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SYNTHESIS OF INDOLYLPYRIMIDINES *VIA* CROSS-COUPLING OF INDOLYLBORONIC ACID WITH CHLOROPYRIMIDINES: FACILE SYNTHESIS OF MERIDIANIN D

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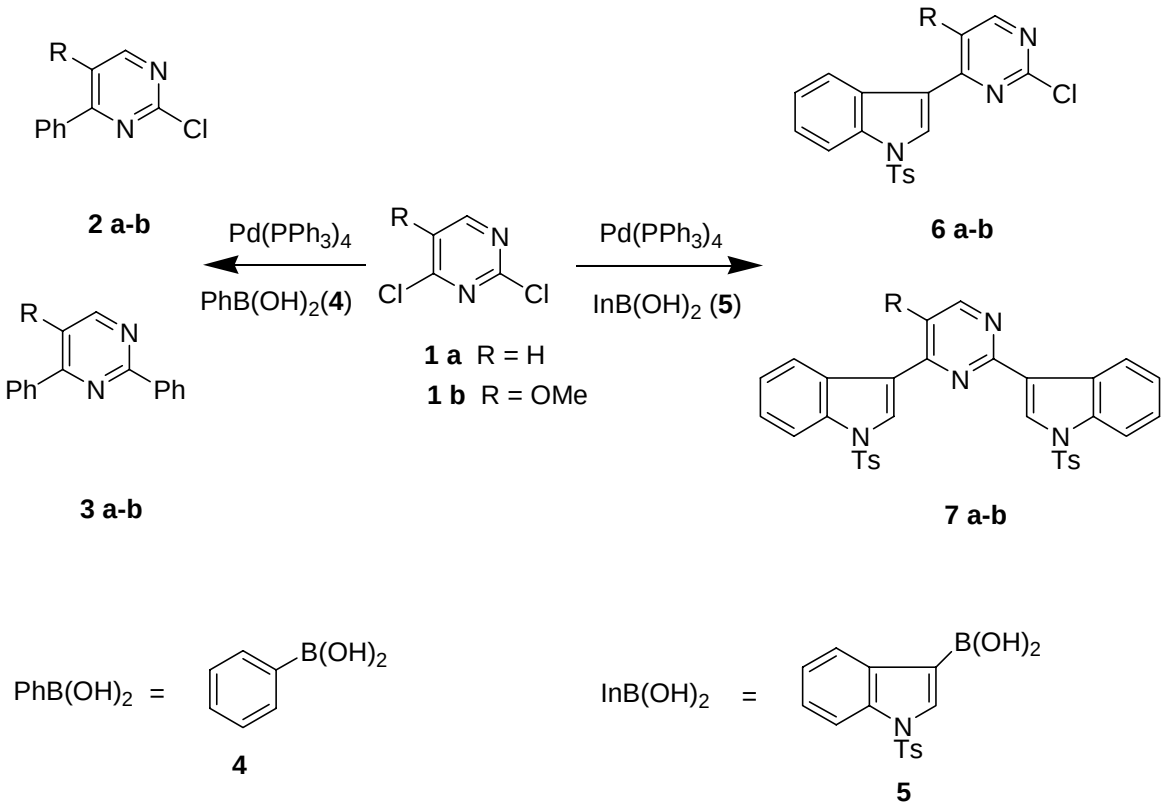
Abstract - Palladium catalyzed cross-coupling reaction of 3-indolylboronic acid with 2,4-dichloropyrimidines proceeded regioselectively to yield indolyl- or bis(indolyl)pyrimidines in high yield, depending on the projection of 3-indolylboronic acid. The marine indole alkaloid meridianin D and an analogue were synthesised *via* the palladium catalyzed cross-coupling reaction as a key step.

Marine invertebrates are a very important source of antitumor secondary metabolites. Numerous biologically active indole alkaloids have been isolated from the marine environment over the past few years.[1-4] Interest in methodology for preparation of marine indole alkaloids has been stimulated both by their novel molecular structures and by their wide range of biological properties. The palladium catalyzed cross-coupling reaction of aryl bromides, aryl iodides, and triflates with arylboronic acids has emerged as an extremely powerful method employed for the formation of C-C bonds.[5] Recently, nortopsentins A-D, antifungal marine 1,4-bis(indolyl)imidazole alkaloids, were synthesised through palladium catalyzed cross-coupling of halogenoimidazoles with 3-indolylboronic and 6-bromo-3-indolylboronic acids.[6] It was noted that the synthesis of bis(indolyl)pyrazine was achieved in low yield (10-15%) by palladium catalyzed reaction of dichloropyrazine with substituted indole.[7] To the best of our knowledge there are few reports about cross-coupling reactions between indole derivatives and halogenopyrimidines. In this paper we report an efficient synthesis of indolylpyrimidines and bis(indolyl)pyrimidines *via* cross-coupling reaction of 3-indolylboronic acid with 2,4-dichloropyrimidines and its application to the synthesis of meridianin D.

