

Synthesis and Antibacterial Activity of Some Imidazo[1,2-*a*]pyrimidine Derivatives

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A series of 75 imidazo[1,2-*a*]pyrimidine derivatives were synthesized. The “*in vitro*” antibacterial activity of these compounds and their corresponding α -bromoketones against a variety of gram (+), gram (–) bacteria and *Mycobacterium* species is reported. Some of the prepared derivatives exhibited potent antimicrobial activity.

Keywords imidazo[1,2-*a*]pyrimidine; azaindolizine; α -bromoketone; *Mycobacterium smegmatis*; antibacterial activity

Azaindolizines and particularly imidazo[1,2-*a*]pyrimidine derivatives (i), were among the various heterocycles that have received a great deal of attention during the last two decades, especially as antimicrobial agents.^{1–3} That was how there were some imidazo[1,2-*a*]pyrimidine or pyrimidine derivatives which had antifungal and even antibacterial activities. In 1975, Rewankar tested the “*in vitro*” antimicrobial activity of some 5- and 7-substituted imidazo[1,2-*a*]pyrimidine derivatives against several bacteria.⁴ The compound A was the only imidazo[1,2-*a*]pyrimidine which afforded significant activity against all bacteria tested. Then Mandrichenko *et al.* showed that the imidazo[1,2-*a*]pyrimidines B and C were active against *Staphylococcus aureus*, *Escherichia coli* and *Pseudomonas aeruginosa*.^{5,6}

Therefore, we have synthesized a series of 75 imidazo[1,2-*a*]pyrimidine derivatives (ii) with different substitutions on the heterocyclic ring in order to examine their antimicrobial activity.

Chemistry Imidazo[1,2-*a*]pyrimidines (I) were synthesized according to Tschitschibabin by condensation of an amino-pyrimidine with the appropriate α -bromoketone.^{7,8–22} The 3-nitroso derivatives (II) were obtained by direct nitrosation of the imidazopyrimidines using sodium nitrite in acetic acid^{23–28} (Chart 1). The 3-nitroimidazo[1,2-*a*]pyrimidines (III) were prepared either by direct nitration by means of a mixture of fuming nitric acid and sulfuric acid or by nitric oxidation of the corresponding

3-nitroso compounds^{1,29} (Chart 2). The 3-bromoimidazo[1,2-*a*]pyrimidines (IV) were prepared using *N*-bromosuccinimide (NBS) in CCl₄ solution^{1,30} (Chart 3). The 3-amino derivatives (V) were obtained either by reduction of the 3-nitroimidazo[1,2-*a*]pyrimidines with a mixture of Sn and HX, either by reduction of the 3-nitroso derivative using Zn and CH₃COOH or Sn and HX, or hydrogenation over Raney nickel^{31–35} (Chart 4). The 5,6,7,8-tetrahydro derivative (VI) was prepared by hydrogenation over Adams catalyst³⁶ (Chart 5).

All compounds tested are listed in Table I. New compounds synthesized are marked (a).

Biological Evaluation All compounds have been tested for “*in vitro*” antimicrobial activity against 12 gram-positive, 8 gram-negative bacteria and against 1 *Mycobacterium* (*Mycobacterium smegmatis* (MYCO)) (Table II). Tests on gram-positive, gram-negative bacteria and on MYCO were carried out according to the agar dilution method (with serial twofold dilution).

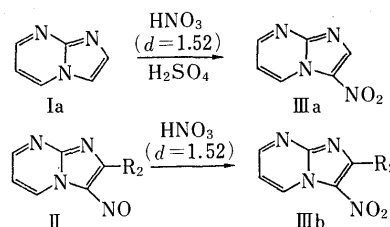


Chart 2

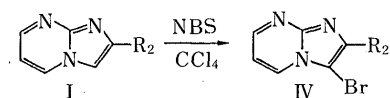


Chart 3

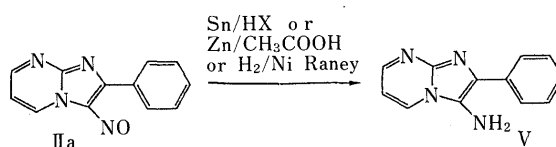


Chart 4

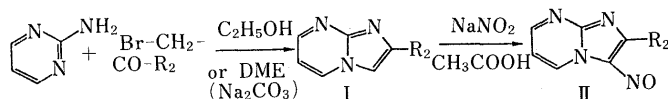
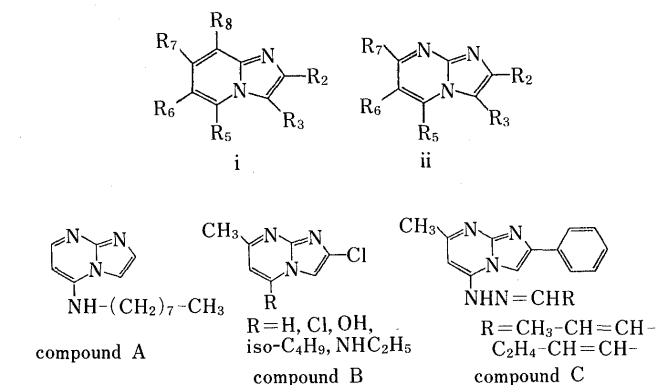


Chart 1

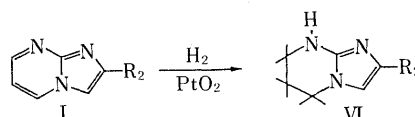
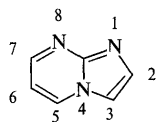


