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A new, one-pot, multi-component synthesis of imines of 3-amino-2-arylimidazo[1,2-*a*]pyridines, 3-amino-2-arylimidazo[1,2-*a*]pyrazines, and 3-amino-2-arylimidazo[1,2-*a*]pyrimidines

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3-Amino-2-arylimidazo[1,2-*a*]pyrazines
3-Amino-2-arylimidazo[1,2-*a*]pyrimidines
Multi-component reactions

ABSTRACT

An efficient, one-pot, multi-component synthesis of 3-amino-2-arylimidazo[1,2-*a*]pyridines, 3-amino-2-arylimidazo[1,2-*a*]pyrazines, and 3-amino-2-arylimidazo[1,2-*a*]pyrimidines is described. Heating a mixture of a 2-aminopyridine, 2-aminopyrazine or 2-aminopyrimidine, a benzaldehyde, and imidazoline-2,4,5-trione under solvent-free conditions afforded imine derivatives of the title compounds in excellent yields. Single-crystal X-ray analysis conclusively confirms the structure of these bridgehead bicyclic 5–6 heterocycles.

1. Introduction

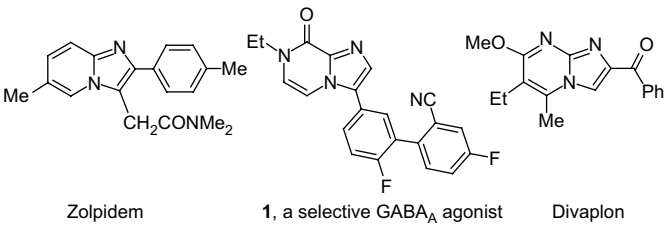
Multi-component reactions (MCRs) have emerged as an efficient and powerful tool in modern synthetic organic chemistry due to their valued features such as atom economy, straightforward reaction design, and the opportunity to construct target compounds by the introduction of several diversity elements in a single chemical event. Typically, purification of products resulting from MCRs is also simple since all the organic reagents employed are consumed and are incorporated into the target compound.[1] MCRs, leading to interesting heterocyclic scaffolds, are particularly useful for the construction of diverse chemical libraries of 'drug-like' molecules.

Imidazo[1,2-*a*]pyridines, -pyrazines, and -pyrimidines, nitrogen-bridgehead fused heterocycles containing an imidazole ring, are a common structural motif in pharmacologically important molecules, with activities spanning a diverse range of targets.[2,3]

Compounds containing imidazo[1,2-*a*]pyridine ring system have been shown to possess antibacterial, anthelmintic, antiinflammatory, anticonvulsant, hypnotic (e.g., zolpidem; Fig. 1), gastrointestinal, and immunomodulatory activities.[2]

Some imidazo[1,2-*a*]pyrazines have exhibited chemi- and bioluminescence reactivities.[4] Compound **1** (Fig. 1) is a selective $GABA_A$ $\alpha2/\alpha3$ agonist for the treatment of anxiety.[5] Some examples have also been used in the treatment of kinase-implicated disorders.[6]

Derivatives containing the imidazo[1,2-*a*]pyrimidine ring system have been shown to possess antiinflammatory, analgesic,



Zolpidem **1**, a selective $GABA_A$ agonist Divaplon

Figure 1. Examples of imidazo[1,2-*a*]pyridines, -pyrazines, and -pyrimidines with pharmaceutical and/or pharmacological activity.

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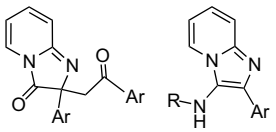
antipyretic, bronchodilator, anxiolytic (e.g., divaplon; Fig. 1), and antifungal activities.[7]

There are several methods reported in the literature for the preparation of 2- or 3-substituted imidazo[1,2-*a*]pyridines with the majority relying on the condensation of 2-aminopyridine with α-bromoketones to form the five-membered cyclic system.[2] Particularly interesting are those structures that contain an amino group at C-2 or C-3. There are well established methods for the preparation of 3-aminoimidazo[1,2-*a*]pyridines; these include nitration at C-3 of the already formed heterocycle and subsequent reduction,[8] a multi-component reaction between 2-aminopyridines, aldehydes, and isonitriles[9–11] or preparation from pyridinium fluorides,[12] Strecker-type reaction between 2-aminopyridines, cyanide ions, and a limited number of aldehydes,[13a] ionic liquid promoted reaction between an 2-aminoazine, an aldehyde, and trimethylsilylcyanide,[13b] or by use of benzotriazole as an auxiliary group.[14] Most of these methods involve three or more sequential synthetic steps, the use of harsh reaction conditions that give low yields, and in some cases, use of hazardous or expensive starting materials.

To date, the most common synthetic methods reported for the preparation of imidazo[l,2-*a*]pyrazine and imidazo[1,2-*a*]pyrimidine ring systems involve closure of the imidazole ring by the condensation of 2-aminopyrazine or 2-aminopyrimidine and closure of the pyrazine or pyrimidine ring by the condensation of 2-aminoimidazole with appropriate electrophilic compounds.[3]

2. Results and discussion

As part of our continuing efforts on the development of new routes for the preparation of biologically active heterocyclic compounds,[15] we recently described two new syntheses of fused imidazoles: imidazo[1,2-*a*]pyridin-3-ones **2** via condensation reaction of 2-aminopyridines with diaroylacetylenes[16] and imidazo[1,2-*a*]pyridines **3** via a catalyst-free reaction between 2-aminopyridines, aldehydes, and isocyanides in water.[17]



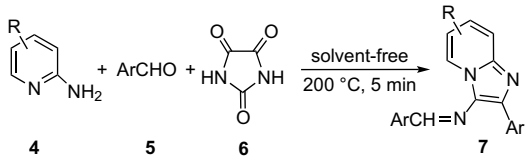
2 **3**

Considering the important biological properties of imidazo[1,2-*a*]pyridines, imidazo[1,2-*a*]pyrazines, and imidazo[1,2-*a*]pyrimidines we report herein[18] an efficient simple synthesis of these nuclei using simple starting materials bearing in mind previously reported syntheses. Thus, a mixture of 2-aminopyridines **4** or 2-aminoazines **8**, benzaldehydes **5**, and imidazoline-2,4,5-trione **6** were found to undergo a new one-pot multi-component reaction at 200 °C within 5 min under solvent-free conditions to produce 3-amino-2-arylimidazo[1,2-*a*]pyridines **7a–i** (Table 1), 3-amino-2-arylimidazo[1,2-*a*]pyrazines, and 3-amino-2-arylimidazo[1,2-*a*]-pyrimidines **9a–j** in 92–97% yields (Table 2).