Phenylboronic acid (**4**) was initially chosen to examine its cross-coupling with 2,4-dichloropyrimidine catalyzed by tetrakis(triphenylphosphine)palladium (**Scheme 1**). The results are summarized in **Table 1**.



Scheme 1

Table 1. Palladium Catalyzed Cross-Coupling of Phenyl and Indolyl Boronic Acids with Dichloropyrimidines[a]

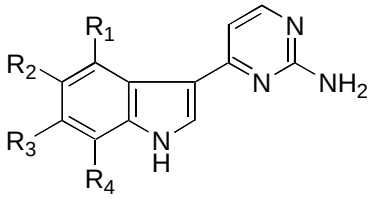
entry	boronic acid (eq)	R in 1	time (h)	product	yield (%)[b]
1	$PhB(OH)_2$ (1 eq)	H	4	**2a**	80
				3a	10
2	$PhB(OH)_2$ (1 eq)	OCH_3	4	**2b**	86
				3b	9
3	$PhB(OH)_2$ (2 eq)	H	6	**3a**	90
4	$PhB(OH)_2$ (2 eq)	OCH_3	6	**3b**	92
5	$InB(OH)_2$ (1 eq)	H	4	**6a**	91
6	$InB(OH)_2$ (1 eq)	OCH_3	6	**6b**	90
7	$InB(OH)_2$ (2 eq)	H	5	**7a**	82
8	$InB(OH)_2$ (2 eq)	OCH_3	8	**7b**	81

[a] All reactions were carried out with 0.1 molar eq. of tetrakis(triphenylphosphine)palladium and 1 eq. molar of 2M Na_2CO_3 in benzene-methanol under reflux; [b] Isolated yields.

Thus, 2,4-dichloropyrimidine (**1a)** was refluxed with two equivalents of phenylboronic acid (**4**) in a mixture of benzene and methanol for 6 h in the presence of palladium catalyst and aqueous sodium carbonate to give the corresponding 2,4-diphenylpyrimidine (**3a**) in good yield (entry 3). The carbon-chlorine bond at the 4-position in pyrimidine (**1**) was more reactive than that at the 2-position, and treatment of dichloropyrimidine (**1a**) with one equivalent of phenylboronic acid (**4**) gave 2-chloro-4-phenylpyrimidine (**2a**) and 2,4-diphenylpyrimidine (**3a**) in a ratio of 8:1 in 90% yield (entry 1). Reaction of 2-chloro-4-phenylpyrimidine (**2a**) with additional equivalent of phenylboronic acid (**4**) furnished 2,4-diphenylpyrimidine (**3a**) in 92% yield. 5-Methoxy-2,4-dichloropyrimidine (**1b**) with one or two equivalents of phenylboronic acid (**4**) gave phenyl or diphenylpyrimidine (**2b** or **3b**) respectively in high yields (entries 2 and 4).

With the above results in mind, we further examined the reaction of 2,4-dichloropyrimidines (**1a-b**) with *N*-tosyl-3-indolylboronic acid (**5)** under the same condition (**Scheme 1, Table 1**). When 2,4-dichloropyrimidines (**1a-b**) were treated with one equivalent of *N*-tosyl-3-indolylboronic acid (**5**), the reaction proceeded exclusively at the 4-position of the pyrimidine to afford 2-chloro-4-indolylpyrimidines (**6a-b**) (entries 5 and 6). While it was reacted with two equivalents of *N*-tosyl-3-indolylboronic acid (**5**) the 2,4-bis(indolyl)pyrimidines (**7a-b**) were obtained in high yields (entries 7 and 8).

