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A facile diversity-oriented synthesis of imidazo[1,2-*a*]pyrazinones via gold-catalyzed regioselective heteroannulation of propynylaminopyrazinones

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ABSTRACT

A gold-catalyzed regioselective heteroannulation strategy has been developed for the concise and efficient synthesis of imidazo[1,2-*a*]pyrazinones. The protocol allows the introduction of diversity via the application of substituted propargyl amines or via Suzuki-coupling of the generated imidazo[1,2-*a*]pyrazinones with various (het)aryl boronic acids.

1. Introduction

The imidazo[1,2-*a*]pyrazines[1] and imidazo[1,2-*a*]pyrazine-8(7*H*)-ones[2] constitute important classes of heterocyclic compounds possessing anticancer-,[1c] antiviral-,[1d] GABAA agonist[2a,d] and antiarrhythmic[2e] activities. They are also known to inhibit PI3K,[1b] cyclin-dependent kinase (CDK),[1e] and gastric secretion.[1f] The prevalent synthetic approaches towards imidazo[1,2-*a*]pyrazinones predominantly involve multiple step sequences,[2b,e] harsh conditions[2a] and are limited in scope of substitution pattern[2] of the pyrazinone ring. Consequently, it would be highly desirable to develop more versatile and milder routes for these compounds.

The synthesis of fused heterocycles via transition metal-catalyzed[3] inter/intra-molecular carbocyclization[4] or heteroannulation[5] strategies, utilizing substituted propargyl amines as substrates, has recently attracted considerable attention owing to its selectivity and mild conditions.[6] In view of our long-standing interest in the synthesis and decoration of the pyrazin-2(1*H*)-one scaffold,[7,8] we became interested in exploring the utility of pyrazinones for accessing the imidazo[1,2-*a*]pyrazine-8(7*H*)-one framework. Herein, we report a methodology via a Au-catalyzed heteroannulation of propynylaminopyrazinones (Table 1).

2. Results and discussion

We have recently reported a chemoselective Ag(I)[9]- and Au(I)[10]-catalyzed protocol for the synthesis of pyrazino[2,1-*b*]quinazolines and 3-indolyl- pyrazin-2(1*H*)-ones.[11] Now we were wondering if this Ag-catalyst system could also afford the selective heteroannulation of propynylaminopyrazinones **2a**–**j** into imidazo[1,2-*a*]pyrazinone.

Compounds **2a**–**j** were obtained in one-step by treatment of readily synthesized 3,5-dichloro-pyrazin-2(1*H*)-ones[12] **1a**–**j** with propargyl amine using diisopropylethylamine (DIPEA) as a base in acetonitrile at 70 °C for 8–24 h (Scheme 1).

Subsequently, **2a** was treated at rt with 5 mol % of AgOTf and trifluoroacetic acid (TFA) (2 equiv) in $CDCl_3$. TLC and GC/MS analysis indicated that **2a** was entirely consumed within 60 min and two different products were formed. ^{1}H NMR analysis revealed that the desired imidazo-pyrazinone **3a** was formed in 62% yield via 5-*exo*-dig cyclization (Table 1, entry 1), along with 2*H*-pyrazino[1,2-*a*]-pyrimidine-9(8*H*)-one **4a** in 38% yield.

Encouraged by these initial findings, a detailed optimization study was undertaken. Various transition metal-catalysts and solvents were evaluated (Table 1). Ag(I)-catalysts gave efficient conversions in short reaction times, although they resulted in a poor selectivity towards the desired product (Table 1, entries 1, 4 and 6). On the other hand, the Au(I)- and Au(III)-catalysts afforded higher selectivities, but incomplete conversions, even after prolonged reaction times (Table 1, entries 2, 5 and 8). Similarly, CuCl was not

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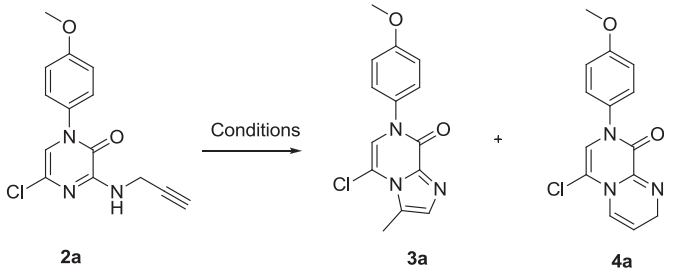
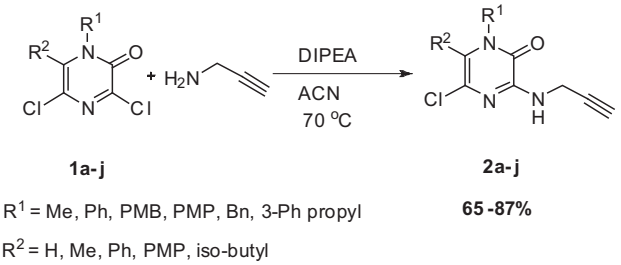
Table 1
Optimization of the heteroannulation of propynyl-aminopyrazinone[a]



Entry	Catalyst (mol %)	Reaction time (h)	Solvent	Conv.	Yield[b] (%) **3a**:**4a**
1	AgOTf (5)	1	$CDCl_3$	100	62:38
2	AuCl (5)	15	$CDCl_3$	81	77:23
3	CuCl (5)	15	$CDCl_3$	41	44:56
4	$AgOCOCF_3$ (5)	1	$CDCl_3$	100	61:39
5	$Au(PPh_3)Cl$ (5)	15	$CDCl_3$	85	91:9
6	$AgSbF_6$ (5)	1	$CDCl_3$	100	62:38
7	$Cu(OTf)_2$ (5)	15	$CDCl_3$	76	82:18
8	$AuCl_3$ (5)	15	$CDCl_3$	79	77:23
9	$Au(PPh_3)OTf$ (5)	1	$CDCl_3$	100	92:8 (90)
10	Au(L)Cl (5)	1	$CDCl_3$	100	93:7
11	$Au(PPh_3)OTf$ (5)[c]	15	$CDCl_3$	16	84:16
12	Au(L)Cl (2)	8	$CDCl_3$	100	93:7
13	$Au(PPh_3)OTf$ (2)	90 min	$CDCl_3$	100	90:10 (87)
14	$Au(PPh_3)OTf$ (1)	15	$CDCl_3$	89	87:13
15	$Au(PPh_3)OTf$ (2)	15	MeOH	29	73:27
16	$Au(PPh_3)OTf$ (2)	15	THF	27	74:26
17	—	48	$CDCl_3$	nd	nd

nd=not detected.
L=2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl.
[a] Unless otherwise stated all reactions were carried out using **2a** (0.2 mmol) and TFA (2 equiv) at rt.
[b] Conversion and ratio of **3a**:**4a** were determined by ^1H NMR. Values in parenthesis represent isolated yields.
[c] Reaction was carried out without TFA.