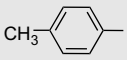
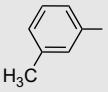
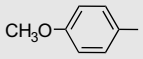
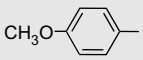
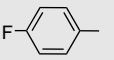
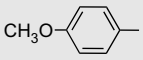
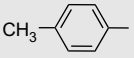
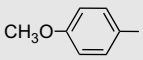
When the reaction was performed using equivalent ratios of 2-aminopyridine (**4**, R=H), benzaldehyde (**5**, Ar=C_6H_5), and imidazoline-2,4,5-trione **6**, ^{1}H NMR analysis of the reaction mixture indicated the formation of imidazo[1,2-*a*]pyridine **7a** in nearly 45% yield. Almost half of the 2-aminopyridine **4** was recovered unreacted at the end of the reaction. The best results were obtained when the reactions were carried out using the three components in a ratio of 1:2.5:1.5 (see Section 4).

The structures of imidazo[1,2-*a*]pyridines **7a–i** were confirmed by IR, ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry, and elemental analysis. The mass spectrum of **7d** displayed the molecular ion (M^+) peak at *m*/*z* 357, which was consistent with the product

Table 1
Multi-component synthesis of imidazo[1,2-*a*]pyridines



4 **5** **6** **7**

7	R	Ar	% Yield[a]
a	H		95
b	H		92
c	H		92
d	H		94
e	6-CH_3		97
f	6-CH_3		97
g	7-CH_3		94
h	6-CH_3		92
i	8-CH_3		93

[a] Isolated yields.

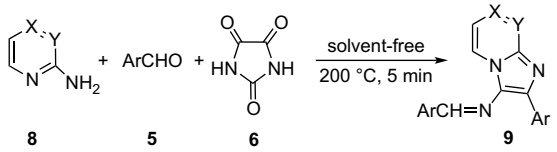
structure. The ^{1}H NMR spectrum of **7d** exhibited three sharp singlets, arising from the two CH_3O (δ 3.81 and 3.82 ppm) and aldimine (δ 8.67 ppm) groups along with characteristic multiplets with appropriate chemical shifts and coupling constants for the four H atoms of the electron-rich diene moiety of the six-membered ring and the eight H atoms of the two aryl substituents. The ^{1}H-decoupled ^{13}C NMR spectrum of **7d** showed 18 distinct resonances, in agreement with the proposed structure.

The isolated imidazo[l,2-*a*]azines **9a–h** were characterized on the basis of their elemental analyses and IR, ^{1}H NMR, and ^{13}C NMR spectra. The nature of these products was apparent from their mass spectra, which displayed molecular ion peaks at the appropriate *m*/*z* values. The ^{1}H NMR spectrum of **9f** exhibited three sharp singlets, arising from the two methyl (δ 2.37 and 2.41 ppm) and aldimine (δ 8.80 ppm) groups along with four doublets with appropriate chemical shifts and coupling constants for the eight H atoms of the two aryl substituents. Three characteristic doublet of doublets (δ 6.87, 8.50, and 8.63 ppm; *J*=6.8, 4.1, and 2.0 Hz) were seen for the three mutually coupling CHs in positions 5, 6, and 7 of the bicyclic ring. The ^{1}H-decoupled ^{13}C NMR spectrum of **9f** showed 17 distinct resonances, in agreement with the suggested structure. Partial assignments of these resonances are given in Section 4.

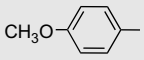
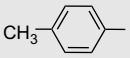
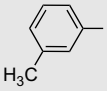
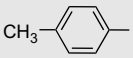
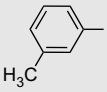
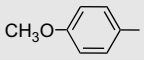
Single-crystal X-ray analysis of **7d** confirmed conclusively the structure of the isolated products. An ORTEP diagram of **7d** is shown in Figure 2.[19]

Although we have not yet established the mechanism of the reaction between 2-aminopyridines or 2-aminoazines, benzaldehydes, and imidazoline-2,4,5-trione in an experimental manner, a mechanistic rationalization for this reaction is provided in

Table 2
Multi-component synthesis of imidazo[1,2-*a*]pyrazines and imidazo[1,2-*a*]-pyrimidines

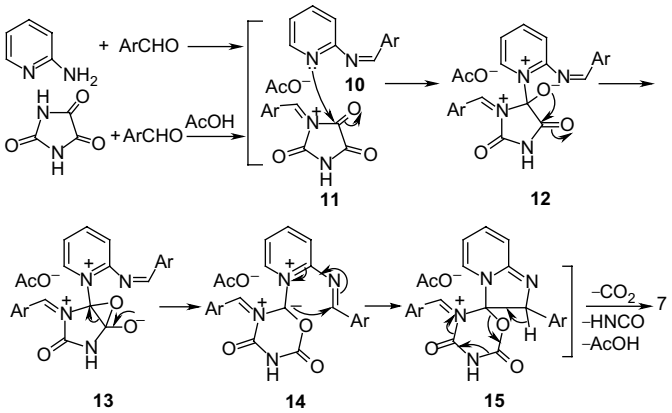


8 5 6 9

9	X, Y	Ar	% Yield[a]
a	X=N, Y=CH		95
b	X=N, Y=CH		92
c	X=N, Y=CH		92
d	X=N, Y=CH		94
e	X=CH, Y=N		96
f	X=CH, Y=N		94
g	X=CH, Y=N		97
h	X=CH, Y=N		97

[a] Isolated yields.

