Synthesis of Diaryl-Substituted Imidazo[1,2-*a*]pyridines Designed as Potential Aromatase Inhibitors

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From a pharmacophore model of bicyclic heterocycles as aromatase inhibitors we have designed three series of imidazo[1,2-*a*]pyridine derivatives. The synthesis and the spectroscopy determination of various compounds are reported. The crystal data of one of these compounds (10b) was obtained. The aromatase inhibition potency was evaluated *in vitro* and no activity was found.

Key words non-steroidal P450 aromatase inhibitors; imidazo[1,2-*a*]pyridine; synthesis; crystal structure

As part of our studies concerning the chemistry of imidazo[1,2-*a*]pyridine structures,[1] we are developing now a program for the design and the preparation of compounds as potential inhibitors of cytochrome P450 aromatase. Non-steroidal aromatase inhibitors are known to prevent estrogen biosynthesis and their implication in the treatment of estrogen dependent diseases such as breast cancer is increasing.[2] The present study was based on the pharmacophore model designed by Rault's group[3] to fit the catalytic site of the human enzyme. This model consisted of a bicyclic skeleton bearing an azine group for interacting with the heme iron atom and an aryl group that is known to favour this interaction by occupying the extra-hydrophobic pocket located in the active site. Concomitantly, a series of 3-(azol-1-ylmethyl)-1*H*-indoles I revealed potent *in vitro* P450 aromatase inhibition (Chart 1).[4] These results led us to investigate the aromatase inhibition properties of new aryl-substituted imidazo[1,2-*a*]pyridine derivatives following the structural requirements of the pharmacophore model. The azole fragment was alternatively introduced on the 2- and 3-positions of the imidazo[1,2-*a*]pyridine leading to structures A and B. A di-heteroaryl compound (structure C) was also included in this study.

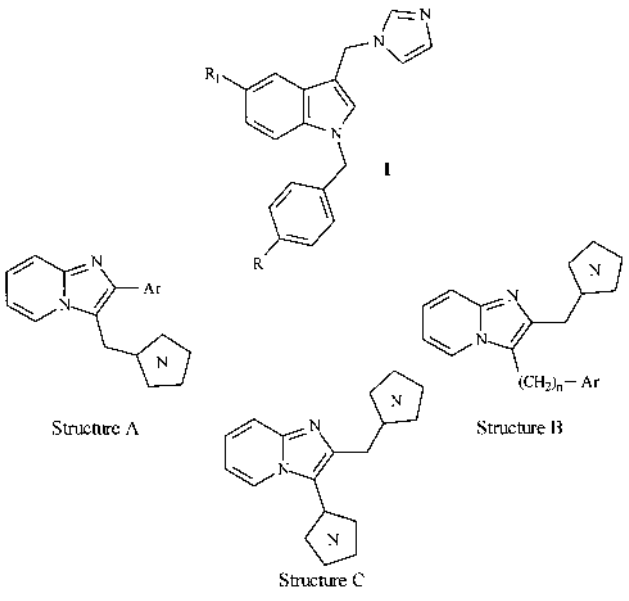

Chart 1

Results and Discussion

The 3-hydroxymethylation of 2-phenylimidazo[1,2-*a*]pyridine **1**[5] was easily achieved using reaction with formaldehyde and sodium acetate in acetic acid media according to our previously described procedure.[6] The transformation of the expected alcohol **2** into the azolyl compounds **3a**—**b** was carried out through a treatment with refluxing thionyl chloride, followed by attack of the intermediary chloro derivative with imidazole or triazole in acetonitrile at 50 °C for 48 h (Chart 2). The structure of the imidazolyl compound **3a** was easily demonstrated from NMR spectra. In the case of triazole derivative the 1 and 4 regioisomers could be formed. Usually the N-4 isomer gives a single signal in ^{1}H- and ^{13}C-NMR while the N-1 derivative gives two signals for H-3′/C-3′ and H-5′/C-5′.[7] The ^{1}H-NMR spectrum of **3b** in $CDCl_3$ presented a singlet at δ 8.05 for H-3′ and H-5′ while C-3′ and C-5′ resonate at δ 152.3 and 142.4. The ambiguity was solved by performing the ^{1}H-NMR spectrum in DMSO-d_6 that gave two singlets at δ 8.02 and 8.87 confirming **3b** to be the N-1 isomer.

Our second investigation was to incorporate the aryl group on the 3-position followed by the introduction of an imidazole ring on the 2-position to provide the geometric isomers.

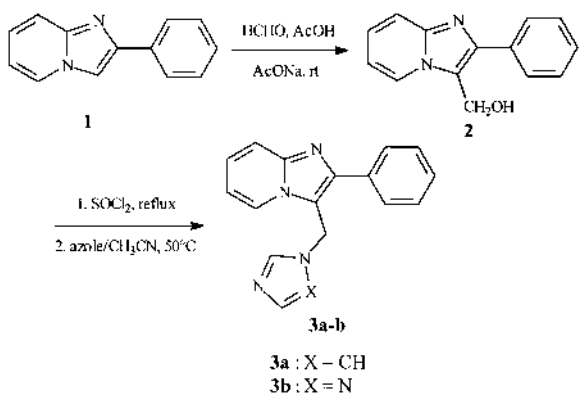

Chart 2

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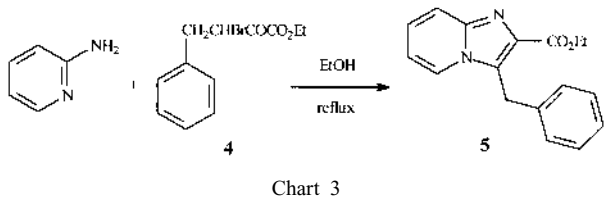