Chart 5

TABLE I(a). Imidazo[1,2-*a*]pyrimidines Tested

No.	R ₂	R ₃	R ₅	R ₆	R ₇
1	H	H	H	H	H
2	H	H	CH ₃	H	CH ₃
3	-COOC ₂ H ₅	H	CH ₃	H	CH ₃
4	-COOC ₂ H ₅	H	Cl	H	CH ₃
5	-CH ₂ Cl	H	H	H	H
6	-CH ₂ Cl	H	Cl	H	Cl
7		H	H	H	H
8		H	H	H	H
9		H	H	H	H
10 ^{a)}		H	H	H	H
11 ^{a)}		H	H	H	H
12 ^{a)}		H	H	H	H
13 ^{a)}		H	H	H	H
14		H	H	H	H
15		H	H	H	H
16 ^{a)}		H	H	H	H
17 ^{a)}		H	H	H	H
18 ^{a)}		H	H	H	H
19		H	H	H	H
20 ^{a)}		H	H	H	H
21		H	H	H	H
22		H	H	H	H
23 ^{a)}		H	H	H	H
24 ^{a)}		H	H	H	H
25 ^{a)}		H	H	H	H

TABLE I(a). (continued)

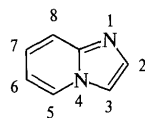
No.	R ₂	R ₃	R ₅	R ₆	R ₇
26 ^{a)}		H	H	H	H
27 ^{a)}		H	H	H	H
28		NO	H	H	H
29		NO	H	H	H
30		NO	H	H	H
31		NO	H	H	H
32		NO	H	H	H
33		NO	H	H	H
34 ^{a)}		NO	H	H	H
35		NO	H	H	H
36 ^{a)}		NO	H	H	H
37		NO	H	H	H
38		NO	H	H	H
39 ^{a)}		NO	H	H	H
40		NO	H	H	H
41 ^{a)}		NO	H	H	H
42		NO	H	H	H
43		NO	H	H	H
44 ^{a)}		NO	H	H	H
45 ^{a)}		NO	H	H	H
46 ^{a)}		NO	H	H	H
47		NO	H	H	H
48		NO	H	H	H

TABLE I(a). (continued)

No.	R ₂	R ₃	R ₅	R ₆	R ₇
49 ^{a)}		NO	H	H	H
50	H	NO ₂	H	H	H
51 ^{a)}	-COOC ₂ H ₅	NO ₂	H	H	H
52		NO ₂	H	H	H
53		NO ₂	H	H	H
54		NO ₂	H	H	H
55		NO ₂	H	H	H
56		NO ₂	H	H	H
57 ^{a)}		NO ₂	H	H	H
58		NH ₂	H	H	H
59		NH ₂	H	H	H
60		NH ₂	H	H	H
61		NH ₂	H	H	H
62	H	Cl	H	H	H
63	H	Br	H	H	H
64	H	Br	CH ₃	H	CH ₃
65 ^{a)}	H	H	H	H	H
66 ^{a)}	-COOC ₂ H ₅	H	H	H	H
67 ^{a)}		H	H	H	H
68		H	H	H	H
69 ^{a)}		H	H	H	H
70 ^{a)}		H	H	H	H

a) New compounds synthesized. b) Heterocyclic structure is 5,6,7,8-tetrahydroimidazo[1,2-a]pyrimidine.

TABLE I(b). Imidazo[1,2-a]pyridines Tested



No.	R ₂	R ₃	R ₅	R ₆	R ₇	R ₈
71		H	H	H	H	H
72	-COOC ₂ H ₅	H	H	H	H	H
73	-CH ₂ Cl	H	H	H	H	H
74		NO	H	H	H	H
75	-COOC ₂ H ₅	NO ₂	H	H	H	H

The imidazo[1,2-a]pyrimidine derivatives and the α -bromoketones were dissolved in dimethyl sulfoxide (DMSO) at concentrations of 10 mg/ml and subsequently diluted in distilled and sterilized water. From these solutions,

TABLE I(c). (A) α -Bromoketones Tested, (B) Ketones Tested

Br-CH ₂ -CO-R A		CH ₃ -CO-R B	
No.	R	No.	R
7b		7a	
8b		8a	
9b		9a	
10b		10a	
11b		11a	
12b		12a	
13b		13a	
14b		14a	
15b		15a	
19b		16a	
23b		17a	
24b		19a	
51b		20a	
		21a	
		23a	

1 ml was incorporated into Petri dishes containing 19 ml of test medium. Inhibition by the diluent (DMSO) was not recorded at this concentration. The minimum inhibitory concentrations (MICs) were determined in trypticase-soja agar with 10 μ l steril sheep blood for all strains listed in Table II. Each bacterium strain was tested with a dilution of an overnight broth culture containing approximately 2×10^6 cells/ml. After 2 d of incubation at 37 °C, the MIC in μ g/ml was determined (Table III).

Results and Discussion

The activities of the most potent compounds against 21 bacteria strains (Table II) are reported in Table III. Among

the potent compounds were essentially 3-nitrosoimidazo[1,2-*a*]pyrimidines, 3-nitroimidazo[1,2-*a*]pyrimidines, some α -bromoketones and four imidazo[1,2-*a*]pyrimidines unsubstituted in position-3. Among all the tested compounds, 5 compounds (**15a**, **15b**, **32**, **36**, **38**) showed antibacterial properties over all the strains without any resistance. Concerning the activity against MYCO, 8 compounds (**14**, **15a**, **29**, **30**, **32**, **35**, **36**) were active. The substituent in position-3 plays a crucial role insofar that only nitroso substitution in this position led to active compounds.