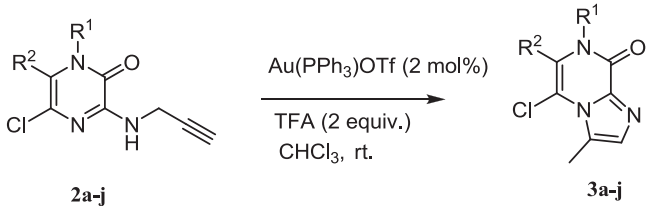


Scheme 1.

found to be effective while $Cu(OTf)_2$ failed to achieve complete conversion (Table 1, entries 3 and 7). Interestingly the cationic gold complex,[10] formed in situ by mixing 5 mol % $Au(PPh_3)Cl$ and 5 mol % AgOTf, dramatically improved the selectivity and also reduced the reaction time (Table 1, entry 9). Importantly, the loading of the above Au-catalyst could be reduced to 2 mol % without a significant loss in reaction performance, upon extending the reaction time to 90 min (Table 1, entry 13). The combination of Au(I)-catalyst with Buchwald phosphine ligand (2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl, X-Phos) was also effective, but the catalyst loading could not be sufficiently reduced in comparison with the cationic gold complex (Table 1, entries 10, 12 and 13). In order to further enhance the reaction performance, different solvents were also evaluated (Table 1, entries 15 and 16), although with little success. A very low conversion or no reaction was observed when the cyclization was carried out without TFA or catalyst (Table 1, entries 11 and 17).

Having established the optimum conditions, the scope and limitations of the process were evaluated. A diverse set of substituted 3-(prop-2-ynylamino)-pyrazin-2(1*H*)-ones (**2a**–**j**) underwent complete conversion at rt to afford the corresponding imidazo[1,2-*a*]pyrazine-8(7*H*)-ones **3a**–**j** in good to excellent yields (Table 2). In the case of 6-methyl substituted pyrazinones (Table 2, **3e**,**h**), an increase in catalyst loading was found to be necessary.

Table 2
Au-catalyzed heteroannulation of propynylamino-pyrazinones[a]



Entry	Product **3**	R^1	R^2	Yield (%)[b]
1	**3a**	*p*-OMe Ph	H	90
2	**3b**	PMB	H	87
3	**3c**	Bn	H	82
4	**3d**	Me	Ph	72
5	**3e**	Ph	Me	71[c]
6	**3f**	*p*-OMe Ph	*p*-OMe Ph	81
7	**3g**	PMB	*i*-Bu	75
8	**3h**	PMB	Me	65[c]
9	**3i**	PMB	*p*-OMe Ph	79
10	**3j**	3-Ph Pr	H	78[c]

[a] Conditions: **2** (0.5 mmol), $Au(PPh_3)Cl$ (2 mol %), AgOTf (2 mol %) and TFA (2 equiv) in $CHCl_3$, rt.
[b] Isolated yields.
[c] $Au(PPh_3)Cl$ (4 mol %) and AgOTf (4 mol %) were used.

In order to further evaluate the utility of the protocol on 3-(prop-2-ynylamino)-pyrazin-2(1*H*)-ones bearing a substituted acetylenic moiety, the corresponding substrates **6a**–**e** were synthesized via Sonogashira-coupling of **2b**–**d**,**f** with various (het)aryl iodides (1.1 equiv) in the presence of $Pd(PPh_3)_2Cl_2$ (2 mol %) and CuI (3 mol %) in a mixture of TEA/DMSO (4:1) at 40 °C for 1 h. Having successfully obtained (het)aryl-(3-phenylprop-2-ynylamino)pyrazin-2(1*H*)-ones **6a**–**e**, we were keen to investigate the subsequent heteroannulation (Table 3). Gratifyingly, high regioselectivity was observed in all cases. However the double bond remains outside the ring with (*Z*)-configuration.[14]

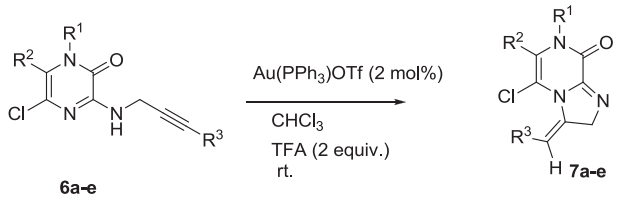
Finally, we became interested to further decorate the synthesized imidazo[1,2-*a*]pyrazine-8(7*H*)-ones using the 5-Cl group as a convenient synthetic handle. It is noteworthy to mention that such Suzuki-coupling could not be performed before the heteroannulation was done.[13] The developed approach (Table 4) proved beneficial, as it allowed to install diversity on both 5- and 6-position of the imidazo[1,2-*a*]pyrazin-8(7*H*)-one skeleton, which is rather difficult to achieve otherwise.[2]

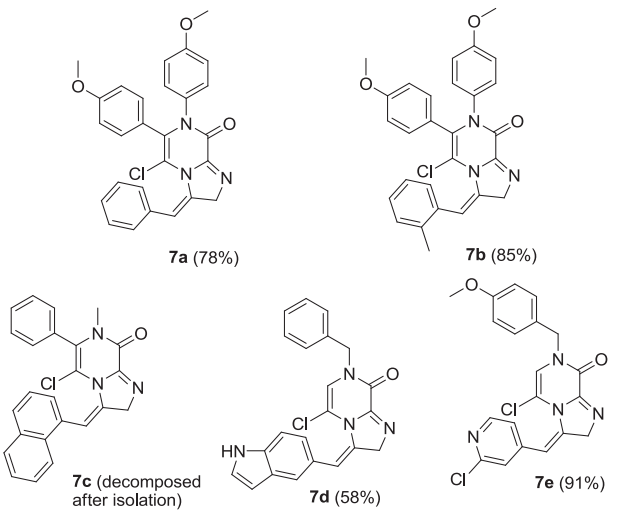
A plausible mechanism for the cationic gold-catalyzed 5-*exo* dig heteroannulation is depicted in Scheme 2. Nucleophilic attack of nitrogen on the activated alkyne generates intermediate **B**, which on subsequent deprotonation and protodeauration produces **7**. However, in case of terminal alkyne, 1,3-proton shift led to product **3**.

