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Synthesis of 7-arylimidazo[1,2-*a*]pyrazin-8(7*H*)-one derivatives

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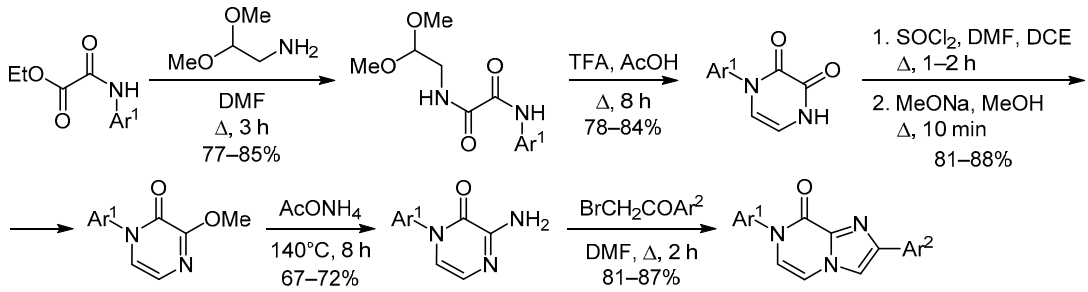


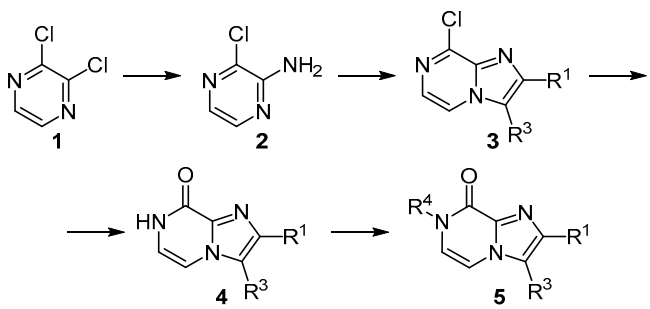
A suitable approach to the synthesis of 7-arylimidazo[1,2-*a*]pyrazin-8(7*H*)-ones starting from esters of oxalic acid monoamides *via* cyclization of intermediate 3-aminopyrazin-2-ones with α-halocarbonyl compounds has been suggested.

Keywords: 3-aminopyrazin-2(1*H*)-one, 2-halophenylethanone, imidazo[1,2-*a*]pyrazin-8(7*H*)-one, 3-methoxypyrazin-2(1*H*)-one, pyrazine-2,3-dione, cyclization.

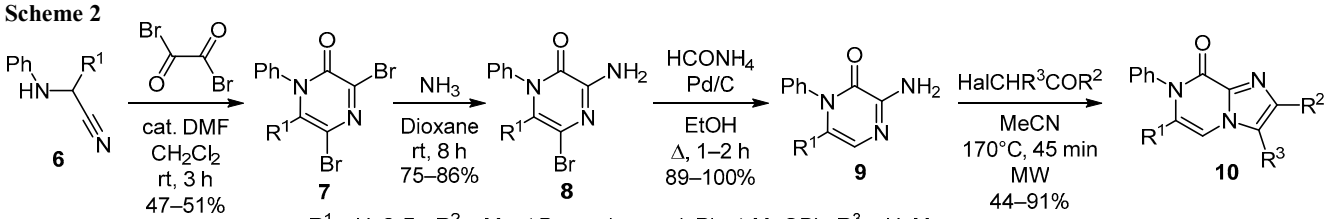
Imidazo[1,2-*a*]pyrazin-8(7*H*)-one ring system is relatively new, but constitutes a scaffold possessing diverse biological activity. Imidazo[1,2-*a*]pyrazin-8(7*H*)-ones have been reported as antiarrhythmics,[1] as $GABA_A$ receptor agonists for the treatment of anxiety,[2] as inhibitors of various kinases[3–6] and CXCR3 antagonists with anti-inflammatory action,[7] as AMPA receptor modulators[8] and useful compounds for treatment neurological and psychiatric deseases.[9–11]

The most common imidazo[1,2-*a*]pyrazin-8(7*H*)-one synthesis starts from 2,3-dichloropyrazine (**1**) and consists of cyclization of the intermediate 3-amino-2-chloropyrazine (**2**) by action of α-halocarbonyl reagents followed by hydrolysis of the resulting 8-chloroimidazo[4,3-*a*]-pyrazines **3** to imidazo[1,2-*a*]pyrazin-8(7*H*)-ones **4**, which can be alkylated by standard methods (Scheme 1).[1–5,7–10,12] However, synthesis of 7-arylimidazo[1,2-*a*]pyrazin-8(7*H*)-ones **5** according to this method presents a problem, in our opinion, and there are no examples reported.

