RSC Advances

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2014, **4**, 9885

Received 2nd December 2013
Accepted 18th December 2013

DOI: 10.1039/c3ra47192f

www.rsc.org/advances

Palladium catalyzed novel monoarylation and symmetrical/unsymmetrical diarylation of imidazo-[1,2-*a*]pyrazines and their *in vitro* anticancer activities†

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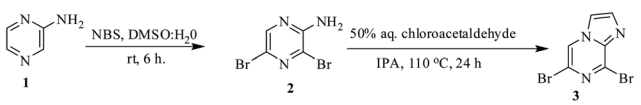
Palladium catalyzed Suzuki–Miyaura cross-coupling reactions are reported for the synthesis of monoarylated (at the C8 position) and symmetrical diarylated (at the C6 and C8 positions) imidazo[1,2-*a*]-pyrazines. Monoarylated products have also been used to synthesize unsymmetrical C6/C8 diarylated products. These compounds were screened for *in vitro* antitumor activities against a preliminary tumor cell line panel assay.

Fused heterocyclic molecular frameworks are found in a large number of biologically active natural and synthetic components.[1] Halogenated heteroaromatic ring systems are valuable monomers because of their ability to participate in established cross-coupling reactions including the Heck, Stille and Suzuki reactions.[2] Several procedures for transition-metal-catalyzed direct C–C functionalization of imidazoazines have been developed, notably in the imidazo[1,2-*a*]pyridine[3] and imidazo-[1,2-*a*]pyrimidine[4] series. Imidazo[1,2-*a*]pyrazine, consisting of bicyclic N-fused imidazole and pyrazine rings, is a privileged structural motif present in several natural products and pharmacologically relevant structures with a wide range of activities such as aurora kinase inhibitors,[5] antiinflammatory,[6] antibronchospastic,[7] antiulcer,[8] anticancer[9] and controlling allergic reactions.[10]

A variety of classical methods have been developed for the functionalization of imidazo[1,2-*a*]pyrazine *viz.*, arylation of 8-methoxy or 8-methylthio-6-bromo-imidazo[1,2-*a*]pyrazines,[11] 3-aryl/alkylamino and 2-aryl/alkyl substituted imidazo[1,2-*a*]-pyrazines,[12] diarylurea,[13] 8-morpholinyl[14] and 3,6-di(hetero)aryl-imidazo[1,2-*a*]pyrazines[15] through palladium catalyzed cross-coupling reactions. But, the imidazo[1,2-*a*]pyrazine series remains almost unexplored for palladium catalyzed direct C–C monoarylation at C8 and diarylation at C6 and C8 positions. Palladium catalyzed cross-coupling reactions of aryl halides with organometallic reagents serve as a straightforward and powerful method for the formation of carbon–carbon bonds. Most magnesium, tin and zinc reagents are sufficiently reactive to undergo transmetalation with palladium without the need for a ligand or an additive; boron and silicon reagents, on the other hand, are usually reluctant to transmetalate in the absence of an activator. So Suzuki is typically carried out in the presence of a ligand, the role of which is to form a higher valent, more reactive complex.[2b] Herein we report the monoarylation at the C8 position and symmetrical/unsymmetrical diarylation at the C6 and C8 positions of imidazo[1,2-*a*]pyrazine catalyzed by palladium with and without ligands.

To obtain 6,8-dibromo-imidazo[1,2-*a*]pyrazine, we have used the readily available starting material 2-aminopyrazine **1**. Bromination of **1** with *N*-bromosuccinamide (NBS) in DMSO and water at room temperature for 6 h gave 2-amino-3,5-dibromopyrazine **2** (ref. 16) in 90% yield followed by cyclization with chloroacetaldehyde in the absence of base to obtain 6,8-dibromo-imidazo[1,2-*a*]pyrazine **3** in 80% yield (Scheme 1).