3. Conclusion

We have developed an efficient and mild approach for the synthesis of biologically important (dihydro)imidazo[1,2-*a*]pyrazin-8(7*H*)-one via a cationic gold-catalyzed regioselective 5-*exo* dig heteroannulation strategy. Low catalyst loading, good to excellent yields and tolerance towards a variety of functional groups

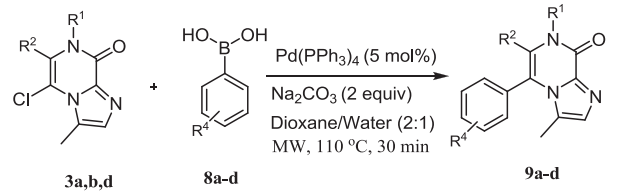
Table 3
Au-catalyzed heteroannulation approach towards dihydroimidazo[1,2-*a*] pyrazinone[a]





[a] Conditions: **6** (0.5 mmol), $Au(PPh_3)Cl$ (2 mol%), AgOTf (2 mol%) and TFA (2 equiv) in $CHCl_3$, rt. Isolated yields.

Table 4
Synthesis of polysubstituted imidazo[1,2,*a*]pyrazin-8(7*H*)-one[a]



Entry	Product **9**	R^1	R^2	R^3	Yield (%)[b]
1	**9a**	*p*-OMe Ph	H	*p*-Tolyl	94
2	**9b**	*p*-OMe Ph	H	Ph	75
3	**9c**	Me	Ph	*m*-Cl Ph	60
4	**9d**	PMB	H	3-Thiophene	89

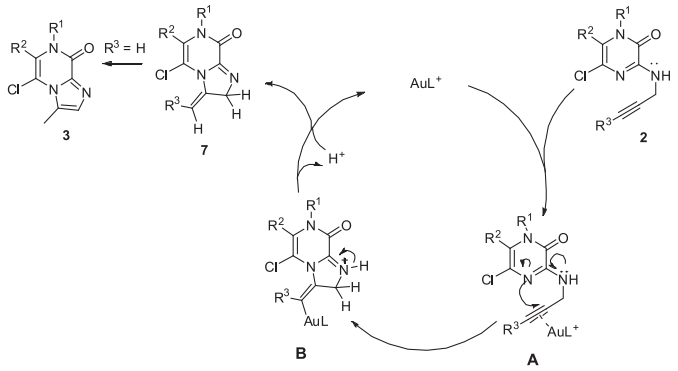
[a] Conditions: **3** (0.5 mmol), **8** (1.5 equiv), Na_2CO_3 (2 equiv), $Pd(PPh_3)_4$ (5 mol %), dioxane/water (2:1) 2 mL, 110 °C, MW, 30 min.
[b] Isolated yields.

are the merits of this protocol. Importantly, the above heteroannulation also allowed installation of further diversity via Suzuki-coupling, thereby, furnishing a convenient access to polysubstituted imidazo[1,2-*a*]pyrazine-8(7*H*)-ones.

4. Experimental section

4.1. General

NMR spectra were recorded on a Bruker Avance 300 MHz instrument using $CDCl_3$ or DMSO-d_6 as solvent unless otherwise stated. The ^1H and ^{13}C NMR chemical shifts are reported in parts per million relative to tetramethylsilane using the residual solvent signal as an internal reference. Mass spectra were recorded by using a Kratos MS50TC and a Kratos Mach III system. The ion source temperature was 150–250 °C, as required. High-resolution electron impact (EI) mass spectra were performed with a resolution of 10,000. The low-resolution spectra were obtained with a HP5989A MS instrument. For, TLC, analytical TLC plates (Alu-gram SIL G/UV254) and 70–230 mesh silica gel (E.M. Merck) were used.



Scheme 2. Plausible mechanism for the gold-catalyzed regioselective 5-*exo* dig heteroannulation.

4.2. Microwave irradiation experiments

All microwave irradiation experiments were carried out in a dedicated CEM-Discover monomode microwave apparatus, operating at a frequency of 2.45 GHz with continuous irradiation of 300 W maximum power. The reactions were carried out in 10 mL glass tubes, sealed with a Teflon septum and placed in the microwave cavity. Initially, microwave irradiation of required watts was used and the temperature was ramped from room temperature to the desired temperature. Once this was reached the reaction mixture was held at this temperature for the required time. The reaction mixture was continuously stirred with magnetic stirring during the reaction. The temperature was measured with an IR sensor on the outer surface of the process vial. After irradiation, air jet cooling cooled the reaction vessel rapidly to ambient temperature.

4.3. General procedure for the synthesis of 3-(prop-2-ynylamino)pyrazin-2(1*H*)-ones (2a–j)

To a solution of substituted 3,5-dichloro-pyrazine-2(1*H*)-one **1** (2 mmol) in THF (25 mL) were added propargyl amine (1.5 equiv) and diisopropylethylamine (DIPEA) (2 equiv). The reaction mixture was stirred at 70 °C for 8–24 h. After completion, THF was distilled under reduced pressure and the mixture was partitioned between ethyl acetate (2×50 mL) and water (50 mL). The organic layer was separated, washed with brine and dried over $MgSO_4$. The solvent was distilled off and the residue was subjected to silica gel chromatography (30–60% ethyl acetate in heptane) to afford compound **2a–j**.