Scheme 1

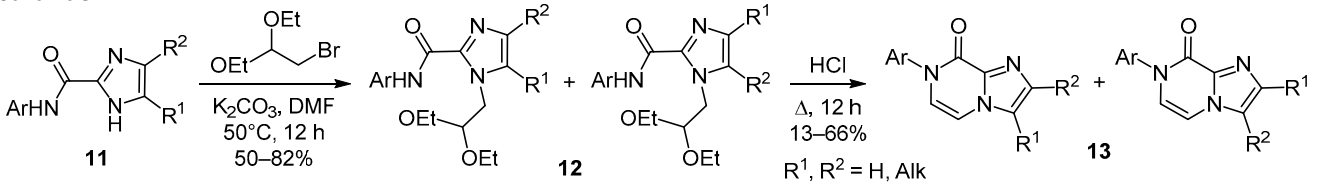


Scheme 2



R^1 = H, 2-Pr, R^2 = Me, *t*-Bu, cyclopropyl, Ph, 4-MeOPh, R^3 = H, Me

Scheme 3



R^1, R^2 = H, Alk

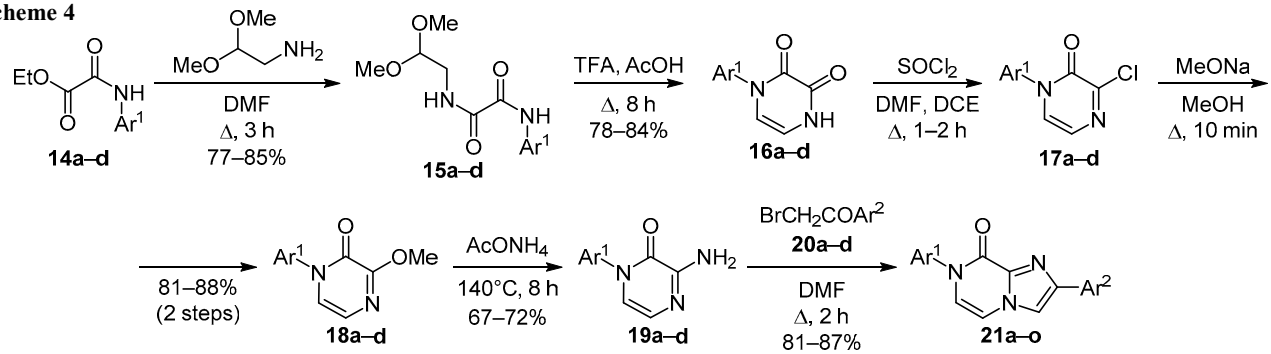
7-Arylimidazo[1,2-*a*]pyrazin-8(7*H*)-ones **10** have been synthesized by another method (Scheme 2).[13] Starting α-aminonitriles **6** were treated with oxalyl bromide providing the requisite 3,5-dibromo-2(1*H*)-pyrazinones **7**. Regioselective nucleophilic substitution of bromine by 35% aqueous ammonia in 1,4-dioxane led to 3-amino-5-bromo-2(1*H*)-pyrazinones **8**. After reductive substitution of bromine, 3-amino-2(1*H*)-pyrazinones **9** were obtained and were condenced with α-halocarbonyl reagents by microwave irradiation resulted in imidazo[1,2-*a*]pyrazin-8(7*H*)-ones **10**. The disadvantage of this method is limited set of commercially available α-aminonitriles **6** and usage of high toxic cyanides for their synthesis.

7-Arylimidazo[1,2-*a*]pyrazin-8(7*H*)-ones **13** could be synthesized *via* condensation of the corresponding imidazole-2-carboxamides **11**.[6,11,14] But this approach led to a mixture of regioisomers, both intermediate imidazoles **12** and final imidazo[1,2-*a*]pyrazin-8(7*H*)-ones **13**, in the case of different substituents in starting imidazole **11**[14] (Scheme 3).

We suggest here a suitable method of synthesis, which allows to obtain more diverse imidazo[1,2-*a*]pyrazin-8(7*H*)-ones **21a**–**o**, containing aromatic substituents both in pyrazine (position 7) and imidazole (position 2) rings (Scheme 4). The starting esters of oxalic acid monoamides **14a**–**d**, already having the substituent, which shall occupy position 7 of target imidazo[1,2-*a*]pyrazin-8(7*H*)-ones **21a**–**o**, could be easily obtained from corresponding amines and diethyl oxalate or ethyl oxalyl chloride.[15,16] Detailed procedure for the synthesis of intermediate 3-chloropyrazin-2(1*H*)-ones **17a**–**d** was described in our previous publication.[17]

The chlorine atom in 3-chloropyrazin-2(1*H*)-ones **17** can be easily replaced by the action of nucleophilic reagents.[17] Therefore, compounds **17a**–**d** were used without additional purification and were converted into more stable 3-methoxypyrazin-2(1*H*)-ones **18a**–**d** by treatment with MeONa in MeOH. Nucleophilic substitution of methoxy group was carried out by heating of products **18a**–**d** in molten dry ammonium acetate and led to 3-amino-2(1*H*)-pyrazinones **19a**–**d**, while 3-chloropyrazin-2(1*H*)-one **17d** by the same procedure gave product **19d** in mixture with 20% of pyrazin-2,3-dione **16d** as side product. A mixture of these two products was also obtained by treatment of 3-chloropyrazin-2(1*H*)-one **17d** with aqueous ammonia or solution of aqueous ammonia in 1,4-dioxane. 3-Methoxypyrazin-2(1*H*)-one **18d** reacted with aqueous ammonia or solution of aqueous ammonia in DMF very slowly and gave a mixture of pyrazine-2,3-dione **16d** and 3-amino-2(1*H*)-pyrazinone **19d** by prolonged reflux in DMF.

Scheme 4



14–**19** **a** Ar^1 = 3-FC_6H_4, **b** Ar^1= 4-$MeOC_6H_4$, **c** Ar^1 = 4-ClC_6H_4, **d** Ar^1 = 3,5-$Me_2C_6H_3$;
20 **a** Ar^2 = 4-EtC_6H_4, **b** Ar^2 = 4-$EtOC_6H_4$, **c** Ar^2 = 3,4-$(MeO)_2C_6H_3$, **d** Ar^2 = 4-ClC_6H_4;
21 **a** Ar^1 = 3-FC_6H_4, Ar^2 = 4-EtC_6H_4; **b** Ar^1 = 3-FC_6H_4, Ar^2 = 4-$EtOC_6H_4$; **c** Ar^1 = 3-FC_6H_4, Ar^2 = 3,4-$(MeO)_2C_6H_3$;
d Ar^1 = 3-FC_6H_4, Ar^2 = 4-ClC_6H_4; **e** Ar^1 = 4-$MeOC_6H_4$, Ar^2 = 4-EtC_6H_4; **f** Ar^1 = 4-$MeOC_6H_4$, Ar^2 = 4-$EtOC_6H_4$;
g Ar^1 = 4-$MeOC_6H_4$, Ar^2 = 3,4-$(MeO)_2C_6H_3$; **h** Ar^1 = 4-$MeOC_6H_4$, Ar^2 = 4-ClC_6H_4; **i** Ar^1 = 4-ClC_6H_4, Ar^2 = 4-EtC_6H_4;
j Ar^1 = 4-ClC_6H_4, 4-$EtOC_6H_4$; **k** Ar^1 = 4-ClC_6H_4, Ar^2 = 3,4-$(MeO)_2C_6H_3$; **l** Ar^1 = 3,5-$Me_2C_6H_3$, Ar^2 = 4-EtC_6H_4;
m Ar^1 = 3,5-$Me_2C_6H_3$, Ar^2 = 4-$EtOC_6H_4$; **n** Ar^1 = 3,5-$Me_2C_6H_3$, Ar^2 = 3,4-$Me_2OC_6H_3$; **o** Ar^1 = 3,5-$Me_2C_6H_3$, Ar^2 = 4-ClC_6H_4

Condensation of 3-amino-2(1*H*)-pyrazinones 1**9a**–**d** with α-halocarbonyl reagents **20a**–**d** was carried out in DMF by reflux for 2 h and resulted in imidazo[1,2-*a*]-pyrazin-8(7*H*)-ones **21a**–**o**. The purity and structures of synthesized compounds were confirmed by ^{1}H NMR spectroscopy, as well as by ^{13}C NMR spectroscopy for imidazo[1,2-*a*]pyrazin-8(7*H*)-ones **21a**–**o**.

