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*]pyridine 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*]pyridine 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 CCl_4 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 CH_3COOH 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 catalyst[36] (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).

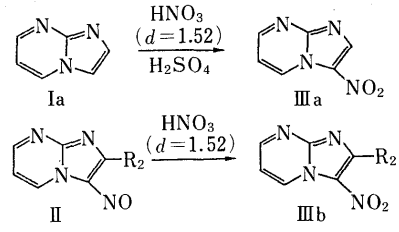


Chart 2

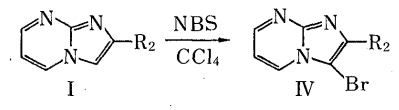


Chart 3

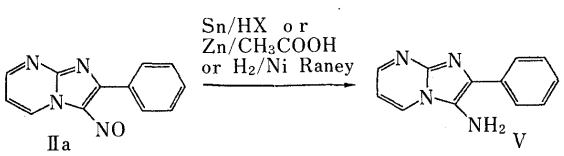


Chart 4

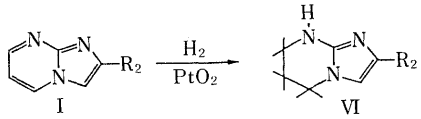
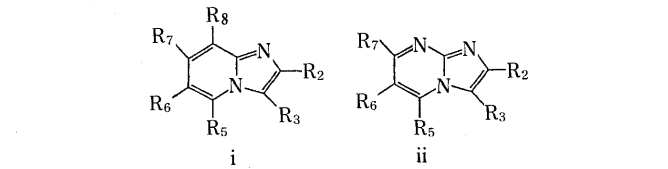


Chart 5



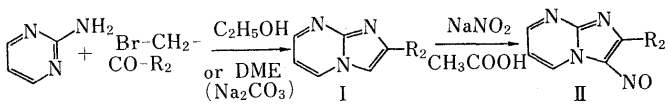
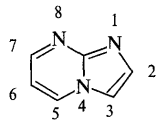


Chart 1

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



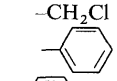
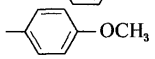
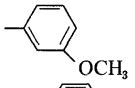
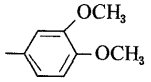
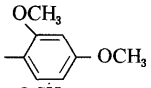
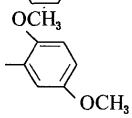
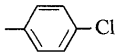
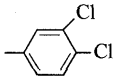
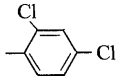
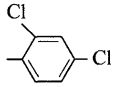
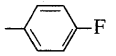
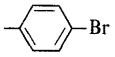
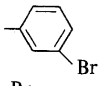
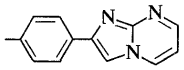
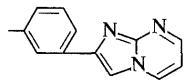
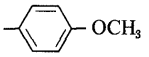
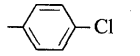
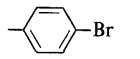
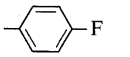
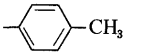
No.	R_2	R_3	R_5	R_6	R_7
1	H	H	H	H	H
2	H	H	CH_3	H	CH_3
3	$-COOC_2H_5$	H	CH_3	H	CH_3
4	$-COOC_2H_5$	H	Cl	H	CH_3
5	$-CH_2Cl$	H	H	H	H
6	$-CH_2Cl$	H	Cl	H	Cl
7		H	H	H	H
8		H	H	H	H
9		H	H	H	H
10[a]		H	H	H	H
11[a]		H	H	H	H
12[a]		H	H	H	H
13[a]		H	H	H	H
14		H	H	H	H
15		H	H	H	H
16[a]		H	H	H	H
17[a]		H	H	H	H
18[a]		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
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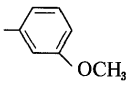
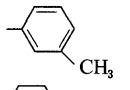
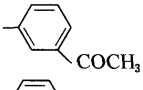
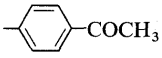
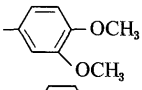
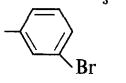
35		NO	H	H	H
36[a]		NO	H	H	H
37		NO	H	H	H
38		NO	H	H	H
39[a]		NO	H	H	H
40		NO	H	H	H
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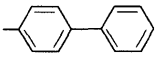
42		NO	H	H	H
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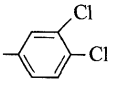
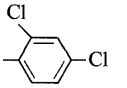
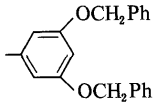
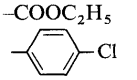
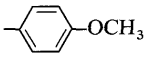
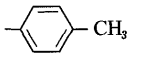
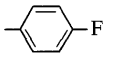
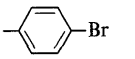
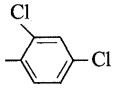
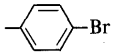
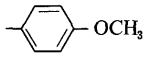
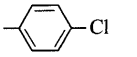
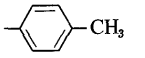
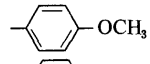
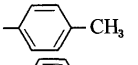
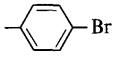
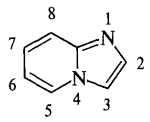
44[a]		NO	H	H	H
45[a]		NO	H	H	H
46[a]		NO	H	H	H
47		NO	H	H	H
48		NO	H	H	H