Palladium catalyzed Suzuki–Miyaura coupling of 6,8-dibromo-imidazo[1,2-*a*]pyrazine **3** with different aryl boronic acids afforded substituted monoarylated and symmetrical diarylated products. During our study of imidazo[1,2-*a*]pyrazine derivatives, thiophen-2-boronic acid served as a model reactant for the optimization of the reaction conditions as the thiophene moiety is considered a structural alert in drug design and discovery. Thiophene and the thienyl core have attracted the



Scheme 1 Synthesis of 6,8-dibromo-imidazo[1,2-*a*]pyrazine.

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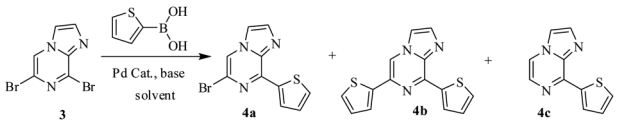
† Electronic supplementary information (ESI) available: Experimental section, ^{1}H and ^{13}C NMR spectra of all new compounds **4–12** and **16–30**, antitumor methodology and activities of all selected compounds **4a–b**, **5a–b**, **7a**, **8a–b**, **9a–b**, **11a–b**, **13b**, **18–19**, **21–23**, **27–28** and **30**. CCDC 960038 and 960039. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3ra47192f

attention of the scientific community due to their therapeutic uses as anti HIV,[17] antitubercular,[18] antimicrobial,[19] tyrosine kinase inhibitor[20] and anticancer agents.[21]

The Suzuki–Miyaura coupling reaction between **3** and thiophen-2-boronic acid was carried out with different palladium based catalysts such as $Pd(PPh_3)_4$, $Pd(PPh_3)_2Cl_2$ and $Pd_2(dba)_3$.$Pd(PPh_3)_4$ proved to be an effective catalyst for monoarylated and diarylated products giving 70% and 10% yields respectively (Table 1, entries 1–3). A survey of different bases (Cs_2CO_3, Na_2CO_3, K_2CO_3 and DIPEA) revealed that Cs_2CO_3 was found to be the best choice (Table 1, entries 3–6). Recent developments have been reported for in Suzuki–Miyaura coupling employing ligandless palladium catalysts and phase-transfer catalysis or a mixture of organic solvents along with water as a cosolvent.[22] Use of water is suitable in this coupling reaction as boronic acids are stable in aqueous conditions. Its ability to dissolve various bases helps in activating boronic acids and enhancing the rate of reaction.[23] The effect of different solvents was also studied and it was observed that the reaction proceeds in both protic and aprotic solvents although significant variations in yield were noticed. The polar protic solvents such as MeCN–H_2O (Table 1, entries 1–6 and 15–20), THF–H_2O (Table 1, entry 11) and acetone (Table 1, entry 12) were found to be the most effective solvents and gave excellent results. On the other hand, the protic nonpolar solvent, toluene–H_2O (Table 1, entries 7–10), and aprotic polar solvents *viz.*, DMF and 1,4-dioxane (Table 1, entry 13 and 14) gave comparatively lower yields. A lower yield was also obtained in the absence of water (Table 1, entry 21). Polar protic solvents like isopropyl alcohol ((IPA) (Table 1, entries 22–24)) with Cs_2CO_3 gave very interesting results as 8-thiophen-2-yl-imidazo-[1,2-*a*]pyrazine was formed **4c** in 60% yield along with 6-bromo-8-thiophen-2-yl-imidazo[1,2-*a*]pyrazine **4a** in 30% yield due to dehalogenation and C–C coupling respectively. However, K_2CO_3 in IPA gave only 8-thiophen-2-yl-imidazo[1,2-*a*]pyrazine **4c** in 55% yield. A mixture of acetonitrile and water (9 : 1) proved to

Table 1 Optimization of palladium catalyzed Suzuki–Miyaura coupling[a]