Chart 3

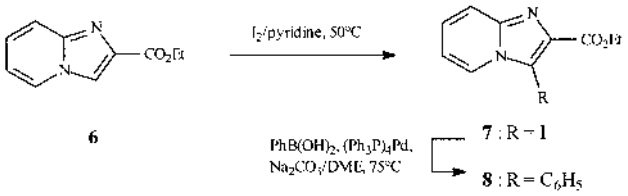

Chart 4

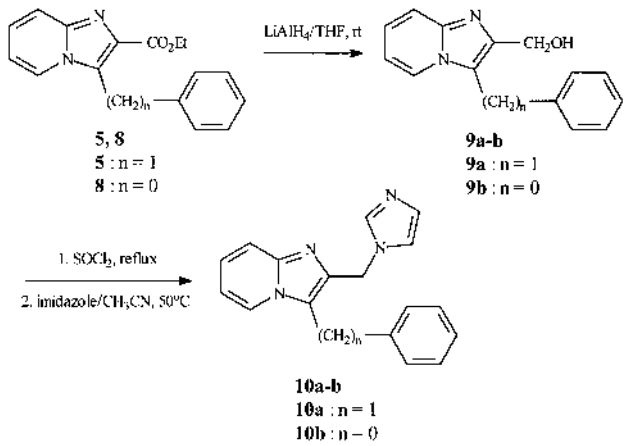

Chart 5

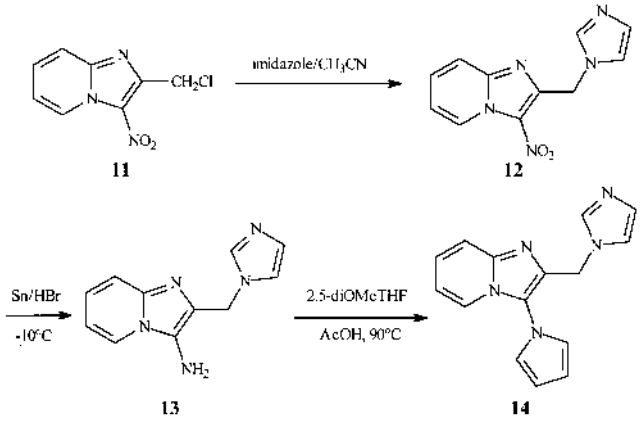

Chart 6

Commercially available ethyl 2-oxo-4-phenylbutyrate was readily brominated to give the α-bromocarbonyl intermediate **4** which was condensed as previously described[5] with 2-aminopyridine to yield **5** (Chart 3). Synthesis of the lesser homologue **8** through the same synthetic pathway was difficult due to the troublesome access to the ethyl 2-oxo-3-phenylpropanoate. Recently 3-arylation of imidazo[1,2-*a*]pyridine was achieved using Stille conditions[8] while we have studied the palladium catalyzed Suzuki-type cross coupling reaction.[9] We chose our strategy to introduce the 3-phenyl ring starting from the appropriate iodo intermediate **7** (Chart 4). This compound was obtained from ethyl imidazo[1,2-*a*]pyridine-2-carboxylate **6** using iodine in pyridine[10] in 46% yield. ^{13}C-NMR spectrum of **7** was characterized by the C-3 signal high field shielding to 68 ppm. Suzuki reaction was performed using phenylboronic acid in the presence of sodium carbonate in DME at 75 °C for 0.5 h to give **8** (91% yield).[9]

The ester function of **5** and **8** was reduced using lithium aluminium hydride in tetrahydrofuran at room temperature for 1 h (Chart 5). Proof of the structure was found in ^{1}H-NMR spectra. Depending on the $CDCl_3$ solution concentration, a variation of 0.4 ppm could be observed for the H-8 signal due to the formation of a hydrogen bond between the hydroxyl group and the N-1 atom. The substitution of the expected alcohols **9a**—**b** into the 2-(imidazol-1-ylmethyl)imidazo[1,2-*a*]pyridines **10a**—**b** was carried out using the synthetic pathway reported for **3a**—**b**.

Finally, in order to prepare diheteroaryl derivatives, we have changed the phenyl ring of **10b** to a pyrrole fragment (Chart 6). The 2-chloromethyl-3-nitroimidazo[1,2-*a*]pyridine **11**[11] was first substituted with imidazole in acetonitrile and then reduced with tin in hydrobromic acid media.[12] The expected aminoderivative **13** was then involved in a Clauson–Kaas reaction,[13] using 2,5-dimethoxytetrahydrofuran in acetic acid but 2-(imidazol-1-ylmethyl)-3-(pyrrol-1-yl)imidazo[1,2-*a*]pyridine **14** was obtained in only poor yield.

With a view to further developing the structure–activity relationship study, we were then interested in the crystallographic data for one of the synthesized compounds. Our studies were focused on derivatives of structure B and a crystal of compound **10b** was obtained.

Crystal Structure The fractional coordinates and the equivalent thermal factors (U_{eq}) are listed in Table 1. The thermal ellipsoid representation and the labelling of non-hydrogen atoms of both conformations for one molecule is presented in Fig. 1.[14] The bond lengths and bond angles are given in Tables 2 and 3 respectively and agree quite well with the literature.[15] The interesting torsion angles which entirely define the molecule conformation are reported in Table 4.

The imidazo[1,2-*a*]pyridine ring ø1 (atoms N1 to C8A), imidazole ring ø2 (atoms N1′ to C5′), and phenyl ring ø3 (atoms C1″ to C6″) are planar with the dihedral angles reported in Table 5.

The packing of the molecule is shown in Fig. 2. There are numerous weak van der Waals interactions so the crystal cohesion is assumed through several hydrogen bonds (Fig. 3). The molecule I is involved in the following hydrogen bond between the OH group and N atoms (Table 6).

Conclusion

The present paper deals with the synthesis of 2,3-disubstituted imidazo[1,2-*a*]pyridine derivatives as potential aromatase inhibitors. On the basis of a pharmacophore model three types of structures were designed. From the synthesized compounds the crystal data obtained from **10b** was studied. Unfortunately the spatial structure showed the compound does not fit well with the proposed pharmacophore. This result was ascertained by determining the inhibition of the enzyme *in vitro* which showed that these compounds are inactive. Despite this fact, the crystal data of **10b** serve as a start

