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CONVENIENT SYNTHESIS OF NOVEL 2-SUBSTITUTED IMIDAZOPYRAZINONE DERIVATIVES

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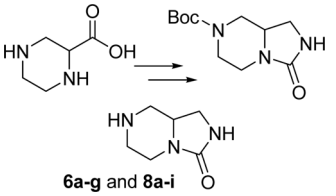
GRAPHICAL ABSTRACT



Abstract *Starting from commercially available piperazine-2-carboxylic acid, a series of novel 2-aryl and 2-benzyl substituted imidazopyrazinone were prepared. The intermediates* ***5a–g*** *were obtained through facile Buchwald–Hartwig coupling reaction, and the effects of catalyst, base, and solvent on the coupling reaction were investigated. The optimal reaction conditions for the coupling reaction were* $PdCl_2(dppf)$*/NaO-t-Bu/toluene.*

Keywords Buchwald–Hartwig coupling; catalyst; imidazopyrazinone; Mitsunobu reaction

INTRODUCTION

The piperazine ring system undoubtedly belongs to the most important heterocycles in nature, as it represent the main structure of many biologically significant compounds. For this reason many analogs and derivatives of piperazine have been synthesized and developed as pharmacologically active compounds or drugs.[1–3] In addition, a large number of fused piperazines were recently created and introduced as the key moieties of dipeptidyl peptidase IV (DPP-IV) inhibitor for the treatment of type 2 diabetes.[4]

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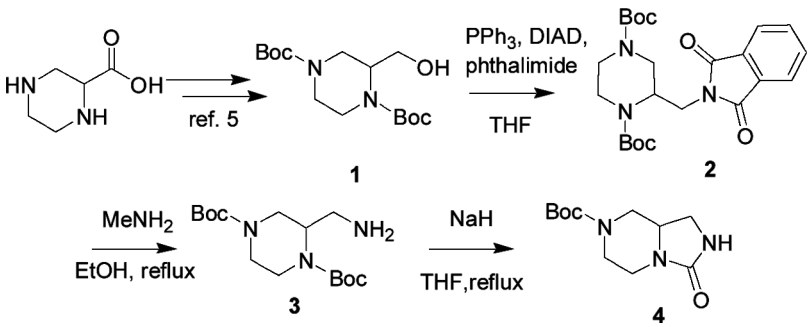
This article described the synthesis of 2-aryl and 2-benzyl substituted imidazopyrazinone analogs **6a**–**g** and **8a**–**i**, as part of our ongoing research work, which might have potential for inhibition of the DPP-IV enzyme.

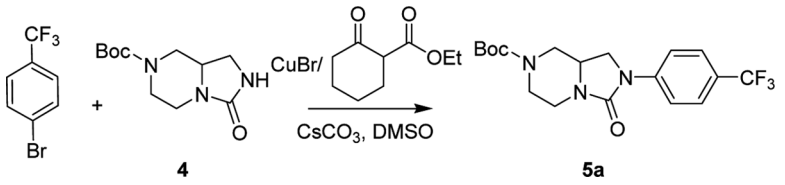
RESULTS AND DISCUSSION

Various imidazopyrazinone derivatives were synthesized via the routes depicted in Schemes 1–3. As shown in Scheme 1, compound **1** was easily accessible in two steps starting from piperazine-2-carboxylic acid through a known procedure.[5] Subsequently, the conversion of **1** to primary amine **3** was completed under a standard Mitsunobu reaction condition, followed by ammonolysis in refluxing methylamine ethanol solution. The key intermediate **4** was successfully obtained in excellent yield by refluxing **3** in tetrahydrofuran (THF) with NaH. No catalyst, such as reported $W(CO)_6$ [6] and Ph_3SbO/P_4O_{10}, [7] was needed, and the selective deprotection of the Boc-group at the 7-position of the piperazine group was also unnecessary when NaH was used. The coupling reaction of aryl halides and lactams **4** was then investigated. When the coupling reaction was catalyzed by CuBr/ethyl 2-oxocyclohexanecarboxylate with Cs_2CO_3 as base[8] (Scheme 2), only 19% of desired compound **5a** was gained.

Thus, the Buchwald–Hartwig reaction conditions were optimized by using the coupling of 4-(trifluoromethyl)bromobenzene with **4** as the model reaction. First, three palladium-containing catalysts, namely tris(dibenzylideneacetone) dipalladium [$Pd_2(dba)_3$], $Pd(OAc)_2$, and [1,1′-bis(diphenylphosphino)ferrocene] dichloropalladium [$PdCl_2$(dppf)], were examined. As shown in Table 1, $PdCl_2$(dppf) could catalyze the coupling reaction with much greater efficiency than the other two catalysts. Second, several bases including Cs_2CO_3, K_2CO_3, and NaO-*t*-Bu were examined in the $Pd_2(dba)_3$-catalyzed coupling reaction. The yields with different bases were in the order NaO-*t*-Bu > K_2CO_3 > Cs_2CO_3 (entries 1–3). Finally, the effect of solvents such as toluene, 1,4-dioxane, and tetrahydrofuran (THF) was investigated (entries 7–9). Weak influence of solvents on yield was observed while relatively good yield was obtained in toluene. $PdCl_2$(dppf)/NaO-*t*-Bu/toluene was regarded as the optimal reaction condition for the coupling reaction. It has the advantages such as (1) excellent yields; (2) less catalyst (0.5 mol%) than previously reported (1–4 mol%) [9]; and (3) no use of auxiliary ligands.