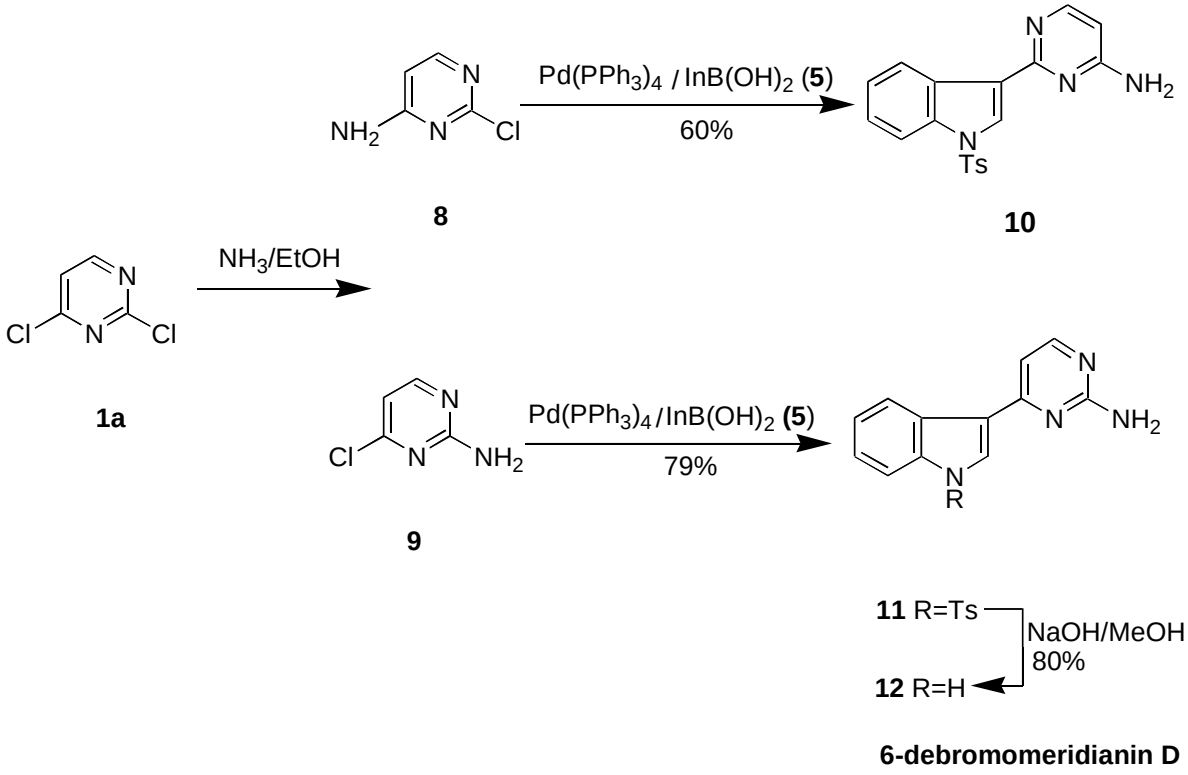
With the view to extend the synthetic utility of cross-coupling reaction of the chloropyrimidines with 3-indolylboronic acid, we contemplated its incorporation into a reaction aimed at the synthesis of the indole alkaloid. Five novel indole alkaloids, meridianin A-E, have been isolated from the tunicate *Aplidium meridianum* recently.[8] All of these compounds have a brominated and/or hydroxylated indole ring linking a 2-aminopyrimidine at 3-position of indole and showed cytotoxicity toward murine tumer cell lines.



Meridianin A $R_1 = OH, R_2 = R_3 = R_4 = H$
Meridianin B $R_1 = OH, R_2 = R_4 = H, R_3 = Br$
Meridianin C $R_1 = R_3 = R_4 = H, R_2 = Br$
Meridianin D $R_1 = R_2 = R_4 = H, R_3 = Br$
Meridianin E $R_1 = OH, R_2 = R_3 = H, R_4 = Br$

Meridianin D was chosen as a representative of meridianin family to be synthesised. Retrosynthetically, a strategy for the synthesis of meridianin D would be palladium catalyzed cross-coupling reaction between 2-amino-4-halogenopyrimidine and 3-indolylboronic acid. Thus, 2-amino-4-chloropyrimidine (**9**) was prepared simply by amination of 2,4-dichloropyrimidine (**1a**) in ethanolic ammonia at room temperature along with its isomer 2-chloro-4-aminopyrimidine (**8**) in a ratio of 1:1, which could be separated by recrystallization.[9] Examining the palladium catalyzed cross-coupling reaction of both **8** and **9**, it was found that the reaction of 4-amino-2-chloropyrimidine (**8**) with *N*-tosyl-3-indolylboronic acid (**5**) was sluggishly and completed after prolonged heating for 10 h in 60% yield, while 2-amino-4-

