Imidazo[4,5-*b*]pyridine Derivatives of Potential Tuberculostatic Activity, II[1]:

Synthesis and Bioactivity of Designed and Some Other 2-Cyanomethylimidazo[4,5-*b*]pyridine Derivatives

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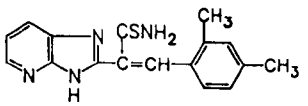
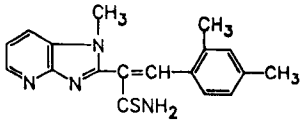
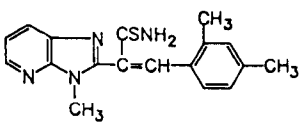
Based on the analysis of Quantitative Structure - Activity Relationships (QSAR)[1] three representatives of imidazo[4,5-*b*]pyridine derivatives of predicted high antibacterial activity against *Mycobacterium tuberculosis* were synthetized and tested bacteriologically. Excellent agreement of the predicted and experimentally observed bioactivity was noted. Additional new derivatives of 4-methyl-4*H*-2-cyanomethylimidazo[4,5-*b*]pyridine (7) and 2-(α-methylcyanomethyl)imidazo[4,5-*b*]pyridine (22) were also synthesized and some of them were tested for tuberculostatic activity. The compounds synthesized according to a standard "trial and error" approach appeared generally inactive.

Imidazo[4,5-*b*]pyridin-Derivate mit potentiell tuberkulostatischer Wirkung, 2. Mitt.: Synthese und Bioaktivität einiger 2-Cyanomethylimidazo[4,5-*b*]pyridin-Derivate

Auf Grund der Analyse von Quantitativen Struktur-Wirkung-Beziehungen (QSAR), die in der 1. Mitt. beschrieben wurden, wurden drei Imidazo[4,5-*b*]pyridin-Derivate mit der vorhergesehenen hohen antibakteriellen Aktivität gegen *Mycobacterium tuberculosis* entworfen, synthetisiert und bakteriologisch geprüft. Ausgezeichnete Übereinstimmung wurde zwischen der vorhergesehenen und experimentellen Bioaktivität festgestellt. Nachträglich wurden auch neue Derivate von 4-Methyl-4*H*-2-Cyanomethylimidazo[4,5-*b*]pyridin **7** und 2-(α-Methylcyanomethyl)imidazo[4,5-*b*]pyridin **22** synthetisiert und manche von ihnen wurden auf tuberkulostatische Wirkung geprüft. Die Verbindungen, die nach der "Versuch und Fehler" Methode synthetisiert wurden, stellten sich als inaktiv heraus.

In Part I of this report[1] a QSAR analysis was performed of a group of 29 imidazo[4,5-*b*]pyridines comprising a subgroup of newly synthesized 3-methyl-3*H*-2-cyanomethylimidazo[4,5-*b*]pyridine derivatives and subgroups of previously obtained[2,3] 2-cyanomethylimidazo[4,5-*b*]pyridines and 1-methyl-1*H*-2-cyanomethylimidazo[4,5-*b*]pyridines. In effect, a highly significant statistically QSAR equation was derived relating the *in vitro*

Table 1: Structure, structural parameters and bioactivity data of imidazo[4,5-*b*]pyridine derivatives designed and synthesized basing on QSAR.

No.	Compound	Structural parameters		MIC (μg/ml) against Mycobacterium tuberculosis $H_{37}Rv$	
		Hydrophobicity Σf	Indicator variable D	Obsd	Calcd *
4		-0.18	0	15.6	6.6
5		0.48	1	62.5	7.7
6		0.48	1	31.2	7.7