Table 1a. Atomic Coordinates and Equivalent U_{eq} Factors for Molecule I

	x/a	*y/b*	*z/c*	U_{eq}
O1	0.3666 (2)	0.0436 (2)	0.3202 (1)	0.0644 (4)
O2	0.5978 (2)	0.9606 (2)	0.2151 (1)	0.0725 (5)
O3	0.9144 (3)	0.9796 (2)	0.1802 (1)	0.0879 (6)
O4	0.0474 (3)	0.0788 (4)	0.2964 (1)	0.1246 (10)
N1	0.4676 (2)	0.2940 (2)	0.8292 (1)	0.0472 (4)
C2	0.5885 (2)	0.3468 (2)	0.8503 (1)	0.0426 (4)
C3	0.5548 (2)	0.4823 (2)	0.8639 (1)	0.0400 (4)
N4	0.4052 (2)	0.5148 (2)	0.8498 (1)	0.0400 (4)
C5	0.3096 (2)	0.6343 (2)	0.8562 (1)	0.0492 (5)
C6	0.1651 (2)	0.6365 (2)	0.8424 (1)	0.0574 (5)
C7	0.1117 (2)	0.5183 (2)	0.8222 (1)	0.0571 (5)
C8	0.2049 (2)	0.4002 (2)	0.8157 (1)	0.0532 (5)
C8A	0.3565 (2)	0.3970 (2)	0.8297 (1)	0.0433 (4)
C9	0.7338 (2)	0.2573 (2)	0.8577 (1)	0.0499 (5)
N1′	0.7382 (2)	0.1868 (2)	0.9323 (1)	0.0441 (4)
C2′	0.8617 (2)	0.1544 (2)	0.9671 (1)	0.0566 (5)
N3′	0.8291 (2)	0.0922 (2)	1.0336 (1)	0.0592 (5)
C4′	0.6761 (2)	0.0844 (2)	1.0410 (1)	0.0552 (5)
C5′	0.6190 (2)	0.1418 (2)	0.9798 (1)	0.0542 (5)
C1″	0.6426 (2)	0.5805 (2)	0.8900 (1)	0.0415 (4)
C2″	0.7155 (2)	0.5397 (2)	0.9518 (1)	0.0516 (5)
C3″	0.7976 (3)	0.6311 (3)	0.9772 (1)	0.0626 (6)
C4″	0.8061 (3)	0.7645 (3)	0.9424 (1)	0.0630 (6)
C5″	0.7349 (3)	0.8059 (2)	0.8809 (1)	0.0575 (5)
C6″	0.6545 (2)	0.7146 (2)	0.8547 (1)	0.0490 (5)

Table 1b. Atomic Coordinates and Equivalent U_{eq} Factors for Molecule II

	x/a	*y/b*	*z/c*	U_{eq}
N1	0.5664 (2)	0.6846 (2)	0.6751 (1)	0.0448 (4)
C2	0.4397 (2)	0.6437 (2)	0.6529 (1)	0.0406 (4)
C3	0.4616 (2)	0.5092 (2)	0.6373 (1)	0.0389 (4)
N4	0.6091 (2)	0.4643 (2)	0.6515 (1)	0.0387 (3)
C5	0.6940 (2)	0.3391 (2)	0.6447 (1)	0.0463 (5)
C6	0.8388 (2)	0.3246 (2)	0.6596 (1)	0.0544 (5)
C7	0.9033 (2)	0.4356 (2)	0.6812 (1)	0.0562 (5)
C8	0.8207 (2)	0.5589 (2)	0.6883 (1)	0.0508 (5)
C8A	0.6686 (2)	0.5745 (2)	0.6735 (1)	0.0417 (4)
C9	0.2988 (2)	0.7410 (2)	0.6508 (1)	0.0510 (5)
N1′	0.2817 (2)	0.8125 (2)	0.5774 (1)	0.0440 (4)
C2′	0.3900 (2)	0.8526 (2)	0.5239 (1)	0.0507 (5)
N3′	0.3333 (2)	0.9123 (2)	0.4648 (1)	0.0527 (4)
C4′	0.1807 (2)	0.9089 (2)	0.4819 (1)	0.0557 (5)
C5′	0.1465 (2)	0.8486 (2)	0.5506 (1)	0.0571 (5)
C1″	0.3650 (2)	0.4226 (2)	0.6078 (1)	0.0398 (4)
C2″	0.3422 (2)	0.2879 (2)	0.6396 (1)	0.0503 (5)
C3″	0.2546 (3)	0.2074 (2)	0.6100 (1)	0.0618 (6)
C4″	0.1865 (3)	0.2607 (3)	0.5487 (1)	0.0658 (6)
C5″	0.2054 (2)	0.3949 (3)	0.5176 (1)	0.0613 (6)
C6″	0.2946 (2)	0.4752 (2)	0.5464 (1)	0.0493 (5)

point in the design of further derivatives.

Experimental

Melting points were determined on a Kofler block and are uncorrected. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Brüker DPX 200 MHz (50 MHz for ^{13}C). Splitting patterns have been designated as follows: s=singlet; bs=broad singlet; d=doublet; t=triplet; q=quartet; dd=double doublet; m=multiplet. Analyses indicated by the symbols of the elements were within ±0.5% of the theoretical values. The organic solutions were dried over anhydrous calcium chloride. Previously reported imidazo[1,2-*a*]pyridines synthesized by the described procedure were: 2-phenylimidazo[1,2-*a*]pyridine (**1**),[16] [2-phenylimidazo[1,2-*a*]pyridin-3-yl]methanol (**2**),[6] ethyl imidazo[1,2-*a*]pyridine-2-carboxylate (**6**),[17] 2-chloromethyl-3-nitroimidazo[1,2-*a*]pyridine (**11**).[11] Possible inversion of two values in the NMR spectra is expressed by an asterisk.