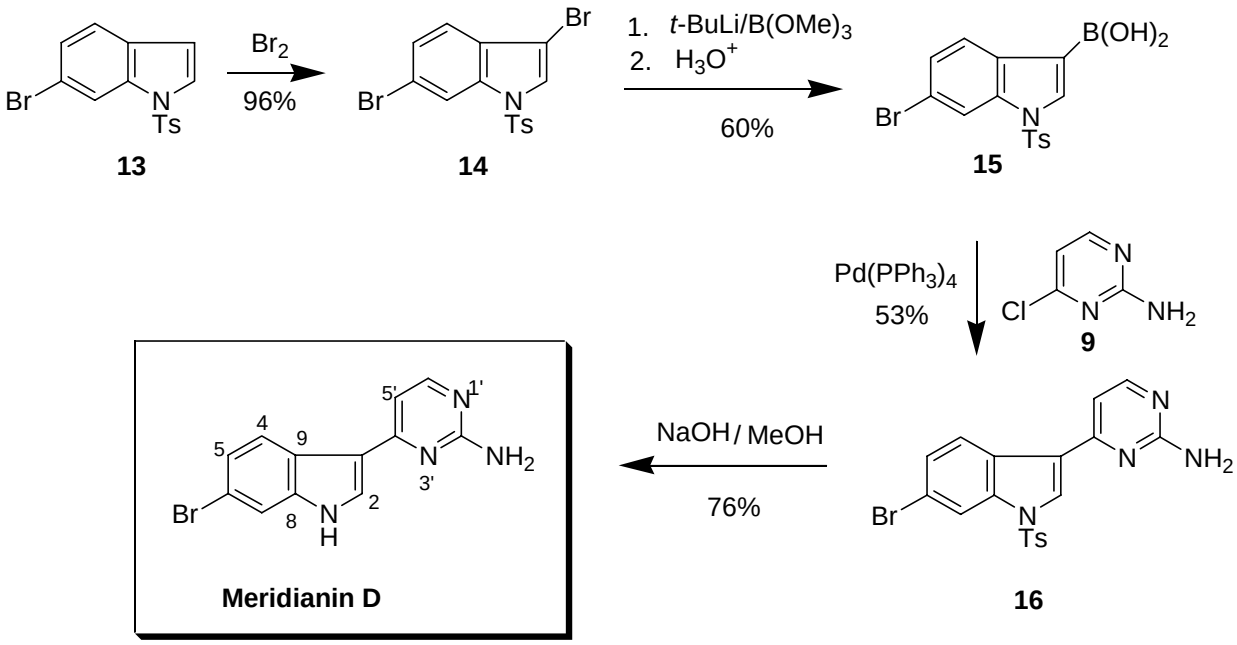
chloropyrimidine (**9**) proceeded smoothly within 5 h to offer 2-amino-4-(*N*-tosyl-3′-indolyl)pyrimidine (**11**) in 79% yield (**Scheme 2**). Deprotection of *N*-tosyl group in **11** with sodium hydroxide in methanol afforded 6-debromomeridianin D (**12**) in 80% yield, an analogue of meridianin.



Scheme 2

Finally meridianin D was synthesised from 3-bromoindole as following steps. *N*-Tosyl-3-bromoindole (**13**) was converted to *N*-tosyl-3,6-dibromoindole (**14**), which was treated with *tert*-butyllithium in tetrahydrofuran at -78 ^{o}C followed by addition of trimethoxyborane and aqueous work-up to give *N*-tosyl-6-bromo-3-indolylboronic acid (**15**).[10] The crude *N*-tosyl-6-bromo-3-indolylboronic acid (**15**) was reacted with one equivalent of 2-amino-4-chloropyrimidine (**9**) under the above-mentioned condition to afford *N*-tosylmeridianin D (**16**) in 53% yield. A trace amount of the homo-coupling product of **15** between C-$B(OH)_2$ and C-Br was also observed by GC-MS in this process. Removal of the *N*-tosyl group with sodium hydroxide yielded meridianin D in 76% yield (**Scheme 3**). ^{1}H NMR and ^{13}C NMR chemical shifts of synthetic meridianin D correspond to those reported for meridianin D isolated from nature (**Table 2**).

In summary, indolyl- and bis(indolyl)pyrimidines were synthesised efficiently by the Suzuki type cross-coupling reaction of 3-indolylboronic acid with 2,4-dichloropyrimidines in high yield. The coupling reaction between 2-amino-4-chloropyrimidine and 3-indolylboronic acid offered a practical method for the synthesis of meridianins and their analogues.



Scheme 3

Table 2. ^{1}H NMR and ^{13}C NMR Data (*DSMO-d_6*) for Synthetic and Natural Meridianin D

Position of proton	^{1}H NMR synthetic	^{1}H NMR natural	Position of carbon	^{13}C NMR synthetic	^{13}C NMR natural
1-NH	11.81 (br s)	11.76 (br s)	2	129.1	129.2
2	8.24 (d, J = 2.4 Hz)	8.21 (d, J = 2.6 Hz)	3	114.7	114.8
4	8.58 (d, J = 8.6 Hz)	8.55 (d, 8.4)	4	124.2	124.3
5	7.25 (dd, J = 8.6 and 1.5 Hz)	7.24 (dd, J = 8.4 and 1.8 Hz)	5	123.0	123.1
7	7.64 (d, J = 1.5 Hz)	7.63 (d, J = 1.8 Hz)	6	113.8	113.9
2′-NH_2	6.49 (s, 2H)	6.43 (s, 2H)	7	114.4	114.5
5′	7.02 (d, J = 5.3 Hz)	7.00 (d, J = 5.1 Hz)	8	137.9	138.0
6′	8.13 (d, J = 5.3 Hz)	8.12 (d, J = 5.1 Hz)	9	124.4	124.5
			2′	163.5	163.6
			4′	162.2	162.3
			5′	105.3	105.4
			6′	157.2	157.2