The ^{1}H NMR spectra of imidazo[1,2-*a*]pyrazin-8(7*H*)-ones **21a**–**o** are characterized by the presence of the signals of protons H-3 as singlets at 8.15–8.35 ppm and the signals of protons H-5,6 as doublets at 7.12–7.16 and 7.57–7.62 ppm, respectively. The chemical shifts of these signals are in good correlation with those of analogous compounds described previously.[13] The signals of protons H-5,6 in the ^{1}H NMR spectra of 3-aminopyrazin-2(1*H*)-ones **19a**–**d** are overlapped by the signals of the NH_2 protons at 6.65–6.85 ppm. Therefore, it is impossible both to determine their multiplicity and use their integral intensity to estimate the amount of 3-amino-1-(3,5-dimethylphenyl)pyrazin-2(1*H*)-one (**19d**) in crude products in the failed attempts to obtain this compound. However, the molar percentage of 1-(3,5-dimethylphenyl)-1,4-dihydropyrazine-2,3-dione (**16d**) in crude product could be estimated by the ratio of integral intensity of the triplet of H-5 proton at 6.36 ppm to integral intensity of the singlet of CH_3 protons at 2.28 ppm. Similarly, molar content of 1-(3,5-dimethylphenyl)-3-methoxypyrazin-2(1*H*)-one (**18d**) was evaluated by the ratio of integral intensity of the singlet of OCH_3 protons at 3.82 ppm to integral intensity of the singlet of CH_3 protons at 2.28 ppm.

In summary, we have proposed a suitable approach to the synthesis of imidazo[1,2-*a*]pyrazin-8(7*H*)-ones starting from esters of oxalic acid monoamides *via* intermediate pyrazine-2,3-diones which are converted into 3-amino-pyrazin-2-ones. The cyclization of the latter with α-halocarbonyl reagents leads to imidazo[1,2-*a*]pyrazin-8(7*H*)-ones having various substituents both at 2 and 7 position.

Experimental

^{1}H NMR spectra were recorded on a Varian WXR-400 (200 MHz) spectrometer. ^{13}C NMR spectra were recorded on a Bruker DRX-300 (75 MHz) spectrometer. For all NMR spectra, DMSO-d_6 was used as solvent, and the chemical shift values were referred to residual protons (δ 2.49 ppm) and carbons (δ 39.6 ppm) of the solvent as internal standard. Elemental analysis was performed on a EuroEA-3000 CHNS-O Analyzer. Melting points were determined with a Buchi B-520 melting point apparatus.

Ethyl phenylamino(oxo)acetates **14a**,**c** were commercially available. Detailed procedure of 1-(4-methoxyphenyl)-1,4-dihydropyrazine-2,3-dione (**16b**) synthesis have been reported.[17]

Ethyl [2-(3,5-dimethylphenyl)amino]-2-oxoacetate (14d). A solution of 3,5-dimethylaniline (24.2 g, 0.2 mol) in diethyl oxalate (100 ml, 0.74 mol) was heated at 150°C for 6 h. After cooling, the solution was diluted with EtOH (100 ml) and left overnight to form a precipitate of the diamide side product, which was separated by filtration. The filtrate was diluted with water (200 ml). On next day, the oil that formed on the bottom was dissolved in EtOH (50 ml) under reflux. After cooling, the precipitate formed was filtered off. Yield 28.3 g (64%), white solid, mp 75–76°C (EtOH) (mp 130°C[18], mp 124–126°C[19]). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.28 (3H, t, *J* = 7.4, C<u>H</u>$_3$CH$_2$); 2.22 (6H, s, 2CH$_3$); 4.26 (2H, q, *J* = 7.4, OCH$_2$); 6.76 (1H, s, H-4 Ar); 7.32 (2H, s, H-2,6 Ar); 10.50 (1H, s, NH). Found, %: C 64.96; H 6.98; N 6.28. $C_{12}H_{15}NO_3$. Calculated, %: C 65.14; H 6.93; N 6.33.

Synthesis of *N*-substituted *N*'-(2,2-dimethoxyethyl)-ethanediamides 15a,c,d (General method). 2,2-Dimethoxyethanamine (34.5 g, 0.33 mol) was added to an agitated solution of the corresponding ethyl amino(oxo)acetate **14a**,**c**,**d** (0.3 mol) in DMF (300 ml). The reaction mixture was refluxed for 3 h. After cooling, the solution was diluted with *i*-PrOH (500 ml) and left overnight. The precipitate was filtered off, washed with *i*-PrOH (300 ml), and recrystallized from mixture of DMF (50 ml) and *i*-PrOH (200 ml). Amides **15a**,**c**,**d** were obtained as white solids.

***N*-(2,2-Dimethoxyethyl)-*N*'-(3-fluorophenyl)ethanediamide (15a)**. Yield 64.1 g (79%). Decomp. temp. >200°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.20 (6H, s, 2OCH$_3$); 3.28 (2H, t, *J* = 5.4, NCH$_2$); 4.50 (1H, t, *J* = 5.4, CH); 6.96 (1H, td, *J* = 8.2, *J* = 0.8, H-4 Ar); 7.38 (1H, q, *J* = 5.3, H-5 Ar); 7.63–7.77 (2H, m, H Ar); 8.94 (1H, t, *J* = 5.4, N<u>H</u>CH$_2$); 10.90 (1H, s, NH). Found, %: C 53.15; H 5.54; N 10.40. $C_{12}H_{15}FN_2O_4$. Calculated, %: C 53.33; H 5.59; N 10.37.