No clear-cut conclusions can be drawn about substituent effects on the aromatic ring in position-2. The compounds **12**, **14**, **26**, **29**, **30**, **33**, **51**, **53** showed a complete inactivity over all the gram (–) PROT, PROV, PSEU and SERR

well known for their resistance. Concerning the MIC values, the best potency is 2 μ g/ml for BACC (**30**, **53**), 12 μ g/ml for BACM (**14**, **36**), 0.7 μ g/ml for CORY (**14**), 3 μ g/ml for PROP (**30**, **35**), 3 μ g/ml for STAA (**30**), 6 μ g/ml for STAE (**35**), 23 μ g/ml for STEA (**14**) 23 μ g/ml for STEE (**14**), 24 μ g/ml for STEC (**36**), 6 μ g/ml for STEG (**35**), 16 μ g/ml for STEL (**15a**), 7 μ g/ml for STEN (**30**), 24 μ g/ml for ENTE (**36**), 13 μ g/ml for ESCH (**35**), 24 μ g/ml for KLEB (**36**), 3 μ g/ml for NEIS (**30**), 12 μ g/ml for PROT (**9b**), 15.8 μ g/ml for PROV (**15a**), 24 μ g/ml for PSEU and SERR (**36**) and 23 μ g/ml for MYCO (**14**). These values are favorably situated in comparison to that found for the reference compounds (Table IV).

Experimental

Melting points were determined on a Kofler apparatus and are uncorrected. Infrared (IR) spectra were measured on a Spectrometer Perkin-Elmer 983 G and proton nuclear magnetic resonance ($^1\text{H-NMR}$) spectra were determined on a Bruker WM 250 (250 MHz). Microanalyses are indicated only by symbols of the elements analyzed; the results obtained had a maximum deviation of 0.4% from the theoretical value.

Preparation of α -Bromoketones Bromine (0.1 mol) was slowly added to a solution of ketone (0.1 mol) in dry mixture dioxane–ether (1 : 2). The reaction mixture was stirred until 1 h after the end of bromine addition. The mixture was washed with water and the ether separated, dried and evaporated under reduced pressure. The pure compound was obtained by recrystallization in a mixture of ethanol–water.

7b: mp 49 °C (lit.³⁷) 50 °C). **8b**: mp 73 °C (lit.^{38,50}) 73–74 °C). **9b**: mp 63 °C (lit.³⁹) 63 °C). **10b**: mp 69 °C (lit.⁴⁰) 69–71 °C). **11b**: mp 80 °C (lit.⁴¹) 80–81 °C). **12b**: mp 83 °C (lit.⁴²) 83–85 °C). **13b**: mp 88 °C (lit.⁴²) 89 °C). **14b**: mp 78 °C (lit.⁴³) 77–79 °C). **15b**: mp 97 °C (lit.⁴⁴) 97.5–98 °C). **19b**: mp 49 °C (lit.⁴⁴) 48–49 °C). **23b**: mp 87 °C (lit.⁴⁵) 86–87 °C). **24b**: mp 55 °C (lit.⁴⁶) 55–56 °C). **51b**: (lit.⁴⁷) bp 98–100 °C).

Preparation of Imidazo[1,2-*a*]pyrimidines Unsubstituted in Position-2: 2-Aminopyrimidine (0.5 mol) was dissolved in 50% aqueous alcohol solution in the presence of sodium hydrogencarbonate (0.6 mol). To this mixture, an aqueous solution (40%) of chloroacetaldehyde (1 mol) was slowly added under nitrogen with vigorous stirring and was refluxed for 48 h. After this period, the reaction mixture was cooled, concentrated under reduced pressure, poured into water and extracted with hot chloroform. The organic layer was dried (MgSO_4) and evaporated under reduced pressure. Pure imidazo[1,2-*a*]pyrimidine was obtained after chromatog-

TABLE II. Bacteria Strains

Strain	Gram	Abbreviation
<i>Bacillus cereus</i>	+	BACC
<i>Bacillus megatherium</i>	+	BACM
<i>Corynebacterium hoffmanii</i>	+	CORY
<i>Propionibacterium spe.</i>	+	PROP
<i>Staphylococcus aureus</i> CNCM 53154	+	STAA
<i>Staphylococcus epidermitis</i>	+	STAE
<i>Streptococcus A</i>	+	STEA
<i>Streptococcus faecium</i>	+	STEE
<i>Streptococcus faecalis</i> CNCM 5855	+	STEC
<i>Streptococcus G</i>	+	STEG
<i>Streptococcus salivarius</i>	+	STEL
<i>Streptococcus sanguis</i>	+	STEN
<i>Enterobacter cloacae</i>	–	ENTE
<i>Escherichia coli</i> CNCM 54127	–	ESCH
<i>Klebsiella pneumoniae</i>	–	KLEB
<i>Neisseria flava</i>	–	NEIS
<i>Proteus mirabilis</i>	–	PROT
<i>Providencia</i>	–	PROV
<i>Pseudomonas aeruginosa</i> CNCM A22	–	PSEU
<i>Serratia</i>	–	SERR
<i>Mycobacterium smegmatis</i> CNCM 7326	/	MYCO