EXPERIMENTAL

All melting points were measured with a WRS-1A digital melting point apparatus, without correction. IR spectra were determined with a Shimadzu IR-440 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AM-300 instrument. The chemical photo shifts are expressed in ppm and coupling constants are given in Hz. Low-resolution MS spectra were obtained on a VG-Quattro or HP-5969A spectrometer and high-resolution MS spectra were recorded on a Finnigan MAT-95 spectrometer. Elemental analyses were carried out on a Heraeus Rapid-CHNO instrument. Column chromatography was performed on silica gel H (10-40 μm). Reagents purchased commercially were used without further purification. Solvents were dried using standard procedures.

General procedure for palladium catalyzed cross-coupling reaction of 2,4-dichloropyrimidines (1a-b) with phenylboronic acid (4) or *N*-tosyl-3-indolylboronic acid (5):

A mixture of phenylboronic acid (**4**) or *N*-tosyl-3-indolylboronic acid (**5**) (1 or 2 mmol), 2,4-dichloropyrimidines (**1a-b**) (1 mmol), benzene (20 mL), methanol (4 mL), aqueous sodium carbonate (1 or 2 mL, 2 M) and tetrakis(triphenylphosphine)palladium (0.1 or 0.2 mmol) was refluxed under an argon atmosphere. The reaction was monitored with TLC. When the reaction completed, anhydrous sodium sulfate was added. The mixture was filtered and the filtrate was evaporated under reduced pressure. The residue was subjected to flash column chromatography (eluted with ethyl acetate/hexane) to give cross-coupling products.

2-Chloro-4-phenylpyrimidine (2a): mp 86.9-88.7 ^{o}C (CH_2Cl_2/Hexane) (lit.,[11] 89 ^{o}C); IR (KBr) ν_{max} 3064, 2927, 1570, 1532, 1450, 1348, 1287, 1180 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.54 (m, 3H), 7.66 (dd, J = 5.2 and 1.3 Hz, 1H), 8.08 - 8.12 (m, 2H), 8.64 (d, J = 5.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 115.1, 127.4, 129.1, 131.8, 135.0, 159.7, 161.8, 167.1; EIMS *m/z* (%) 190 (M^+, 100), 155 (52), 129 (83), 77 (29), 51 (25).

2-Chloro-5-methoxy-4-phenylpyrimidine (2b): mp 61.8-62.7 ^{o}C (CH_2Cl_2/Hexane); IR (KBr) ν_{max} 3062, 1565, 1531, 1429, 1359, 1295, 1209, 1163, 1060, 1009 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.98 (s, 3H), 7.45-7.52 (m, 3H), 8.08-8.31 (m, 2H), 8.30 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 56.6, 128.2, 129.6, 130.7, 133.9, 142.9, 150.4, 152.2, 156.6; EIMS *m/z* (%) 220 (M^+, 72), 219 (100), 155 (18), 102 (41), 89 (40); *Anal*. Calcd for $C_{11}H_9N_2OCl$: C, 59.88; H, 4.11; N, 12.69. Found: C, 60.17; H, 4.10; N, 12.49.

2,4-Diphenylpyrimidine (3a): mp 62-63.7 ^{o}C (CH_2Cl_2/Hexane) (lit.,[12] 69-70 ^{o}C); IR (KBr) ν_{max} 1586, 1562, 1546, 1425, 1382, 1282, 1024 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.50 - 7.56 (m, 6H), 7.60 (d, J = 5.3 Hz, 1H), 8.22 - 8.25 (m, 2H), 8.58 - 8.62 (m, 2H), 8.84 (d, J = 5.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 114.5, 127.4, 128.5, 128.7, 129.0, 131.2, 131.4, 136.4, 136.6, 156.5, 163.7, 164.8; EIMS *m/z* (%) 232 (M^+, 100), 231 (17), 129 (34), 103 (51), 77 (21).

5-Methoxy-2,4-diphenylpyrimidine (3b): mp 74.4-75.8 ^{o}C (CH_2Cl_2/Hexane); IR (KBr) ν_{max} 3059, 1561, 1540, 1452, 1429, 1380, 1288, 1233, 1014 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.99 (s, 3H), 7.44 - 7.54 (m, 6H), 8.22 - 8.25 (m, 2H), 8.46 - 8.49 (m, 2H), 8.51 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 56.4, 127.8, 128.2, 128.6, 129.9, 130.2, 130.4, 135.4, 136.7, 139.8, 150.0, 154.3, 156.6; EIMS *m/z* (%) 262 (M^+, 76), 144 (13), 116 (64), 103 (42), 89 (100), 77 (29); *Anal*. Calcd for $C_{17}H_{14}N_2O$: C, 77.84; H, 5.38; N, 10.68. Found: C, 77.72; H, 5.40; N, 10.55.