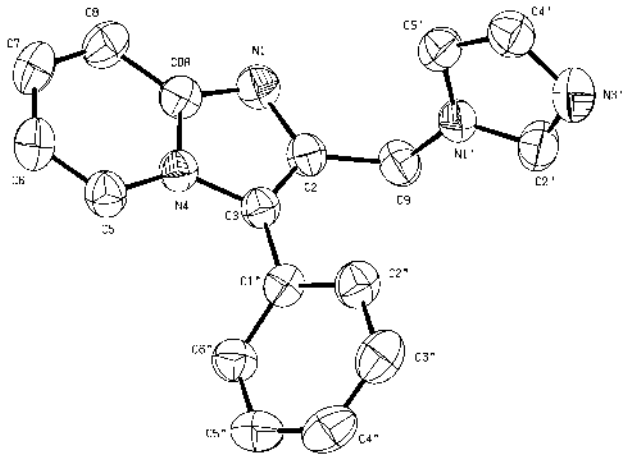

Fig. 1. Ellipsoid Representation (Probability 50%) of One Molecule and Atomic Labelling of **10b**

Table 2. Bond Lengths (Å) and Standard-Deviations in Parenthesis

	Molecule I	Molecule II
N1–C8A	1.333 (2)	1.332 (2)
N1–C2	1.370 (2)	1.372 (2)
C2–C3	1.374 (3)	1.369 (3)
C2–C9	1.495 (3)	1.493 (3)
C3–N4	1.392 (2)	1.391 (2)
C3–C1″	1.470 (3)	1.473 (3)
N4–C5	1.377 (2)	1.377 (2)
N4–C8A	1.385 (2)	1.382 (2)
C5–C6	1.347 (3)	1.347 (3)
C6–C7	1.408 (3)	1.408 (3)
C7–C8	1.355 (3)	1.354 (3)
C8–C8A	1.409 (3)	1.410 (3)
C9–N1′	1.468 (2)	1.468 (2)
N1′–C2′	1.342 (2)	1.339 (3)
N1′–C5′	1.358 (3)	1.363 (2)
C2′–N3′	1.313 (3)	1.313 (3)
N3′–C4′	1.363 (3)	1.358 (3)
C4′–C5′	1.341 (3)	1.343 (3)
C1″–C6″	1.389 (3)	1.390 (3)
C1″–C2″	1.391 (3)	1.393 (3)
C2″–C3″	1.381 (3)	1.378 (3)
C3″–C4″	1.377 (3)	1.381 (3)
C4″–C5″	1.378 (3)	1.375 (3)
C5″–C6″	1.378 (3)	1.379 (3)

Ethyl 3-Bromo-2-oxo-4-phenylbutyrate (4) To a solution of ethyl 2-oxo-4-phenylbutyrate (5 g, 24.2 mmol) in chloroform (30 ml) was added dropwise bromine (1.24 ml, 24.2 mmol). After stirring for 1 h at room temperature, the reaction mixture was washed with water (3×20 ml), dried and concentrated *in vacuo* to give a translucent oil (87%); ^{1}H-NMR ($CDCl_3$) δ: 7.44—7.32 (5H, m, Ph); 5.36 (1H, m, CH); 4.45 (2H, q, J=7.1 Hz, CH_2); 3.62 (1H, m, AB system, CH_2); 3.33 (1H, m, AB system, CH_2); 1.46 (3H, t, CH_3); *Anal.* Calcd for $C_{12}H_{13}BrO_3$: C, 50.55; H, 4.60. Found: C, 50.21; H, 4.72.

Ethyl 3-Benzylimidazo[1,2-*a*]pyridine-2-carboxylate (5) A solution of 2-aminopyridine (0.66 g, 7.0 mmol) and ethyl 3-bromo-2-oxo-4-phenylbutyrate (2.4 g, 8.4 mmol) was refluxed in ethanol (50 ml) for 4 h. After cooling, the solution was concentrated *in vacuo*, poured into water and made alkaline with sodium carbonate. The aqueous layer was extracted with dichloromethane. The combined and dried organic phases were evaporated to dryness and the residue chromatographed on neutral alumina eluting with dichloromethane to give colorless crystals (51%); mp 88 °C; ^{1}H-NMR ($CDCl_3$) δ: 7.85 (1H, d, $J_{H\text{-}5\ H\text{-}6}$=6.8 Hz, H-5); 7.72 (1H, d, $J_{H\text{-}7\ H\text{-}8}$=9.0 Hz, H-8); 7.31—7.23 (6H, m, Ph, H-7); 6.81 (1H, t, $J_{H\text{-}6\ H\text{-}7}$=6.8 Hz, H-6); 4.79 (2H, s, CH_2); 4.57 (2H, q, J=7.1 Hz, CH_2); 1.50 (3H, t, CH_3); ^{13}C-NMR

Table 3. Bond Angles (°) and Standard-Deviations in Parenthesis

	Molecule I	Molecule II
C8A–N1–C2	105.42 (15)	105.35 (15)
N1–C2–C3	111.93 (16)	111.83 (16)
N1–C2–C9	120.16 (17)	128.14 (18)
C3–C2–C9	127.88 (18)	119.98 (17)
C2–C3–N4	104.54 (16)	104.72 (15)
C2–C3–C1″	132.44 (17)	132.14 (16)
N4–C3–C1″	122.99 (16)	123.05 (16)
C5–N4–C8A	121.80 (16)	121.58 (16)
C5–N4–C3	130.74 (16)	131.08 (16)
C8A–N4–C3	107.38 (15)	107.31 (14)
C6–C5–N4	118.94 (19)	118.99 (18)
C5–C6–C7	120.7 (2)	120.79 (19)
C8–C7–C6	120.77 (19)	120.73 (19)
C7–C8–C8A	118.97 (19)	118.81 (19)
N1–C8A–N4	110.72 (16)	110.78 (16)
N1–C8A–C8	130.46 (18)	130.10 (18)
N4–C8A–C8	118.79 (17)	119.09 (17)
N1′–C9–C2	111.76 (16)	112.91 (16)
C2′–N1′–C5′	106.30 (17)	106.48 (16)
C2′–N1′–C9	126.56 (17)	128.67 (16)
C5′–N1′–C9	127.15 (16)	124.84 (17)
N3′–C2′–N1′	112.36 (19)	112.16 (18)
C2′–N3′–C4′	104.28 (18)	104.63 (17)
C5′–C4′–N3′	110.67 (19)	110.70 (18)
C4′–C5′–N1′	106.39 (18)	106.03 (19)
C6″–C1″–C2″	118.49 (18)	118.30 (18)
C6″–C1″–C3	121.79 (17)	121.74 (17)
C2″–C1″–C3	119.73 (17)	119.96 (17)
C3″–C2″–C1″	120.4 (2)	120.8 (2)
C4″–C3″–C2″	120.4 (2)	120.2 (2)
C3″–C4″–C5″	119.7 (2)	119.7 (2)
C4″–C5″–C6″	120.1 (2)	120.3 (2)
C5″–C6″–C1″	120.84 (19)	120.7 (2)

Table 4. Significative Torsion Angles (°) with Standard Deviations in Parenthesis