***N*'-(4-Chlorophenyl)-*N*-(2,2-dimethoxyethyl)ethanediamide (15c)**. Yield 69.7 g (81%). Decomp. temp. >200°C (mp 130–132°C[19,20]). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.22–3.28 (8H, m, NCH$_2$, 2OCH$_3$); 4.55 (1H, t, *J* = 5.0, CH); 7.42 (2H, d, *J* = 8.0, H Ar); 7.83 (2H, d, *J* = 8.0, H Ar); 8.90 (1H, t, *J* = 5.4, N<u>H</u>CH$_2$); 10.80 (1H, s, NH). Found, %: C 50.46; H 5.30; N 9.82. $C_{12}H_{15}ClN_2O_4$. Calculated, %: C 50.27; H 5.27; N 9.77.

***N*-(2,2-Dimethoxyethyl)-*N*'-(3,5-dimethylphenyl)ethanediamide (15d)**. Yield 64.8 g (77%). Decomp. temp. >200°C (mp 134–136°C[19,20]). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.23 (6H, s, 2CH$_3$); 3.25 (6H, s, 2OCH$_3$); 3.32 (2H, t, *J* = 5.4, NCH$_2$); 4.52 (1H, t, *J* = 5.4, CH); 6.85 (1H, s, H-4 Ar); 7.42 (2H, s, H-2,6 Ar); 8.80 (1H, t, *J* = 5.4, N<u>H</u>CH$_2$); 10.40 (1H, s, NH). Found, %: C 60.15; H 7.14; N 11.09. $C_{14}H_{20}N_2O_4$. Calculated, %: C 59.99; H 7.19; N 9.99.

Synthesis of 1,4-dihydropyrazine-2,3-diones 16a,c,d (General method). A solution of the appropriate oxalamide **15a**,**c**,**d** (0.2 mol) in a mixture of AcOH (200 ml) and TFA (20 ml) was refluxed for 8 h. After cooling, the reaction mixture was diluted with *i*-PrOH (500 ml) and left overnight. The precipitate was filtered off, washed with *i*-PrOH (200 ml), and recrystallized from mixture of DMF (50 ml) and *i*-PrOH (200 ml). Compounds **16a**,**c**,**d** were obtained as white solids.

1-(3-Fluorophenyl)-1,4-dihydropyrazine-2,3-dione (16a). Yield 32.2 g (78%). Mp >300°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 6.37 (1H, t, *J* = 4.8, H-5); 6.53 (1H, d, *J* = 4.8, H-6); 7.22–7.38 (3H, m, H-2,4,5 Ar); 7.54 (1H, q, *J* = 5.2, H-6 Ar); 11.33 (1H, s, NH). Found, %: C 58.42; H 3.40; N 13.50. $C_{10}H_7FN_2O_2$. Calculated, %: C 58.26; H 3.42; N 13.59.

1-(4-Chlorophenyl)-1,4-dihydropyrazine-2,3-dione (16c). Yield 37.4 g (84%). Mp >300°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 6.36 (1H, t, *J* = 4.8, H-5); 6.51 (1H, d, *J* = 4.8, H-6); 7.45 (2H, d, *J* = 8.0, H Ar); 7.56 (2H, d, *J* = 8.0, H Ar); 11.30 (1H, s, NH). Found, %: C 54.16; H 3.24; N 12.46. $C_{10}H_7ClN_2O_2$. Calculated, %: C 53.95; H 3.17; N 12.58.

1-(3,5-Dimethylphenyl)-1,4-dihydropyrazine-2,3-dione (16d). Yield 34.2 g (79%). Mp >300°C (mp 200–202°C[19,20]). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.23 (6H, s, 2CH_3); 6.36 (1H, t, *J* = 4.8, H-5); 6.44 (1H, d, *J* = 4.8, H-6); 6.97 (2H, s, H-2,6 Ar); 7.05 (1H, s, H-4 Ar); 11.30 (1H, s, NH). Found, %: C 66.46; H 5.54; N 13.08. $C_{12}H_{12}N_2O_2$. Calculated, %: C 66.65; H 5.59; N 12.96.

Synthesis of 3-methoxypyrazin-2(1*H*)-ones 18a–d (General method). Anhydrous DMF (8 ml, 0.1 mol) was added to a stirred suspension of the appropriate 1,4-dihydropyrazine-2,3-dione **16a–d** (0.1 mol) in dichloroethane (200 ml). Then $SOCl_2$ (8 ml, 0.11 mol) was added dropwise with vigorous stirring. The suspension was refluxed with stirring until the dissolution of the precipitate (1–2 h). After cooling, the reaction mixture was diluted with hexane (500 ml). Formed precipitate was filtered off and washed with hexane (200 ml) to obtain crude 3-chloropyrazin-2(1*H*)-one **17a–d** that was used for the next step without additional purification and immediately added to a solution of MeONa (from 9.16 g of Na, 0.4 mol) in dry MeOH (300 ml). The reaction mixture was refluxed for 10 min. The excess of MeOH was evaporated to final volume of the reaction mixture about 100 ml. The reaction mixture was diluted with water (500 ml). On the next day, the precipitate formed was filtered off, washed with water (200 ml), and recrystallized from a mixture of DMF (30 ml) and *i*-PrOH (200 ml). Compounds **18a–d** were obtained as cream-colored solids.

1-(3-Fluorophenyl)-3-methoxypyrazin-2(1*H*)-one (18a). Yield 18.1 g (82%). Mp 206–208°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.84 (3H, s, 3-OCH_3); 6.88 (1H, d, *J* = 4.0, H-5); 7.24 (1H, d, *J* = 4.0, H-6); 7.40–7.64 (4H, m, H Ar). Found, %: C 59.84; H 4.05; N 12.59. $C_{11}H_9FN_2O_2$. Calculated, %: C 60.00; H 4.12; N 12.72.

3-Methoxy-1-(4-methoxyphenyl)pyrazin-2(1*H*)-one (18b). Yield 19.7 g (85%). Mp 198–199°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.78 (3H, s, 4-OCH_3 Ar); 3.84 (3H, s, 3-OCH_3); 6.85 (1H, d, *J* = 4.0, H-5); 7.04 (2H, d, *J* = 7.8, H Ar); 7.17 (1H, d, *J* = 4.0, H-6); 7.35 (2H, d, *J* = 7.8, H Ar). Found, %: C 61.91; H 5.20; N 11.89. $C_{12}H_{12}N_2O_3$. Calculated, %: C 62.06; H 5.21; N 12.06.