2-Chloro-4-(*N*-tosyl-3′-indolyl)pyrimidine (6a): mp 171.8-173.2 ^{o}C (CH_2Cl_2/Hexane); IR (KBr) ν_{max} 3113, 1574, 1525, 1444, 1385, 1335, 1288, 1199, 1173, 1138, 1091 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.34 (s, 3H), 7.24 - 7.27 (m, 2H), 7.35 - 7.44 (m, 2H), 7.57 (d, J = 5.3 Hz, 1H), 7.83 (d, J = 8.4 Hz, 2H), 8.00 - 8.03 (m, 1H), 8.33 (s, 1H), 8.36 - 8.40 (m, 1H), 8.58 (d, J = 5.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 21.6, 113.5, 115.4, 118.6, 122.4, 124.6, 125.7, 127.1, 127.3, 128.6, 130.2, 134.5, 135.5, 145.8, 158.8, 161.4, 163.1; EIMS *m/z* (%) 383 (M^+, 30), 228 (25), 201 (12), 155 (45), 91 (100), 65 (29); *Anal*. Calcd for $C_{19}H_{14}N_3O_2ClS$: C, 59.45; H, 3.68; N, 10.95. Found: C, 59.66; H, 3.69; N, 10.79.

2-Chloro-5-methoxy-4-(*N*-tosyl-3′-indolyl)pyrimidine (6b): mp 239.6-241.7 ^{o}C (CH_2Cl_2/Hexane); IR (KBr) ν_{max} 3178, 1598, 1560, 1550, 1475, 1446, 1421, 1379, 1355, 1267, 1176, 1136 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.34 (s, 3H), 4.13 (s, 3H), 7.22 - 7.26 (m, 2H), 7.35 - 7.65 (m, 2H), 7.81 (d, J = 8.4 Hz, 2H), 7.96 - 8.00 (m, 1H), 8.27 (s, 1H), 8.62 (s, 1H), 8.72 - 8.76 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 21.6, 56.7, 113.0, 115.1, 123.9, 124.4, 125.5, 127.0, 128.5, 130.0, 132.1, 134.5, 134.7, 140.4, 145.6, 149.5, 151.4, 152.3; EIMS *m/z* (%) 413 (M^+, 100), 258 (99), 155 (23), 102 (24), 91 (67), 65 (24); HRMS Calcd for $C_{20}H_{16}N_3O_3ClS$: 413.0578. Found: 413.0589; *Anal*. Calcd for $C_{20}H_{16}N_3O_3ClS$: C, 58.04; H, 3.87; N, 10.16. Found: C, 58.34; H, 4.06; N, 9.91.

2,4-Bis(*N*-tosyl-3′-indolyl)pyrimidine (7a): mp 132.8-134.7 ^{o}C (CH_2Cl_2/Hexane); IR (KBr) ν_{max} 3055, 1733, 1556, 1444, 1373, 1306, 1250, 1174, 1090 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.32 (s, 3H), 2.34 (s, 3H), 7.21 - 7.27 (m, 4H), 7.35 - 7.44 (m, 4H), 7.50 (d, J = 5.3 Hz, 1H), 7.86 (d, J = 8.4 Hz, 4H), 8.05 (m, 2H), 8.32 (s, 1H), 8.47 (m, 1H), 8.63 (s, 1H), 8.70 (m, 1H), 8.78 (d, J = 5.3 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 21.0, 113.2, 113.3, 115.8, 119.5, 121.2, 122.3, 122.8, 124.0, 124.3, 125.3, 125.5, 127.0, 127.4, 127.7, 128.4, 129.1, 130.4, 133.6, 134.8, 146.0, 157.6, 159.6, 161.1; EIMS *m/z* (%) 618 (M^+, 100), 463 (45), 308 (82), 262 (54), 183 (38), 91 (80); HRMS Calcd for $C_{34}H_{26}N_4O_4S_2$: 618.1361. Found: 618.1378.

5-Methoxy-2,4-bis(*N*-tosyl-3′-indolyl)pyrimidine (7b): mp 178.6-180.3 ^{o}C (CH_2Cl_2/Hexane); IR (KBr) ν_{max} 2926, 1725, 1558, 1452, 1373, 1280, 1175, 1129, 1090, 964, 669, 574 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.31 (s, 3H), 2.34 (s, 3H), 4.15 (s, 3H), 7.19 - 7.44 (m, 8H), 7.85 (dd, J = 8.4 and 2.4 Hz, 4H), 8.05 (d, J = 9.5 Hz, 2H), 8.46 (s, 1H), 8.51 (s, 1H), 8.61 (s, 1H), 8.63 (m, 1H), 8.81 (m, 1H); ^{13}C NMR (DMSO-d_6) δ 21.0, 56.7, 113.2, 115.6, 121.2, 122.6, 123.0, 123.9, 124.0, 125.2, 125.5, 126.8, 126.9, 127.7, 128.3,

130.4, 133.6, 133.7, 134.8, 140.7, 145.8, 146.0, 147.8, 148.5, 153.2; EIMS *m/z* (%) 648 (M^+, 100), 493 (91), 338 (42), 155 (15), 127 (25), 91 (66); HRMS Calcd for $C_{35}H_{28}N_4O_5S_2$: 648.1515. Found: 648.1508.