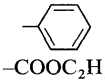
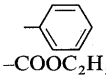
TABLE I(a). (continued)

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]	$-COOC_2H_5$	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	b)
66[a]	$-COOC_2H_5$	H	H	H	H	b)
67[a]		H	H	H	H	b)
68		H	H	H	H	b)
69[a]		H	H	H	H	b)
70[a]		H	H	H	H	b)

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

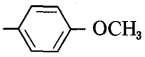
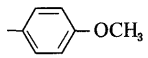
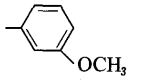
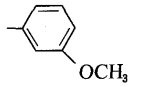
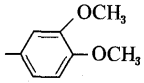
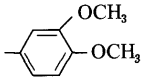
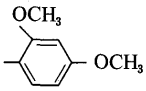
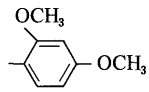
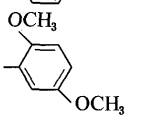
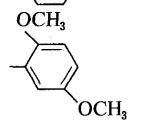
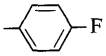
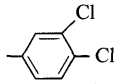
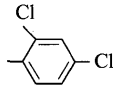
TABLE I(b). Imidazo[1,2-*a*]pyridines Tested



No.	R_2	R_3	R_5	R_6	R_7	R_8
71		H	H	H	H	H
72	$-COOC_2H_5$	H	H	H	H	H
73	$-CH_2Cl$	H	H	H	H	H
74		NO	H	H	H	H
75	$-COOC_2H_5$	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 steriled 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	$-COOC_2H_5$	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 tryptycase-soja agar with 10 μl 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 μg/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 in sofar 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 μg/ml for BACC (**30**, **53**), 12 μg/ml for BACM (**14**, **36**), 0.7 μg/ml for CORY (**14**), 3 μg/ml for PROP (**30**, **35**), 3 μg/ml for STAA (**30**), 6 μg/ml for STAE (**35**), 23 μg/ml for STEA (**14**) 23 μg/ml for STEE (**14**), 24 μg/ml for STEC (**36**), 6 μg/ml for STEG (**35**), 16 μg/ml for STEL (**15a**), 7 μg/ml for STEN (**30**), 24 μg/ml for ENTE (**36**), 13 μg/ml for ESCH (**35**), 24 μg/ml for KLEB (**36**), 3 μg/ml for NEIS (**30**), 12 μg/ml for PROT (**9b**), 15.8 μg/ml for PROV (**15a**), 24 μg/ml for PSEU and SERR (**36**) and 23 μg/ml for MYCO (**14**). These values are favorably situated in comparison to that found for the reference compounds (Table IV).

TABLE II. Bacteria Strains

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

Experimental

Melting points were determined on a Kofler apparatus and are uncorrected. Infrared (IR) spectra were measured on a Spectrometer Perking-Elmer 983 G and proton nuclear magnetic resonance (^{1}H-NMR) spectra were determined on a Brucker 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 imidazol[1,2-*a*]pyrimidine was obtained after chromatog-