Entry	Time (h)	Catalyst/ligand	Base	Solvent	Yield[b] (%) **4a**/**4b**/**4c**
1	12	$Pd(PPh_3)_2Cl_2$	Cs_2CO_3	MeCN–H_2O	30/10/0
2	12	$Pd_2(dba)_3$	Cs_2CO_3	MeCN–H_2O	43/7/0
3	8	$Pd(PPh_3)_4$	Cs_2CO_3	MeCN–H_2O	70/10/0
4	10	$Pd(PPh_3)_4$	Na_2CO_3	MeCN–H_2O	62/11/0
5	12	$Pd(PPh_3)_4$	K_2CO_3	MeCN–H_2O	60/15/0
6	12	$Pd(PPh_3)_4$	DIPEA	MeCN–H_2O	54/10/0
7	18	$Pd(PPh_3)_4$	Na_2CO_3	Toluene–H_2O	45/5/0
8	19	$Pd(PPh_3)_4$	K_2CO_3	Toluene–H_2O	36/13/0
9	18	$Pd(PPh_3)_4$	DIPEA	Toluene–H_2O	15/0/0
10	12	$Pd(PPh_3)_4$	Cs_2CO_3	Toluene–H_2O	20/10/0
11	19	$Pd(PPh_3)_4$	Cs_2CO_3	THF–H_2O	55/0/0
12	10	$Pd(PPh_3)_4$	K_2CO_3	Acetone	52/15/0
13	10	$Pd(PPh_3)_4$	Cs_2CO_3	DMF	52/0/0
14	15	$Pd(PPh_3)_4$	Cs_2CO_3	1,4-Dioxane	44/0/0
15	14	$Pd(PPh_3)_2Cl_2$	Na_2CO_3	MeCN–H_2O	52/7/0
16	14	$Pd(PPh_3)_2Cl_2$	K_2CO_3	MeCN–H_2O	50/5/0
17	15	$Pd(PPh_3)_2Cl_2$	DIPEA	MeCN–H_2O	38/10/0
18	12	$Pd_2(dba)_3$	Na_2CO_3	MeCN–H_2O	43/0/0
19	12	$Pd_2(dba)_3$	K_2CO_3	MeCN–H_2O	65/0/0
20	12	$Pd_2(dba)_3$	DIPEA	MeCN–H_2O	45/0/0
21	20	$Pd(PPh_3)_4$	Cs_2CO_3	MeCN	30/15/0
22	12	$Pd(PPh_3)_4$	Na_2CO_3	IPA	0/0/45
23	8	$Pd(PPh_3)_4$	K_2CO_3	IPA	0/0/55
24	12	$Pd(PPh_3)_4$	Cs_2CO_3	IPA	30/0/60
25	11	$Pd(PPh_3)_4$ + XantPhos	K_2CO_3	MeCN–H_2O	62/10/0
26	10	$Pd(PPh_3)_4$ + JohnPhos	K_2CO_3	MeCN–H_2O	65/0/0
27	10	$Pd(PPh_3)_4$ + cyclohexyl John Phos	K_2CO_3	MeCN–H_2O	61/5/0
28	9	$Pd(PPh_3)_4$ + BINAP	K_2CO_3	MeCN–H_2O	59/0/0
29	12	$Pd(PPh_3)_4$ + PPh_3	K_2CO_3	MeCN–H_2O	53/0/0

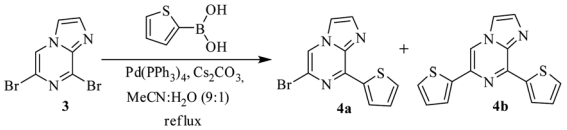
[a] *Reaction conditions*: 1.0 eq. thiophen-2-boronic acid, 5 mol% catalyst, 5 mol% ligand, 1.0 eq. base, solvent : cosolvent (9 : 1), reflux, 8–20 h. [b] Isolated yields.

be best solvent for this transformation. Reaction conditions were also optimized by using a Pd catalyst in the presence of different ligands. Use of ligands XantPhos, JohnPhos, cyclohexyl JohnPhos, BINAP and PPh_3 (Table 1, entries 25–29) were not able to increase the diarylated products or improve the yields of the monoarylated products.

Further, by using 1.5 equivalents of thiophen-2-boronic acid in the same ratio of Cs_2CO_3, there was not much variation in monosubstituted and disubstituted products. But by using 2.0 eq. of boronic acid, monosubstituted and disubstituted products were formed in 28% and 54% yields respectively. When 3.0 eq. of boronic acid was used, predominantly disubstituted products were formed with monosubstituted products only in traces (Table 2).