	Molecule I	Molecule II
N1–C2–C9–N1′	−91.8 (2)	98.9 (2)
C2–C9–N1′–C2′	−147.1 (2)	−32.8 (2)
C2–C3–C1″–C6″	130.8 (2)	47.9 (3)

Table 5. Table of Dihedral Angles (°) with Standard Deviations in Parenthesis

	Molecule I	Molecule II
ø2/ø1	81.48 (7)	83.68 (6)
ø3/ø1	52.06 (6)	50.93 (6)
ø3/ø2	55.49 (9)	58.47 (9)

($CDCl_3$) δ: 164.8 (CO), 144.8 (C-8a), 136.9 (C-2), 133.8 (Ph-1), 129.5 (Ph-2,6), 128.7 (C-3), 128.6 (Ph-3,5), 127.5 (Ph-4*), 126.3 (C-7*), 124.4 (C-5), 119.7 (C-8), 114.1 (C-6), 61.7 (CH_2), 30.1 (CH_2), 15.1 (CH_3); *Anal.* Calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.58; H, 5.69; N, 10.20.

Ethyl 3-Iodoimidazo[1,2-*a*]pyridine-2-carboxylate (7) To a solution of **6** (3 g, 15.8 mmol) in pyridine (10 ml) was added iodine (6 g, 23.6 mmol). The reaction mixture was heated at 50 °C for 5 h and then poured into water (20 ml). The aqueous solution was extracted with dichloromethane. The combined organic extracts were washed with water (3×20 ml), dried and evaporated to dryness. The residual material was purified by column chromatography (neutral alumina, dichloromethane as eluant) to give brown

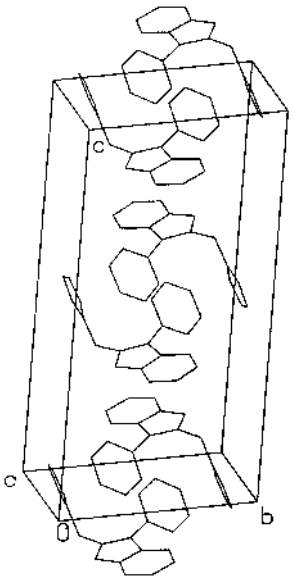

Fig. 2. Packing Representation of **10b**

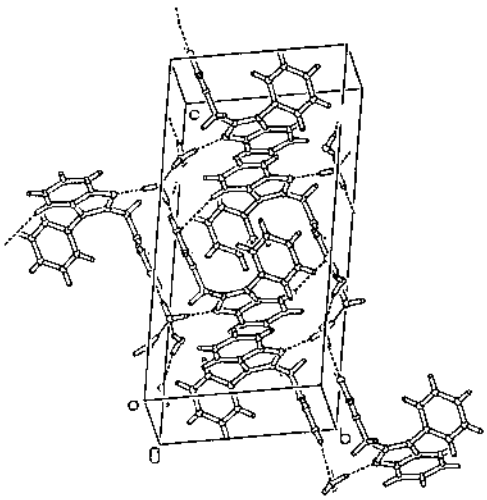

Fig. 3. Packing Representation of **10b**

Table 6. Table of Hydrogen Bond

D–H···A	D–H–A (°)	*d*(D···A) (Å)	Symmetry
O1–H1A_I···N1_II	179.70	2.795	[−*x*+1, −*y*+1, −*z*+1]
O1–H1B_I···N3′_II	168.50	2.814	[*x*, *y*−1, *z*]
O2–H2A_I···N1_I	171.25	2.862	[−*x*+1, −*y*+1, −*z*+1]
O2–H2B_I···O1_I	173.13	2.777	[*x*, *y*+1, *z*]
O3–H3A_I···O2_I	161.48	2.830	
O3–H3B_I···N3′_I	163.84	2.971	[*x*, *y*+1, *z*−1]
O4–H4A_I···O3_I	162.81	2.926	[*x*−1, *y*−1, *z*]
O4–H4B_I···O1_I	161.39	2.920	

crystals (46%); mp 144 °C; ^{1}H-NMR ($CDCl_3$) δ: 8.31 (1H, dt, $J_{H\text{-}5\ H\text{-}6}$= 6.9 Hz, $J_{H\text{-}5\ H\text{-}7}$=1.1 Hz, H-5); 7.72 (1H, dt, $J_{H\text{-}7\ H\text{-}8}$=9.2 Hz, $J_{H\text{-}6\ H\text{-}8}$=1.1 Hz, H-8); 7.38 (1H, ddd, $J_{H\text{-}6\ H\text{-}7}$=6.9 Hz, H-7); 7.05 (1H, td, H-6); 4.54 (2H, q, J=7.1 Hz, CH_2); 1.51 (3H, t, CH_3); ^{13}C-NMR ($CDCl_3$) δ: 163.1 (CO), 148.2 (C-8a), 138.5 (C-2), 127.5 (C-5, C-7), 119.6 (C-8), 115.1 (C-6), 68.5 (C-3), 61.9 (CH_2), 14.8 (CH_3); *Anal.* Calcd for $C_{10}H_9IN_2O_2$: C, 38.00; H, 2.87; N, 8.86. Found: C, 38.33; H, 2.91; N, 8.81.

Ethyl 3-Phenylimidazo[1,2-*a*]pyridine-2-carboxylate (8) To a solution of **7** (0.3 g, 0.95 mmol) in DME (7.6 ml) was added tetrakis(triphenylphosphine)palladium (55 mg, 0.048 mmol), phenylboronic acid (127 mg, 1.05

mmol) and a solution of sodium carbonate (201 mg, 1.90 mmol) in water (3.8 ml). The reaction mixture was heated for 0.5 h at 75 °C with vigorous stirring under nitrogen atmosphere. After **7** was consumed, the solution was concentrated *in vacuo* and the residue diluted in water (100 ml). After extraction with dichloromethane, the dried organic layers were evaporated to dryness. The oily residue was purified by column chromatography (silica gel eluting with dichloromethane) (91%); mp 96 °C (lit.[18] mp 88—90 °C); ^{13}C-NMR ($CDCl_3$) δ: 163.8 (CO), 144.7 (C-8a), 133.4 (C-2), 131.0 (Ph-1,2,6), 129.8 (Ph-4), 129.2 (Ph-3,5), 128.5 (C-3), 126.6 (C-7), 124.4 (C-5), 119.4 (C-8), 114.1 (C-6), 61.3 (CH_2), 14.7 (CH_3).