1-(4-Chlorophenyl)-3-methoxypyrazin-2(1*H*)-one (18c). Yield 20.8 g (88%). Mp 238–239°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.84 (3H, s, 3-OCH_3); 6.88 (1H, d, *J* = 4.0, H-5); 7.22 (1H, d, *J* = 4.0, H-6); 7.45 (2H, d, *J* = 8.0, H Ar); 7.56 (2H, d, *J* = 8.0, H Ar). Found, %: C 55.61; H 3.91; N 11.69. $C_{11}H_9ClN_2O_2$. Calculated, %: C 55.83; H 3.83; N 11.84.

1-(3,5-Dimethylphenyl)-3-methoxypyrazin-2(1*H*)-one (18d). Yield 18.6 g (81%). Mp 182–183°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.28 (6H, s, 2CH_3); 3.82 (3H, s, 3-OCH_3); 6.85 (1H, d, *J* = 4.0, H-5); 7.02 (2H, s, H-2,6 Ar); 7.08 (1H, s, H-4 Ar); 7.16 (1H, d, *J* = 4.0, H-6). Found, %: C 67.71; H 6.04; N 12.30. $C_{13}H_{14}N_2O_2$. Calculated, %: C 67.81; H 6.13; N 12.17.

Synthesis of 3-aminopyrazin-2(1*H*)-ones 19a–d (General method). 3-Methoxypyrazin-2(1*H*)-one **18a–d** (0.05 mol) was added to a stirred liquid melt of NH_4OAc (38.5 g, 0.5 mol), and the mixture was stirred for 8 h at 140°C. After cooling to 80–90°C, the reaction mixture was poured into water (500 ml). The formed precipitate was filtered off, washed with water (100 ml), and purified by crystallization from a mixture of $CHCl_3$ (200 ml) and hexane (200 ml). Compounds **19a–d** were obtained as cream-colored solids.

3-Amino-1-(3-fluorophenyl)pyrazin-2(1*H*)-one (19a). Yield 6.98 g (68%). Decomp. temp. >250°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 6.70 (1H, d, *J* = 4.0, H-5(6)); 6.75–6.85 (3H, m, H-6(5), NH_2); 7.40–7.64 (4H, m, H Ar). Found, %: C 58.76; H 4.02; N 20.36. $C_{10}H_8FN_3O$. Calculated, %: C 58.53; H 3.93; N 20.48.

3-Amino-1-(4-methoxyphenyl)pyrazin-2(1*H*)-one (19b). Yield 7.49 g (69%). Decomp. temp. >250°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.78 (3H, s, 4-OCH_3 Ar); 6.65–6.85 (4H, m, H-5,6, NH_2); 7.04 (2H, d, *J* = 7.8, H Ar); 7.35 (2H, d, *J* = 7.8, H Ar). Found, %: C 60.53; H 5.02; N 19.46. $C_{11}H_{11}N_3O_2$. Calculated, %: C 60.82; H 5.10; N 19.34.

3-Amino-1-(4-chlorophenyl)pyrazin-2(1*H*)-one (19c). Yield 7.98 g (72%). Decomp. temp. >250°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 6.65–6.85 (4H, m, H-5,6, NH_2); 7.45 (2H, d, *J* = 8.0, H Ar); 7.56 (2H, d, *J* = 8.0, H Ar). Found, %: C 54.29; H 3.56; N 19.13. $C_{10}H_8ClN_3O$. Calculated, %: C 54.19; H 3.64; N 18.96.

3-Amino-1-(3,5-dimethylphenyl)pyrazin-2(1*H*)-one (19d). Yield 7.21 g (67%). Decomp. temp. >250°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.28 (6H, s, 2CH_3); 6.65–6.85 (4H, m, H-5,6, NH_2); 7.02 (2H, s, H-2,6 Ar); 7.08 (1H, s, H-4 Ar). Found, %: C 66.74; H 6.12; N 19.36. $C_{12}H_{13}N_3O$. Calculated, %: C 66.96; H 6.09; N 19.52.

Reaction of 3-chloro-1-(3,5-dimethylphenyl)pyrazin-2(1*H*)-one (17d) with NH_4OAc. Crude 3-chloro-1-(3,5-dimethylphenyl)pyrazin-2(1*H*)-one (**17d**) (2.35 g, 0.01 mol) was added to a stirred liquid melt of NH_4OAc (5.7 g, 0.01 mol), and the mixture was stirred for 8 h at 140°C. After cooling to 80–90°C, the reaction mixture was poured into water (100 ml). The formed precipitate was filtered off, washed with water (20 ml), and dried. The crude product (2.09 g) contained compound **19d** with 20% molar admixture of compound **16d**.

Reaction of 3-chloro-1-(3,5-dimethylphenyl)pyrazin-2(1*H*)-one (17d) with ammonia. Crude 3-chloro-1-(3,5-dimethylphenyl)pyrazin-2(1*H*)-one (**17d**) (2.35 g, 0.01 mol) was added to a mixture of 35% aqueous NH_3 (1 ml, 0.16 mol) and dry 1,4-dioxane (30 ml). The reaction mixture was refluxed for 1 h. After cooling, the reaction mixture was diluted with water (100 ml). The formed precipitate was filtered off, washed with water (20 ml), and dried. The crude product (2.06 g) contained compound **19d** with 35% molar admixture of compound **16d**.

Reaction of 3-methoxy-1-(3,5-dimethylphenyl)pyrazin-2(1*H*)-one (18d) with ammonia. 3-Methoxy-1-(3,5-dimethylphenyl)pyrazin-2(1*H*)-one (**18d**) (2.30 g, 0.01 mol) was dissolved in a mixture of 35% aqueous NH_3 (1 ml, 0.16 mol) and dry DMF (15 ml). The solution was refluxed

for 12 h. After cooling, the reaction mixture was diluted with water (100 ml). The formed precipitate was filtered off, washed with water (20 ml), and dried. The crude product (2.06 g) contained compound **19d** with 25% molar admixture of compound **16d** and 10% molar of the starting compound **18d**.