With the optimized reaction conditions in hand, we have used 1.0 equivalent of thiophen-2-boronic acid, 5 mol% of $Pd(PPh_3)_4$, Cs_2CO_3 (1 eq.) in MeCN–H_2O (9 : 1) and evaluated the scope of arylation with a variety of aryl boronic acids, providing a library of monosubstituted (**4a–15a**) and disubstituted imidazo[1,2-*a*]pyrazines (**4b–15b**) (Table 3). Electron withdrawing as well as electron donating substituents on aryl boronic acids were well tolerated. The reaction worked well with thiophen-2-boronic acid, furan-2-boronic acid, 4-fluoro, 4-chloro, 4-bromo, 4-methoxy, 4-formyl and 2-hydroxyphenyl boronic acids and good yields of monoarylated and diarylated products were obtained (Table 3, entries 1–8). Among the halides, 4-chloro and 4-bromo gave higher yields of the monoarylated products compared to the 4-fluoro analogue. The structures of all novel compounds were confirmed by NMR (ESI†) as well as mass spectroscopic techniques. The structure of compound **9b** was also confirmed by X-ray crystallography (Fig. 1).[24] In the case of naphthalen-1-boronic acid, only the monoarylated product at the C8 position was formed in 64% yield and arylation at the C6 position did not occur (Table 3, entry 9). This is due to the steric hindrance of the bulky naphthyl ring at the C8 position of the imidazo[1,2-*a*]pyrazine. In the case of phenyl boronic acid, 3-methylphenyl boronic acid and 4-

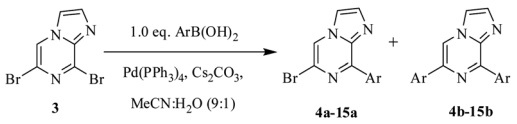
Table 2 Reactions of 6,8-dibromo-imidazo[1,2-*a*]pyrazine with varying equivalences of boronic acid

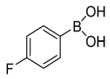
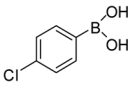
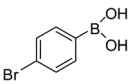
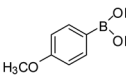
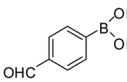
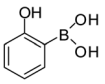
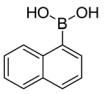
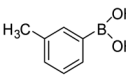
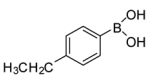


Entry	Thiophen-2-boronic acid (eq.)	Cs_2CO_3	Yield[a] (%) 4a	4b
1	1.0	1.0	70	10
2	1.5	1.5	65	20
3	2.0	2.0	28	54
4	2.5	2.5	20	60
5	3.0	3.0	Trace	90

[a] Isolated yields.

Table 3 Reactions of 6,8-dibromo-imidazo[1,2-*a*]pyrazine with different boronic acids



Entry	Time (h)	Ar	Products[a] (%)	
1	8		**4a** (70)	**4b** (10)
2	12		**5a** (56)	**5b** (12)
3	10		**6a** (52)	**6b** (25)
4	8		**7a** (70)	**7b** (16)
5	8		**8a** (68)	**8b** (20)
6	8		**9a** (69)	**9b** (14)
7	7		**10a** (70)	**10b** (15)
8	8		**11a** (57)	**11b** (30)
9	10		**12a** (64)	—
10	10		**13a** (50)[b]	**13b** (20)[b]
11	10		**14a** (53)[b]	**14b** (10)[b]
12	11		**15a** (65)[b]	**15b** (13)[b]

[a] Isolated yields. [b] GC-MS yields.

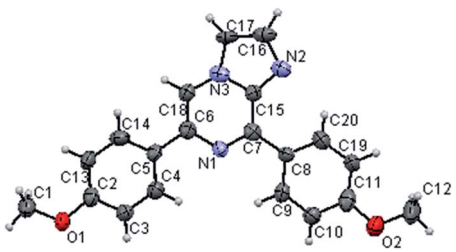


Fig. 1 X-ray structure of **9b**.

ethylphenyl boronic acid, monoaryl and diaryl substituted imidazo[1,2-*a*]pyrazine could not be isolated in pure form, but were confirmed by NMR and GCMS (Table 3, entries 10–12). Attempting to achieve arylation with 4-acetylphenyl boronic acid in all the reaction conditions proved unsuccessful and only the starting material was recovered.