TABLE III. MICs (μ g/ml) of the Most Potent Compounds

Strains	Compounds																			
	7b	9b	12	14	15	15a	15b	23b	24b	26	29	30	31	32	33	35	36	38	40	48
BACC	41	12	>200	12	47	15.8	23.8	57	50	>200	20	2	31	18	24	3	24	54	62	55
BACM	41	23	104	12	94	15.8	48	113	50	>200	26	26	31	25	49	26	12	54	62	57
CORY	20	23	>200	0.7	12	1	23.8	7	50	127	>200	105	124	99	97	>200	24	27	124	55
PROP	81	23	>200	12	47	15.8	23.8	57	50	>200	26	3	31	12	24	3	24	54	62	55
STAA	41	47	>200	>200	47	15.8	23.8	57	50	>200	26	3	31	25	49	6	24	54	62	55
STAE	>200	47	>200	23	47	15.8	23.8	57	50	>200	26	26	31	12	24	6	24	54	62	55
STEA	>200	47	>200	23	47	32	48	113	50	>200	>200	53	62	49	200	26	24	109	124	110
STEE	>200	93	>200	23	47	32	48	113	50	>200	>200	>200	124	99	200	52	24	109	124	110
STEC	>200	>200	>200	>200	94	32	95	113	50	>200	>200	105	62	99	200	26	24	109	200	>200
STEG	>200	47	>200	>200	94	32	48	113	50	>200	104	26	31	25	97	6	24	27	62	55
STEL	>200	23	>200	04	47	16	48	28	50	>200	>200	>200	31	99	200	52	24	54	62	55
STEN	81	47	>200	12	94	15.8	23.8	28	100	>200	13	7	>200	12	24	13	12	54	62	27
ENTE	200	>200	>200	94	94	32	48	113	50	>200	>200	>200	>200	99	200	>200	24	109	200	>200
ESCH	81	47	>200	47	94	15.8	48	113	100	>200	200	105	124	49	200	13	24	109	124	>200
KLEB	>200	>200	>200	47	94	32	48	57	25	>200	>200	>200	200	99	200	52	24	109	200	>200
NEIS	>200	47	>200	47	47	15.8	23.8	28	50	>200	104	3	31	12	49	13	12	54	62	27
PROT	41	12	>200	>200	>200	16	48	57	100	>200	>200	>200	124	49	200	13	24	54	124	27
PROV	41	93	>200	>200	47	15.8	23.0	57	100	>200	>200	>200	200	99	200	52	24	109	200	>200
PSEU	>200	>200	>200	>200	47	32	95	57	100	>200	>200	>200	200	99	200	>200	24	109	200	>200
SERR	41	93	>200	>200	94	32	48	113	>200	>200	>200	>200	200	49	200	>200	24	109	200	>200
MYCO	81	47	104	23	94	32	48	>200	100	127	26	26	31	25	49	26	24	109	124	110

TABLE IV. Reference Compounds

Nifuroxazide ³⁵⁾ (Ercefuryl)		Thiophenicol ³⁶⁾	
	MIC ($\mu\text{g/ml}$)		MIC ($\mu\text{g/ml}$)
STAA	16	STAA	32
STEC	32		
ESCH	16	ESCH	128
KLEB	64	KLEB	156
		PROT	16
		PROV	256

raphy on a silica gel column (eluent, ethyl acetate).

1: mp 132°C (lit.¹⁰⁾ 130–131°C). 2: mp 127°C (lit.³²⁾ 124°C).

Substituted in Position-2: A solution of 2-aminopyrimidine (0.02 mol) in dry 1,2-dimethoxyethane (DME) was slowly added to a mixture of bromoketone (0.5 mol) in DME. The reaction mixture was refluxed for 48 h and after cooling, was filtered. The filtrate was alkalized; the solid was dissolved in water, alkalized and added to the alkalized filtrate. This aqueous alkalized phase was extracted with chloroform. The solvent was dried and evaporated under reduced pressure. The compounds were obtained after chromatography on a silica gel column (eluent, ethyl acetate).