General Procedure for (Imidazo[1,2-*a*]pyridin-2-yl)methanol Derivatives To a stirred solution of **5** or **8** (6 mmol) in THF (15 ml) was added a suspension of lithium aluminium hydride (12 mmol) in THF (5 ml). After 1 h, water (20 ml) was added dropwise and then the reaction media filtered off. The filtrate was extracted with dichloromethane and the dried organic layers were evaporated to dryness to give white crystals.

(3-Benzylimidazo[1,2-*a*]pyridin-2-yl)methanol (**9a**): Colorless crystals (81%); mp 163 °C; ^{1}H-NMR ($CDCl_3$) δ: 7.94 (1H, d, $J_{H\text{-}7\ H\text{-}8}$=8.8 Hz, H-8); 7.70 (1H, d, $J_{H\text{-}5\ H\text{-}6}$=6.8 Hz, H-5); 7.25—7.20 (4H, m, Ph, H-7); 7.05 (2H, dd, J=7.2 Hz, J=3.4 Hz, Ph-2,6); 6.72 (1H, t, $J_{H\text{-}6\ H\text{-}7}$=6.8 Hz, H-6); 4.99 (2H, s, CH_2); 4.81 (1H, s, OH); 4.25 (2H, s, CH_2); ^{13}C-NMR ($CDCl_3$) δ: 144.0 (C-8a, C-2), 137.0 (Ph-1), 129.3 (Ph-2,6), 128.4 (Ph-3,5), 127.3 (Ph-4), 124.9 (C-7), 123.9 (C-5), 119.0 (C-3), 117.8 (C-8), 112.7 (C-6), 57.5 (CH_2), 29.5 (CH_2); *Anal.* Calcd for $C_{15}H_{14}N_2O$: C, 75.61; H, 5.92; N, 11.76. Found: C, 75.89; H, 5.97; N, 11.94.

(3-Phenylimidazo[1,2-*a*]pyridin-2-yl)methanol (**9b**): Colorless crystals (75%); mp 66 °C (dec.); ^{1}H-NMR ($CDCl_3$) δ: 8.18 (1H, d, $J_{H\text{-}5\ H\text{-}6}$=6.8 Hz, H-5); 7.67 (1H, d, $J_{H\text{-}7\ H\text{-}8}$=9 Hz, H-8); 7.70—7.44 (5H, m, Ph); 7.21 (1H, dd, $J_{H\text{-}6\ H\text{-}7}$=6.8 Hz, H-7); 6.77 (1H, t, H-6); 6.60 (1H, bs, OH); 4.89 (2H, s, CH_2); ^{13}C-NMR ($CDCl_3$) δ: 145.2 (C-8a*), 144.3 (C-2*), 130.1 (Ph-2,6), 129.6 (Ph-3,5), 129.0 (Ph-1*), 128.9 (Ph-4*), 125.4 (C-7), 123.9 (C-5), 122.9 (C-3), 117.8 (C-8), 113.0 (C-6), 57.2 (CH_2); *Anal.* Calcd for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.39; N, 12.49. Found: C, 74.59; H, 5.33; N, 12.72.

General Procedure for Arylmethylimidazo[1,2-*a*]pyridine Derivatives A solution of imidazo[1,2-*a*]pyridinylmethanol derivative **2** or **9a**—**b** (6 mmol) in thionyl chloride (20 ml) was refluxed for 2 h. After evaporation to dryness, the chloro derivative was washed with petroleum ether (2× 50 ml), poured into acetonitrile (20 ml) and imidazole or triazole (13.2 mmol) was added. After 48 h of stirring at 50 °C, the solution was concentrated *in vacuo* and the residue diluted in water (20 ml). The solution was extracted with dichloromethane, the dried organic layers evaporated to dryness and the residue was chromatographed on neutral alumina eluting with dichloromethane.

3-(1*H*-Imidazol-1-ylmethyl)-2-phenylimidazo[1,2-*a*]pyridine (**3a**): Colorless crystals (13%); mp 139 °C; ^{1}H-NMR ($CDCl_3$) δ: 7.79—7.73 (4H, m, Ph, H-5); 7.59 (1H, bs, Im-2); 7.57—7.42 (3H, m, Ph, H-8); 7.32 (1H, ddd, $J_{H\text{-}7\ H\text{-}8}$=8.8 Hz, $J_{H\text{-}6\ H\text{-}7}$=6.8 Hz, $J_{H\text{-}5\ H\text{-}7}$=1.1 Hz, H-7); 7.15 (1H, bs, Im-4); 6.93 (1H, bs, Im-5); 6.89 (1H, td, $J_{H\text{-}5\ H\text{-}6}$=6.8 Hz, $J_{H\text{-}6\ H\text{-}8}$=1.1 Hz, H-6); 5.61 (2H, s, CH_2); ^{13}C-NMR ($CDCl_3$) δ: 146.7 (C-2), 145.7 (C-8a), 136.3 (Im-2), 133.3 (Ph-1), 130.4 (Im-4), 129.0 (Ph-2,6*), 128.6 (Ph-4), 128.4 (Ph-3,5*), 125.7 (C-7), 122.9 (C-5), 118.1 (Im-5), 118.0 (C-8), 113.4 (C-6), 112.6 (C-3), 40.8 (CH_2); *Anal.* Calcd for $C_{17}H_{14}N_4$: C, 74.43; H, 5.14; N, 20.42. Found: C, 74.58; H, 5.18; N, 20.22.