We took advantage of the monoarylated products to implement an additional cross-coupling reaction which aimed at providing straightforward access to unsymmetrical imidazo[1,2-*a*]-pyrazine. Thus, reactions of C8 monosubstituted imidazo[1,2-*a*]-pyrazines were carried out with 1.0 equivalent of a variety of boronic acids in the presence of $Pd(PPh_3)_4$ and Cs_2CO_3 in MeCN–H_2O to give unsymmetrical diarylated imidazo[1,2-*a*]pyrazine derivatives. Monoarylation at the C8 position was confirmed by considering 2D NOE difference experiments (Fig. 2) that showed negative NOE signals for the singlet from the C5H proton of imidazo[1,2-*a*]pyrazine and doublet from the C2′H of 4-formylphenyl (**10a**). For the unsymmetrical diarylation, substitution of 4-formylphenyl at the C8 position and 2-thiophene at C6 position (**25**) was also confirmed by 2D NOE experiment (positive NOE signals for the singlet from the C5H proton of imidazo[1,2-*a*]pyrazine with a doublet from the thiophene and negative NOE signals for the singlet from the C5H proton of imidazo[1,2-*a*]pyrazine and doublet from the C2′H of 4-formylphenyl). 4-Fluoro, 4-chloro, 4-methoxy and 4-formylphenyl imidazo[1,2-*a*]pyrazine derivatives were reacted with thiophen-2-boronic acid, furan-2-boronic acid, 4-methoxy, 2-hydroxy, 4-formyl, 4-chloro and 4-fluorophenyl boronic acids to form the corresponding unsymmetrical imidazo[1,2-*a*]pyrazines (**16–30**) in 52–85% yields (Table 4). The reaction of monosubstituted 4-methoxyphenyl derivative was slow and only traces of the desired product was observed when naphthalen-1-boronic acid was reacted under the same reaction conditions. The structure of compound **20** was also confirmed by measuring X-ray crystallography (Fig. 3).[24] All synthesized compounds were screened for *in vitro* anticancer activity.

Preliminary anticancer activity studies revealed that monoarylated, symmetrical diarylated compounds (**4a**, **4b**, **5a**, **5b**, **7a**, **8a**, **8b**, **9a**, **9b**, **11a**, **11b** and **13b**) and unsymmetrical diarylated compounds (**18**, **19**, **21–23**, **27**, **28** and **30**) were selected by National Cancer Institute, Bethesda, Maryland, USA on the basis of structure variation for evaluation of their anticancer activity. The selected compounds were subjected to *in vitro* anticancer assay against tumor cells in a full panel of 60-cell lines at single dose concentration of 10 μM, and the percentages of growth inhibition over sixty tested cancer cell lines were determined[25–27] (Tables 1 and 2, ESI†). Monosubstituted compounds (**4a–5a**, **7a–9a** and **11a**) displayed modest potency against the tested tumor cell lines and were considered to be the least effective. Similarly disubstituted compounds (**4b**, **5b**, **9b** and **13b**) showed lower activity for cancer cell lines but were more active than the monosubstituted compounds. Diarylated compounds 4-bromophenyl and 2-hydroxyphenyl imidazo[1,2-*a*]-pyrazine (**8b** and **11b**) showed a broad spectrum of anticancer activity compared to their corresponding monoarylated products (**8a** and **11a**), indicating that arylation at both C6 and C8 positions is essential for activity. Disubstituted compound **4b** showed selective potency towards breast cancer cell lines MCF7, T-47D and MDA-MB-468 with GI values of 75.44%, 78.80% and 88.28%, respectively, while compound **5b** showed selectivity towards breast cancer cell line MCF7 with a GI value of 75.20%. Compound **8b** also showed excellent inhibition against leukaemia cancer cell lines K-562 (83.21%), SR (86.61%), non-small cell lung cancer cell line NCI-H460 (83.24%), colon cancer cell lines COLO205 (92.17%), HCT-15 (78.38%), HT29 (90.12%) and SW-620 (74.59%), melanoma cancer cell line MDA-MB-435 (96.92%), ovarian cancer cell line NCI/ADR-RES (80.29%) and breast cancer cell lines BT-549 (82.44%), MCF7 (77.96%), and is lethal to non-small lung cancer cell line NCI-H522. Compound **11b** also showed selectivity towards colon cancer cell line HCT-15, renal cancer cell line A-498, breast cancer cell lines MCF7 and MDA-MB-231/ATCC with GI values of 59.04%, 68.01%, 59.64% and 69.32% respectively.