* Calculated from the equation: log 1/MIC = -0.7671 + 0.2985 Σf - 0.2609 D

  0365-6233/91/0909-0537 $ 3.50 + .25/0

Table 2: Physical data and tuberculostatic activity of compounds **1-28**

Comp.	Mp.(°C) Recryst.sol.	Yield %	Mol.formula M. wt.	Analysis calcd/found C	H	N	Tuberculostatic activity MIC µg/ml Mycobacterium: $H_{37}Rv$	109^{x}	193^{xx}
1	2	3	4	5	6	7	8	9	10
1	284-286 DMF/W	80	$C_{17}H_{14}N_4$ 274.3	74.4 74.6	5.14 5.02	20.4			
2	182-184 Me	71	$C_{18}H_{16}N_4$ 288.3	75.0 74.6	5.59 5.72	19.4			
3	145-147 Me	66	$C_{18}H_{16}N_4$ 288.3	75.0 75.2	5.59 5.43	19.4			
4	226-228 Et	54	$C_{17}H_{16}N_4S$ 308.3	66.2 66.5	5.23 5.02	18.2	15.6	7.8	7.8
5	192-195 W	58	$C_{18}H_{18}N_4S$ 322.3	67.1 66.8	5.63 5.40	17.4	62.5	31.2	31.2
6	194-196 W	52	$C_{18}H_{18}N_4S$ 322.3	67.1 67.1	5.63 5.38	17.4	31.2	31.2	15.6
7	168-170 B	42	$C_9H_8N_4$ 172.2	62.8 62.7	4.68 4.52	32.5 32.6			
8	182-184 B	15	$C_{10}H_{10}N_4$ 186.2	64.5 64.6	5.41 5.21	30.1 30.1			
9	126-128 B/C	67	$C_{10}H_{11}N_3O_2$ 205.2	58.5 58.6	5.40 5.32	20.5			
10	219-221 Me	64	$C_9H_{10}N_4O$ 190.2	56.8 56.7	5.30 5.18	29.5			
11	184-187 Me	56	$C_9H_{11}N_5O$ 205.2	52.7 52.4	5.40 5.24	34.1	250	250	250
12	244-246 Et	62	$C_9H_{11}N_5O$ 205.2	52.7 52.5	5.40 5.61	34.1	500	125	500
13	146-148 B/C	58	$C_8H_9N_3$ 147.2	65.3 65.4	6.16 6.42	28.6			
14	220-222 Et	68	$C_{16}H_{12}N_4$ 260.3	73.8 74.1	4.65 4.46	21.5			
15	218-220 DMF/W	67	$C_{18}H_{16}N_4O_2$ 320.3	67.5 67.7	5.03 4.92	17.5			
16	276-278 DMF/W	75	$C_{17}H_{14}N_4O_2$ 306.3	66,7 66.7	4.61 4.36	18.3			
17	225-227 DMF/W	69	$C_{20}H_{21}N_5$ 331.4	72.5 72.2	6.39 6.31	21.1			
18	107-110 C	60	$C_{11}H_{13}N_3O_2$ 219.2	60.3 60.4	5.98 6.12	19.2			
19	158-160 Me	52	$C_{10}H_{12}N_4O$	58.8 59.1	5.92 6.18	27.4			
20	170-172 Me	65	$C_{10}H_{13}N_5O$ 219.2	54.9 54.9	5.98 6.04	31.9	500	250	250
21	250-252 Ch	63	$C_9H_{11}N_3$ 161.2	67.1 67.2	6.88 6.91	26.1 26.3			

Table 2: (Cont.)

1	2	3	4	5	6	7	8	9	10
22	212-214 W	52	$C_9H_8N_4$	62.8	4.68	32.5			
			172.2	63.1	4.43	32.8			
23	106-109 C	67	$C_{10}H_{11}N_3O_2$	58.5	5.40	20.5			
			205.2	58.7	5.28				
24	241-243 W	63	$C_9H_{10}N_4O$	56.8	5.30	29.5			
			190.2	56.6	5.42				
25	122-125 Me	52	$C_9H_{11}N_5O$	52.7	5.40	34.1	500	125	1000
			205.2	52.5	5.24				
26	167-170 Me	56	$C_9H_{11}N_5O$	52.7	5.40	34.1	1000	500	1000
			205.2	52.9	5.18				
27	213-215 W	58	$C_9H_{10}N_4S$	52.4	4.89	27.2	31	16	125
			206.2	52.2	4.63				
28	152-154 C	47	$C_8H_9N_3$	65.3	6.16	28.6			
			147.1	65.4	6.04				

Solvent: DMF: dimethylformamide, W: H_2O, Me: CH_3OH, Et: C_2H_5OH, B: benzene, C: cyclohexane, Ch: $CHCl_3$.