Scheme 1. Synthesis of intermediate **4**.



Scheme 2. Synthesis of compound **5a**.

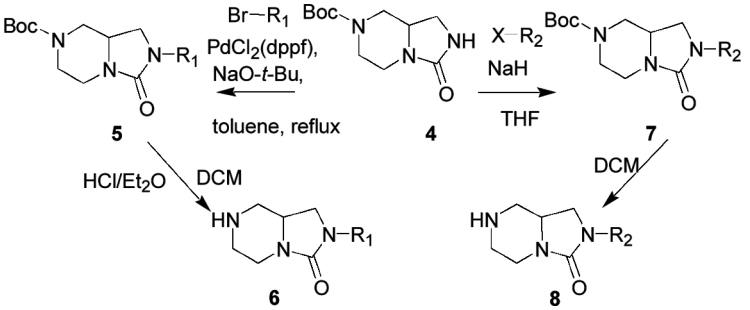
To obtain the desired derivatives **5b**–**g**, the optimized conditions were then applied to the coupling reactions of intermediate **4** with various aryl bromides bearing electron-withdrawing substitutes (Table 2). It was found that the electronic effect of substituted groups exerted important influence on the yields of the coupling reactions. Buchwald–Hartwig reactions of **4** with aryl bromides bearing electron-donating substitutes proceeded sluggishly. For an example, 4-fluorobromobenzene, which possesses a relatively weak electron-withdrawing substitute, resulted in poor yield although the reaction time had been prolonged. On the other hand, according to the synthesis of tetramethylurea derivatives,[10] the intermolecular amidation of aryl or benzyl halides with lactams **4** was carried out successfully in the presence of NaH in THF, without use of expensive Pd catalysts. Various corresponding benzyl substituted products **7a**–**i** were then obtained in acceptable yields (48–90%, Table 3).

Finally, after the removal of Boc-protection groups of **5a**–**g** and **7a**–**i** in HCl/Et_2O solution, the targeted free amines, **6a**–**g** and **8a**–**i**, were precipitated from the reaction mixture and easily isolated by filtration in good yields (77–99%, Scheme 3). The final products were pure enough for normal use even without further purification.

In conclusion, a series of novel 2-aryl and 2-benzyl substituted imidazopyrazinone derivatives had been prepared, and the facile protocol for the preparation of target products by Buchwald–Hartwig coupling reaction or electrophilic substitution was described. The application of these free amines in the development of novel DPP-IV inhibitors is in progress and will be reported later.

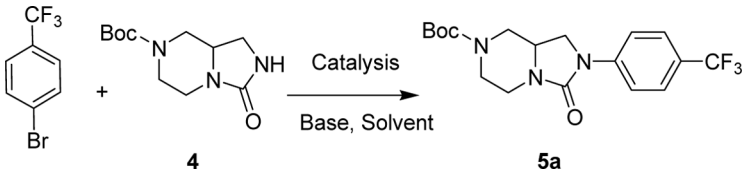
EXPERIMENTAL

Melting points were obtained with a Mel-Temp apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded respectively on Varian Mercury



Scheme 3. Synthesis of **6a**–**g** and **8a**–**i**.

Table 1. Optimization of catalyst, base, and solvent in the synthesis of **5a**



4 **5a**

Entry	Catalyst	Base	Solvent	Conditions	Yield (%)[a]
1	$Pd_2(dba)_3$	Cs_2CO_3	Toluene	reflux, 24 h	34
2	$Pd_2(dba)_3$	K_2CO_3	Toluene	reflux, 24 h	41
3	$Pd_2(dba)_3$	NaO-*t*-Bu	Toluene	reflux, 24 h	55
4	$Pd(OAc)_2$	Cs_2CO_3	Toluene	reflux, 24 h	0
5	$Pd(OAc)_2$	K_2CO_3	Toluene	reflux, 24 h	0
6	$Pd(OAc)_2$	NaO-*t*-Bu	Toluene	reflux, 24 h	0
7	$PdCl_2$(dppf)	NaO-*t*-Bu	Toluene	reflux, 12 h	98
8	$PdCl_2$(dppf)	NaO-*t*-Bu	1,4-Dioxane	reflux, 12 h	92
9	$PdCl_2$(dppf)	NaO-*t*-Bu	THF	reflux, 12 h	89

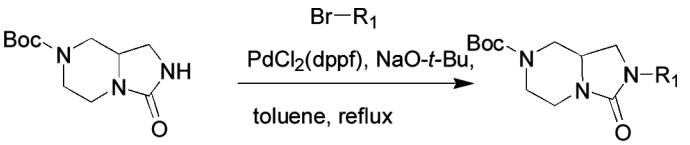
[a]Isolated yields.