Compounds **18**, **27** and **28** are the least effective in the unsymmetrical disubstituted imidazo[1,2-*a*]pyrazine series indicating that 4-chlorophenyl, 2-hydroxyphenyl and 4-fluorophenyl at the C6 position to their corresponding 4-fluorophenyl and 4-methoxyphenyl at C8 positions of imidazo[1,2-*a*]pyrazine is not essential for activity. Compounds **23** and **30**, having 4-fluorophenyl and 2-thiophene moieties at the C8 position with respective 4-chlorophenyl and 4-methoxyphenyl groups at the C6 position of imidazo[1,2-*a*]pyrazine, showed moderate antitumor activity while compounds **21** and **22**, with 2-hydroxyphenyl and 2-furan at the C6 position with 4-chlorophenyl at the C8 positions showed a broad spectrum of antitumor activity. Leukaemia cancer cell line K-562 proved to be sensitive towards compounds **19**, **21** and **23** with GI values of 73.90%, 78.51% and 70.71% respectively. Non-small lung cancer cell lines NCI-H322M and NCI-H460 showed sensitivity towards compound **22** with GI values of 88.56% and 85.47% respectively while NCI-H522 showed sensitivity towards compound **21** with a GI value of 82.59%. Compound **19** showed selectivity towards melanoma cancer cell line MDA-MB-435, breast cancer cell lines MCF7 and T-47D with GI values of 76.92%, 80.94% and 83.67% respectively. Compound **22** showed selectivity towards CNS cancer cell line SF-295 with a GI value of 84.86% and renal cancer cell line ACHN, TK-10 and UO-31 with GI values of 91.41%, 88.07% and 92.94% respectively. These results revealed that unsymmetrical diarylated compounds have been found to be more effective for anticancer activity than monoarylated or symmetrical diarylated compounds.

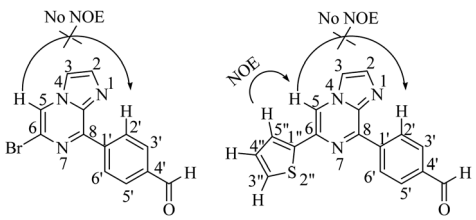
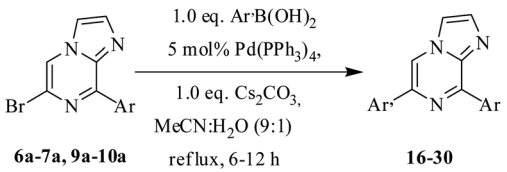


Fig. 2 2D NOE ^1H, ^1H correlations used for structural assignment of compounds **10a** and **25**.

Table 4 Reactions of 8-aryl-6-bromo-imidazo[1,2-*a*]pyrazines with aryl boronic acids