[x] Bacterial strain isolated from patients resistant against isonicotinhydrazide, ethambutol and rifampicine.

[xx] Bacterial strain isolated from patients succeptible towards isonicotinhydrazide, ethambutol and rifampicine.

antibacterial activity of the agents against *Mycobacterium tuberculosis* $H_{37}Rv$ to their hydrophobicity and to an indicator variable, discriminating compounds unsubstituted and methyl substituted at the imidazole-N. In such a situation it seemed reasonable to design active compounds basing on the QSAR equation derived. Next step would be the synthesis and testing of antimicrobial activity.

Since the beginning of the QSAR studies in the 1960s many bioactivity-predicting equations have been published. Prevailing majority of those equations were derived retrospectively, however, and were not used for rational design and synthesis of active congeners[4].

Some QSAR equations are unsuitable for direct predicting and designing purposes, although they may be of value for getting insight into molecular mechanism of a given physicochemical or pharmacological process[5].

Such are the QSARs in which the independent variables describing bioactivity are physicochemical parameters obtained by measurements, *e.g.*, chromatographic data, spectroscopic parameters, dissociation constants, etc.

From the point of view of drug design especially valuable are QSARs in which the independent structural variables are nonempirical molecular descriptors which can be derived basing on structural formula of chemical compounds. Certainly, the nonempirical structural parameters are less precise and reliable than the well measured data. In the case of related compounds the reliability of nonempirical structural descriptors is usually satisfactory, however.

In this work we designed three compounds which should be active according to the previously derived QSAR equation[1]. Designing the active structures we also had in mind feasibility of the corresponding synthetic procedure required.

From a purely chemical point of view the present work was aimed at a further exploration of synthetic possibilities in the group of imidazo[4,5-*b*]pyridines. Possibilities of methyl-substitution, different from those so far reported, were considered, namely at positions 4 and 2-α side chain. Thus, besides the derivatives designed due to QSAR also several other new derivatives were obtained. Comparison of bioactivity of the rationally designed agents and of the compounds resulting from the classical "trial and error" approach seemed interesting and instructive.

Synthesis

Basing on the QSAR equation[1] and taking into consideration synthetic feasibility we designed three imidazo[4,5-*b*]pyridine derivatives representing 2-cyanomethylimidazo[4,5-*b*]pyridine derivatives (compound **4**), 1-methyl-1*H*-2-cyanomethylimidazo[4,5-*b*]pyridine derivatives (compound **5**) and 3-methyl-3*H*-2-cyanomethylimidazo[4,5-*b*] pyridine derivatives (compound **6**). These compounds were synthesized according to procedures described[1-3]. The structures of the compounds are given in Table 1, their physicochemical data are collected in Table 2.