400-MHz or Mercury 300-MHz (Varian Inova) instruments with tetramethylsilane (TMS) as an internal standard. Mass spectra (MS-ESI) were recorded with a Finnigan MAT 95. Compound **1** was prepared following the literature procedure.[5]

Di-*tert*-butyl 2-((1,3-Dioxoisoindolin-2-yl)methyl)-piperazine-1,4-dicarboxylate (2)

PPh_3(16.2 g, 61.8 mmol) and phthalimide (9.1 g, 61.8 mmol) were added to a solution of **1** (15.0 g, 47.5 mmol) in anhydrous THF (250 mL) at 10 °C. DIAD (12.0 mL,

Table 2. Palladium-catalyzed coupling of **4** with aryl bromides

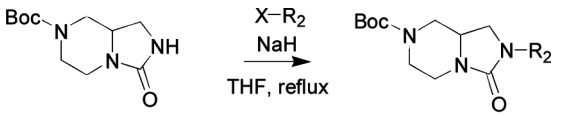


4 **5**

Entry	R_1	Reaction time (h)	Yield (%)[a]	Mp (°C)[b]
5a	4-$CF_3C_6H_4$	12	98	188–190
5b	2-pyridinyl	12	82	126–128
5c	4-FC_6H_4	48	15	168–170
5d	4-ClC_6H_4	24	52	123–125
5e	4-CNC_6H_4	24	78	194–195
5f	4-$NO_2C_6H_4$	24	52	216–218
5g	4-$MeSO_2C_6H_4$	24	67	244–245

[a]Isolated yields.
[b]Melting points are uncorrected.

Table 3. Substitution reaction of lactam **4** with benzylhalides



4 **7**

Entry	R_2-X	R_2	Yield[a] (%)	Mp[b] (°C)
7a	BnBr	Bn	64	130–131
7b	4-$FC_6H_4CH_2Br$	4-$FC_6H_4CH_2$	90	130–131
7c	4-$ClC_6H_4CH_2Br$	4-$ClC_6H_4CH_2$	83	119–120
7d	4-$OMeC_6H_4CH_2Cl$	4-$OMeC_6H_4CH_2$	86	111–112
7e	4-$MeC_6H_4CH_2Br$	4-$MeC_6H_4CH_2$	48	106–107
7f	3-$FC_6H_4CH_2Br$	3-$FC_6H_4CH_2$	86	129–130
7g	3-$CNC_6H_4CH_2Br$	3-$CNC_6H_4CH_2$	88	125–126
7h	CH_3I	Me	83	121–122
7i	CH_3CH_2Br	Et	65	110–112

[a]Isolated yields.
[b]Melting points are uncorrected.

61.8 mmol) was then added slowly to the reaction mixture at 10 °C. The reaction was stirred at 10 °C for an additional 2 h. After the reaction was completed, the reaction mixture was treated with 1*N* HCl (100 mL) and then extracted with ethyl acetate. The extract was washed with 5% aqueous $NaHCO_3$ (100 mL), dried and concentrated in vacuo. The residue was purified by silica-gel chromatography to give the title compound (19.9 g, 93%) as a white solid. Mp 95–96 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.02 (m, 9H), 1.44 (m, 9H), 2.73–2.84 (m, 1H), 2.93–3.01 (m, 1H), 3.28–3.40 (m, 1H), 3.55 (m, 1H), 3.65–4.15 (m, 4H), 4.48–4.66 (m, 1H), 7.67–7.84 (m, 4H).

Di-*tert*-butyl 2-(Aminomethyl)piperazine-1,4-dicarboxylate (3)

The solution of **2** (14.1 g, 31.7 mmol) in EtOH (100 mL) was treated with methylamine alcohol solution (32%, 100 mL), heated at reflux for 4 h, cooled to room temperature, and concentrated. The resulting residue was dissolved in H_2O (50 mL), acidified to pH = 3 with 2*N* HCl, and extracted with methyl-*tert*-butyl ether. The pH was adjusted to 10 with 2*N* NaOH, and the mixture was extracted with ethyl acetate. The extract was dried and filtered, and the solvent was removed under reduced pressure to give the title compound (7.7 g, 77%) as a white solid. Mp 92–93 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.45 (s, 18H), 2.73–2.92 (m, 5H), 3.82–4.16 (m, 4H); MS (ESI) m/z: 316.2 $(M+H)^+$.

tert-Butyl Hexahydro-3-oxoimidazo[1,5-*a*]pyrazine-7(1*H*)-carboxylate (4)

The solution of **3** (7.7 g, 24.2 mmol) in anhydrous THF (50 mL) was added dropwise to a suspension of NaH (60% dispersion in mineral oil, 0.7 g, 48.4 mmol)

in THF (50 mL) at 0 °C. The reaction mixture was heated at reflux for 3 h. Upon cooling to room temperature, the mixture was poured into ice H_2O (50 mL) and extracted with ethyl acetate. The extracts were washed with H_2O and brine, dried, filtered, and concentrated to give the desired product (5.3 g, 90%). mp 212–213 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.44 (s, 9H), 2.68–2.87 (m, 3H), 3.03 (m, 1H), 3.53 (t, $J = 12.0$ Hz, 1H), 3.62–3.71 (m, 1H), 3.76 (d, $J = 12.8$ Hz, 1H), 3.98–4.19 (m, 2H), 5.18–5.36 (m, 1H); MS (ESI) m/z: 264.2 $(M + Na)^+$.