3: mp 153°C (lit.¹⁴⁾ 154°C). 4: mp 230°C (lit.¹⁴⁾ 231°C). 5: mp 130°C (lit.⁴⁾ 129°C). 6: mp 124°C (lit.⁴⁾ 126°C). 7: mp 195°C (lit.^{9,11)} 202°C). 8: mp 183°C (lit.¹⁸⁾ 190°C). 9: mp 226°C (lit.⁴⁸⁾ 226°C). 10: mp 130°C. IR $\nu_{\text{cm}^{-1}}$: 1641, 1611, 1080, 730, 669. ¹H-NMR (DMSO-*d*₆) δ : 8.5 (1H, s, H-3), 7.7 (4H, m, phenyl), 7.1 (1H, m, H-6), 8.55 (1H, dd, H-7), 9.05 (1H, dd, H-5). *Anal.* Calcd for C₁₂H₈ClN₃: C, 62.74; H, 3.48; N, 18.30. Found: C, 62.75; H, 3.52; N, 18.26. 11: mp 146°C. IR $\nu_{\text{cm}^{-1}}$: 1641, 1611, 1080, 730, 669. ¹H-NMR (DMSO-*d*₆) δ : 8.5 (1H, s, H-3), 7.7 (4H, m, phenyl), 7.1 (1H, m, H-6), 8.55 (1H, dd, H-7), 9.05 (1H, dd, H-5). *Anal.* Calcd for C₁₂H₈ClN₃: C, 62.74; H, 3.48; N, 18.30. Found: C, 62.75; H, 3.52; N, 18.26. 12: mp 158°C. IR $\nu_{\text{cm}^{-1}}$: 1641, 1611, 1080, 730, 669. ¹H-NMR (DMSO-*d*₆) δ : 8.5 (1H, s, H-3), 7.7 (4H, m, phenyl), 7.1 (1H, m, H-6), 8.55 (1H, dd, H-7), 9.05 (1H, dd, H-5). *Anal.* Calcd for C₁₂H₈ClN₃: C, 62.74; H, 3.48; N, 18.30. Found: C, 62.75; H, 3.52; N, 18.26. 13: mp 178°C. IR $\nu_{\text{cm}^{-1}}$: 1641, 1611, 1080, 730, 669. ¹H-NMR (DMSO-*d*₆) δ : 8.5 (1H, s, H-3), 7.7 (4H, m, phenyl), 7.1 (1H, m, H-6), 8.55 (1H, dd, H-7), 9.05 (1H, dd, H-5). *Anal.* Calcd for C₁₂H₈ClN₃: C, 62.74; H, 3.48; N, 18.30. Found: C, 62.75; H, 3.52; N, 18.26. 14: mp 270°C (lit.¹⁸⁾ 274°C). 15: mp 225°C (lit.⁴⁸⁾ 225°C). 16: mp 228°C. IR $\nu_{\text{cm}^{-1}}$: 1658, 1611, 1085, 730, 675. ¹H-NMR (DMSO-*d*₆) δ : 8.56 (1H, dd, H-7), 8.66 (1H, dd, H-5), 8.06 (1H, s, H-3), 7.65 (3H, m, phenyl), 6.89 (1H, m, H-6). *Anal.* Calcd for C₁₂H₇Cl₂N₃: C, 56.25; H, 2.73; N, 16.40. Found: C, 56.21; H, 2.74; N, 16.43. 17: mp 244°C. IR $\nu_{\text{cm}^{-1}}$: 1642, 1610, 1046, 710, 670. ¹H-NMR (DMSO-*d*₆) δ : 8.72 (1H, dd, H-5), 8.60 (1H, dd, H-7), 8.10 (1H, s, H-3), 7.5 (3H, m, phenyl), 6.91 (1H, m, H-6). *Anal.* Calcd for C₁₂H₇Cl₂N₃: C, 54.75; H, 2.66; N, 15.96. Found: C, 54.83; H, 2.64; N, 15.92. 18: mp 218°C. IR $\nu_{\text{cm}^{-1}}$: 1677, 1610, 1088, 711, 673. ¹H-NMR (DMSO-*d*₆) δ : 8.60 (1H, dd, H-5), 8.30 (1H, dd, H-7), 8.28 (1H, s, H-3), 7.35 (3H, m, phenyl), 6.90 (1H, m, H-6). *Anal.* Calcd for C₁₂H₇Cl₂N₃: C, 54.75; H, 2.66; N, 15.96. Found: C, 54.80; H, 2.64; N, 15.93. 19: mp 239°C (lit.¹⁹⁾ 238°C). 20: mp 191°C. IR $\nu_{\text{cm}^{-1}}$: 1639, 1612, 1095, 1065, 1013. ¹H-NMR (DMSO-*d*₆) δ : 9 (1H, dd, H-5), 8.6 (1H, dd, H-7), 8.2 (1H, s, H-3), 8.3 (4H, m, phenyl), 7.1 (1H, m, H-6). *Anal.* Calcd for C₁₂H₆FN₃: C, 67.60; H, 3.75; N, 19.71. Found: C, 67.53; H, 3.78; N, 19.75. 21: mp 224°C (lit.^{22,23)} 226°C). 22: mp 220°C (lit.⁴⁸⁾ 220°C). 23: mp 174°C. IR $\nu_{\text{cm}^{-1}}$: 1643, 1610, 1053, 603. ¹H-NMR (DMSO-*d*₆) δ : 8.56 (1H, dd, H-5), 8.46 (1H, dd, H-7), 8.36 (4H, m, phenyl), 8.26 (1H, s, H-3), 6.91 (1H, m, H-6). *Anal.* Calcd for C₁₂H₈BrN₃: C, 52.55; H, 2.91; N, 15.32. Found: C, 52.59; H, 2.89; N, 15.34. 24: mp 261°C. IR $\nu_{\text{cm}^{-1}}$: 1666, 1617, 1475, 1075. ¹H-NMR (DMSO-*d*₆) δ : 8.8 (1H, dd, H-5), 8.56 (1H, dd, H-7), 8.2 (4H, m, phenyl), 8.12 (1H, s, H-3), 7 (1H, m, H-6). *Anal.* Calcd for C₁₂H₈N₄O₂: C, 60.00; H, 3.33; N, 23.33. Found: C, 60.09; H, 3.30; N, 23.27. 25: mp 106°C. IR $\nu_{\text{cm}^{-1}}$: 1645, 1610, 1079, 999. ¹H-NMR (DMSO-*d*₆) δ : 9 (1H, dd, H-5), 8.58 (1H, dd, H-7), 7.10 (1H, m, H-6), 4.5 (8H, m, CH₂). *Anal.* Calcd for C₁₀H₁₁N₃: C, 69.36; H, 6.35; N, 24.27. Found: C, 69.40; H, 6.34; N, 24.24. 26: mp 178°C. IR $\nu_{\text{cm}^{-1}}$: 1671, 1606, 1031, 801. ¹H-NMR (DMSO-*d*₆) δ : 8.90 (1H, dd, H-5), 8.59 (1H, dd, H-7), 8.2 (4H, m, phenyl), 8 (1H, s, H-3), 7.15 (1H, m, H-6). *Anal.* Calcd for C₁₈H₁₂N₆: C, 72.00; H, 4.00; N, 28.00. Found: C, 72.08; H, 3.98; N, 27.94. 27: mp 210°C. IR