Scheme 1 (exemplified by **4**, R=H). The first step may involve condensation of the aldehyde with 2-aminopyridine and imidazoline-2,4,5-trione with formation of aldimine **10** and imidazolium ion **11**, respectively. Then the imidazolium ion **11** is probably attacked by the pyridine-*N* atom of the aldimine **10** leading to adduct **12**. Intramolecular nucleophilic addition of alkoxide to the adjacent carbonyl group would yield epoxide intermediate **13**, which may undergo ring opening to form ylide **14**. This ylide may undergo intramolecular cyclization to dihydroimidazo[1,2-*a*]pyridine intermediate **15** from which a carbon dioxide, an isocyanic acid, and an acetic acid molecule may be removed to afford the imidazo[1,2-*a*]pyridine **7**.



Scheme 1.

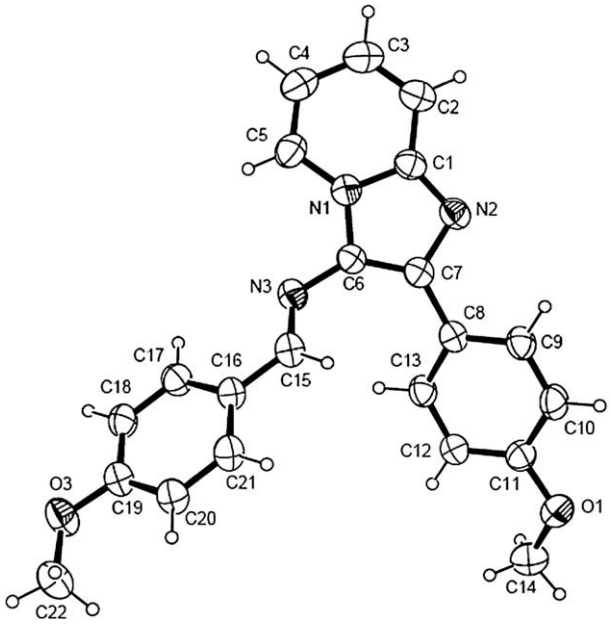


Figure 2. ORTEP diagram of the structure of **7d**.

3. Conclusion

In conclusion, we have developed a new, efficient, one-pot multi-component synthesis of 3-amino-2-arylimidazo[1,2-*a*]pyridine, 3-amino-2-arylimidazo[1,2-*a*]pyrazine, and 3-amino-2-arylimidazo[1,2-*a*]pyrimidine imine derivatives of potential synthetic and pharmacological interest. Solvent-free conditions, excellent yields of the products, and use of simple starting materials are the main advantages of this method. The simplicity of this method makes it an interesting alternative to other approaches.

4. Experimental

4.1. General

2-Aminopyridines, 2-aminopyrazine, 2-aminopyrimidine, and aromatic aldehydes were obtained from Merck (Germany) and were used without further purification. Imidazoline-2,4,5-trione was prepared according to the procedure.[20] Melting points were measured on an Electrothermal 9100 apparatus. Elemental analyses for C, H, and N were performed using a Heraeus CHN-O-Rapid analyzer. Mass spectra were recorded on an Agilent Technologies (HP) 5973 mass spectrometer operating at an ionization potential of 20 eV. ^{1}H and ^{13}C NMR spectra were measured with Bruker DRX-500 AVANCE (at 500.1 and 125.8 MHz) spectrometer using $CDCl_3$ solvent with TMS as an internal standard. IR spectra were recorded on a Shimadzu IR-460 spectrometer. Chromatography columns were prepared from Merck silica gel 60 mesh.

4.2. General procedure

A mixture of the appropriate 2-aminopyridine or 2-aminoazine, **4** or **8** (2 mmol), the appropriate aldehyde (5 mmol), and imidazoline-2,4,5-trione (0.342 g, 3 mmol) was stirred at 200 °C for 5 min. Then the reaction mixture was cooled to room temperature and the residue was purified by column chromatography using *n*-hexane–ethyl acetate (1:3) as eluent. The solvent was removed and the product was recrystallized from 1:2 *n*-hexane–EtOAc.

*4.2.1. 2-Phenyl-N^3-[(E)-1-phenylmethylidene]imidazo[1,2-a]pyridin-3-amine (**7a**)*

Yellow crystals, mp 161–163 °C, yield: 0.56 g, 95% (relative to 2-aminopyridine). IR (KBr) (ν_{max}/cm^{-1}): 1604, 1575, 1497, 1435, 1416, 1362, 1301, 1275, 1239, 1214, 1100, 1043, 804, 765, 690. MS *m*/*z* (%): 297 (M^+, 100), 208 (19), 194 (15), 181 (63), 105 (21), 91 (16), 78 (39), 68 (21), 52 (43). Anal. Calcd for $C_{20}H_{15}N_3$ (297.36): C, 80.78; H, 5.08; N, 14.13. Found: C, 80.9; H, 5.2; N, 14.0%. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 6.89 (1H, t, *J*=6.7 Hz, CH), 7.24 (1H, dd, *J*=7.5 and 7.6 Hz, 1CH), 7.36 (1H, t, *J*=7.4 Hz, CH), 7.40–7.48 (5H, m, 5CH), 7.60 (1H, d, *J*=9.0 Hz, 1CH), 7.83 (2H, d, *J*=7.5 Hz, 2CH), 7.84 (2H, d, *J*=7.5 Hz, 2CH), 8.46 (1H, d, *J*=6.8 Hz, CH), 8.79 (1H, s, CH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 113.0, 118.0, 123.9, 125.7, 128.5, 128.9, 129.0, 129.3, 129.4 and 131.9 (10CH), 135.5, 137.1 and 143.6 (3C), 157.9 (CH).