General Procedure for the Synthesis of Compounds 5a–g

Compound **4** (480 mg, 2.0 mmol) was dissolved in toluene (20 mL) under nitrogen. Then aryl bromides (4.0 mmol), NaO-*t*-Bu (384 mg, 4.0 mmol), and $PdCl_2$(dppf) (10 mg, 0.01 mmol) were added to the mixture and refluxed for 12–48 h. Upon cooling, the mixture was concentrated, and the residue was dissolved in H_2O (30 mL) and extracted with ethyl acetate. The extract was washed with brine, dried, filtered, and concentrated. The residue was purified by column chromatography to give the compounds **5a**–**g**.

General Procedure for the Synthesis of Compounds 7a–i

Benzylhalide (2.0 mmol) was added to the solution of **4** (241 mg, 1.0 mmol) in anhydrous THF (10 mL). Then the mixed solution was added dropwise to a suspension of NaH (60% dispersion in mineral oil, 4.0 mmol) in THF (20 mL) at 0 °C. The mixture was refluxed for 3–8 h. Upon cooling, the mixture was poured into ice H_2O (50 mL) and extracted with ethyl acetate. The combined extracts were washed with H_2O and brine, dried, filtered, and concentrated to give the desired products **7a**–**i** as yellow solids.

General Procedure for the Synthesis of Compounds 6a–g and 8a–i

HCl/Et_2O solution (1.7 mL, 4.0 M, 6.8 mmol) was added to a solution of **5a**–**g** or **7a**–**i** (1.0 mmol) in CH_2Cl_2 (15 mL). After being stirred overnight, the precipitated solids were filtered and washed with Et_2O to give the desired compounds.

Data

***tert*-Butyl 2-(4-(trifluoromethyl)phenyl)-hexahydro-3-oxoimidazo[1,5-*a*]pyrazine-7(1*H*)-carboxylate (5a).** Yield: 98%; mp 188–190 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.47 (m, 9H), 2.64–2.71 (m, 1H), 2.81–2.86 (m, 1H), 2.93–3.02 (m, 1H), 3.43–3.57 (m, 1H), 3.73–3.81 (m, 1H), 3.92–3.98 (m, 2H), 4.06–4.15 (m, 1H), 4.28–4.33 (m, 1H), 7.57 (d, $J = 9.4$ Hz, 2H), 7.66 (d, $J = 8.5$ Hz, 2H); MS (ESI) m/z: 408.4 $(M + Na)^+$.

***tert*-Butyl 2-(pyridin-2-yl)-hexahydro-3-oxoimidazo[1,5-*a*]pyrazine-7(1-*H*)-carboxylate (5b).** Yield: 82%; mp 126–128 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.47 (m, 9H), 2.60–2.72 (m, 1H), 2.78–2.83 (m, 1H), 3.00 (m, 1H), 3.67–3.73

(m, 2H), 3.93 (m, 1H), 4.11–4.26 (m, 3H), 6.89–6.94 (m, 1H), 7.60–7.66 (m, 1H), 8.27 (m, 2H); MS (ESI) m/z: 319.3 $(M + H)^+$.

***tert*-Butyl 2-(4-fluorophenyl)-hexahydro-3-oxoimidazo[1,5-*a*]pyrazine-7(1*H*)-carboxylate (5c).** Yield: 15%; mp 168–170 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.42–1.48 (m, 9H), 2.66–2.72 (m, 1H), 2.80–2.88 (m, 1H), 2.90–3.00 (m, 1H), 3.41 (m, 1H), 3.67–3.77 (m, 1H), 3.87–3.94 (m, 2H), 4.06–4.12 (m, 1H), 4.18–4.24 (m, 1H), 7.00–7.06 (m, 2H), 7.46–7.51 (m, 2H); MS (ESI) m/z: 358.3 $(M + Na)^+$.

***tert*-Butyl 2-(4-chlorophenyl)-hexahydro-3-oxoimidazo[1,5-*a*]pyrazine-7(1*H*)-carboxylate (5d).** Yield: 52%; mp 123–125 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.47 (m, 9H), 2.60–2.74 (m, 1H), 2.80–2.87 (m, 1H), 2.94 (m, 1H), 3.41 (m, 1H), 3.73 (m, 1H), 3.87–3.94 (m, 2H), 4.02–4.15 (m, 1H), 4.20–4.37 (m, 1H), 7.28 (d, $J = 10.0$ Hz, 2H), 7.49 (d, $J = 9.9$ Hz, 2H); MS (ESI) m/z : 374.3 $(M + Na)^+$.

***tert*-Butyl 2-(4-cyanophenyl)-hexahydro-3-oxoimidazo[1,5-*a*]pyrazine-7(1*H*)-carboxylate (5e).** Yield: 78%; mp 194–195 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.46 (m, 9H), 2.64–2.71 (m, 1H), 2.82–2.89 (m, 1H), 2.94–3.04 (m, 1H), 3.43–3.48 (m, 1H), 3.73–3.83 (m, 1H), 3.93–3.99 (m, 2H), 4.09–4.40 (m, 2H), 7.62 (d, $J = 9.0$ Hz, 2H), 7.68 (d, $J = 9.0$ Hz, 2H); MS (ESI) m/z: 365 $(M + Na)^+$.