*4.3.1. 5-Chloro-1-(4-methoxyphenyl)-3-(prop-2-ynylamino)pyrazin-2(1H)-one (**2a**).* White solid, mp 170–172 °C, yield 84%, ^1H NMR (300 MHz, $CDCl_3$): δ 7.30 (d, J=8.85 Hz, 2H), 6.99 (d, J=8.85 Hz, 2H), 6.68 (s, 1H), 6.52 (bs, 1H), 4.26 (dd, J=2.39, 5.63 Hz, 2H), 3.85 (s, 3H), 2.28 (t, J=2.39 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.4, 144.8, 144.5, 126.4, 121.5, 121.3, 109.4, 109.1, 73.7, 66.7, 50.3, 25.6. HRMS (EI): calcd for $C_{14}H_{12}ClN_3O_2$: 289.0618, found: 289.0591.

*4.3.2. 5-Chloro-1-(4-methoxybenzyl)-3-(prop-2-ynylamino)pyrazin-2(1H)-one (**2b**).* White solid, mp 197–199 °C, yield 87%, ^1H NMR (300 MHz, $CDCl_3$): δ 7.28–7.20 (m, 2H), 6.88 (d, J=8.49 Hz, 2H), 6.52 (s, 1H), 6.44 (bs, 1H), 4.94 (s, 2H), 4.21 (dd, J=2.39, 5.57 Hz, 2H), 3.80

(s, 3H), 2.26 (t, *J*=2.40 Hz, 1H). HRMS (EI): calcd for $C_{15}H_{14}ClN_3O_2$: 303.0775, found: 303.0771.

*4.3.3. 1-Benzyl-5-chloro-3-(prop-2-ynylamino)pyrazin-2(1H)-one (**2c**).* White solid, mp 170–172 °C, yield 67%, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41–7.24 (m, 5H), 6.54 (s, 1H), 6.46 (bs, 1H), 5.01 (s, 2H), 4.26–4.16 (m, 2H), 2.27 (bs, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 149.6, 149.5, 136.0, 128.6, 127.9, 127.8, 124.8, 113.7, 80.7, 72.6, 51.0, 29.7. HRMS (EI): calcd for $C_{14}H_{12}ClN_3O$: 273.0669, found: 273.0668.

*4.3.4. 5-Chloro-1-methyl-6-phenyl-3-(prop-2-ynylamino)pyrazin-2(1H)-one (**2d**).* White solid, mp 119–121 °C, yield 78%, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60–7.45 (m, 3H), 7.33–7.28 (m, 2H), 6.41 (b, 1H), 4.27 (q, *J*=2.4 Hz, 2H), 3.22 (s, 3H), 2.28 (t, *J*=2.3 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 151.0, 148.2, 132.2, 130.2, 129.4, 129.0, 125.7, 124.8, 79.2, 71.8, 34.2, 30.7. HRMS (EI): calcd for $C_{14}H_{12}ClN_3O$: 273.0669, found: 273.0680.

*4.3.5. 5-Chloro-6-methyl-1-phenyl-3-(prop-2-ynylamino)pyrazin-2(1H)-one (**2e**).* Off white solid, mp 165–167 °C, yield 79%, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59–7.44 (m, 3H), 7.17 (d, *J*=7.17 Hz, 2H), 6.23 (bs, 1H), 4.25 (dd, *J*=2.27, 5.67 Hz, 2H), 2.26 (t, *J*=2.40 Hz, 1H), 1.94 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 151.4, 147.8, 137.4, 129.9, 129.3, 127.4, 124.9, 120.5, 79.4, 71.6, 30.6, 16.9. HRMS (EI): calcd for $C_{14}H_{12}ClN_3O$: 273.0669, found: 273.0662.

*4.3.6. 5-Chloro-1,6-bis(4-methoxyphenyl)-3-(prop-2-ynylamino) pyrazin-2(1H)-one (**2f**).* Light yellow solid, mp 137–139 °C, yield 79%, ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.99 (d, *J*=8.46 Hz, 2H), 6.90 (d, *J*=8.85 Hz, 2H), 6.80–6.65 (m, 4H), 6.47 (t, *J*=5.57 Hz, 1H), 4.31 (dd, *J*=2.24, 5.75 Hz, 2H), 3.73 (s, 3H), 2.30 (bs, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.2, 159.0, 151.3, 148.7, 132.3, 130.1, 129.1, 126.0, 125.1, 124.5, 114.2, 113.4, 79.3, 71.8, 55.3, 55.1, 30.7. HRMS (EI): calcd for $C_{21}H_{18}ClN_3O_3$: 395.1037, found: 395.1030.

*4.3.7. 5-Chloro-6-isobutyl-1-(4-methoxybenzyl)-3-(prop-2-ynylamino)pyrazin-2(1H)-one (**2g**).* Orange viscous liquid, yield 72%, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.04 (d, *J*=8.49 Hz, 2H), 6.84 (d, *J*=8.49 Hz, 2H), 6.25 (t, *J*=5.11 Hz, 1H), 5.21 (s, 2H), 4.22 (dd, *J*=2.42, 5.42 Hz, 2H), 3.78 (s, 3H), 2.55 (d, *J*=7.35 Hz, 2H), 2.26 (t, *J*=2.44 Hz, 1H), 2.01–1.86 (m, 1H), 0.99 (d, *J*=6.78 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.1, 151.6, 147.6, 127.8, 127.6, 126.8, 123.5, 114.3, 79.5, 71.7, 55.2, 47.5, 37.2, 30.6, 29.1, 22.3. HRMS (EI): calcd for $C_{19}H_{22}ClN_3O_2$: 359.1401, found: 359.1388.

*4.3.8. 5-Chloro-1-(4-methoxybenzyl)-6-methyl-3-(prop-2-ynylamino)pyrazin-2(1H)-one (**2h**).* White solid, mp 121–123 °C, yield 70%, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.10 (d, *J*=8.10 Hz, 2H), 6.85 (d, *J*=8.10 Hz, 2H), 6.25 (bs, 1H), 5.21 (s, 2H), 4.21 (d, *J*=3.03 Hz, 2H), 3.78 (s, 3H), 2.31–2.25 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.2, 151.5, 147.5, 128.1, 127.2, 125.5, 120.5, 114.3, 79.4, 71.7, 55.3, 47.9, 30.7, 15.6. HRMS (EI): calcd for $C_{16}H_{16}ClN_3O_2$: 317.0931, found: 317.0932.