*4.2.2. 2-(4-Methylphenyl)-N^3-[(E)-1-(4-methylphenyl)-methylidene]imidazo[1,2-a]pyridin-3-amine (**7b**)*

Yellow crystals, mp 154–155 °C, yield: 0.60 g, 92%. IR (KBr) (ν_{max}/cm^{-1}): 1601, 1574, 1502, 1435, 1414, 1366, 1340, 1304, 1271, 1236, 1188, 1175, 1109, 1067, 1043, 1020, 926, 825, 779, 752, 745. MS *m*/*z* (%): 325 (M^+, 45), 310 (7), 220 (10), 198 (47), 183 (10), 145 (25), 135 (24), 121 (100), 105 (31), 91 (82), 84 (60), 78 (88), 67 (32), 56 (55). Anal. Calcd for $C_{22}H_{19}N_3$ (325.41): C, 81.20; H, 5.89; N, 12.91. Found: C, 81.3; H, 5.9; N, 12.8%. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 2.37 and 2.38 (6H, 2s, $2CH_3$), 6.79 (1H, t, *J*=6.7 Hz, CH), 7.15 (1H, dt, *J*=1.2 and 6.7 Hz, CH), 7.20 (2H, d, *J*=8.1 Hz, 2CH), 7.22 (2H, d, *J*=8.0 Hz, 2CH), 7.53 (1H, d, *J*=9.0 Hz, CH), 7.69 (2H, d, *J*=8.0 Hz, 2CH), 7.72 (2H, d, *J*=8.1 Hz, 2CH), 8.35 (1H, d, *J*=6.7 Hz, CH), 8.73 (1H, s, CH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 21.3 and 21.6 ($2CH_3$), 112.1, 117.3, 123.2, 124.7, 128.2 and 128.3 (6CH), 128.9 (C), 129.4 and 129.5 (2CH), 132.1, 133.8, 134.0, 137.6, 141.8 and 142.8 (6C), 157.4 (CH).

*4.2.3. 2-(3-Methylphenyl)-N^3-[(E)-1-(3-methylphenyl)-methylidene]imidazo[1,2-a]pyridin-3-amine (**7c**)*

Yellow crystals, mp 165 °C, yield: 0.60 g, 92%. IR (KBr) (ν_{max}/cm^{-1}): 1606, 1580, 1499, 1435, 1364, 1303, 1273, 1240, 1215, 1151, 1094, 1043, 910, 885, 788, 752, 690. MS *m*/*z* (%): 325 (M^+, 100), 310 (9), 221 (13), 195 (91), 135 (13), 121 (82), 105 (12), 94 (48), 86 (15), 84 (22), 78 (97), 67 (13). Anal. Calcd for $C_{22}H_{19}N_3$ (325.41): C, 81.20; H, 5.89; N, 12.91. Found: C, 81.2; H, 5.8; N, 12.7%. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 2.37 and 2.38 (6H, 2s, $2CH_3$), 6.79 (1H, dt, *J*=1.0 and 6.7 Hz, CH), 7.12–7.15 (2H, m, 2CH), 7.22 (1H, d, *J*=7.8 Hz, CH), 7.25–7.29 (2H, m, 2CH), 7.53–7.60 (3H, m, 3CH), 7.61 (1H, s, CH), 7.70 (1H, s, CH), 8.36 (1H, d, *J*=6.7 Hz, CH), 8.72 (1H, s, CH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 21.3 and 21.5 ($2CH_3$), 112.3, 117.3, 123.3, 124.9, 125.2, 125.7, 128.6, 128.7, 128.8 and 128.9 (10CH), 129.0 (C), 129.4 and 132.1 (2CH), 134.0, 134.9, 136.5, 138.4, 138.5 and 142.9 (6C), 157.5 (CH).

*4.2.4. 2-(4-Methoxyphenyl)-N^3-[(E)-1-(4-methoxyphenyl)-methylidene]imidazo[1,2-a]pyridin-3-amine (**7d**)*

Yellow crystals, mp 175 °C, yield: 0.67 g, 94%. IR (KBr) (ν_{max}/cm^{-1}): 1605, 1575, 1517, 1475, 1362, 1310, 1239, 1169, 1097, 1067, 1036, 825, 769, 751. MS *m*/*z* (%): 357 (M^+, 100), 342 (8), 239 (9), 211 (88), 196 (9), 178 (5), 78 (72). Anal. Calcd for $C_{22}H_{19}N_3O_2$ (357.41): C, 73.93; H, 5.36; N, 11.76. Found: C, 73.8; H, 5.4; N, 11.6%. ^{1}H NMR (300.1 MHz, $CDCl_3$): δ 3.81 and 3.82 (6H, 2s, $2CH_3$), 6.79 (1H, dt, *J*=1.0 and 6.8 Hz, CH), 6.91 (2H, d, *J*=8.7 Hz, 2CH), 6.93 (2H, d, *J*=8.8 Hz, 2CH), 7.14 (1H, ddd, *J*=1.3, 6.6, and 6.7 Hz, CH), 7.54 (1H, d, *J*=9.0 Hz, CH), 7.74 (2H, d, *J*=8.7 Hz, 2CH), 7.76 (2H, d, *J*=8.8 Hz, 2CH), 8.32 (1H, d, *J*=6.8 Hz, CH), 8.67 (1H, s, CH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 55.2 and 55.4 ($2CH_3$), 112.2, 114.1, 114.2, 116.9, 123.1 and 124.8 (6CH), 126.9, 128.8 and 129.3 (3C), 129.5 and 130.0 (2CH), 132.6 and 142.3 (2C), 157.3 (CH), 159.3 and 162.3 (2C).