***tert*-Butyl 2-(4-nitrophenyl)-hexahydro-3-oxoimidazo[1,5-*a*]pyrazine-7(1*H*)-carboxylate (5f).** Yield: 52%; mp 216–218 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.42–1.51 (m, 9H), 2.64–2.70 (m, 1H), 2.83–2.89 (m, 1H), 2.96–3.02 (m, 1H), 3.50 (m, 1H), 3.77–3.82 (m, 1H), 3.93–4.03 (m, 2H), 4.11–4.18 (m, 1H), 4.23–4.37 (m, 1H), 7.71 (d, $J = 7.3$ Hz, 2H), 8.22 (d, $J = 7.3$ Hz, 2H); MS (ESI) m/z: 385.3 $(M + Na)^+$.

***tert*-Butyl 2-(4-(methylsulfonyl)phenyl)-hexahydro-3-oxoimidazo[1,5-*a*]pyrazine-7(1*H*)-carboxylate (5g).** Yield: 67%; mp 244–245 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.49 (m, 9H), 2.64–2.71 (m, 1H), 2.80–2.87 (m, 1H), 2.88–2.99 (m, 1H), 3.03 (s, 3H), 3.48 (m, 1H), 3.75–3.82 (m, 1H), 3.92–4.01 (m, 2H), 4.09–4.13 (m, 1H), 4.15–4.37 (m, 1H), 7.75 (d, $J = 9.0$ Hz, 2H), 7.89 (d, $J = 8.9$ Hz, 2H); MS (ESI) m/z: 418.3 $(M + Na)^+$.

***tert*-Butyl 2-benzyl-hexahydro-3-oxoimidazo[1,5-*a*]pyrazine-7(1*H*)-carboxylate (7a).** Yield: 64%; mp 130–131 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.43 (s, 9H), 2.59–2.91 (m, 4H), 3.26–3.31 (m, 1H), 3.54 (m, 1H), 3.84–3.89 (m, 1H), 3.98–4.06 (m, 2H), 4.38 (s, 2H), 7.23–7.36 (m, 5H); MS (ESI) m/z: 354.3 $(M + Na)^+$.

***tert*-Butyl 2-(4-fluorobenzyl)-hexahydro-3-oxoimidazo[1,5-*a*]pyrazine-7(1*H*)-carboxylate (7b).** Yield: 90%; mp 130–131 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.45 (s, 9H), 2.53–2.58 (m, 1H), 2.78 (q, $J = 4.8$ Hz, 2H), 2.89 (dt, $J_1 = 12.9$ Hz, $J_2 = 3.0$ Hz, 1H), 3.28 (t, $J = 8.7$ Hz, 1H), 3.51–3.58 (m, 1H), 3.85 (d, $J = 10.2$ Hz, 1H), 3.95–4.08 (m, 2H), 4.30–4.69 (m, 2H), 6.98–7.04 (m, 2H), 7.21 (m, 2H); MS (ESI) m/z: 372.3$(M + Na)^+$.

***tert*-Butyl 2-(4-chlorobenzyl)-hexahydro-3-oxoimidazo[1,5-*a*]pyrazine-7(1*H*)-carboxylate (7c).** Yield: 83%; mp 119–120 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.45 (s, 9H), 2.52–2.60 (m, 1H), 2.75 (q, $J = 4.6$ Hz, 2H), 2.90 (dt, $J_1 = 13.1$ Hz, $J_2 = 3.1$ Hz, 1H), 3.28 (t, $J = 8.9$ Hz, 1H), 3.51–3.58 (m, 1H), 3.85 (dd, $J_1 = 13.1$ Hz, $J_2 = 3.1$ Hz, 1H), 3.95–4.12 (m, 2H), 4.30–4.38 (m, 2H), 7.18 (m, 2H), 7.28–7.31 (m, 2H); MS (ESI) m/z: 388.2 $(M + Na)^+$.

***tert*-Butyl 2-(4-methoxybenzyl)-hexahydro-3-oxoimidazo[1,5-*a*]pyrazine-7(1*H*)-carboxylate (7d).** Yield: 86%; mp 111–112 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.45 (s, 9H), 2.53–2.60 (m, 1H), 2.77 (q, $J = 4.8$ Hz, 2H), 2.88 (dt, $J_1 = 12.9$ Hz, $J_2 = 2.8$ Hz, 1H), 3.26 (t, $J = 8.4$ Hz, 1H), 3.49–3.56 (m, 1H), 3.79 (s, 3H), 3.84 (d, $J = 10.5$ Hz, 1H), 3.95–4.12 (m, 2H), 4.31 (m, 2H), 6.98 (d, $J = 6.6$ Hz, 2H), 7.29 (d, $J = 6.7$ Hz, 2H); MS (ESI) m/z: 384.3 $(M + Na)^+$.

***tert*-Butyl 2-(4-methylbenzyl)-hexahydro-3-oxoimidazo[1,5-*a*]pyrazine-7(1*H*)-carboxylate (7e).** Yield: 48%; mp 106–107 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.45 (s, 9H), 2.33 (s, 3H), 2.53–2.60 (m, 1H), 2.77 (q, $J = 6.0$ Hz, 2H), 2.90 (dt, $J_1 = 17.2$ Hz, $J_2 = 4.0$ Hz, 1H), 3.27 (t, $J = 8.4$ Hz, 1H), 3.48–3.57 (m, 1H), 3.86 (d, $J = 14.0$ Hz, 1H), 3.94–4.10 (m, 2H), 4.33 (s, 2H), 7.11 (s, 4H); MS (ESI) m/z: 368.3 $(M + Na)^+$.