*4.3.9. 5-Chloro-1-(4-methoxybenzyl)-6-(4-methoxyphenyl)-3-(prop-2-ynylamino)pyrazin-2(1H)-one (**2i**).* Yellow solid, mp 113–115 °C, yield 81%, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.01 (d, *J*=8.46 Hz, 2H), 6.89 (d, *J*=8.49 Hz, 2H), 6.81–6.67 (m, 4H), 6.45 (t, *J*=5.25 Hz, 1H), 4.94 (s, 2H), 4.27 (dd, *J*=2.37, 5.45 Hz, 2H), 3.85 (s, 3H), 3.75 (s, 3H), 2.29 (bs, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.1, 159.0, 151.1, 148.6, 132.1, 128.6, 127.8, 126.6, 124.4, 124.0, 113.9, 113.6, 79.2, 71.8, 55.3, 55.2, 48.8, 30.7. HRMS (EI): calcd for $C_{22}H_{20}ClN_3O_3$: 409.1193, found: 409.1200.

*4.3.10. 5-Chloro-1-(3-phenylpropyl)-3-(prop-2-ynylamino)pyrazin-2(1H)-one (**2j**).* Light yellow solid, mp 91–93 °C, yield 65%, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34–7.13 (m, 5H), 6.48 (s, 1H), 6.42 (bs, 1H), 4.20 (d, *J*=4.46 Hz, 2H), 3.84 (t, *J*=7.22 Hz, 2H), 2.68 (t, *J*=7.52 Hz, 2H), 2.27 (bs, 1H), 2.14–2.01 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 150.0, 149.4, 140.2, 128.5, 128.2, 126.5, 126.3, 113.3, 79.0, 71.9, 48.8, 32.6, 30.7, 29.7. HRMS (EI): calcd for $C_{16}H_{16}ClN_3O$: 301.0982, found: 301.0974.

4.4. General procedure for the synthesis of substituted imidazo[1,2-*a*]pyrazin-8(7*H*)-ones (3a–j)

To an oven dried 10 mL screw cap vial equipped with a stir-bar and charged with **2** (0.5 mmol, 1 equiv) was added silver triflate (2 mol %), Au(PPh$_3$)Cl (2 mol %) and Trifluoroacetic acid (2 equiv). Dry $CHCl_3$ (2 mL) was added by syringe and the reaction was allowed to stir at rt. After completion of the reaction as indicated by TLC analysis, a saturated solution of K_2CO_3 (5 mL) was added and the mixture was stirred for 5 min more. The resulting mixture was diluted with ethyl acetate (50 mL) and washed with water (50 mL) and brine (50 mL). The organic phase was dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude sample was purified by silica gel column chromatography (5–20% diethylether in dichloromethane) to obtain compounds **3a**–**j**.

*4.4.1. 5-Chloro-7-(4-methoxyphenyl)-3-methylimidazo[1,2-a]pyrazin-8(7H)-one (**3a**).* White solid, mp 197–199 °C, yield 87%, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35–7.28 (m, 3H), 6.99 (d, *J*=8.85 Hz, 2H), 6.77 (s, 1H), 3.84 (s, 3H), 2.72 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.5, 152.2, 138.2, 133.5, 131.5, 128.0, 127.5, 118.8, 114.7, 109.5, 55.6, 12.6. HRMS (EI): calcd for $C_{14}H_{12}ClN_3O_2$: 289.0618, found: 289.0619.

*4.4.2. 5-Chloro-7-(4-methoxybenzyl)-3-methylimidazo[1,2-a]pyrazin-8(7H)-one (**3b**).* White solid, mp 241–242 °C, yield 87%, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31–7.22 (m, 2H), 6.88 (d, *J*=8.64 Hz, 1H), 6.53 (s, 1H), 5.05 (s, 2H), 3.80 (s, 3H), 2.66 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.7, 152.6, 138.2, 133.3, 129.9, 127.8, 127.6, 116.8, 114.4, 109.6, 55.3, 49.7, 12.6. HRMS (EI): calcd for $C_{15}H_{14}ClN_3O_2$: 303.0775, found: 303.0775.

*4.4.3. 7-Benzyl-5-chloro-3-methylimidazo[1,2-a]pyrazin-8(7H)-one (**3c**).* White solid, mp 167–169 °C, yield 82%, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40–7.30 (m, 4H), 7.29–7.24 (m, 1H), 5.12 (s, 2H), 2.67 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 152.6, 138.1, 135.6, 133.3, 129.0, 128.4, 128.3, 127.8, 117.0, 109.7, 50.2, 12.6. HRMS (EI): calcd for $C_{14}H_{12}ClN_3O$: 273.0669, found: 273.0673.

*4.4.4. 5-Chloro-3,7-dimethyl-6-phenylimidazo[1,2-a]pyrazin-8(7H)-one (**3d**).* White solid, mp 242–243 °C, yield 72%, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59–7.49 (m, 3H), 7.38–7.27 (m, 3H), 3.20 (s, 3H), 2.70 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.3, 137.7, 133.4, 131.7, 129.9, 129.8, 129.3, 128.9, 128.0, 109.1, 33.5, 13.3. HRMS (EI): calcd for $C_{14}H_{12}ClN_3O$: 273.0669, found: 273.0683.

*4.4.5. 5-Chloro-3,6-dimethyl-7-phenylimidazo[1,2-a]pyrazin-8(7H)-one (**3e**).* White solid, mp 181–183 °C, yield 71%, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.56–7.42 (m, 3H), 7.28 (s, 1H), 7.25–7.18 (m, 2H), 2.74 (s, 3H), 2.01 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.1, 137.5, 137.4, 133.5, 129.8, 129.2, 128.5, 128.0, 124.5, 108.0, 17.3, 13.6. HRMS (EI): calcd for $C_{14}H_{12}ClN_3O$: 273.0669, found: 273.0645.

*4.4.6. 5-Chloro-6,7-bis(4-methoxyphenyl)-3-methylimidazo[1,2-a]pyrazin-8(7H)-one (**3f**).* White solid, mp 201–203 °C, yield 81%, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33 (s, 1H), 7.03 (d, *J*=8.85 Hz, 2H), 6.93 (d, *J*=8.85 Hz, 2H), 6.77–6.68 (m, 4H), 3.75 (s, 3H), 3.72 (s, 3H), 2.74 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.6, 158.9, 153.3, 137.9, 133.7, 132.0, 130.1 (2), 129.3, 128.4, 123.8, 114.1, 113.7, 109.4, 55.3, 55.1, 13.5. HRMS (EI): calcd for $C_{21}H_{18}ClN_3O_3$: 395.1037, found: 395.1037.