*4.2.5. 2-(4-Methoxyphenyl)-N^3-[(E)-1-(4-methoxyphenyl)-methylidene]-6-methylimidazo[1,2-a]pyridin-3-amine (**7e**)*

Yellow crystals, mp 189–190 °C, yield: 0.72 g, 97%. IR (KBr) (ν_{max}/cm^{-1}): 1610, 1580, 1537, 1514, 1348, 1302, 1252, 1163, 1109, 1080, 1028, 852, 802, 731. MS *m*/*z* (%): 371 (M^+, 25), 364 (6), 325 (13), 225 (20), 195 (11), 149 (10), 135 (16), 114 (21), 92 (11), 84 (100). Anal. Calcd for $C_{23}H_{21}N_3O_2$ (371.44): C, 74.37; H, 5.70; N, 11.31. Found: C, 74.4; H, 5.8; N, 11.2%. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 2.37 (3H, s, CH_3), 3.85 and 3.87 (6H, 2s, $2CH_3$), 6.94 (2H, d, *J*=8.8 Hz, 2CH), 6.97 (2H, d, *J*=8.8 Hz, 2CH), 7.06 (1H, dd, *J*=1.6 and 9.1 Hz, CH), 7.50 (1H, d, *J*=9.1 Hz, CH), 7.73 (2H, d, *J*=8.8 Hz, 2CH), 7.79 (2H, d, *J*=8.8 Hz, 2CH), 8.16 (1H, d, *J*=1.6 Hz, CH), 8.70 (1H, s, CH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 18.4 (CH_3), 55.3 and 55.5 ($2CH_3$), 114.2, 114.3, 116.4 and 120.8 (4CH), 121.9 and 127.3 (2C), 127.9 (CH), 128.7 (C), 129.6 and 130.0 (2CH), 132.8 and 141.7 (2C), 157.0 (CH), 159.3 and 162.4 (2C–O).

*4.2.6. 2-(4-Fluorophenyl)-N^3-[(E)-1-(4-fluorophenyl)methylidene]-6-methylimidazo[1,2-a]pyridin-3-amine (**7f**)*

Yellow crystals, mp 154–156 °C, yield: 0.67 g, 97%. IR (KBr) (ν_{max}/cm^{-1}): 1608, 1597, 1539, 1504, 1474, 1414, 1393, 1340, 1223, 1215, 1157, 1145, 1096, 842, 816. MS *m*/*z* (%): 347 (M^+, 100), 279 (13), 213 (80), 167 (31), 149 (83), 137 (13), 123 (14), 113 (13), 92 (90), 81 (41), 69 (81), 57 (50). Anal. Calcd for $C_{21}H_{15}F_2N_3$ (347.37): C, 72.61; H, 4.35; N, 12.10. Found: C, 72.4; H, 4.5; N, 11.9%. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 2.39 (3H, s, CH_3), 7.08 (1H, d, *J*=9.1 Hz, CH), 7.11 (2H, dd, $^3J_{FH}$=8.6 Hz, $^3J_{HH}$=8.7 Hz, 2CH), 7.16 (2H, dd, $^3J_{FH}$=8.6 Hz, $^3J_{HH}$=8.7 Hz, 2CH), 7.48 (1H, d, *J*=9.1 Hz, CH), 7.77 (2H, dd, $^4J_{FH}$=5.4 Hz, $^3J_{HH}$=8.7 Hz, 2CH), 7.82 (2H, dd, $^4J_{FH}$=5.5 Hz, $^3J_{HH}$=8.7 Hz, 2CH), 8.17 (1H, br s, CH), 8.67 (1H, s, CH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 18.4 (CH_3), 115.8 (d, $^2J_{FC}$=21.6 Hz, CH), 116.0 (d, $^2J_{FC}$=22.1 Hz, CH), 116.7 and 120.9 (2CH), 122.3 and 128.4 (2C), 128.5 (CH), 130.1 (d, $^3J_{FC}$=8.5 Hz, CH), 130.2 (d, $^3J_{FC}$=8.8 Hz, CH), 131.0 (d, $^4J_{FC}$=4.0 Hz, C), 132.7 (d, $^4J_{FC}$=3.1 Hz, C), 132.8 and 142.1 (2C), 155.5 (CH), 162.5 (d, $^1J_{FC}$=247.5 Hz, C–F), 164.7 (d, $^1J_{FC}$=252.9 Hz, C–F).

*4.2.7. 2-(4-Methoxyphenyl)-N^3-[(E)-1-(4-methoxyphenyl)-methylidene]-7-methylimidazo[1,2-a]pyridin-3-amine (**7g**)*

Yellow crystals, mp 176 °C, yield: 0.70 g, 94%. IR (KBr) (ν_{max}/cm^{-1}): 1603, 1572, 1514, 1366, 1306, 1254, 1167, 1134, 1107, 1018, 827, 804. MS *m*/*z* (%): 371 (M^+, 100), 364 (5), 325 (6), 250 (9), 225 (61), 167 (8), 149 (20), 135 (12), 114 (42), 92 (36), 86 (28), 81 (11), 69 (18). Anal. Calcd for $C_{23}H_{21}N_3O_2$ (371.44): C, 74.37; H, 5.70; N, 11.31. Found: C, 74.5; H, 5.7; N, 11.1%. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 2.42 (3H, s, CH_3), 3.86 and 3.88 (6H, 2s, $2CH_3$), 6.68 (1H, dd, *J*=1.2 and 7.0 Hz, CH), 6.94 (2H, d, *J*=8.7 Hz, 2CH), 6.96 (2H, d, *J*=8.7 Hz, 2CH), 7.32 (1H, d, *J*=1.2 Hz, CH), 7.75 (2H, d, *J*=8.7 Hz, 2CH), 7.78 (2H, d, *J*=8.7 Hz, 2CH), 8.28 (1H, d, *J*=7.0 Hz, CH), 8.7 (1H, s, CH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 21.4 (CH_3), 55.3 and 55.5 ($2CH_3$), 114.2, 114.3, 114.8, 115.6 and 122.4 (5CH), 127.5 and 128.5 (2C), 129.6 (CH), 129.7 (C), 129.9 (CH), 133.5, 135.2 and 143.1 (3C), 156.2 (CH), 159.3 and 162.3 (2C–O).