3-(1*H*-1,2,4-Triazol-1-ylmethyl)-2-phenylimidazo[1,2-*a*]pyridine (**3b**): Colorless crystals (31%); mp 132 °C; ^{1}H-NMR ($CDCl_3$) δ: 8.24 (1H, d, $J_{H\text{-}5\ H\text{-}6}$=6.8 Hz, H-5); 8.05 (2H, s, Tr-3,5); 7.79—7.75 (3H, m, Ph); 7.59—7.48 (3H, m, Ph, H-8); 7.37 (1H, ddd, $J_{H\text{-}7\ H\text{-}8}$=8.9 Hz, $J_{H\text{-}6\ H\text{-}7}$=6.8 Hz, $J_{H\text{-}5\ H\text{-}7}$=1.2 Hz, H-7); 6.95 (1H, td, $J_{H\text{-}6\ H\text{-}8}$=1.1 Hz, H-6); 5.82 (2H, s, CH_2); ^{1}H-NMR (DMSO-d_6) δ: 8.87 (1H, s, Tr-5); 8.61 (1H, d, $J_{H\text{-}5\ H\text{-}6}$=6.6 Hz, H-5); 8.02 (1H, s, Tr-3); 7.95 (2H, d, Ph); 7.69 (1H, d, $J_{H\text{-}7\ H\text{-}8}$=8.8 Hz, H-8); 7.56—7.35 (4H, m, Ph, H-7); 7.04 (1H, t, $J_{H\text{-}6\ H\text{-}7}$=6.6 Hz, H-6); 5.97 (2H, s, CH_2); ^{13}C-NMR ($CDCl_3$) δ: 152.7 (Tr-3), 147.1 (C-2), 146.2 (C-8a), 142.9 (Tr-5), 133.7 (Ph-1), 129.4 (Ph-2,6*), 129.1 (Ph-4), 129.0 (Ph-3,5*), 126.4 (C-7), 124.2 (C-5), 118.3 (C-8), 113.7 (C-6), 113.1 (C-3), 43.9 (CH_2); *Anal.* Calcd for $C_{16}H_{13}N_5$: C, 69.80; H, 4.76; N, 25.44. Found: C, 69.45; H, 4.77; N, 25.78.

3-Benzyl-2-(1*H*-imidazol-1-ylmethyl)imidazo[1,2-*a*]pyridine (**10a**): Colorless crystals (13%); mp 128 °C; ^{1}H-NMR ($CDCl_3$) δ: 7.74 (1H, dt, $J_{H\text{-}5\ H\text{-}6}$ =6.8 Hz, $J_{H\text{-}5\ H\text{-}7}$=1.2 Hz, H-5); 7.64 (1H, dt, $J_{H\text{-}7\ H\text{-}8}$=9.1 Hz, $J_{H\text{-}6\ H\text{-}8}$ =1.2 Hz, H-8); 7.60 (1H, bs, Im-2); 7.36—7.26 (3H, m, Ph); 7.23 (1H, ddd, $J_{H\text{-}6\ H\text{-}7}$=6.8 Hz, H-7); 7.05—7.00 (4H, m, Ph, Im-4,5); 6.77 (1H, td, H-6); 5.31 (2H, s, CH_2); 4.29 (2H, s, CH_2); ^{13}C-NMR ($CDCl_3$) δ: 145.2 (C-8a), 139.3 (C-2), 137.5 (Im-2), 136.3 (Ph-1), 130.0 (Im-4), 129.5 (Ph-2,6), 128.2 (Ph-3,5), 127.6 (Ph-4), 125.1 (C-7), 124.0 (C-5), 120.0 (C-3), 119.6 (Im-5), 118.2 (C-8), 113.0 (C-6), 44.6 (CH_2), 29.4 (CH_2); *Anal.* Calcd for $C_{18}H_{16}N_4$: C, 74.98; H, 5.59; N, 19.43. Found: C, 74.58; H, 5.61; N, 19.01.

2-(1*H*-Imidazol-1-ylmethyl)-3-phenylimidazo[1,2-*a*]pyridine (**10b**): Colorless crystals (20%); mp 143 °C; ^{1}H-NMR ($CDCl_3$) δ: 8.06 (1H, d, $J_{H\text{-}5\ H\text{-}6}$ =6.8 Hz, H-5); 7.68 (1H, d, $J_{H\text{-}7\ H\text{-}8}$=9.0 Hz, H-8); 7.61—7.53 (4H, m, Ph, Im-2); 7.42—7.37 (2H, m, Ph); 7.28 (1H, ddd, $J_{H\text{-}6\ H\text{-}7}$=6.8 Hz, $J_{H\text{-}5\ H\text{-}7}$ =1.3 Hz, H-7); 7.03 (2H, m, Im-4,5); 6.83 (1H, td, $J_{H\text{-}6\ H\text{-}8}$=1.1 Hz, H-6); 5.25 (2H, s, CH_2); ^{13}C-NMR ($CDCl_3$) δ: 145.2 (C-8a), 138.9 (C-2), 137.4 (Im-2), 130.3 (Ph-2,6), 130.0 (Ph-3,5), 129.8 (Ph-1), 129.6 (Im-4), 128.2 (Ph-4), 125.8 (C-7), 124.1 (C-5), 123.8 (C-3), 119.5 (Im-5), 118.2 (C-8), 113.3 (C-6), 44.5 (CH_2); *Anal.* Calcd for $C_{17}H_{14}N_4$: C, 74.43; H, 5.14; N, 20.42. Found: C, 74.65; H, 4.98; N, 20.17.

2-(1*H*-Imidazol-1-ylmethyl)-3-nitroimidazo[1,2-*a*]pyridine (12) A solution of 2-chloromethyl-3-nitroimidazo[1,2-*a*]pyridine **11**[11] (3 g, 14.2 mmol) and imidazole (2.1 g, 30.8 mmol) in acetonitrile (15 ml) was stirred at 50 °C for 24 h. After removal of the solvent *in vacuo*, the reaction mixture was diluted in water (50 ml) and extracted with dichloromethane (2×50 ml). The dried organic layers were evaporated to dryness and the oily residue triturated in diethyl ether to give a brown solid (43%); mp 180 °C; ^{1}H-NMR ($CDCl_3$) δ: 9.46 (1H, d, $J_{H\text{-}5\ H\text{-}6}$=6.9 Hz, H-5); 7.85 (1H, d, $J_{H\text{-}7\ H\text{-}8}$=9.0 Hz, H-8); 7.78 (1H, bs, Im-2); 7.72 (1H, ddd, $J_{H\text{-}6\ H\text{-}7}$=6.9 Hz, $J_{H\text{-}5\ H\text{-}7}$=1.3 Hz, H-7); 7.37 (1H, td, $J_{H\text{-}6\ H\text{-}8}$=1.1 Hz, H-6); 7.19 (1H, bs, Im-4); 7.10 (1H, bs, Im-5); 5.73 (2H, s, CH_2); ^{13}C-NMR ($CDCl_3$) δ: 147.0 (C-8a*), 145.0 (C-2*), 137.9 (Im-2), 131.3 (C-7), 129.5 (C-3), 128.9 (Im-4), 127.7 (C-5), 119.8 (Im-5), 118.6 (C-8); 117.3 (C-6), 45.1 (CH_2); *Anal.* Calcd for $C_{11}H_9N_5O_2$: C, 54.32; H, 3.73; N, 28.79. Found: C, 54.65; H, 3.78; N, 28.67.