Synthesis of imidazo[1,2-*a*]pyrazin-8(7*H*)-ones 21a–o (General method). The appropriate 2-bromoacetophenone **20a–d** (1.1 mmol) was added to a stirred solution of 3-aminopyrazin-2(1*H*)-one **19a–d** (1 mmol) in anhydrous DMF (5 ml). The reaction mixture was refluxed for 2 h. After cooling, the reaction mixture was diluted with 10% aqueous NH_3 solution (50 ml). The precipitate that formed was filtered off, washed with MeOH (5 ml), and recrystallized from a mixture of DMF (5 ml) and MeOH (20 ml). Compounds **21a–o** were obtained as white solids.

2-(4-Ethylphenyl)-7-(3-fluorophenyl)imidazo[1,2-*a*]pyrazin-8(7*H*)-one (21a). Yield 0.28 g (85%). Mp >300°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.22 (3H, t, *J* = 7.7, C<u>H</u>$_3$CH$_2$); 2.62 (2H, q, *J* = 7.7, CH$_3$C<u>H</u>$_2$); 7.14 (1H, d, *J* = 4.0, H-5); 7.20–7.66 (7H, m, H-6, H Ar^1, H Ar^2); 7.84 (2H, d, *J* = 7.8, H Ar^2); 8.26 (1H, s, H-3). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 15.5 (CH$_3$); 28.0 (CH$_2$); 107.4; 113.1; 114.3–115.2 (2C, m); 121.1; 123.1; 125.4 (2C); 128.2 (2C); 130.6; 130.8 (d, J_{CF} = 9.0, C Ar^1); 137.2; 141.2 (d, J_{CF} = 9.0, C Ar^1); 143.6; 144.3; 152.3; 161.8 (d, J_{CF} = 245.0, C-3 Ar^1). Found, %: C 71.89; H 4.89; N 12.58. $C_{20}H_{16}FN_3O$. Calculated, %: C 72.06; H 4.84; N 12.61.

2-(4-Ethoxyphenyl)-7-(3-fluorophenyl)imidazo[1,2-*a*]pyrazin-8(7*H*)-one (21b). Yield 0.29 g (82%). Mp >300°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.30 (3H, t, *J* = 7.7, C<u>H</u>$_3$CH$_2$); 4.00 (2H, q, *J* = 7.7, CH$_3$C<u>H</u>$_2$); 6.98 (2H, d, *J* = 7.8, H Ar^2); 7.18 (1H, d, *J* = 4.0, H-5); 7.40–7.64 (5H, m, H-6, H Ar^1); 7.82 (2H, d, *J* = 7.8, H Ar^2); 8.18 (1H, s, H-3). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 14.7 (<u>C</u>H$_3$CH$_2$); 63.1 (OCH$_2$); 107.4; 112.7; 114.3–115.2 (4C, m); 121.2; 123.0; 125.6; 126.7 (2C); 130.7 (d, J_{CF} = 9.0, C Ar^1); 137.3; 141.2 (d, J_{CF} = 9.0, C Ar^1); 144.3; 152.4; 158.4; 161.8 (d, J_{CF} = 245.0, C-3 Ar^1). Found, %: C 68.96; H 4.66; N 11.86. $C_{20}H_{16}FN_3O_2$. Calculated, %: C 68.76; H 4.62; N 12.03.

2-(3,4-Dimethoxyphenyl)-7-(3-fluorophenyl)imidazo-[1,2-*a*]pyrazin-8(7*H*)-one (21c). Yield 0.31 g (85%). Mp >300°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.78 (3H, s, OCH$_3$); 3.84 (3H, s, OCH$_3$); 7.02 (1H, d, *J* = 7.8, H-5 Ar^2); 7.16 (1H, d, *J* = 4.0, H-5); 7.28–7.68 (7H, m, H Ar); 8.25 (1H, s, H-3). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 55.6 (2OCH$_3$); 107.4; 109.0; 112.2; 113.1; 114.5–115.3 (2C, m); 117.9; 121.0; 123.2; 125.9; 130.8 (d, J_{CF} = 9.0, C Ar^1); 136.8; 141.1 (d, J_{CF} = 10.0, C Ar^1); 144.5; 148.9; 149.1; 152.3; 161.8 (d, J_{CF} = 245.0, C-3 Ar^1). Found, %: C 65.92; H 4.47; N 11.38. $C_{20}H_{16}FN_3O_3$. Calculated, %: C 65.75; H 4.41; N 11.50.

2-(4-Chlorophenyl)-7-(3-fluorophenyl)imidazo[1,2-*a*]pyrazin-8(7*H*)-one (21d). Yield 0.29 g (84%). Mp >300°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.22 (1H, d, *J* = 4.0, H-5); 7.26–7.66 (7H, m, H Ar^1); 7.96 (2H, d, *J* = 8.0, H Ar^2); 8.35 (1H, s, H-3). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 107.4; 114.1; 114.3–115.2 (m, 2C Ar^1); 121.2; 123.0; 127.2 (2C); 128.8 (2C); 130.7 (d, J_{CF} = 9, C Ar^1); 132.1; 132.5; 137.3; 141.2 (d, J_{CF} = 9, C Ar^1); 143.3; 152.3; 162.0 (d, J_{CF} = 246, C-3 Ar^1). Found, %: C 63.85; H 3.31; N 12.18. $C_{18}H_{11}ClFN_3O$. Calculated, %: C 63.63; H 3.26; N 12.37.

2-(4-Ethylphenyl)-7-(4-methoxyphenyl)imidazo[1,2-*a*]pyrazin-8(7*H*)-one (21e). Yield 0.28 g (82%). Mp >300°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.22 (3H, t, *J* = 7.7, C<u>H</u>$_3$CH$_2$); 2.62 (2H, q, *J* = 7.7, CH$_3$C<u>H</u>$_2$); 3.78 (3H, s, OCH$_3$); 7.06 (2H, d, *J* = 7.8, H Ar^1); 7.12 (1H, d, *J* = 4.0, H-5); 7.24 (2H, d, *J* = 7.8, H Ar^2); 7.38 (2H, d, *J* = 7.8, H Ar^1); 7.59 (1H, d, *J* = 4.0, H-6); 7.84 (2H, d, *J* = 7.8, H Ar^2); 8.26 (1H, s, H-3). ^{13}C NMR spectrum, δ, ppm: 15.5 (CH$_3$); 28.0 (CH$_2$); 55.5 (OCH$_3$); 107.0; 113.2; 114.3 (2C); 121.4; 125.4 (2C); 128.1 (2C); 128.2 (2C); 130.6; 132.6; 137.2; 143.6; 144.3; 152.7; 158.8. Found, %: C 72.86; H 5.62; N 12.36. $C_{21}H_{19}N_3O_2$. Calculated, %: C 73.03; H 5.54; N 12.17.