6a-7a, 9a-10a **16-30**

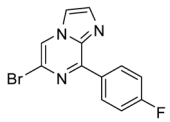
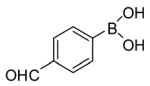
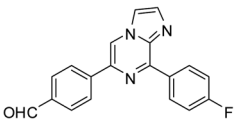
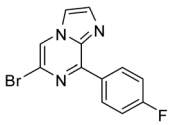
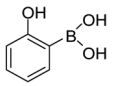
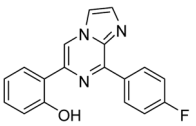
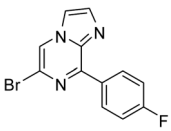
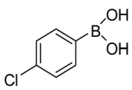
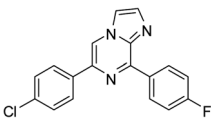
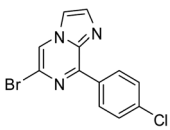
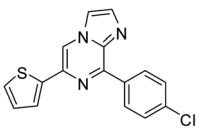
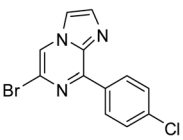
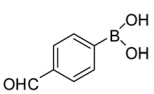
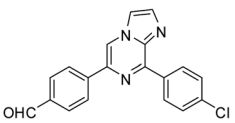
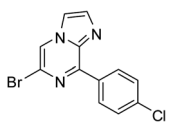
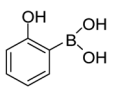
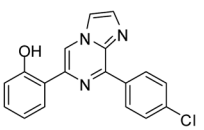
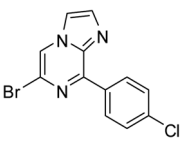
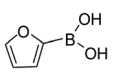
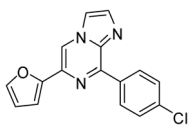
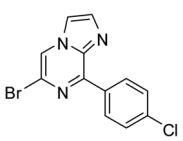
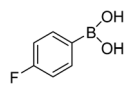
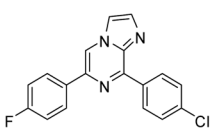
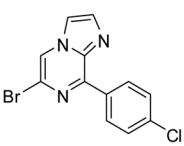
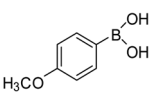
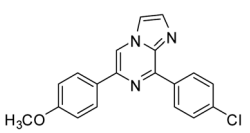
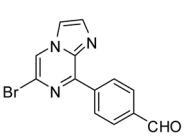
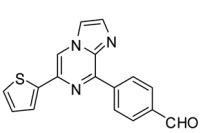
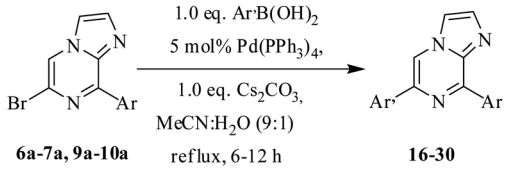
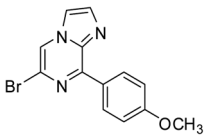
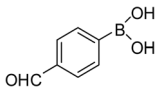
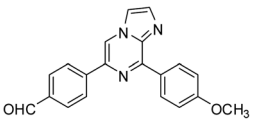
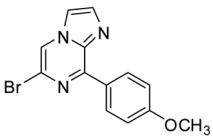
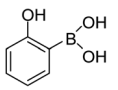
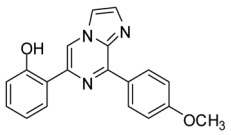
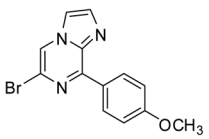
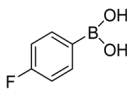
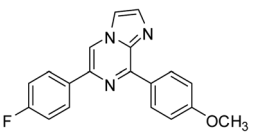
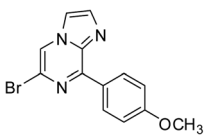
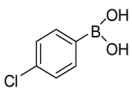
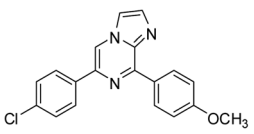
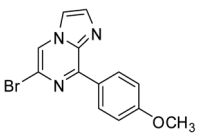
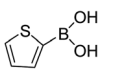
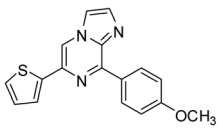
Entry	Time (h)	Monoarylated imidazopyrazine	Ar'B(OH)$_2$	Product	Yield (%)	mp (°C)
1	6				(**16**) 82	208–210
2	7				(**17**) 80	158–160
3	6				(**18**) 62	136–138
4	9				(**19**) 70	135–137
5	8				(**20**) 65	204–207
6	8				(**21**) 68	172–174
7	10				(**22**) 72	159–161
8	7				(**23**) 70	134–135
9	7				(**24**) 74	115–117
10	9				(**25**) 52	165–167