*4.4.7. 5-Chloro-6-isobutyl-7-(4-methoxybenzyl)-3-methylimidazo [1,2-a]pyrazin-8(7H)-one (**3g**).* Off white solid, mp 116–118 °C, yield

75%, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.27 (s, 1H), 7.10 (d, *J*=8.49 Hz, 2H), 6.82 (d, *J*=8.46 Hz, 2H), 5.31 (s, 2H), 3.76 (s, 3H), 2.71 (s, 3H), 2.61 (d, *J*=7.35 Hz, 2H), 2.09–1.94 (m, 1H), 1.03 (d, *J*=6.60 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.0, 153.8, 137.4, 133.6, 128.5, 128.0, 127.9, 127.2, 114.2, 109.5, 55.2, 46.2, 36.6, 28.9, 22.2, 13.7. HRMS (EI): calcd for $C_{19}H_{22}ClN_3O_2$: 359.1401, found: 359.1404.

*4.4.8. 5-Chloro-7-(4-methoxybenzyl)-3,6-dimethylimidazo[1,2-a]pyrazin-8(7H)-one (**3h**).* Off white solid, mp 116–119 °C, yield 65%, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.27 (s, 1H), 7.16 (d, *J*=8.28 Hz, 2H), 6.83 (d, *J*=8.46 Hz, 2H), 5.30 (s, 2H), 3.77 (s, 3H), 2.70 (s, 3H), 2.35 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.1, 153.6, 137.3, 133.5, 128.3, 128.1, 127.8, 124.4, 114.2, 108.1, 55.3, 46.8, 15.6, 13.6. HRMS (EI): calcd for $C_{16}H_{16}ClN_3O_2$: 317.0931, found: 317.0927.

*4.4.9. 5-Chloro-7-(4-methoxybenzyl)-6-(4-methoxyphenyl)-3-methylimidazo[1,2-a]pyrazin-8(7H)-one (**3i**).* Light yellow solid, mp 204–205 °C, yield 79%, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31 (s, 1H), 6.99 (d, *J*=8.34 Hz, 2H), 6.92 (d, *J*=8.67 Hz, 2H), 6.77 (d, *J*=8.67 Hz, 2H), 6.67 (d, *J*=8.67 Hz, 2H), 4.99 (s, 2H), 3.87 (s, 3H), 3.74 (s, 3H), 2.68 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.5, 158.9, 153.5, 137.9, 133.6, 131.8, 128.9, 128.8, 128.5, 128.1, 123.3, 114.1, 113.6, 109.8, 55.4, 55.2, 47.7, 13.4. HRMS (EI): calcd for $C_{22}H_{20}ClN_3O_3$: 409.1193, found: 409.1181.

*4.4.10. 5-Chloro-3-methyl-7-(3-phenylpropyl)-imidazo[1,2-a]pyrazin-8(7H)-one (**3j**).* White solid, mp 114–116 °C, yield 78%, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30–7.24 (m, 3H), 7.21–7.15 (m, 3H), 6.49 (s, 1H), 3.94 (t, *J*=7.33 Hz, 2H), 2.70 (t, *J*=7.54 Hz, 2H), 2.67 (s, 3H), 2.15–2.05 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 152.5, 140.5, 138.2, 133.2, 128.4, 128.2, 127.7, 126.1, 117.6, 109.2, 47.6, 32.7, 30.2, 12.6. HRMS (EI): calcd for $C_{16}H_{16}ClN_3O$: 301.0982, found: 301.0983.

4.5. General procedure for the synthesis of 3-(prop-2-ynylamino)pyrazin-2(1*H*)-ones (6a–e)

An oven dried 25 mL two necked flask equipped with a stir-bar was charged with **2** (0.7 mmol, 1 equiv), (het)aryl iodide **5** (0.77 mmol, 1.1 equiv), $PdCl_2(PPh_3)_2$ (2 mol %) and CuI (3 mol %) under argon. The flask was evacuated and filled back with argon (× three times). Dry TEA/DMSO (4:1) (10 mL) was added by syringe and suspension was allowed to stir at 45 °C for 30 min. After the completion of reaction as indicated by TLC and MS analysis, the mixture was cooled to room temperature. The crude mixture was diluted with ethyl acetate (50 mL) and organic phase was washed with H_2O (50 mL) and brine (50 mL). The organic phase was dried over anhydrous $MgSO_4$, filtered and was concentrated under reduced pressure. The crude sample was purified by silica gel column chromatography (5–10% diethylether in DCM) to obtain compound **6a–e**.

*4.5.1. 5-Chloro-1,6-bis(4-methoxyphenyl)-3-(3-phenylprop-2-ynylamino)pyrazin-2(1H)-one (**6a**).* Off white solid, mp 179–181 °C, yield 89%, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.48–7.40 (m, 2H), 7.35–7.28 (m, 3H), 6.99 (d, *J*=8.67 Hz, 2H), 6.91 (d, *J*=9.03 Hz, 2H), 6.78–6.67 (m, 4H), 6.52 (t, *J*=5.27 Hz, 1H), 4.53 (d, *J*=5.46 Hz, 2H), 3.76–3.69 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.2, 159.0, 151.3, 148.7, 132.3, 131.7, 130.1, 129.1, 128.4, 128.3, 126.1, 124.9, 124.5, 122.6, 114.1, 113.4, 84.6, 83.5, 55.3, 55.0, 31.5. HRMS (EI): calcd for $C_{27}H_{22}ClN_3O_3$: 471.1350, found: 471.1350.

*4.5.2. 5-Chloro-1,6-bis(4-methoxyphenyl)-3-(3-o-tolylprop-2-ynylamino)pyrazin-2(1H)-one (**6b**).* White solid, mp 168–170 °C, yield 90%, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42 (d, *J*=7.32 Hz, 1H), 7.24–7.09 (m, 3H), 7.00 (d, *J*=8.67 Hz, 2H), 6.91 (d, *J*=8.85 Hz, 2H) 6.78–6.67 (m, 4H), 6.53 (t, *J*=5.32 Hz, 1H), 4.57 (d, *J*=5.46 Hz, 2H), 3.76–3.69 (m, 6H), 2.44 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.2, 159.0, 151.4, 148.7, 140.4, 132.3, 132.1, 130.1, 129.4, 129.1, 128.4, 126.1, 125.5, 124.9, 124.5, 122.3, 114.2, 113.4, 88.3, 82.5, 55.3, 55.1, 31.8, 20.7. HRMS (EI): calcd for $C_{28}H_{24}ClN_3O_3$: 485.1506, found: 485.1513.