***N*-Tosyl-3,6-dibromoindole (14):** A solution of *N*-tosyl-6-bromoindole (**13**) (2.07 g, 6 mmol) in CCl_4 (25 mL) was slowly added dropwise to a solution of bromine (0.36 mL, 7 mmol) in CCl_4 (10 mL) with vigorous stirring for 20 min. The mixture was stirred for 4 h at rt, then CH_2Cl_2 (100 mL) was added to the mixture. It was poured into saturated $NaHCO_3$ (30 mL). Water was separated and the organic layer was washed with a solution of 10% $Na_2S_2O_3$ and brine successively, then dried with anhydrous sodium sulfate overnight. The solvent was removed under vacuum and the crude product was purified with column chromatography to give a white solid **14** (2.46g, 96%). mp 133.2-135.5 ^oC (CH_2Cl_2/Hexane); IR (KBr) ν_{max} 1597, 1418, 1381, 1268, 1174, 1128, 1088, 1032 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.36 (s, 3H), 7.26 (s, 2H), 7.34 (d, J = 8.5 Hz, 1H), 7.42 (dd, J = 8.4 and 1.6 Hz, 1H), 7.57 (s, 1H), 7.77 (d, J = 8.4 Hz, 2H), 8.18 (d, J = 1.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 21.6, 99.2, 116.6, 119.6, 121.2, 125.2, 126.9, 127.3, 128.6, 130.2, 134.6, 134.8, 145.7; EIMS *m/z* (%) 427/431 (M^+, 29/31), 429 (61), 272/276 (28/26), 274 (57), 193/195 (6/6), 155 (86), 114 (30).

***N*-Tosyl-6-bromo-3-indolylboronic acid (15):** A solution of *tert*-BuLi in n-pentane (1.5 M, 1.5 mL, 2.25 mmol) was added dropwise to a solution of *N*-tosyl-3,6-dibromoindole (**14**) (0.86 g, 2 mmol) in THF (15 mL) under an argon atmosphere at -78 ^oC. The mixture was stirred at -78 ^oC for 40 min, then trimethoxyborane (1.1 mL, 9 mmol) was added dropwise at -78 ^oC. The reaction was remained at -78 ^oC for 2 h. After methanol (2 mL) and water (2 mL) were added, the mixture was stirred for 3 h at rt and extracted with ether. The organic layer was washed with water and dried over anhydrous sodium sulfate overnight and evaporated to give a solid residue **15**, which was used for the next reaction without further purification.

General procedure for amino-(*N*-tosyl-3′-indolyl)pyrimidine:

A mixture of *N*-tosyl-3-indolylboronic acid (**5**) (0.5 mmol), amino-chloropyrimidine (**8** or **9**) (0.5 mmol), benzene (10 mL), methanol (2 mL), aqueous sodium carbonate (0.5 mL, 2 M) and tetrakis(triphenylphosphine)palladium (58 mg, 0.05 mmol) was refluxed under an argon atmosphere. After the reaction was completed, anhydrous sodium sulfate was added. The mixture was filtered and the filtrate was evaporated under reduced pressure. The residue was subjected to flash column chromatography (eluted with ethyl acetate/hexane) to give cross-coupling products.

4-Amino-2-(*N*-tosyl-3′-indolyl)pyrimidine (10): mp 138.9-141.3 ^oC (CH_2Cl_2/Hexane); IR (KBr) ν_{max} 3472, 3389, 1622, 1587, 1556, 1465, 1419, 1370, 1255, 1240, 1172, 1132 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.31 (s, 3H), 6.36 (d, J = 5.8 Hz, 1H), 6.95 (br s, 2H), 7.32 - 7.43 (m, 4H), 7.91 - 7.98 (m, 3H), 8.18 (d, J = 5.8 Hz, 1H), 8.32 (s, 1H), 8.67 (dd, J = 7.9 and 1.0 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 21.0, 103.0, 112.9, 121.7, 123.6, 124.9, 126.8, 127.5, 128.0, 130.3, 133.7, 134.7, 145.7, 155.0, 160.6, 163.2; EIMS *m/z* (%)

364 (M^+, 68), 210 (19), 209 (100), 182 (17), 155 (6), 91 (10); HRMS Calcd for $C_{19}H_{16}N_4O_2S$: 364.1002. Found: 364.0998.