Table 4 (*Contd.*)



6a-7a, 9a-10a 16-30

Entry	Time (h)	Monoarylated imidazopyrazine	Ar'B(OH)$_2$	Product	Yield (%)	mp (°C)
11	7				(**26**) 85	190–192
12	7				(**27**) 75	125–127
13	10				(**28**) 68	108–110
14	10				(**29**) 76	119–121
15	12				(**30**) 70	120–122

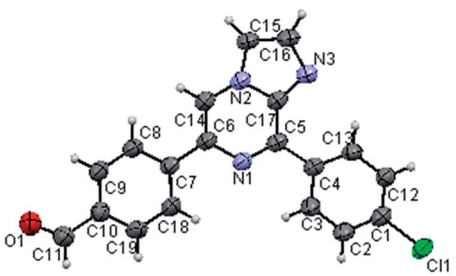


Fig. 3 X-ray structure of **20**.

The structure–activity relationship (SAR) determined from the activity results showed that monoaryl and diaryl imidazo-[1,2-*a*]pyrazines were well tolerated for *in vitro* anticancer activities. (i) The monosubstituted and disubstituted imidazo-[1,2-*a*]pyrazines with variations of different functional groups on the aryl moiety play a key role in varying the efficiency of antitumor activities. (ii) The diaryl imidazo[1,2-*a*]pyrazines positively influence the antitumor effectiveness, inducing better activity than monoaryl imidazo[1,2-*a*]pyrazines against most of the cancer cell lines. (iii) Unsymmetrical diaryl imidazo[1,2-*a*]-pyrazine showed a broader spectrum of antitumor activity than symmetrical diaryl analogues. (iv) Introduction of 2-hydroxy-phenyl (**21**), 2-furanyl (**22**) and 4-fluorophenyl (**23**) at the C6 position with 4-chlorophenyl at the C8 position of imidazo[1,2-*a*]-pyrazine led to a broad spectrum of antitumor activity. Thus 4-chlorophenyl at the C8 position of imidazo[1,2-*a*]pyrazine plays an important role for the activity. (v) The presence of 4-chlor-ophenyl (**19**) and 4-methoxyphenyl (**30**) at the C8 position and 2-thiophene at the C6 position of imidazo[1,2-*a*]pyrazine has slightly improved the activity. (vi) Amongst the symmetrical diaryl analogues, 4-bromophenyl at the C6 and C8 positions of imidazo[1,2-*a*]pyrazine (**8b**) has improved the antitumor activity.

Conclusion

In summary, palladium catalyzed direct C–C coupling has been developed from easily accessible 6,8-dibromo-imidazo[1,2-*a*]-pyrazine, allowing the straightforward functionalization at both C6 and C8 positions to produce a series of monoarylation and

symmetrical diarylation products. In addition, facile access to 8-functionalized imidazo[1,2-*a*]pyrazines were also demonstrated by implementing unsymmetrical diarylation in moderate to high yields. Preliminary analysis of the anticancer activities revealed that unsymmetrical diarylated imidazo[1,2-*a*]pyrazines showed more selectivity than monoarylated and symmetrical diarylated analogues. Compounds **21** and **22** showed a broad spectrum antitumour activities in most of the cancer cell lines amongst these series. Overall, we believe that the developed reaction method and novel series of arylated imidazo[1,2-*a*]-pyrazines should be considered as an important advance in medicinal and pharmaceutical chemistry.

Acknowledgements

KP wishes to thank CSIR, New Delhi (02(0034)/11/EMR-II) for providing funds. RG is indebted to CSIR for SRF (09/677(0020)/2013.EMR-I). We wish to thank IISER, Mohali and Punjab University, Chandigarh for carrying out crystallographic and mass analysis respectively. NCI, USA is greatly acknowledged for anticancer activity studies.

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