*4.5.3. 5-Chloro-1-methyl-3-(3-(naphthalen-1-yl)prop-2-ynylamino)-6-phenylpyrazin-2(1H)-one (**6c**).* White solid, mp 172–174 °C, yield 80%, ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.36 (d, *J*=8.10 Hz, 1H), 7.88–7.78 (m, 2H), 7.68 (d, *J*=6.96 Hz, 1H), 7.62–7.38 (m, 6H), 7.34–7.28 (m, 2H), 6.60 (bs, 1H), 4.64 (d, *J*=5.46 Hz, 2H), 3.23 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 151.1, 148.3, 133.4, 133.0, 132.2, 130.6, 130.2, 129.3, 128.9, 128.8, 128.1, 126.8, 126.4, 126.2, 125.9, 125.1, 124.7, 120.2, 89.5, 81.5, 34.2, 31.8. HRMS (EI): calcd for $C_{24}H_{18}ClN_3O$: 399.1139, found: 399.1149.

*4.5.4. 3-(3-(1H-indol-5-yl)prop-2-ynylamino)-1-benzyl-5-chloropyrazin-2(1H)-one (**6d**).* Light yellow solid, mp 160–162 °C, yield 78%, ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.21 (s, 1H), 7.76 (s, 1H), 7.41–7.17 (m, 8H), 6.61–6.48 (m, 3H), 5.02 (s, 2H), 4.45 (d, *J*=5.10 Hz, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 149.7, 149.6, 136.1, 135.4, 128.6, 127.9, 127.8, 127.4, 126.4, 125.0, 124.3, 123.7, 113.5, 112.3, 111.6, 101.2, 83.3, 83.2, 51.0, 30.6. HRMS (EI): calcd for $C_{22}H_{17}ClN_4O$: 388.1091, found: 388.1079.

*4.5.5. 5-Chloro-3-(3-(2-chloropyridin-4-yl)prop-2-ynylamino)-1-(4-methoxybenzyl)pyrazin-2(1H)-one (**6e**).* Light yellow solid, mp 142–144 °C, yield 92%, ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.34 (d, *J*=5.09 Hz, 1H), 7.33 (s, 1H), 7.30–7.17 (m, 3H), 6.89 (d, *J*=8.10 Hz, 2H), 6.60–6.45 (m, 2H), 4.96 (s, 2H), 4.46 (d, *J*=5.28 Hz, 2H), 3.80 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.8, 151.6, 150.1, 149.5, 149.4, 133.6, 129.9, 126.6 (2), 126.2, 124.4, 114.4, 113.0, 91.1, 79.8, 55.3, 51.5, 31.3. HRMS (EI): calcd for $C_{20}H_{16}Cl_2N_4O_2$: 414.0650, found: 414.0666.

4.6. General procedure for the synthesis of dihydroimidazo[1,2-*a*]pyrazin-8(7*H*)-ones (7a–e)

To an oven dried 10 mL screw cap vial equipped with a stir-bar and charged with **6** (0.5 mmol, 1 equiv) was added silver triflate (2 mol %), Au(PPh_3)Cl (2 mol %) and Trifluoroacetic acid (2 equiv). Dry $CHCl_3$ (2 mL) was added by syringe and the reaction was allowed to stir at rt. After completion of the reaction as indicated by TLC analysis, a saturated solution of K_2CO_3 (5 mL) was added and the mixture was stirred for 5 min more. The resulting mixture was diluted with ethyl acetate (50 mL) and washed with water (50 mL) and brine (50 mL). The organic phase was dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude sample was purified by silica gel column chromatography (5–20% diethylether in DCM) to obtain compounds **7a–e**.

*4.6.1. (Z)-3-Benzylidene-5-chloro-6,7-bis(4-methoxyphenyl)-2,3-dihydroimidazo[1,2-a]pyrazin-8(7H)-one (**7a**).* Off white solid, mp 212–214 °C, yield 78%, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50–7.33 (m, 5H), 7.09 (d, *J*=8.46 Hz, 2H), 6.98 (d, *J*=8.28 Hz, 2H), 6.76 (d, *J*=8.49 Hz, 2H), 6.66 (d, *J*=8.28 Hz, 2H), 5.23 (s, 1H), 4.31 (s, 2H), 3.73 (s, 3H), 3.70 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.2, 158.5, 157.1, 146.7, 138.6, 134.7, 132.0, 130.3, 129.3, 128.8, 128.7, 126.1, 123.9, 123.2, 113.9 (2), 113.3, 107.6, 55.2, 55.0, 46.4. HRMS (EI): calcd for $C_{27}H_{22}ClN_3O_3$: 471.1350, found: 471.1353.

*4.6.2. (Z)-5-Chloro-6,7-bis(4-methoxyphenyl)-3-(2-methylbenzylidene)-2,3-dihydroimidazo[1,2-a]pyrazin-8(7H)-one (**7b**).* Light yellow solid, mp 100–102 °C, yield 85%, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36–7.18 (m, 5H), 7.01 (d, *J*=8.64 Hz, 2H), 6.91 (d, *J*=8.46 Hz, 2H), 6.73 (d, *J*=8.67 Hz, 2H), 6.63 (d, *J*=8.49 Hz, 2H), 5.08 (t, *J*=4.33 Hz, 1H), 4.32 (d, *J*=3.51 Hz, 2H), 3.71 (s, 3H), 3.68 (s, 3H), 2.35 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.2, 158.5, 156.8, 146.5, 138.7, 135.8, 134.3, 132.0, 130.6, 130.3, 130.0, 129.2, 128.9, 126.0, 123.9, 123.1,

113.9, 113.8, 113.3, 108.3, 55.2, 55.0, 46.4, 19.2. HRMS (EI): calcd for $C_{28}H_{24}ClN_3O_3$: 485.1506, found: 485.1496.