$\nu_{\text{cm}^{-1}}$: 1642, 1629, 1082, 786. ¹H-NMR (DMSO-*d*₆) δ : 8.88 (1H, dd, H-5), 8.61 (1H, dd, H-7), 8.40 (4H, m, phenyl), 8.06 (1H, s, H-3), 6.99 (1H, m, H-6). *Anal.* Calcd for C₁₈H₁₂N₆: C, 72.00; H, 4.00; N, 28.00. Found: C, 72.09; H, 3.96; N, 27.95.

Preparation of the 3-Nitrosoimidazo[1,2-*a*]pyrimidines A saturated sodium nitrite solution was added with stirring to imidazo[1,2-*a*]pyrimidine derivative (0.01 mol) in acetic acid (40 ml). A green solid was obtained which was filtered and recrystallized from methanol or purified by chromatography on a silica gel column (eluent, ethyl acetate-methanol (90:10)).

28: mp 221°C (lit.²⁵⁻²⁸⁾ 223.5–224.5°C). 29: mp 247°C (lit.²⁵⁻²⁸⁾ 247–248°C). 30: mp 225°C (lit.²⁵⁻²⁸⁾ 228°C). 31: mp 217°C (lit.²⁵⁻²⁸⁾ 220°C). 32: mp 210°C (lit.²⁵⁻²⁸⁾ 211°C). 33: mp 251°C (lit.²⁵⁻²⁸⁾ 253–254°C). 34: mp 157°C. IR $\nu_{\text{cm}^{-1}}$: 1670, 1596, 1572, 1254. ¹H-NMR (DMSO-*d*₆) δ : 9.94 (1H, dd, H-5), 8.98 (1H, dd, H-7), 7.40 (4H, m, phenyl), 7.33 (1H, m, H-6). *Anal.* Calcd for C₁₃H₁₀N₄O₂: C, 61.41; H, 3.93; N, 22.04. Found: C, 61.47; H, 3.91; N, 22.00. 35: mp 236°C (lit.⁴⁸⁾ 236°C). 36: mp 226°C. IR $\nu_{\text{cm}^{-1}}$: 2917, 1602, 1580, 1526. ¹H-NMR (DMSO-*d*₆) δ : 10.05 (1H, dd, H-5), 9.02 (4H, m, phenyl), 8.95 (1H, dd, H-7), 7.25 (1H, m, H-6). *Anal.* Calcd for C₁₃H₁₀N₄O: C, 65.54; H, 4.20; N, 23.52. Found: C, 65.47; H, 4.22; N, 23.25. 37: mp 240°C (lit.⁴⁸⁾ 240°C). 38: mp 223°C (lit.⁴⁸⁾ 223°C). 39: mp 260°C. IR $\nu_{\text{cm}^{-1}}$: 1603, 1590, 1582, 1245. ¹H-NMR (DMSO-*d*₆) δ : 10.10 (1H, dd, H-5), 8.93 (1H, dd, H-7), 7.26 (1H, m, H-6), 7.20 (3H, m, phenyl). *Anal.* Calcd for C₁₄H₁₂N₄O₃: C, 59.15; H, 4.22; N, 19.71. Found: C, 59.21; H, 4.20; N, 19.75. 40: mp 244°C (lit.⁴⁸⁾ 224°C). 41: mp 134°C. IR $\nu_{\text{cm}^{-1}}$: 1600, 1590, 1558, 590. ¹H-NMR (DMSO-*d*₆) δ : 10 (1H, dd, H-5), 9.16 (4H, m, phenyl), 8.99 (1H, dd, H-7), 7.34 (1H, m, H-6). *Anal.* Calcd for C₁₂H₇BrN₄O: C, 47.52; H, 2.31; N, 18.48. Found: C, 47.61; H, 2.26; N, 18.44. 42: mp 254°C (lit.²⁵⁻²⁸⁾ 257°C). 43: mp 147°C (lit.⁴⁸⁾ 147°C). 44: mp 252°C. IR $\nu_{\text{cm}^{-1}}$: 1648, 1610, 1559, 675. ¹H-NMR (DMSO-*d*₆) δ : 10.09 (1H, dd, H-5), 8.98 (1H, dd, H-7), 7.8 (3H, m, phenyl), 7.32 (1H, m, H-6). *Anal.* Calcd for C₁₂H₆Cl₂N₄O: C, 49.31; H, 2.05; N, 19.17. Found: C, 49.26; H, 2.07; N, 19.20. 45: mp 234°C. IR $\nu_{\text{cm}^{-1}}$: 1632, 1605, 1562, 710. ¹H-NMR (DMSO-*d*₆) δ : 10.15 (1H, dd, H-5), 9.02 (1H, dd, H-7), 7.65 (3H, m, phenyl), 7.34 (1H, m, H-6). *Anal.* Calcd for C₁₂H₆Cl₂N₄O: C, 49.31; H, 2.05; N, 19.17. Found: C, 49.38; H, 2.02; N, 19.13. 46: mp 208°C. IR $\nu_{\text{cm}^{-1}}$: 1659, 1611, 1560, 711. ¹H-NMR (DMSO-*d*₆) δ : 10.03 (1H, dd, H-5), 8.72 (1H, dd, H-7), 7.5 (3H, m, phenyl), 7.33 (1H, m, H-6). *Anal.* Calcd for C₁₂H₆Cl₂N₄O: C, 49.31; H, 2.05; N, 19.17. Found: C, 49.27; H, 2.06; N, 19.20. 47: mp 260°C (lit.²⁵⁻²⁸⁾ 263°C). 48: mp 240°C (lit.⁴⁸⁾ 240°C). 49: mp 155°C. IR $\nu_{\text{cm}^{-1}}$: 1636, 1604, 1592, 1286. ¹H-NMR (DMSO-*d*₆) δ : 10.30 (1H, dd, H-5), 8.98 (1H, dd, H-7), 7.90 (1H, m, H-6), 7.5 (3H, m, phenyl). *Anal.* Calcd for C₂₆H₂₀N₄O₃: C, 71.55; H, 4.58; N, 12.84. Found: C, 71.62; H, 4.55; N, 12.80.