TABLE III. MICs (μg/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**	**51**	**53**
BACC	41	12	>200	12	47	15.8	23.8	57	50	>200	20	2	31	18	24	3	24	54	62	55	>200	2
BACM	41	23	104	12	94	15.8	48	113	50	>200	26	26	31	25	49	26	12	54	62	57	23	55
CORY	20	23	>200	0.7	12	1	23.8	7	50	127	>200	105	124	99	97	>200	24	27	124	55	>200	110
PROP	81	23	>200	12	47	15.8	23.8	57	50	>200	26	3	31	12	24	3	24	54	62	55	>200	200
STAA	41	47	>200	>200	47	15.8	23.8	57	50	>200	26	3	31	25	49	6	24	54	62	55	>200	200
STAE	>200	47	>200	23	47	15.8	23.8	57	50	>200	26	26	31	12	24	6	24	54	62	55	>200	200
STEA	>200	47	>200	23	47	32	48	113	50	>200	>200	53	62	49	200	26	24	109	124	110	>200	110
STEE	>200	93	>200	23	47	32	48	113	50	>200	>200	>200	124	99	200	52	24	109	124	110	>200	110
STEC	>200	>200	>200	>200	94	32	95	113	50	>200	>200	105	62	99	200	26	24	109	200	>200	>200	200
STEG	>200	47	>200	>200	94	32	48	113	50	>200	104	26	31	25	97	6	24	27	62	55	>200	200
STEL	>200	23	>200	04	47	16	48	28	50	>200	>200	>200	31	99	200	52	24	54	62	55	>200	200
STEN	81	47	>200	12	94	15.8	23.8	28	100	>200	13	7	>200	12	24	13	12	54	62	27	110	110
ENTE	200	>200	>200	94	94	32	48	113	50	>200	>200	>200	>200	99	200	>200	24	109	200	>200	>200	200
ESCH	81	47	>200	47	94	15.8	48	113	100	>200	200	105	124	49	200	13	24	109	124	>200	>200	200
KLEB	>200	>200	>200	47	94	32	48	57	25	>200	>200	>200	200	99	200	52	24	109	200	>200	>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	110	110
PROT	41	12	>200	>200	>200	16	48	57	100	>200	>200	>200	124	49	200	13	24	54	124	27	>200	200
PROV	41	93	>200	>200	47	15.8	23.0	57	100	>200	>200	>200	200	99	200	52	24	109	200	>200	>200	200
PSEU	>200	>200	>200	>200	47	32	95	57	100	>200	>200	>200	200	99	200	>200	24	109	200	>200	>200	200
SERR	41	93	>200	>200	94	32	48	113	>200	>200	>200	>200	200	49	200	>200	24	109	200	>200	>200	200
MYCO	81	47	104	23	94	32	48	>200	100	127	26	26	31	25	49	26	24	109	124	110	45	110