*4.6.3. (Z)-3-((1H-Indol-5-yl)methylene)-7-benzyl-5-chloro-2,3-dihydroimidazo[1,2-a]pyrazin-8(7H)-one (**7d**).* Light brown solid, mp>300 °C, yield 58%, ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.23 (s, 1H), 7.51–7.30 (m, 8H), 6.97 (d, J=8.10 Hz, 1H), 6068 (s, 1H), 6.41 (s, 1H), 5.18 (s, 1H), 4.95 (s, 2H), 4.04 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 155.3, 146.2, 139.2, 136.5, 135.8, 128.6, 128.0, 127.7, 127.6, 127.5, 126.4, 125.1, 119.4, 117.8, 113.2, 111.6, 105.7, 101.4, 49.8, 45.5. HRMS (EI): calcd for $C_{22}H_{17}ClN_4O$: 388.1091, found: 388.1087.

*4.6.4. (Z)-5-Chloro-3-((2-chloropyridin-4-yl)methylene)-7-(4-methoxybenzyl)-2,3-dihydroimidazo[1,2-a]pyrazin-8(7H)-one (**7e**).* White solid, mp 151–153 °C, yield 91%, ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.31 (d, J=5.16 Hz, 1H), 7.35 (s, 1H), 7.30 (d, J=8.28 Hz, 2H), 7.05 (s, 1H), 6.96 (d, J=4.62 Hz, 1H), 6.89 (d, J=8.10 Hz, 2H), 6.56 (s, 1H), 5.06 (s, 2H), 4.44 (s, 2H), 3.80 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.8, 152.4, 152.1, 150.5, 150.0, 139.2, 134.9, 130.1, 127.2, 126.9, 123.7, 122.1, 117.6, 114.4, 108.7, 55.3, 49.9, 31.0. HRMS (EI): calcd for $C_{20}H_{16}Cl_2N_4O_2$: 414.0650, found: 414.0650.

4.7. General procedure for the synthesis of polysubstituted imidazo[1,2-*a*]pyrazine-8(7*H*)-one via Suzuki-coupling (9a–d)

In a 10 mL reaction vial charge with compound **3** (0.5 mmol, 1 equiv) was added boronic acid **8** (0.75 mmol, 1.5 equiv), $Pd(PPh_3)_4$ (0.025 mmol, 5 mol %) and Na_2CO_3 (1.0 mmol, 2 equiv). Then water/dioxane (2:1) 2 mL was added and the vial was sealed tightly with Teflon cap. The mixture was irradiated for 30 min at a preselected temperature of 110 °C, with maximum irradiation power of 300 W. After the completion of reaction as monitored by TLC and MS analysis, the resulting crude mixture was added water (50 mL) and extracted with ethyl acetate (2×50 mL). The combined organic layer was washed with brine (50 mL) and dried over $MgSO_4$. After filtration, solvent was evaporated under reduced pressure and crude product was subjected to silica gel column chromatography (20% diethylether in DCM) to afford corresponding compounds **9a–d.**

*4.7.1. 7-(4-Methoxyphenyl)-3-methyl-5-p-tolylimidazo[1,2-a]pyrazin-8(7H)-one (**9a**).* White solid, mp 263–265 °C, yield 94%, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41–7.31 (m, 4H), 7.29–7.24 (m, 2H), 6.98 (d, J=8.67 Hz, 2H), 6.56 (s, 1H), 3.83 (s, 3H), 2.43 (s, 3H), 1.80 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.2, 152.9, 140.0, 138.0, 133.3, 132.2, 130.7, 129.1, 127.8, 127.5, 127.2, 120.1 (2), 114.5, 55.5, 21.4, 12.3. HRMS (EI): calcd for $C_{21}H_{19}ClN_3O_2$: 345.1477, found: 345.1479.

*4.7.2. 7-(4-Methoxyphenyl)-3-methyl-5-phenylimidazo[1,2-a]pyrazin-8(7H)-one (**9b**).* White solid, mp>300 °C, yield 75%, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.56–7.42 (m, 5H), 7.38 (d, J=8.10 Hz, 2H), 7.28 (s, 1H), 6.98 (d, J=8.10 Hz, 2H), 6.60 (s, 1H), 3.83 (s, 3H), 1.79 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.2, 152.9, 138.1, 133.4, 132.2, 130.8, 129.8, 128.5, 128.4, 127.6, 127.1, 120.2, 120.0, 114.6, 55.5, 12.3. HRMS (EI): calcd for $C_{20}H_{17}ClN_3O_2$: 331.1321, found: 331.1320.

*4.7.3. 5-(3-Chlorophenyl)-3,7-dimethyl-6-phenylimidazo[1,2-a]pyrazin-8(7H)-one (**9c**).* White solid, mp>300 °C, yield 60%, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34 (m, 10H), 3.23 (s, 3H), 1.63 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.9, 137.4, 133.9, 133.4, 133.1, 132.1, 131.8, 130.6, 130.5, 130.4, 129.3, 129.2, 129.1, 128.7, 128.5, 126.7, 117.3, 32.9, 12.2. HRMS (EI): calcd for $C_{20}H_{16}ClN_3O$: 349.0982, found: 349.0973.

*4.7.4. 7-(4-Methoxybenzyl)-3-methyl-5-(thiophen-3-yl)imidazo[1,2-a]pyrazin-8(7H)-one (**9d**).* Grey solid, mp 190–192 °C, yield 89%, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43–7.37 (m, 2H), 7.30 (d, J=8.49 Hz, 2H), 7.23 (s, 1H), 7.11 (dd, J=1.55, 4.65 Hz, 1H), 6.86 (d, J=8.46 Hz, 2H), 6.43 (s, 1H), 5.09 (s, 2H), 3.78 (s, 3H), 1.80 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.4, 153.2, 137.8, 133.0, 130.7, 130.1, 129.9, 128.2, 127.8, 126.9, 126.1, 118.7, 115.1, 114.2, 55.2, 49.5, 11.3. HRMS (EI): calcd for $C_{17}H_{19}ClN_3O_2S$: 351.1041, found: 351.1052.

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Supplementary data

Complete experimental details and spectroscopic data of all compounds are available online. Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.tet.2012.10.019.

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