*4.2.8. 6-Methyl-2-(4-methylphenyl)-N^3-[(E)-1-(4-methylphenyl)-methylidene]imidazo[1,2-a]pyridin-3-amine (**7h**)*

Yellow crystals, mp 139–140 °C, yield: 0.62 g, 92%. IR (KBr) (ν_{max}/cm^{-1}): 1626, 1574, 1510, 1500, 1407, 1400, 1344, 1278, 1248, 1200, 1175, 1162, 1105, 1054, 964, 825, 800, 766, 725. MS *m*/*z* (%): 339 (M^+, 100), 325 (78), 312 (15), 297 (15), 234 (26), 209 (77), 195 (55), 92 (32), 78 (30), 65 (15). Anal. Calcd for $C_{23}H_{21}N_3$ (339.44): C, 81.38; H, 6.24; N, 12.38. Found: C, 81.5; H, 6.4; N, 12.2%. ^{1}H NMR (250.1 MHz, $CDCl_3$): δ 2.37, 2.38, and 2.42 (9H, 3s, $3CH_3$), 7.04 (1H, dd, *J*=1.5 and 9.0 Hz, CH), 7.21 (2H, d, *J*=8.0 Hz, 2CH), 7.26 (2H, d, *J*=8.3 Hz, 2CH), 7.46 (1H, d, *J*=9.0 Hz, CH), 7.70 (2H, d, *J*=8.0 Hz, 2CH), 7.72 (2H, d, *J*=8.3 Hz, 2CH), 8.18 (1H, d, *J*=1.5 Hz, CH), 8.75 (1H, s, CH). ^{13}C NMR

(62.9 MHz, $CDCl_3$): δ 18.4, 21.3, and 21.6 ($3CH_3$), 116.6 and 120.9 (2CH), 121.8 (C), 127.9, 128.1, and 128.3 (3CH), 128.8 (C), 129.4 and 129.5 (2CH), 132.2, 133.8, 134.0, 137.4, 141.7, and 142.0 (6C), 157.2 (CH).

4.2.9. 2-(4-Methoxyphenyl)-N^3-[(E)-1-(4-methoxyphenyl)-methylidene]-8-methylimidazo[1,2-a]pyridin-3-amine (**7i**)

Yellow crystals, mp 155–156 °C, yield: 0.69 g, 93%. IR (KBr) (ν_{max}/cm^{-1}): 1601, 1572, 1539, 1514, 1481, 1423, 1367, 1344, 1308, 1246, 1184, 1167, 1123, 1101, 1067, 1032, 831, 750. MS *m*/*z* (%): 371 (M^+, 55), 364 (12), 325 (100), 253 (13), 234 (12), 225 (32), 195 (84), 149 (14), 92 (23), 83 (15), 78 (39), 69 (23), 57 (21). Anal. Calcd for $C_{23}H_{21}N_3O_2$ (371.44): C, 74.37; H, 5.70; N, 11.31. Found: 74.4; H, 5.7; N, 11.2%. ^{1}H NMR (250.1 MHz, $CDCl_3$): δ 2.63 (3H, s, CH_3), 3.85 and 3.87 (6H, 2s, $2CH_3$), 6.77 (1H, t, *J*=6.8 Hz, CH), 6.94 (2H, d, *J*=8.5 Hz, 2CH), 6.96 (2H, d, *J*=8.5 Hz, 2CH), 7.01 (1H, t, *J*=6.8 Hz, CH), 7.74 (2H, d, *J*=8.5 Hz, 2CH), 7.76 (2H, d, *J*=8.5 Hz, 2CH), 8.28 (1H, d, *J*=6.8 Hz, CH), 8.67 (1H, s, CH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 16.7 (CH_3), 55.3 and 55.5 ($2CH_3$), 112.2, 114.2, 114.3, 121.0 and 123.8 (5CH), 126.9, 127.5, 129.2 and 129.6 (4C), 129.9 and 130.0 (2CH), 132.6 and 142.8 (2C), 156.7 (CH), 159.3 and 162.3 (2C–O).

4.2.10. 2-Phenyl-N^3-[(E)-1-phenylmethylidene]imidazo[1,2-a]pyrazin-3-amine (**9a**)

Yellow crystals, mp 219–220 °C, yield: 0.57 g, 95%. IR (KBr) (ν_{max}/cm^{-1}): 1604, 1580, 1545, 1479, 1450, 1356, 1220, 802, 766. MS *m*/*z* (%): 298 (M^+, 30), 196 (24), 182 (47), 149 (14), 129 (13), 95 (100), 89 (10), 79 (38), 68 (62). Anal. Calcd for $C_{19}H_{14}N_4$ (298.35): C, 76.49; H, 4.73; N, 18.78. Found: 76.5; H, 4.7; N, 18.7%. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 7.41 (1H, t, *J*=7.4 Hz, CH), 7.45–7.54 (4H, m, 4CH), 7.53 (1H, t, *J*=7.4 Hz, CH), 7.84 (2H, d, *J*=7.5 Hz, 2CH), 7.86 (2H, d, *J*=7.5 Hz, 2CH), 7.96 (1H, d, *J*=4.6 Hz, CH), 8.30 (1H, dd, *J*=1.3 and 4.6 Hz, CH), 8.80 (1H, s, CH), 9.06 (1H, d, *J*=1.3 Hz, CH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 115.9, 128.4, 128.6, 128.7, 128.9, 129.0, and 129.8 (7CH), 130.0 (C), 132.2 (CH), 133.8, 135.8, 136.2, and 137.9 (4C), 143.6 and 160.8 (2CH).

4.2.11. 2-(4-Methoxyphenyl)-N^3-[(E)-1-(4-methoxyphenyl)-methylidene]imidazo[1,2-a]pyrazin-3-amine (**9b**)

Yellow crystals, mp 168–170 °C, yield: 0.66 g, 92%. IR (KBr) (ν_{max}/cm^{-1}): 1605, 1599, 1479, 1408, 1344, 1291, 1218, 1098, 960, 825, 815, 784, 750. MS *m*/*z* (%): 358 (M^+, 45), 343 (9), 251 (12), 212 (78), 134 (20), 107 (18), 95 (36), 79 (41), 52 (21). Anal. Calcd for $C_{21}H_{18}N_4O_2$ (358.40): C, 70.38; H, 5.06; N, 15.63. Found: C, 70.5; H, 5.2; N, 15.3%. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 3.86 and 3.88 (6H, 2s, $2CH_3$), 6.97 (2H, d, *J*=8.7 Hz, 2CH), 6.98 (2H, d, *J*=8.6 Hz, 2CH), 7.77 (2H, d, *J*=8.7 Hz, 2CH), 7.80 (2H, d, *J*=8.6 Hz, 2CH), 7.89 (1H, d, *J*=4.6 Hz, CH), 8.22 (1H, dd, *J*=1.3 and 4.6 Hz, CH), 8.73 (1H, s, CH), 9.00 (1H, d, *J*=1.3 Hz, CH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 55.3 and 55.5 ($2CH_3$), 114.3, 114.4, and 115.7 (3CH), 126.3 and 128.8 (2C), 129.5 (CH), 129.6 and 130.0 (2C), 130.6 (CH), 135.7 (C), 137.6 and 143.2 (2CH), 159.8 (C–O), 160.3 (CH), 163.0 (C–O).

