R and Martin A 1979 *J. Chem. Soc. Perkin Trans. I* 2107
- Krishnamurti M and Seshagiri S N 1976 *Ind. J. Chem.* **14B** 222
- Chatterjea J N, Shaw S C and Fatma A 1985 *J. Ind. Chem. Soc.* **62** 990
- Bhardwaj D K, Jain R K, Malhotra V P and Sharma A K 1983 *Proc. Ind. Nat. Sci. Acad.* **49A** 168
- (a) Ravi Kumar P, Behera M, Sambaiha M, Venu K, Nagaraju P, Jaya Shree A and Satyanarayana Y 2014 *J. Amino Acid* **ID 721291**; (b) Ravi Kumar P, Behera M, Raghavulu K, Jaya Shree A and Satyanarayana Y 2012 *Tetrahedron Lett.* **53** 4108
- Elassar Abdel-Zaher A and El-Khair Adel A 2003 *Tetrahedron* **59** 8463
- Biegasiwicz K F, Denis J D, Carrol V M and Priefer R 2010 *Tetrahedron Lett.* **51** 4408
- Miyaura N and Suzuki A 1995 *Chem. Rev.* **95** 2457
- Kotha S, Lahiri K and Dhurke K 2002 *Tetrahedron* **58** 9633