Preparation of the 3-Nitroimidazo[1,2-*a*]pyrimidines Method A: Aza-indolizine (0.01 mol) was added to an ice-cooled sulfuric acid (15 ml). The solution thus obtained was stirred and cooled. Fuming nitric acid (0.02 mol, *d* = 1.52) was added slowly. After 30 min, the reaction mixture was allowed to reach room temperature and was stirred for 2 h. The mixture was poured into water and the yellow solid was filtered, dissolved in chloroform and purified by chromatography on a short silica gel column (eluent, ethyl acetate).

Method B: 3-Nitrosoimidazo[1,2-*a*]pyrimidine (0.02 mol) was dissolved in fuming nitric acid (30 ml). This mixture was slightly heated at 60°C for 2 h. After cooling, the solution was poured into an ice-water mixture: the yellow solid obtained was filtered and the filtrate was alkalized and extracted with hot chloroform. After removal of the solvent, the residue was purified by chromatography on a silica gel column (eluent, ethyl acetate).

50: mp 199°C (lit.¹⁾ 198°C). 51: mp 96°C (lit.⁴⁸⁾ 96°C). IR $\nu_{\text{cm}^{-1}}$: 1737, 1670, 1616, 1494, 1292. ¹H-NMR (DMSO-*d*₆) δ : 9.6 (1H, dd, H-5), 8.8 (1H, dd, H-7), 7.4 (1H, m, H-6), 4.5 (2H, q, CH₂), 1.4 (3H, t, CH₃). *Anal.* Calcd for C₉H₈N₄O₄: C, 45.76; H, 3.38; N, 23.72. Found: C, 45.70; H, 3.40; N, 28.76. 52: mp 170°C (lit.⁴⁸⁾ 170°C). 53: mp 145°C (lit.⁴⁸⁾ 145°C). 54: mp 215°C (lit.²⁶⁾ 213°C). 55: mp 195°C (lit.²⁶⁾ 198°C). 56: mp 197°C (lit.²⁶⁾ 199°C). 57: mp 204°C. IR $\nu_{\text{cm}^{-1}}$: 1690, 1530, 1485, 668. ¹H-NMR (DMSO-*d*₆) δ : 9.8 (1H, dd, H-5), 9.1 (1H, dd, H-7), 8.4 (3H, m, phenyl), 7.7 (1H, m, H-6). *Anal.* Calcd for C₁₂H₆Cl₂N₄O₂: C, 46.75; H, 1.94; N, 18.18. Found: C, 46.81; H, 1.93; N, 18.13.

Preparation of 3-Aminoimidazo[1,2-*a*]pyrimidines Method A: 3-Nitroso derivative (1 g) was quickly added to a mixture of tin powder (2 g) and concentrated hydrochloric acid (30 ml). The solution was stirred for 2 h at 20°C. The reaction mixture was filtered, alkalized (pH = 9) and extracted with chloroform. After removal of the solvent, the residue was

recrystallized from absolute ethanol.

Method B: 3-Nitroso derivative (1 g) was added to a mixture of granular zinc (2 g) in a mixture of acetic acid and ethanol (15:15). The reaction mixture was stirred for 2 h at room temperature and then filtered. The filtrate was alkalized and extracted with hot chloroform. The chloroform extracts were evaporated and the residue was purified by chromatography on a silica gel column (eluent, ethanol).

Method C: The 3-nitroso compound (1 g) was dissolved in methanol and Raney Ni (4 g) was added. Hydrogenation under atmospheric pressure was carried out. After filtration of the Raney Ni, methanol was evaporated under inert gas. Amine was chromatographed on silica gel column with ethanol as eluent.

58: mp 109°C (lit.⁴⁸) 109°C). **59:** mp 195°C (lit.^{33,34}) 196°C). **60:** mp 130°C (lit.⁴⁸) 130°C). **61:** mp 200°C (lit.^{33,34}) 198°C).

Preparation of 3-Halogenimidazo[1,2-a]pyrimidines An equimolar mixture of azaindolizine and NBS was refluxed for 12 h in chloroform. After removal of the solvent, the solid was purified by chromatography on a silica gel column (eluent, ethyl acetate-methanol (75:25)).