4.2.12. 2-(4-Methylphenyl)-N^3-[(E)-1-(4-methylphenyl)-methylidene]imidazo[1,2-a]pyrazin-3-amine (**9c**)

Yellow crystals, mp 155–156 °C, yield: 0.60 g, 92%. IR (KBr) (ν_{max}/cm^{-1}): 1609, 1600, 1566, 1483, 1411, 1346, 1294, 1222, 1176, 1107, 1032, 960, 814, 786, 752. MS *m*/*z* (%): 326 (M^+, 79), 235 (7), 196 (100), 118 (25), 103 (9), 91 (16), 79 (50). Anal. Calcd for $C_{21}H_{18}N_4$ (326.40): C, 77.28; H, 5.56; N, 17.17. Found: C, 77.3; H, 5.7; N, 17.1%. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 2.39 and 2.42 (6H, 2 s, $2CH_3$), 7.23 (2H, d, *J*=8.0 Hz, 2CH), 7.26 (2H, d, *J*=7.9 Hz, 2CH), 7.71 (2H, d, *J*=8.0 Hz, 2CH), 7.73 (2H, d, *J*=7.9 Hz, 2CH), 7.89 (1H, d, *J*=4.6 Hz, CH), 8.22 (1H, dd, *J*=1.3 and 4.6 Hz, CH), 8.76 (1H, s, CH), 9.01 (1H, d, *J*=1.3 Hz, CH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 21.4 and 21.7 ($2CH_3$), 115.8, 128.2, 128.8, 129.6 and 129.7 (5CH), 129.8, 130.0, 130.9, 133.3, 136.1, and 137.8 (6C), 138.4 (CH), 142.9 (C), 143.4 and 160.8 (2CH).

4.2.13. 2-(3-Methylphenyl)-N^3-[(E)-1-(3-methylphenyl)-methylidene]imidazo[1,2-a]pyrazin-3-amine (**9d**)

Yellow crystals, mp 149–150 °C, yield: 0.61 g, 94%. IR (KBr) (ν_{max}/cm^{-1}): 1612, 1578, 1492, 1357, 1313, 1256, 1207, 1182, 1111, 1022, 978, 881, 793, 756, 688. MS *m*/*z* (%): 326 (M^+, 95), 235 (6), 196 (100), 122 (13), 114 (32), 86 (26), 79 (50). Anal. Calcd for $C_{21}H_{18}N_4$ (326.40): C, 77.28; H, 5.56; N, 17.17. Found: C, 77.4; H, 5.6; N, 17.0%. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 2.41 and 2.43 (6H, 2s, $2CH_3$), 7.20 (1H, d, *J*=7.6 Hz, CH), 7.30–7.38 (3H, m, 3CH), 7.58 (1H, d, *J*=7.7 Hz, CH), 7.62 (1H, d, *J*=7.7 Hz, CH), 7.68 (1H, s, CH), 7.70 (1H, s, CH), 7.94 (1H, d, *J*=4.6 Hz, CH), 8.28 (1H, dd, *J*=1.3 and 4.6 Hz, CH), 8.78 (1H, s, CH), 9.04 (1H, d, *J*=1.3 Hz, CH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 21.3 and 21.4 ($2CH_3$), 115.9, 125.2, 126.2, 128.7, 128.8, 129.0, 129.2, 129.3, and 129.8 (9CH), 130.1 (C), 133.0 (CH), 133.7, 135.8, 136.2, 137.9, 138.7 and 138.8 (6C), 143.5 and 161.1 (2CH).

4.2.14. 2-Phenyl-N^3-[(E)-1-phenylmethylidene]imidazo[1,2-a]pyrimidin-3-amine (**9e**)

Yellow crystals, mp 194 °C, yield: 0.57 g, 96%. IR (KBr) (ν_{max}/cm^{-1}): 1610, 1579, 1549, 1515, 1479, 1449, 1356, 1222, 799, 760. MS *m*/*z* (%): 298 (M^+, 97), 193 (29), 182 (93), 166 (12), 122 (100), 114 (10), 104 (12), 95 (13), 89 (11), 79 (56), 68 (20), 52 (20). Anal. Calcd for $C_{19}H_{14}N_4$ (298.35): C, 76.49; H, 4.73; N, 18.78. Found: 76.3; H, 4.9; N, 18.6%. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 6.89 (1H, dd, *J*=4.0 and 6.7 Hz, CH), 7.34 (1H, t, *J*=7.2 Hz, CH), 7.39–7.45 (5H, m, 5CH), 7.80 (2H, d, *J*=7.2 Hz, 2CH), 7.88 (2H, d, *J*=7.6 Hz, 2CH), 8.54 (1H, dd, *J*=2.0 and 4.0 Hz, CH), 8.65 (1H, dd, *J*=2.0 and 6.7 Hz, CH), 8.81 (1H, s, CH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 108.7 (CH), 127.3 (C), 128.4, 128.5, 128.6, 128.8, 128.9, 130.7, and 131.8 (7CH), 134.2, 135.3, 136.1, and 146.1 (4C), 150.0 and 159.2 (2CH).