2-Amino-4-(*N*-tosyl-3′-indolyl)pyrimidine (11): mp 222.4-222.8 ^oC (CH_2Cl_2/Hexane); IR (KBr) ν_{max} 3341, 3202, 1656, 1570, 1548, 1462, 1366, 1283, 1219, 1187, 1174 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.31 (s, 3H), 6.68 (br s, 2H), 7.25 (dd, J = 5.2 and 0.9 Hz, 1H), 7.33 - 7.46 (m, 4H), 7.95 - 8.01 (m, 3H), 8.28 (dd, J = 5.2 and 1.2 Hz, 1H), 8.63 (s, 1H), 8.66 (d, J = 8.4 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 21.0, 106.5, 112.9, 120.0, 123.4, 123.8, 125.2, 126.8, 127.8, 130.3, 133.7, 134.7, 145.8, 158.0, 160.0, 163.3; EIMS *m/z* (%) 364 (M^+, 89), 210 (20), 209 (100), 182 (23), 155 (13), 91 (21), 65 (7); HRMS Calcd for $C_{19}H_{16}N_4O_2S$: 364.0972. Found: 364.0983.

2-Amino-4-(*N*-tosyl-6′-bromo-3′-indolyl)pyrimidine (16): mp 194.4 - 194.9 ^oC (CH_2Cl_2/Hexane); IR (KBr) ν_{max} 3489, 3294, 3149, 1744, 1632, 1580, 1467, 1371, 1169, 1149 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.34 (s, 3H), 6.73 (br s, 2H), 7.26 (d, J = 5.2 Hz, 1H), 7.45 (d, J = 8.0 Hz, 2H), 7.51 (dd, J = 8.6 and 1.8 Hz, 1H), 8.00 (d, J = 8.4 Hz, 2H), 8.11 (d, J = 1.4 Hz, 1H), 8.27 (d, J = 5.2 Hz, 1H), 8.66 (d, J = 8.6 Hz, 1H), 8.72 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 21.0, 106.4, 115.4, 118.0, 119.8, 125.3, 126.9, 128.5, 130.4, 133.5, 135.3, 146.1, 158.2, 159.6, 163.3; EIMS *m/z* (%) 442 (M^+, 59.91), 289 (95.62), 287 (100), 260 (16), 208 (63), 155 (22), 91 (84), 65 (39); HRMS Calcd for $C_{19}H_{15}N_4O_2BrS$: 442.0129. Found: 442.0114.

Meridianin D:

2-Amino-4-(*N*-tosyl-6′-bromo-3′-indolyl)pyrimidine (**16**) (100 mg, 0.23 mmol) and sodium hydroxide (160 mg, 4 mmol) in methanol (20 mL) were refluxed for 1.5 h. After cooled to rt, methanol was removed under vacuum and the residue was dispersed into water and ethyl acetate. The organic layer was separated and washed with water and brine successively. Then the organic phase was dried over anhydrous sodium sulfate overnight. After evaporation under vacuum, the solid residue was purified by chromatography to give yellow powder meridianin D (50 mg, 76%). mp 219.5 - 221.8 ^oC (EtOAc/MeOH); IR (KBr) ν_{max} 3432, 3167, 1660, 1571, 1515, 1448, 1389, 1230, 1103, 886, 814 cm^{-1}; ^1H NMR (DMSO-d_6) and ^{13}C NMR (DMSO-d_6) see the **Table 2**; EIMS *m/z* (%) 288 (M^+, 94), 290 (M+2, 100), 249 (29), 247 (30), 208 (12), 168 (14), 140 (13), 104 (22); HRMS Calcd for $C_{12}H_9N_4Br$: 288.0022. Found: 288.0016.

6-Debromomeridianin D (12): Prepared as meridianin D**.** mp 262.2 - 264.3 ^oC (EtOAc/MeOH); IR (KBr) ν_{max} 3408, 3329, 3174, 1661, 1568, 1453, 1414, 1246, 1119 cm^{-1}; ^1H NMR (DMSO-d_6) δ 6.39 (br s, 2H), 7.02 (d, J = 5.3 Hz, 1H), 7.15 (m, 2H), 7.45 (d, J = 7.9 Hz, 1H), 8.11 (d, J = 5.3 Hz, 1H), 8.19 (s, 1H), 8.59 (d, J = 7.4 Hz, 1H), 11.65 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 105.2, 111.7, 113.6, 120.2, 121.9, 122.3, 125.3, 128.1, 136.9, 156.9, 162.6, 163.4; EIMS *m/z* (%) 210 (M^+, 100), 209 (35), 169 (48), 155 (4), 140 (9), 114 (8), 89 (4); HRMS Calcd for $C_{12}H_{10}N_4$: 210.0923. Found: 210.0914.

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