***tert*-Butyl 2-(3-fluorobenzyl)-hexahydro-3-oxoimidazo[1,5-*a*]pyrazine-7(1*H*)-carboxylate (7f).** ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.46 (s, 9H), 2.55–2.60 (m, 1H), 2.80 (q, $J = 4.6$ Hz, 2H), 2.90 (dt, $J_1 = 12.7$ Hz, $J_2 = 2.9$ Hz, 1H), 3.31 (t, $J = 8.7$ Hz, 1H), 3.53–3.60 (m, 1H), 3.86 (d, $J = 9.9$ Hz, 1H), 3.97–4.12 (m, 2H), 4.33–4.41 (m, 2H), 6.94–7.03 (m, 3H), 7.27–7.31 (m, 1H); MS (ESI) m/z: 372.3 $(M + Na)^+$.

***tert*-Butyl 2-(3-cyanobenzyl)-hexahydro-3-oxoimidazo[1,5-*a*]pyrazine-7(1*H*)-carboxylate (7g).** ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.45 (s, 9H), 2.54–2.62 (m, 1H), 2.79 (q, $J = 4.4$ Hz, 2H), 2.91 (dt, $J_1 = 12.7$ Hz, $J_2 = 3.1$ Hz, 1H), 3.31 (t, $J = 8.9$ Hz, 1H), 3.54–3.61 (m, 1H), 3.85 (d, $J = 13.2$ Hz, 1H), 3.97–4.15 (m, 2H), 4.33–4.46 (m, 2H), 7.42–7.58 (m, 4H); MS (ESI) m/z: 379.3 (10%, $M + Na)^+$.

***tert*-Butyl 2-methyl-hexahydro-3-oxoimidazo[1,5-*a*]pyrazine-7(1*H*)-carboxylate (7h).** ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.46 (s, 9 H), 2.60–2.76 (m, 2H), 2.78 (s, 3H), 2.85 (dd, $J_1 = 13.0$ Hz, $J_2 = 3.1$ Hz, 1H), 2.91 (q, $J = 4.8$ Hz, 1H), 3.40 (t, $J = 8.5$ Hz, 1H), 3.51–3.58 (m, 1H), 3.77–3.82 (m, 1H), 4.07–4.12 (m, 2H); MS (ESI) m/z: 278.2 $(M + Na)^+$.

***tert*-Butyl 2-ethyl-hexahydro-3-oxoimidazo[1,5-*a*]pyrazine-7(1*H*)-carboxylate (7i).** ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.08 (t, $J = 7.3$ Hz, 3H), 1.44 (s, 9H), 2.60–2.84 (m, 3H), 2.90 (q, $J = 4.4$ Hz, 1H), 3.23 (q, $J = 6.3$ Hz, 2H), 3.39 (t, $J = 8.4$ Hz, 1H), 3.49–3.56 (m, 1H), 3.75–3.81 (m, 1H), 3.96–4.10 (m, 2H); MS (ESI) m/z: 292.3 $(M + Na)^+$.

Hexahydro-2-(4-trifluoromethylphenyl)-imidazo[1,5-*a*]pyrazin-3-one (6a). Yield: 78%; mp 233–235 °C; ^{1}H NMR (CF_3COOD, 400 MHz) δ 3.29–3.36 (m, 2H), 3.54–3.72 (m, 2H), 3.76 (m, 1H), 3.86 (m, 1H), 4.11–4.29 (m, 2H), 4.48 (m, 1H), 7.48 (d, $J = 8.6$ Hz, 2H), 7.60 (d, $J = 8.5$ Hz, 2H); ^{13}C NMR (DMSO-d_6,

100 MHz) δ 37.3, 42.3, 45.7, 47.1, 50.3, 117.2, 126.3, 126.4, 143.9, 155.3, 160.3; HRMS (ESI): $C_{13}H_{14}N_3OF_3Na$, calc. 308.0987; found 308.0992.

Hexahydro-2-(pyridin-2-yl)-imidazo[1,5-*a*]pyrazin-3(5*h*)-one (6b). Yield: 90%; mp 170–171 °C; ^{1}H NMR (CF_3COOD, 400 MHz) δ 3.41–3.53 (m, 2H), 3.63–3.76 (m, 2H), 3.87–3.97 (m, 2H), 4.30–4.48 (m, 2H), 4.68 (m, 1H), 7.28 (m, 1H), 7.53 (m, 1H), 8.35–8.42 (m, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 28.4, 37.2, 45.0, 45.7, 47.0, 112.3, 118.4, 131.2, 138.1, 148.1, 155.1; HRMS (ESI): $C_{11}H_{14}N_4ONa$, calc. 241.1065; found 241.1057.