2-(4-Ethoxyphenyl)-7-(4-methoxyphenyl)imidazo[1,2-*a*]pyrazin-8(7*H*)-one (21f). Yield 0.29 g (81%). Mp >300°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.30 (3H, t, *J* = 7.7, C<u>H</u>$_3$CH$_2$); 3.78 (3H, s, OCH$_3$); 4.00 (2H, q, *J* = 7.7, CH$_3$C<u>H</u>$_2$); 6.98 (2H, d, *J* = 7.8, H Ar^2); 7.03–7.14 (3H, m, H-5, Ar^1); 7.36 (2H, d, *J* = 7.8, H Ar^1); 7.57 (1H, d, *J* = 4.0, H-6); 7.82 (2H, d, *J* = 7.8, H Ar^2); 8.15 (1H, s, H-3). ^{13}C NMR spectrum, δ, ppm: 14.7 (<u>C</u>H$_3$CH$_2$); 55.5 (OCH$_3$); 63.1 (OCH$_2$); 107.1; 112.6; 114.3 (2C); 114.7 (2C); 121.8; 125.6; 126.7 (2C); 128.0 (2C); 132.8; 137.1; 144.4; 152.4; 158.4; 158.8. Found, %: C 70.01; H 5.25; N 11.55. $C_{21}H_{19}N_3O_3$. Calculated, %: C 69.79; H 5.30; N 11.63.

2-(3,4-Dimethoxyphenyl)-7-(4-methoxyphenyl)imidazo-[1,2-*a*]pyrazin-8(7*H*)-one (21g). Yield 0.32 g (85%). Mp >300°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.78 (3H, s, OCH$_3$); 3.80 (3H, s, OCH$_3$); 3.84 (3H, s, OCH$_3$); 7.02–7.12 (4H, m, H Ar); 7.38 (2H, d, *J* = 7.8, H Ar^1); 7.47 (1H, d, *J* = 7.9, H-6 Ar^2); 7.53 (1H, s, H-2 Ar^2); 7.58 (1H, d, *J* = 4.0, H-6); 8.18 (1H, s, H-3). ^{13}C NMR spectrum, δ, ppm: 55.6 (OCH$_3$); 55.9 (2OCH$_3$); 107.0; 109.9; 112.8 (2C); 114.5 (2C); 118.2; 121.6; 126.3; 128.0 (2C); 132.8; 137.1; 144.5; 149.2; 149.4; 152.7; 158.9. Found, %: C 67.12; H 5.12; N 11.04. $C_{21}H_{19}N_3O_4$. Calculated, %: C 66.83; H 5.07; N 11.13.

2-(4-Chlorophenyl)-7-(4-methoxyphenyl)imidazo[1,2-*a*]pyrazin-8(7*H*)-one (21h). Yield 0.31 g (87%). Mp >300°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.78 (3H, s, 4-OCH$_3$); 7.06 (2H, d, *J* = 7.8, H Ar^1); 7.13 (1H, d, *J* = 4.0, H-5); 7.38 (2H, d, *J* = 7.8, H Ar^1); 7.48 (2H, d, *J* = 8.0, H Ar^2); 7.62 (1H, d, *J* = 4.0, H-6); 7.96 (2H, d, *J* = 8.0, H Ar^2); 8.35 (1H, s, H-3). ^{13}C NMR spectrum, δ, ppm: 55.5 (OCH$_3$); 107.0; 114.0; 114.3 (2C); 121.8; 127.1 (2C); 128.0 (2C); 128.9 (2C); 132.0; 132.3; 132.8; 137.1; 144.6; 152.6; 158.8. Found, %: C 65.09; H 4.07; N 11.84. $C_{19}H_{14}ClN_3O_2$. Calculated, %: C 64.87; H 4.01; N 11.94.

7-(4-Chlorophenyl)-2-(4-ethylphenyl)imidazo[1,2-*a*]pyrazin-8(7*H*)-one (21i). Yield 0.30 g (87%). Mp >300°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.22 (3H, t, *J* = 7.7, C<u>H</u>$_3$CH$_2$); 2.62 (2H, q, *J* = 7.7, CH$_3$C<u>H</u>$_2$); 7.16 (1H, d, *J* = 4.0, H-5); 7.26 (2H, d, *J* = 7.8, H Ar^2); 7.52–7.64 (5H, m, H-6, H Ar^1); 7.84 (2H, d, *J* = 7.8, H Ar^2); 8.24 (1H, s, H-3). ^{13}C NMR spectrum, δ, ppm: 15.3 (CH$_3$); 27.9 (CH$_2$); 107.4; 113.3; 121.0; 125.5 (2C); 128.1 (2C); 128.8 (2C); 129.1

(2C); 130.6; 132.7; 136.9; 138.6; 143.6; 144.6; 152.4. Found, %: C 68.46; H 4.54; N 11.93. $C_{20}H_{16}ClN_3O$. Calculated, %: C 68.67; H 4.61; N 12.01.

7-(4-Chlorophenyl)-2-(4-ethoxyphenyl)imidazo[1,2-*a*]-pyrazin-8(7*H*)-one (21j). Yield 0.31 g (86%). Mp >300°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.30 (3H, t, *J* = 7.7, C<u>H</u>$_3$CH$_2$); 4.00 (2H, q, *J* = 7.7, CH$_3$C<u>H</u>$_2$); 6.98 (2H, d, *J* = 7.8, H Ar^2); 7.16 (1H, d, *J* = 4.0, H-5); 7.52–7.64 (5H, m, H-6, H Ar^1); 7.82 (2H, d, *J* = 7.8, H Ar^2); 8.18 (1H, s, H-3). ^{13}C NMR spectrum, δ, ppm: 14.7 (<u>C</u>H$_3$CH$_2$); 63.1 (OCH$_2$); 107.4; 112.6; 114.7 (2C); 121.0; 125.6; 126.7 (2C); 128.8 (2C); 129.1 (2C); 132.7; 136.9; 138.6; 144.7; 152.4; 158.4. Found, %: C 65.46; H 4.54; N 11.62. $C_{20}H_{16}ClN_3O_2$. Calculated, %: C 65.67; H 4.41; N 11.49.