62: mp 129°C (lit.⁴) 131°C). **63:** mp 158°C (lit.⁴) 157–158.5°C). **64:** mp 246°C (lit.⁴) 247–248°C).

Reduction of the Pyrimidine Ring Imidazo[1,2-a]pyrimidine (0.025 mol) was dissolved in absolute ethanol (250 ml) and PtO₂ catalyst (1 g) was added. Concentrated hydrochloric acid (20 ml) was added and then argon was bubbled through the mixture. The mixture was hydrogenated under atmospheric pressure with stirring. The solution was filtered and the solvent removed. The residue was dissolved in water and the mixture was alkalized, then extracted with hot chloroform. Chromatography on a silica gel column was used for purification of the product (eluent, ethyl acetate).

65: mp dec. IR $\nu_{\text{cm}^{-1}}$: 3421, 1672. ¹H-NMR (DMSO-*d*₆) δ : 6.88 (1H, d, H-2), 6.68 (1H, d, H-3), 4.1 (2H, m, H-5), 3.58 (2H, m, H-7), 2.2 (2H, m, H-6). *Anal.* Calcd for C₆H₆N₃: C, 58.53; H, 7.31; N, 34.14. Found: C, 58.48; H, 7.35; N, 34.15. **66:** mp 166°C. IR $\nu_{\text{cm}^{-1}}$: 3410, 3220, 1690, 1619, 1279. ¹H-NMR (DMSO-*d*₆) δ : 7.2 (1H, s, H-3), 4.3 (2H, q, CH₂), 3.9 (2H, m, H-5), 3.45 (2H, m, H-7), 1.99 (2H, m, H-6), 1.3 (3H, t, CH₃). *Anal.* Calcd for C₉H₁₃N₃O₂: C, 55.38; H, 6.66; N, 21.53. Found: C, 55.42; H, 6.64; N, 21.51. **67:** mp 128°C. IR $\nu_{\text{cm}^{-1}}$: 3416, 1670, 1602. ¹H-NMR (DMSO-*d*₆) δ : 7.5 (5H, m, phenyl), 6.7 (1H, s, H-3), 3.8 (2H, m, H-5), 3.3 (2H, m, H-7), 1.99 (2H, m, H-6). *Anal.* Calcd for C₁₂H₁₃N₃: C, 72.36; H, 6.53; N, 21.10. Found: C, 72.42; H, 6.52; N, 21.05. **68:** mp dec. (lit.⁴⁸) dec.). **69:** mp 149°C. IR $\nu_{\text{cm}^{-1}}$: 3413, 2930, 1648, 1585. ¹H-NMR (DMSO-*d*₆) δ : 7.3 (4H, m, phenyl), 6.56 (1H, s, H-3), 3.78 (2H, m, H-5), 3.3 (2H, m, H-7), 1.96 (2H, m, H-6). *Anal.* Calcd for C₁₃H₁₅N₃: C, 73.23; H, 7.04; N, 19.71. Found: C, 73.18; H, 7.07; N, 19.73. **70:** mp 180°C. IR $\nu_{\text{cm}^{-1}}$: 3415, 1685, 1610, 604. ¹H-NMR (DMSO-*d*₆) δ : 7.3 (4H, m, phenyl), 6.67 (1H, s, H-3), 3.95 (2H, m, H-5), 3.3 (2H, m, H-7), 2.04 (2H, m, H-6). *Anal.* Calcd for C₁₂H₁₂BrN₃: C, 51.79; H, 4.31; N, 15.10. Found: C, 51.88; H, 4.26; N, 15.06.

Preparation of Imidazo[1,2-a]pyridines A solution of 2-aminopyridine (0.02 mol) in dry DME was slowly added to a mixture of α -bromoketone (0.5 mol) in DME. The reaction mixture was refluxed for 48 h and after cooling, was filtered. The filtrate was alkalized; the solid was dissolved in water, alkalized and added to the alkalized filtrate. This aqueous alkalized phase was extracted with chloroform. The solvent was dried and evaporated under reduced pressure. The compounds were obtained after chromatography on a silica gel column (eluent, ethyl acetate).

71: mp 141°C (lit.⁴⁹) 138°C). **72:** mp 82°C (lit.⁴⁹) 85°C). **73:** mp 91°C (lit.¹⁴) 93°C).

Preparation of the 3-Nitroso-2-phenylimidazo[1,2-a]pyridine A saturated sodium nitrite solution was added under stirring to 2-phenylimidazo[1,2-a]pyridine (0.01 mol) in acetic acid (40 ml). A green solid was obtained which was filtered and recrystallized from methanol or purified by chromatography on a silica gel column (eluent, ethyl acetate-methanol (90:10)).

74: mp 165°C (lit.²⁷) 165°C).

Preparation of the Ethyl 3-Nitroimidazo[1,2-a]pyridine-2-carboxylate Ethyl imidazo[1,2-a]pyridine-2-carboxylate (0.01 mol) was added to ice-cooled sulfuric acid (15 ml). The solution thus obtained was stirred and cooled. Fuming nitric acid (0.02 mol, *d*=1.52) was added slowly. After 30 min, the reaction mixture was allowed to reach room temperature and was stirred for 2 h. The mixture was poured into water and the yellow solid was filtered, dissolved in chloroform and purified by chromatography on a short silica gel column (eluent, ethyl acetate).

75: mp 110°C (lit.¹) 110°C).

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