3-Amino-2-(1*H*-imidazol-1-ylmethyl)imidazo[1,2-*a*]pyridine (13) To 48% hydrobromic acid (12 ml) cooled at −10 °C was added portionwise tin powder (1.5 g, 12.6 mmol) and then **12** (1.2 g, 5.2 mmol) keeping the temperature below −5 °C. After stirring at 0 °C for 1 h, the reaction mixture was stirred at room temperature for 2 h. The solution was made basic with sodium carbonate and the water removed *in vacuo.* The residue was chromatographed on neutral alumina eluting with dichloromethane–methanol (90: 10 v/v) to give a brown solid (63%); mp 127—130 °C (dec); ^{1}H-NMR (DMSO-d_6) δ: 8.08 (1H, d, $J_{H\text{-}5\ H\text{-}6}$=7.0 Hz, H-5); 7.74 (1H, bs, Im-2); 7.35 (1H, d, $J_{H\text{-}7\ H\text{-}8}$=9.0 Hz, H-8); 7.20 (1H, bs, Im-4); 7.04 (1H, m, H-7); 6.87 (1H, bs, Im-5); 6.84 (1H, t, $J_{H\text{-}6\ H\text{-}7}$=7.0 Hz, H-6); 5.27 (4H, s, CH_2, NH_2).

2-(1*H*-Imidazol-1-ylmethyl)-3-(pyrrol-1-yl)imidazo[1,2-*a*]pyridine (14) A mixture of **13** (0.75 g, 3.5 mmol) and dimethoxytetrahydrofuran (0.46 ml, 3.5 mmol) in acetic acid (20 ml) was heated at 90 °C for 2 h. After removal of the solvent *in vacuo*, the residue was triturated in diethyl ether (75 ml). After filtration, the filtrate was dried over magnesium sulfate and evaporated to dryness. The residue was chromatographed on neutral alumina eluting with dichloromethane to give **14** as white crystals (13%); mp 153 °C; ^{1}H-NMR ($CDCl_3$) δ: 7.65 (1H, dt, $J_{H\text{-}7\ H\text{-}8}$=9.0 Hz, $J_{H\text{-}6\ H\text{-}8}$=1.1 Hz, H-8); 7.61 (1H, dt, $J_{H\text{-}5\ H\text{-}6}$=6.2 Hz, $J_{H\text{-}5\ H\text{-}7}$=1.1 Hz, H-5); 7.51 (1H, bs, Im-2); 7.32 (1H, ddd, $J_{H\text{-}6\ H\text{-}7}$=6.2 Hz, H-7); 7.04 (1H, bs, Im-4); 6.99 (1H, bs, Im-5); 6.88 (1H, td, H-6); 6.77 (2H, t, J=2.1 Hz, Py-2,5); 6.52 (2H, t, Py-3,4); 5.18 (2H, s, CH_2); ^{13}C-NMR ($CDCl_3$) δ: 142.8 (C-8a), 137.6 (Im-2), 136.3 (C-2), 130.0 (Im-4), 126.4 (C-7), 123.4 (Py-2,5), 122.9 (C-5), 120.7 (C-3), 119.6 (Im-5), 118.4 (C-8), 113.9 (C-6), 112.1 (Py-3,4), 43.4 (CH_2); *Anal.* Calcd for $C_{15}H_{13}N_5$: C, 68.43: H, 4.98; N, 26.60. Found: C, 68.32; H, 4.93; N, 26.22.

X-Ray Diffraction of Compound 10b Colorless crystals of compound **10b** were grown by slow evaporation of an ethanol solution at 293 K. The crystal used for X-ray measurement was lamellar, with dimensions: 0.2×0.2×0.08 mm. The studied compound, $C_{17}H_{14}N_4 \cdot 2H_2O$, M_γ=310.4 crystallizes in the triclinic system, space group P-1 (Z=2), two independent molecules per asymmetric unit. The unit cell parameters were obtained by least-squares fit of the setting angles of 25 reflections and are as follows: a=8.924(1), b=9.752(1), c=18.645(3) Å, α=82.15(1), β=82.07(1) and γ=83.81(1)° with a cell volume of 1585.5(4) Å^3. The calculated density equal to 1.30 g·cm^{-3}. The linear absorption coefficient is μ=0.717 mm^{-1} for the Cu$K\alpha$ radiation.

The diffracted intensities were collected with a CAD-4 Enraf-Nonius diffractometer equiped with a graphite monochromator for θ_{max}=65°: $0 \leq h \leq 10$, $-11 \leq k \leq 11$, $-21 \leq l \leq 21$ and an $\omega-2\theta$ scan. Two standard reflections (3 0 −10, 0 −5 −10) were used to monitor the data collection and detect any decrease of intensity; the crystal absorption correction was performed using the Ψ scan technique.[19] There were 5316 independent reflections of which 4898 were considered as observed ($I>2\sigma(I)$ and R_{int}=0.012).

The crystal structure was solved and refined using the SHELX97 program.[20] Scattering factors were taken from the International Tables for Crystallography.[21] The hydrogen atoms were introduced in their theoretical

positions and allowed to ride with the atoms to which they are attached. The final reliability factors are: $R=0.051$, $wR=0.127$ and the goodness of fit was equal to s=1.22. The weight was equal to: $w=1/[\sigma^2(F_o^2)+(0.0421P)^2+0.6335P]$ where $P=(F_O^2+2F_O^2)/3$. The minimum and maximun residual densities were equal to -0.17 and 0.21 e $Å^{-3}$ respectively; $(\Delta/\sigma)_{max}=0.04$.

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