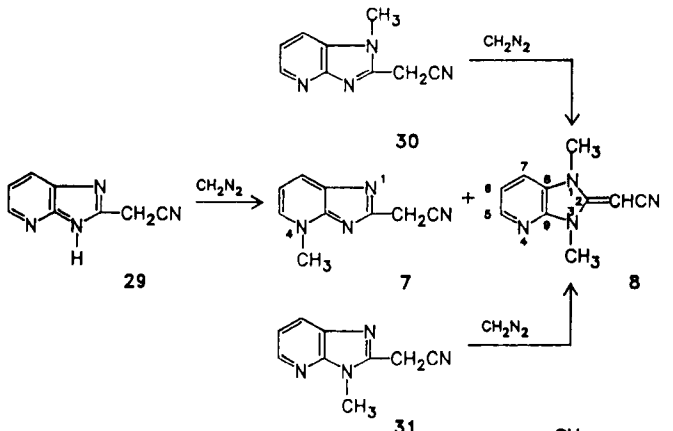
Continuing the search for antituberculotic agents among 2-cyanomethylimidazo[4,5-*b*]pyridines[1-3] in this work the derivatives of 4-methyl-4*H*-2-cyanomethylimidazo[4,5-*b*]-pyridine (**7**) and 2-(α-methylcyanomethyl)imidazo[4,5-*b*] pyridine (**22**) were also studied.

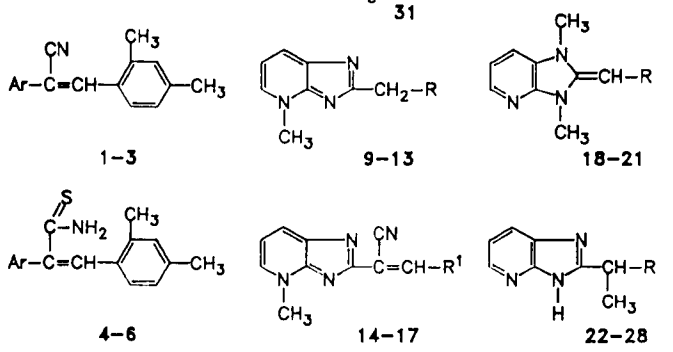
Compound **7** was prepared by reaction of 2-cyanomethylimidazo[4,5-*b*]pyridine (**29**) with CH_2N_2 (Scheme 1), yielding a mixture of compounds **7** and **8** with average yields of 42 and 15%, respectively. Structures **7** and **8** have been assigned by spectral analysis (IR, NMR, MS).

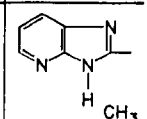
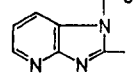
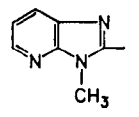
Compound **8** was also obtained from reaction of N^1- or N^3-methyl-2-cyanomethylimidazo[4,5-*b*]pyridine (**30** or **31**) with CH_2N_2.

Substances **7** and **8** appeared homogenous when tested by tlc. However, in the ^{1}H-NMR spectrum of **8** two signals are observed for each *N*-CH_3 group. In the ^{13}C-NMR spectrum a duplication of signals of all C-atoms is evident (intensity of individual double signals is similar). The above observations suggest that compound **8** is a mixture of two isomers at roughly equal amounts.

The already mentioned 2-(α-methylcyanomethyl)imidazo[4,5-*b*]pyridine (**22**) was obtained from the reaction of 2,3-diaminopyridine with ethyl α-cyanopropionate.





Comp.	Ar
1;4	
2;5	
3;6	

Comp.	R
22	- CN
9; 18; 23	- $COOCH_3$
10; 19; 24	- $CONH_2$
11; 20; 25	- $CONHNH_2$
12; 26	- $C(NOH)NH_2$
27	- $CSNH_2$
13; 21; 28	- H

Comp.	R^1
14	- phenyl
15	- 3, 4-dimethoxyphenyl
16	- 4-hydroxy-3-methoxyphenyl
17	- 4-diethylaminophenyl

Using reported methods[1-3] compounds **9** - **28** were obtained from the derivatives **7**, **8**, and **22**. Attempts to obtain the respective thioamides from nitriles **7**, **8**, **14** - **17** appeared unsuccessful. Physical properties and antibacterial activity against *Mycobacterium tuberculosis* of the compounds synthesised are presented in Table 2.

Results and Discussion

All the three designed compounds and six representatives of the randomly synthesized derivatives were subjected to bacteriological analysis in the Institute of Tuberculosis in Warsaw. Minimum inhibitory concentrations (MIC, μg/ml) were determined according to the standard procedure[1,6].