Hexahydro-2-(4-fluorophenyl)-imidazo[1,5-*a*]pyrazin-3-one (6c). Yield: 81%; mp 336–338 °C; ^{1}H NMR (CF_3COOD, 400 MHz) δ 3.37–3.47 (m, 2H), 3.60–3.66 (m, 3H), 3.69–3.76 (m, 1H), 4.14–4.29 (m, 1H), 4.26–4.32 (m, 1H), 4.38–4.52 (m, 1H), 7.05–7.11 (m, 2H), 7.30 (m, 2H); ^{13}C NMR (D_2O, 100 MHz) δ 37.1, 42.4, 45.3, 46.9, 47.6, 115.8, 121.9, 134.8, 157.4, 160.4; HRMS (ESI): $C_{12}H_{14}N_3OFNa$, calc. 258.1019; found 258.1037.

Hexahydro-2-(4-chlorophenyl)-imidazo[1,5-*a*]pyrazin-3-one (6d). Yield: 95%; mp 127–129 °C; ^{1}H NMR (CF_3COOD, 300 MHz) δ 3.30–3.45 (m, 2H), 3.56–3.77 (m, 3H), 3.82–3.89 (m, 1H), 4.15–4.21 (m, 1H), 4.27–4.32 (m, 1H), 4.45–4.52 (m, 1H), 7.25 (d, $J = 7.8$ Hz, 2H), 7.33 (d, $J = 8.9$ Hz, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 37.3, 42.3, 45.6, 45.8, 47.1, 119.0, 126.4, 129.0, 139.5, 155.5; HRMS (ESI): $C_{12}H_{14}N_3OClNa$, calc. 274.0723; found 274.0733.

Hexahydro-2-(4-cyanophenyl)-imidazo[1,5-*a*]pyrazin-3-one (6e). Yield: 79%; mp 154–155 °C; ^{1}H NMR (CF_3COOD, 400 MHz) δ 3.27–3.40 (m, 2H), 3.51–3.59 (m, 1H), 3.67 (m, 1H), 3.74–3.83 (m, 2H), 4.16–4.22 (m, 1H), 4.25–4.30 (m, 1H), 4.38 (m, 1H), 7.58 (d, $J = 8.8$ Hz, 2H), 7.69 (d, $J = 8.8$ Hz, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 37.3, 42.3, 45.5, 45.6, 47.0, 104.0, 117.3, 119.6, 133.5, 144.5, 155.1; HRMS (ESI): $C_{13}H_{14}N_4ONa$, calc. 265.1065; found 265.1087.

Hexahydro-2-(4-nitrophenyl)-imidazo[1,5-*a*]pyrazin-3-one (6f). Yield: 72%; mp 183–184 °C;^{1}H NMR (D_2O, 400 MHz) δ 2.95–3.01 (m, 2H), 3.19–3.36 (m, 1H), 3.19–3.36 (m, 1H), 3.22 (dt, $J_1 = 15.0$ Hz, $J_2 = 3.0$ Hz, 1H), 3.34 (dd, $J_1 = 12.6$ Hz, $J_2 = 2.5$ Hz, 1H), 3.48 (dd, $J_1 = 12.3$ Hz, $J_2 = 3.3$ Hz, 1H), 3.64 (m, 1H), 3.96 (dd, $J_1 = 13.1$ Hz, $J_2 = 2.2$ Hz, 1H), 4.06 (m, 2H), 7.52 (m, 2H), 8.10 (m, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 37.2, 42.2, 45.6, 45.9, 46.9, 116.8, 125.3, 141.5, 146.5, 154.9; HRMS (ESI): $C_{12}H_{15}N_4O_3$, calc. 263.1144; found 263.1131.

Hexahydro-2-(4-(methylsulfonyl)phenyl)-imidazo[1,5-*a*]pyrazin-3-one (6g). Yield: 78%; mp 297–300 °C; ^{1}H NMR (CF_3COOD, 400 MHz) δ 3.13 (s, 3H), 3.20–3.39 (m, 2H), 3.42–4.12 (m, 4H), 4.32 (m, 2H), 4.39–4.46 (m, 1H), 7.76–7.88 (m, 2H), 7.99–8.11 (m, 2H);^{13}C NMR (D_2O+DMSO-d_6, 100 MHz) δ 36.9, 42.4, 43.7, 45.6, 45.9, 47.2, 117.2, 126.4, 132.3, 144.4, 156.3; HRMS (ESI): $C_{13}H_{17}N_3O_3SNa$, calc. 318.0888; found 318.0909.

Hexahydro-2-benzyl-imidazo[1,5-*a*]pyrazin-3-one (8a). Yield: 99%; mp 214–215 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.74 (t, $J = 8.0$ Hz, 1H), 2.82 (dt, $J_2 = 9.6$ Hz, $J_2 = 4.0$ Hz, 1H), 2.91 (dd, $J_2 = 12.4$ Hz, $J_2 = 4.8$ Hz, 1H), 3.16–3.30 (m, 4H), 3.78 (dd, $J_1 = 14.8$ Hz, $J_2 = 3.8$ Hz, 1H), 3.92–3.97 (m, 1H), 4.30 (m, 2H),

7.22–7.27 (m, 3H), 7.33–7.37 (m, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 37.4, 42.2, 44.9, 45.4, 47.3, 47.9, 127.7, 128.1, 129.0, 137.6, 158.8; HRMS (ESI): $C_{13}H_{17}N_3ONa$, calc. 254.1269; found 254.1277.