4.2.15. 2-(4-Methylphenyl)-N^3-[(E)-1-(4-methylphenyl)-methylidene]imidazo[1,2-a]pyrimidin-3-amine (**9f**)

Yellow crystals, mp 165–167 °C, yield: 0.61 g, 94%. IR (KBr) (ν_{max}/cm^{-1}): 1610, 1578, 1565, 1479, 1358, 1229, 1185, 1130, 1039, 999, 802, 729. MS *m*/*z* (%): 326 (M^+, 54), 235 (4), 224 (18), 208 (4), 196 (54), 135 (5), 119 (18), 95 (100), 84 (18), 68 (52). Anal. Calcd for $C_{21}H_{18}N_4$ (326.40): C, 77.28; H, 5.56; N, 17.17. Found: C, 77.4; H, 5.8; N, 17.1%. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 2.37 and 2.41 (6H, 2s, $2CH_3$), 6.87 (1H, dd, *J*=4.1 and 6.8 Hz, CH), 7.22 (2H, d, *J*=7.9 Hz, 2CH), 7.25 (2H, d, *J*=8.0 Hz, 2CH), 7.71 (2H, d, *J*=7.9 Hz, 2CH), 7.76 (2H, d, *J*=8.0 Hz, 2CH), 8.50 (1H, dd, *J*=2.0 and 4.1 Hz, CH), 8.63 (1H, dd, *J*=2.0 and 6.8 Hz, CH), 8.80 (1H, s, CH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 21.3 and 21.6 ($2CH_3$), 108.5 (CH), 127.3 (C), 128.3 and 128.5 (2CH), 129.3 (C), 129.5, 129.6, and 130.6 (3CH), 131.2, 133.5, 138.1, 142.4, and 145.8 (5C), 149.6 and 159.3 (2CH).

4.2.16. 2-(3-Methylphenyl)-N^3-[(E)-1-(3-methylphenyl)-methylidene]imidazo[1,2-a]pyrimidin-3-amine (**9g**)

Yellow crystals, mp 155–157 °C, yield: 0.63 g, 97%. IR (KBr) (ν_{max}/cm^{-1}): 1602, 1578, 1545, 1516, 1479, 1450, 1358, 1326, 1223, 1175, 1040, 802, 730. MS *m*/*z* (%): 326 (M^+, 92), 221 (54), 196 (100), 169 (5), 146 (5), 129 (7), 119 (14), 103 (8), 95 (32), 79 (44), 68 (8). Anal. Calcd for $C_{21}H_{18}N_4$ (326.40): C, 77.28; H, 5.56; N, 17.17. Found: C, 77.3; H, 5.7; N, 16.9%. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 2.37 and 2.40 (6H, 2s, $2CH_3$), 6.89 (1H, dd, *J*=4.0 and 6.7 Hz, CH), 7.16 (1H, d, *J*=7.6 Hz, CH), 7.27 (1H, t, *J*=7.6 Hz, CH), 7.29 (1H, d, *J*=7.6 Hz, CH), 7.33 (1H, t, *J*=7.5 Hz, CH), 7.58 (1H, d, *J*=7.5 Hz, CH), 7.62 (1H, d, *J*=7.5 Hz, CH), 7.64 (1H, s, CH), 7.75 (1H, s, CH), 8.52 (1H, dd, *J*=2.0 and 4.0 Hz, CH), 8.66 (1H, dd, *J*=2.0 and 6.7 Hz, CH), 8.80 (1H, s, CH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 21.3 and 21.4 ($2CH_3$), 108.6, 125.3 and 125.9 (3CH), 127.3 (C), 128.6, 128.7, 128.8, 129.1, 129.4, 130.7, and

132.6 (7CH), 134.0, 135.2, 136.1, 138.5, 138.6, and 145.9 (6C), 149.8 and 159.4 (2CH).

4.2.17. 2-(4-Methoxyphenyl)-N^3-[(E)-1-(4-methoxyphenyl)-methylidene]imidazo[1,2-a]pyrimidin-3-amine (**9h**)

Yellow crystals, mp 160–162 °C, yield: 0.69 g, 97%. IR (KBr) (ν_{max}/cm^{-1}): 1610, 1579, 1539, 1520, 1479, 1455, 1359, 1222, 798, 758. MS *m*/*z* (%): 358 (M^+, 64), 326 (17), 212 (78), 196 (21), 135 (44), 95 (100), 84 (93), 77 (13), 68 (45). Anal. Calcd for $C_{21}H_{18}N_4O_2$ (358.40): C, 70.38; H, 5.06; N, 15.63. Found: C, 70.5; H, 5.2; N, 15.4%. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 3.81 and 3.83 (6H, 2 s, $2CH_3$), 6.83 (1H, dd, J=4.1 and 6.8 Hz, CH), 6.91 (2H, d, J=8.7 Hz, 2CH), 6.93 (2H, d, J=8.8 Hz, 2CH), 7.74 (2H, d, J=8.7 Hz, 2CH), 7.81 (2H, d, J=8.8 Hz, 2CH), 8.46 (1H, dd, J=2.0 and 4.1 Hz, CH), 8.56 (1H, dd, J=2.0 and 6.8 Hz, CH), 8.73 (1H, s, CH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 55.3 and 55.5 ($2CH_3$), 108.4, 114.2, and 114.3 (3CH), 126.6, 127.2, and 129.0 (3C), 129.7, 130.2, and 130.4 (3CH), 134.5 and 145.6 (2C), 149.3 and 159.5 (2CH), 159.6 and 162.7 (2C–O).

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18. The first part of this paper has been published as a preliminary form: Adib, M.; Sheibani, E.; Zhu, L. G.; Mirzaei, P. *Tetrahedron Lett.* **2008**, *49*, 5108–5110.
19. Selected X-ray crystallographic data for compound **7d**: $C_{22}H_{19}N_3O_2$, monoclinic, space group=$P2_1/n$, a=10.4920(16) Å, b=8.7631(13) Å, c=20.768(3) Å, β=91.269(2)°, V=1908.96(5) Å^3, T=295(2) K, Z=4, D_{calcd}=1.24 g cm^{-3}, μ=0.081 mm^{-1}, 1986 observed reflections, final R_1=0.054, wR_2=0.124 and for all data R_1=0.107, wR_2=0.124. CCDC 666888 contains the supplementary crystallographic data for the structure reported in this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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