As evidenced by the MIC values in Table 1 the QSAR - guided synthesis leads to highly active derivatives in all the three instances tested. The antibacterial activity of compounds **4** - **6** appears convincing if one realizes that the MIC value of a known tuberculostatic drug pyrazinamide, determined at identical conditions is 62.5 μg/ml. According to calculations compound **4** should be most active but generally, activity of all the three congeners should be similar. And it is the case here.

Hydrophobicity, Σf, of compounds **5** and **6** is higher than that of **4** but the latter has no methyl substituent at the imidazoline-N, and thus the negative contribution of indicator variable *D* to the activity of **4** is canceled.

The calculated bioactivity data for **4** - **6** tend to be higher than those experimentally found. The discrepancy is fully acceptable, however, and may be explained by experimental error of bioactivity determinations and by limited precision of nonempirical measure of hydrophobicity, Σf. Certainly, the MIC data against *Mycobacterium tuberculosis* $H_{37}Rv$ are no accidental and the prediction of high activity of **4** - **6** is not by chance.

Additional prove for such an assumption is the agreement of the $H_{37}Rv$ data and MIC determined in two other microbiological tests. It may thus be concluded that QSAR analysis provides rational premises for guiding the search for new active congeners in a group of imidazo[4,5-*b*]pyridine derivatives.

The success of the QSAR - guided synthesis of active congeners appears especially evident in view of poor activity of the derivatives synthesized by the standard "trial and error" method (Table 2). Only one of six randomly synthesized derivatives showed activity comparable to that observed for the all rationally designed derivatives.

Experimental Part

Mp. (uncorrected): Boetius apparatus.- IR spectra: Specord 75 spectrophotometer, KBr pellets.- ^{1}H-NMR spectra: 80 MHz Tesla 478.- ^{13}C-NMR spectra: Jeol SX 90 Q spectrometer (22.5 MHz).- Mass spectra: LKS 9000 S apparatus.- Elementary analyses: Department of Physical Chemistry, Medical Academy, Gdansk.

4-Methyl-4H-2-cyanomethylimidazo[4,5-b]pyridine (7)
1,3-Dimethyl-2-cyanomethylene-1,2-dihydroimidazo[4,5-b]pyridine (8)

To a mixture 50 ml of CH_3OH and 50 ml of etheric solution of CH_2N_2[7], 3.2 g (0.02 mol) of compound **29**[2] were added in small portions. Then, to the reaction mixture further etheric solution of CH_2N_2 was added (also in small portions) until evolution of gas ceased. The mixture was left overnight at room temp., then the solvents were evaporated under reduced pressure.

The solid obtained was treated with a small amount of CH_3OH and the unsoluble part of the product was filtered off and recrystallized (comp. **8**). From the filtrate CH_3OH was evaporated and the residue was purified by recrystallization (comp. **7**).

7: IR (cm^{-1}): 2260 (C≡N).- ^{1}H-NMR ($CDCl_3$, TMS int): δ (ppm) = 4.12 (s; 2H, CH_2), 4.33 (s; 3H, NCH_3), 7.03-7.36 (2xd, J_1 = 8 Hz, J_2 = 9 Hz; 1H, C-6), 7.78 (d, J = 6 Hz; 1H, C-7), 8.20 (d, J = 7 Hz; 1H, C-5).- MS [70 eV, m/z (%)]: 173 (9), 172 (100) M^+, 171 (22), 157 (14), 118 (11), 64 (11), 42 (11), 40 (14).