TABLE IV. Reference Compounds

	Nifuroxazide[35] (Ercefuryl) MIC (μg/ml)		Thiophenicol[36] MIC (μg/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 alkalinized; the solid was dissolved in water, alkalinized and added to the alkalinized filtrate. This aqueous alkalinized 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 νcm^{-1}: 1641, 1611, 1080, 730, 669. ^{1}H-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 $C_{12}H_8ClN_3$: C, 62.74; H, 3.48; N, 18.30. Found: C, 62.75; H, 3.52; N, 18.26. **11**: mp 146 °C. IR νcm^{-1}: 1641, 1611, 1080, 730, 669. ^{1}H-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 $C_{12}H_8ClN_3$: C, 62.74; H, 3.48; N, 18.30. Found: C, 62.75; H, 3.52; N, 18.26. **12**: mp 158 °C. IR νcm^{-1}: 1641, 1611, 1080, 730, 669. ^{1}H-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 $C_{12}H_8ClN_3$: C, 62.74; H, 3.48; N, 18.30. Found: C, 62.75; H, 3.52; N, 18.26. **13**: mp 178 °C. IR νcm^{-1}: 1641, 1611, 1080, 730, 669. ^{1}H-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 $C_{12}H_8ClN_3$: 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 νcm^{-1}: 1658, 1611, 1085, 730, 675. ^{1}H-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 $C_{12}H_7Cl_2N_3$: C, 56.25; H, 2.73; N, 16.40. Found: C, 56.21; H, 2.74; N, 16.43. **17**: mp 244 °C. IR νcm^{-1}: 1642, 1610, 1046, 710, 670. ^{1}H-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 $C_{12}H_7Cl_2N_3$: C, 54.75; H, 2.66; N, 15.96. Found: C, 54.83; H, 2.64; N, 15.92. **18**: mp 218 °C. IR νcm^{-1}: 1677, 1610, 1088, 711, 673. ^{1}H-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 $C_{12}H_7Cl_2N_3$: 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 νcm^{-1}: 1639, 1612, 1095, 1065, 1013. ^{1}H-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 $C_{12}H_8FN_3$: 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 νcm^{-1}: 1643, 1610, 1053, 603. ^{1}H-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 $C_{12}H_8BrN_3$: C, 52.55; H, 2.91; N, 15.32. Found: C, 52.59; H, 2.89; N, 15.34. **24**: mp 261 °C. IR νcm^{-1}: 1666, 1617, 1475, 1075. ^{1}H-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 $C_{12}H_8N_4O_2$: C, 60.00; H, 3.33; N, 23.33. Found: C, 60.09; H, 3.30; N, 23.27. **25**: mp 106 °C. IR νcm^{-1}: 1645, 1610, 1079, 999. ^{1}H-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, CH_2). *Anal.* Calcd for $C_{10}H_{11}N_3$: C, 69.36; H, 6.35; N, 24.27. Found: C, 69.40; H, 6.34; N, 24.24. **26**: mp 178 °C. IR νcm^{-1}: 1671, 1606, 1031, 801. ^{1}H-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 $C_{18}H_{12}N_6$: C, 72.00; H, 4.00; N, 28.00. Found: C, 72.08; H, 3.98; N, 27.94. **27**: mp 210 °C. IR νcm^{-1}: 1642, 1629, 1082, 786. ^{1}H-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 $C_{18}H_{12}N_6$: 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 νcm^{-1}: 1670, 1596, 1572, 1254. ^{1}H-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 $C_{13}H_{10}N_4O_2$: 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 νcm^{-1}: 2917, 1602, 1580, 1526. ^{1}H-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 $C_{13}H_{10}N_4O$: 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 νcm^{-1}: 1603, 1590, 1582, 1245. ^{1}H-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 $C_{14}H_{12}N_4O_3$: 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 νcm^{-1}: 1600, 1590, 1558, 590. ^{1}H-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 $C_{12}H_7BrN_4O$: 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 νcm^{-1}: 1648, 1610, 1559, 675. ^{1}H-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 $C_{12}H_6Cl_2N_4O$: C, 49.31; H, 2.05; N, 19.17. Found: C, 49.26; H, 2.07; N, 19.20. **45**: mp 234 °C. IR νcm^{-1}: 1632, 1605, 1562, 710. ^{1}H-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 $C_{12}H_6Cl_2N_4O$: C, 49.31; H, 2.05; N, 19.17. Found: C, 49.38; H, 2.02; N, 19.13. **46**: mp 208 °C. IR νcm^{-1}: 1659, 1611, 1560, 711. ^{1}H-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 $C_{12}H_6Cl_2N_4O$: 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 νcm^{-1}: 1636, 1604, 1592, 1286. ^{1}H-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 $C_{26}H_{20}N_4O_3$: 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: Azaindolizine (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 fitrate was alkalinized 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 νcm^{-1}: 1737, 1670, 1616, 1494, 1292. ^{1}H-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, CH_2), 1.4 (3H, t, CH_3). *Anal.* Calcd for $C_9H_8N_4O_4$: 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 νcm^{-1}: 1690, 1530, 1485, 668. ^{1}H-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 $C_{12}H_6Cl_2N_4O_2$: 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, alkalinized (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 alkalinized 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 chromatographied 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-Halogenoimidazo[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 PtO_2 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 alkalinized, 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 ν cm^{-1}: 3421, 1672. ^{1}H-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 $C_6H_9N_3$: C, 58.53; H, 7.31; N, 34.14. Found: C, 58.48, H, 7.35; N, 34.15. **66**: mp 166 °C. IR ν cm^{-1}: 3410, 3220, 1690, 1619, 1279. ^{1}H-NMR (DMSO-d_6) δ: 7.2 (1H, s, H-3), 4.3 (2H, q, CH_2), 3.9 (2H, m, H-5), 3.45 (2H, m, H-7), 1.99 (2H, m, H-6), 1.3 (3H, t, CH_3). *Anal.* Calcd for $C_9H_{13}N_3O_2$: C, 55.38; H, 6.66; N, 21.53. Found: C, 55.42; H, 6.64; N, 21.51. **67**: mp 128 °C. IR ν cm^{-1}: 3416, 1670, 1602. ^{1}H-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 $C_{12}H_{13}N_3$: 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 ν cm^{-1}: 3413, 2930, 1648, 1585. ^{1}H-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 $C_{13}H_{15}N_3$: C, 73.23; H, 7.04; N, 19.71. Found: C, 73.18; H, 7.07; N, 19.73. **70**: mp 180 °C. IR ν cm^{-1}: 3415, 1685, 1610, 604. ^{1}H-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 $C_{12}H_{12}BrN_3$: 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 alkalinized; the solid was dissolved in water, alkalinized and added to the alkalinized filtrate. This aqueous alkalinized 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 slolwy. 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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