Hexahydro-2-(4-fluorobenzyl)-imidazo[1,5-*a*]pyrazin-3-one (8b). Yield: 91%; mp 219–220 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.69–2.91 (m, 3H), 3.16–3.29 (m, 3H), 3.45–3.62 (m, 1H), 3.76 (m, 1H), 3.91–3.97 (m, 1H), 4.19–4.30 (m, 2H), 7.12–7.17 (m, 2H), 7.23–7.29 (m, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 37.4, 42.2, 44.9, 45.4, 46.5, 47.9, 115.9, 130.1, 130.2, 133.8, 158.7; HRMS (ESI): $C_{13}H_{16}FN_3ONa$, calc. 272.1175; found 272.1181.

Hexahydro-2-(4-chlorobenzyl)-imidazo[1,5-*a*]pyrazin-3-one (8c). Yield: 89%; mp 197–198 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.72–2.93 (m, 3H), 3.15–3.29 (m, 4H), 3.78–4.05 (m, 2H), 4.23–4.34 (m, 2H), 7.25 (d, $J = 8.2$ Hz, 2H), 7.35 (d, $J = 8.2$ Hz, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 37.5, 42.2, 44.9, 45.4, 46.8, 47.9, 129.6, 130.1, 133.6, 135.1, 158.8; HRMS (ESI): $C_{13}H_{16}ClN_3ONa$, calc. 288.0880; found 288.0875.

Hexahydro-2-(4-methoxybenzyl)-imidazo[1,5-*a*]pyrazin-3-one (8d). Yield: 99%; mp 204–205 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.67 (m, 1H), 2.78 (m, 1H), 2.86 (dd, $J_1 = 15.6$ Hz, $J_2 = 4.2$ Hz, 1H), 3.14–3.24 (m, 4H), 3.71 (s, 3H), 3.76 (dd, $J_1 = 13.6$ Hz, $J_2 = 2.4$ Hz, 1H), 3.87–3.93 (m, 1H), 4.16–4.25 (m, 2H), 6.99 (d, J = 8.6 Hz, 2H), 7.14 (d, $J = 8.5$ Hz, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 37.4, 42.2, 44.9, 45.3, 47.0, 47.9, 114.5, 129.6, 128.1, 158.2, 158.8; HRMS (ESI): $C_{14}H_{19}N_3O_2Na$, calc. 284.1375; found 284.1377.

Hexahydro-2-(4-methylbenzyl)-imidazo[1,5-*a*]pyrazin-3-one (8e). Yield: 71%; mp 194–195 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.33 (s, 3H), 2.53 (t, $J = 11.1$ Hz, 1H), 2.66–2.77 (m, 2H), 2.90–2.96 (m, 3H), 3.25 (t, $J = 8.7$ Hz, 1H), 3.51–3.58 (m, 1H), 3.85 (d, $J = 12.9$ Hz, 1H), 4.28–4.38 (m, 2H), 7.13 (s, 4H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 21.6, 37.5, 42.2, 44.9, 45.3, 47.0, 47.9, 128.2, 129.6, 134.4, 136.9, 158.8; HRMS (ESI): $C_{14}H_{19}N_3ONa$, calc. 268.1426; found 268.1414.

Hexahydro-2-(3-fluorobenzyl)-imidazo[1,5-*a*]pyrazin-3-one (8f). Yield: 91%; mp 216–217 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.75–2.96 (m, 3H), 3.18–3.34 (m, 3H), 3.56–3.64 (m, 1H), 3.78–3.87 (m, 1H), 3.93–3.98 (m, 1H), 4.29 (m, 2H), 7.02–7.12 (m, 3H), 7.38 (m, 1H); MS (ESI) m/z: 250.2 $(M + H)^+$.

Hexahydro-2-(3-cyanobenzyl)-imidazo[1,5-*a*]pyrazin-3-one (8g). Yield: 99%; mp 199–201 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.80–2.86 (m, 2H), 2.96 (dd, $J_1 = 9.7$ Hz, $J_2 = 4.2$ Hz, 1H), 3.19–3.27 (m, 3H), 3.32–3.38 (m, 1H), 3.79 (dd, $J_1 = 13.6$ Hz, $J_2 = 2.7$ Hz, 1H), 3.95–3.98 (m, 1H), 4.31–4.40 (m, 2H), 7.54–7.61 (m, 2H), 7.71–7.77 (m, 2H); MS (ESI) m/z: 257.1 $(M + H)^+$.

Hexahydro-2-methyl-imidazo[1,5-*a*]pyrazin-3-one (8h). Yield: 87%; mp 207–208 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.69–2.93 (m, 4H), 3.04 (m, 1H), 3.12–3.58 (m, 5H), 3.89–3.96 (m, 1H), 4.09–4.17 (m, 1H); MS (ESI) m/z: 156.1 $(M + H)^+$.

Hexahydro-2-ethyl-imidazo[1,5-*a*]pyrazin-3-one (8i). Yield: 85%; mp 201–203 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 0.98 (t, $J = 7.3$ Hz, 3H), 2.67–2.78 (m, 2H), 3.02 (m, 1H), 3.08–3.18 (m, 4H), 3.21–3.27 (m, 1H), 3.40 (t, $J = 8.8$ Hz, 1H), 3.70 (m, 1H), 3.91–3.96 (m, 1H); MS (ESI) m/z: 170.1 $(M + H)^+$.

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