8: IR (cm^{-1}): 2170 (C≡N), 1580 (C=C).- ^{1}H-NMR ($CDCl_3$, TMS int): δ ppm = 3.30, 3.37 (2xs; 3H, NCH_3), 3.48 (s; 1H, =CH-), 3.80, 3.87 (2xs; 3H, NCH_3), 6.92-7.07 (m; 2H, C-6 and C-7), 7.99 (d, J = 6 Hz; 1H, C-5).- ^{13}C-NMR ($CDCl_3$, TMS int): δ ppm = 27.36, 29.09 (N-CH_3), 29.25, 30.93 (N-CH_3), 37.11 (=CH-)*, 112.09, 112.26 (C-6), 116.64, 116.81 (C-7), 121.63, 121.79 (C≡N), 126.51, 127.32 (C-2), 140.38, 140.59 (C-5), 145.85, 146.39 (C-8), 153.81, 154.14 (C-9).- MS [70 eV, m/z (%)]: 187 (13), 186 (94) M^+, 185 (11), 171 (21), 147 (10), 146 (100), 79 (16), 78 (26), 66 (11), 52 (18), 51 (14), 39 (8), 38 (11).

*Duplication of the signal was not observed.

Compound **8** was also obtained from reaction of comp. **30**[3] or **31**[1] with diazomethane using the procedure described above.

2-(2-Imidazo[4,5-b]pyridine)propionitrile (22)

2,3-Diaminopyridine (5.4 g, 0.05 mol) and ethyl α-cyanopropionate (9.5 g, 0.075 mol) were heated at 190-195°C with stirring for 30 min. The precipitate obtained after cooling was washed with ether and recrystallized.- IR (cm^{-1}): 2240 (C≡N).- ^{1}H-NMR (DMSO-d_6), (HMDSO exter): δ (ppm) = 1.84 (d, J = 7 Hz; 3H, CH_3), 4.86 (q, J = 7 Hz; 1H, CHCN), 7.30-7.47 (2xd, J_1 = 5 Hz, J_2 = 6 Hz; 1H, C-6), 8.16 (d, J = 8 Hz; 1H, C-7), 8.49 (d, J = 5 Hz; 1H, C-5).- Ms [70 eV, m/z (%)]: 173 (11), 172 (100) M^+, 171 (97), 170 (20), 157 (47), 146 (19), 145 (36), 144 (15), 130 (12), 119 (32), 103 (18), 92 (19), 65 (11), 64 (16).

Methyl ester of 4-Methyl-4H-2-imidazo[4,5-b]pyridineacetic acid (9)
1,3-Dimethyl-2-methoxycarbonylmethylene-1,2-dihydroimidazo [4,5-b]pyridine (18)
Methyl ester of 2-(2-imidazo[4,5-b]pyridine)propionic acid (23)

A solution of nitrile **7**, **8**, or **22** (0.01 mol) in 60 ml of CH_3OH was saturated with dry HCl at room temp. for 8 h. Then, the mixture was cooled in an ice-water bath, made alkaline with $NaHCO_3$ solution and extracted with $CHCl_3$. The chloroform extract was dried ($MgSO_4$) and after evaporation of the solvent the residue was recrystallized.

9: IR (cm^{-1}): 1720 (C=O), 1285, 1260 (C-O-C).

18: IR (cm^{-1}): 1660 (C=O), 1120 (C-O-C).- ^{1}H-NMR ($CDCl_3$, TMS int): δ (ppm) = 3.50 (m; 9H, OCH_3, 2 x NCH_3), 4.33 (s; 1H, =CH-), 6.92-7.25 (2xd, J_1 = 5 Hz, J_2 = 8.7 Hz; 1H, C-6), 7.23 (d, J = 8.7 Hz; 1H, C-7), 8.06 (d, J = 5 Hz; 1H, C-5).- MS [70 eV, m/z (%)]: 220 (10), 219 (100) M^+, 214 (9), 188 (87), 176 (8), 160 (10), 161 (50), 155 (26), 146 (10), 92 (10), 91 (60), 78 (10).

23: IR (cm^{-1}): 1720 (C=O), 1250, 1180 (C-O-C).