7-(4-Chlorophenyl)-2-(3,4-dimethoxyphenyl)imidazo-[1,2-*a*]pyrazin-8(7*H*)-one (21k). Yield 0.32 g (84%). Mp >300°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.78 (3H, s, OCH$_3$); 3.84 (3H, s, OCH$_3$); 7.02 (1H, d, *J* = 7.8, H-5 Ar^2); 7.12 (1H, d, *J* = 4.0, H-5); 7.44–7.66 (7H, m, H Ar); 8.20 (1H, s, H-3). ^{13}C NMR spectrum, δ, ppm: 55.9 (2OCH$_3$); 107.4; 109.9; 112.8; 113.0; 118.2; 120.9; 126.3; 128.8 (2C); 129.1 (2C); 132.7; 136.9; 138.6; 144.7; 149.2; 149.4; 152.4. Found, %: C 63.14; H 4.18; N 10.86. $C_{20}H_{16}ClN_3O_3$. Calculated, %: C 62.91; H 4.22; N 11.01.

7-(3,5-Dimethylphenyl)-2-(4-ethylphenyl)imidazo[1,2-*a*]-pyrazin-8(7*H*)-one (21l). Yield 0.28 g (82%). Mp 290–293°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.22 (3H, t, *J* = 7.7, C<u>H</u>$_3$CH$_2$); 2.28 (6H, s, 2CH$_3$); 2.62 (2H, q, *J* = 7.7, CH$_3$C<u>H</u>$_2$); 7.03–7.14 (4H, m, H-5, H Ar^1); 7.24 (2H, d, *J* = 7.8, H Ar^2); 7.59 (1H, d, *J* = 4.0, H-6); 7.82 (2H, d, *J* = 7.8, H Ar^2); 8.24 (1H, s, H-3). ^{13}C NMR spectrum, δ, ppm: 15.5 (<u>C</u>H$_3$CH$_2$); 20.8 (2CH$_3$); 28.0 (CH$_2$); 107.1; 113.2; 121.5; 124.5 (2C); 125.4 (2C); 128.2 (2C); 129.6; 130.6; 137.1; 138.5 (2C); 139.7; 143.5; 144.4; 152.5. Found, %: C 76.72; H 6.08; N 12.33. $C_{22}H_{21}N_3O$. Calculated, %: C 76.94; H 6.16; N 12.24.

7-(3,5-Dimethylphenyl)-2-(4-ethoxyphenyl)imidazo-[1,2-*a*]pyrazin-8(7*H*)-one (21m). Yield 0.30 g (83%). Mp 287–289°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.30 (3H, t, *J* = 7.7, C<u>H</u>$_3$CH$_2$); 2.28 (6H, s, 2CH$_3$); 4.00 (2H, q, *J* = 7.7, CH$_3$C<u>H</u>$_2$); 6.98 (2H, d, *J* = 7.8, H Ar^2); 7.03–7.14 (4H, m, H-5, H Ar^1); 7.57 (1H, d, *J* = 4.0, H-6); 7.82 (2H, d, *J* = 7.8, H Ar^2); 8.18 (1H, s, H-3). ^{13}C NMR spectrum, δ, ppm: 14.7 (<u>C</u>H$_3$CH$_2$); 20.8 (2CH$_3$); 63.1 (OCH$_2$); 107.1; 112.6; 114.7 (2C); 121.4; 124.5 (2C); 125.6; 126.7 (2C); 129.6; 137.0; 138.5 (2C); 139.7; 144.3; 152.4; 158.4. Found, %: C 73.66; H 6.00; N 11.53. $C_{22}H_{21}N_3O_2$. Calculated, %: C 73.52; H 5.89; N 11.69.

2-(3,4-Dimethoxyphenyl)-7-(3,5-dimethylphenyl)-imidazo[1,2-*a*]pyrazin-8(7*H*)-one (21n). Yield 0.30 g (81%). Mp 304–306°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.28 (6H, s, 2CH$_3$); 3.78 (3H, s, OCH$_3$); 3.84 (3H, s, OCH$_3$); 7.02–7.15 (5H, m, H Ar); 7.47 (1H, d, *J* = 7.9, H-6 Ar^2); 7.54 (1H, s, H-2 Ar^2); 7.58 (1H, d, *J* = 4.0, H-6); 8.18 (1H, s, H-3). ^{13}C NMR spectrum, δ, ppm: 20.7 (2CH$_3$); 55.9 (2OCH$_3$); 107.0; 109.9; 112.9 (2C); 118.2; 121.3; 124.4 (2C); 126.3; 129.5; 137.1; 138.5 (2C); 139.9; 144.6; 149.2; 149.4; 152.4. Found, %: C 70.11; H 5.56; N 11.05. $C_{22}H_{21}N_3O_3$. Calculated, %: C 70.38; H 5.64; N 11.19.

2-(4-Chlorophenyl)-7-(3,5-dimethylphenyl)imidazo-[1,2-*a*]pyrazin-8(7*H*)-one (21o). Yield 0.29 g (84%). Mp >300°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.28 (6H, s, 2CH$_3$); 7.02–7.15 (4H, m, H-5, H Ar^1); 7.48 (2H, d, *J* = 8.0, H Ar^2); 7.62 (1H, d, *J* = 4.0, H-6); 7.96 (2H, d, *J* = 8.0, H Ar^2); 8.35 (1H, s, H-3). ^{13}C NMR spectrum, δ, ppm: 20.8 (2CH$_3$); 107.1; 114.0; 121.7; 124.5 (2C); 127.1 (2C); 128.9 (2C); 129.6; 132.0; 132.3; 137.4; 138.5 (2C); 139.6; 143.0; 152.5. Found, %: C 68.83; H 4.66; N 11.89. $C_{20}H_{16}ClN_3O$. Calculated, %: C 68.67; H 4.61; N 12.01.

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