When the reaction was carried out under reflux instead of the esters **9**, **18**, or **23** the 2,4-dimethyl-4H-imidazo[4,5-*b*]pyridine **13**, 1,3-dimethyl-2-methylene-1,2-dihydroimidazo[4,5-*b*]pyridine **21**, or 2-ethylimidazo[4,5-*b*]pyridine **28**, respectively, were isolated.

13: ^{1}H-NMR ($CDCl_3$, TMS int): δ (ppm) = 2.72 (s; 3H, CH_3), 4.25 (s; 3H, NCH_3), 6.96 (dd, J_1 = 6 Hz; J_2 = 8 Hz; 1H, C-6), 7.56 (d, J = 6 Hz; 1H, C-7), 8.02 (d, J = 8 Hz; 1H, C-5).- UV (N-HCl) λ nm, (ε): 260 (2654), 297 (9608).- MS [70 eV, m/z (%)]: 148 (9), 147 (100) M^+, 146 (40), 132 (18), 105 (16), 78 (9), 18 (15).

21: IR (cm^{-1}): 3030 (CHAr), 2950 (CH_3), 1620 (C=C).- ^{1}H-NMR (DMSO-d_6, TMS int): δ (ppm) = 2.96 (s; 2H, =CH_2), 4.00, 4.06 (2xs; 6H, 2 x NCH_3), 7.70-7.83 (2xd, J_1 = 5 Hz, J_2 = 7.5 Hz; 1H, C-6), 8.62 (d, J = 7.5 Hz; 1H, C-7), 8.75 (d, J = 5 Hz; 1H, C-5).- MS [70 eV, m/z (%)]: 162 (7), 161 (79) M^+, 160 (34), 155 (17), 147 (9), 146 (100), 119 (29), 105 (14), 93 (23), 92 (14), 91 (36), 78 (36).

28: ^{1}H-NMR ($CDCl_3$, TMS int): δ (ppm) = 1.51 (t, J = 7 Hz; 3H, CH_3), 3.06 (q, J = 7 Hz; 2H, CH_2), 7.21 (dd, J_1 = 6 Hz; J_2 = 8 Hz; 1H, C-6), 8.04 (d, J = 8 Hz; 1H, C-7), 8.67 (d, J = 6 Hz; 1H, C-5).- MS [70 eV, m/z (%)]: 148 (5), 147 (65) M^+, 146 (100), 132 (13), 119 (5), 105 (6), 78 (5), 28 (7).

4-Methyl-4H-2-imidazo[4,5-b]pyridineacetamide (10)
1,3-Dimethyl-2-carbamoylmethylene-1,2-dihydroimidazo[4,5-b]pyridine (19)

Ester **9** or **18** (1 g, 0.005 mol) was mixed with CH_3OH, saturated with NH_3 at 0°C (15 ml), and left at room temp. for 3 days. The precipitated solid was filtered off and recrystallized.

10: IR (cm^{-1}): 1640, 1595 (-$CONH_2$).

19: 1640 (C=C); 1620; 1560 (-$CONH_2$).

2-(2-Imidazo[4,5-b]pyridine)propaneamide (24)

Nitrile **22** (1 g, 0.006 mol) was dissolved in 8 ml conc. H_2SO_4 and the solution obtained was left to stand at room temp. for 24 h. Then, the mixture was poured onto a small amount of ice and made alkaline with conc. NH4OH. The precipitate was filtered off and recrystallized. IR (cm^{-1}): 1680; 1620 (-$CONH_2$).

4-Methyl-4H-2-imidazo[4,5-b]pyridineacetic acid hydrazide (11)
1,3-Dimethyl-2-carbazoylmethylene-1,2-dihydroimidazo[4,5-b] pyridine (20)
2-(2-Imidazo[4,5-b]pyridine)propionic acid hydrazide (25)

A solution of ester **9**, **18**, or **23**, respectively, (0.005 mol) in CH_3OH (5 ml) was refluxed for 15 min with a small excess of 100% hydrazine hydrate. After cooling the precipitate was filtered off and recrystallized (Table).

4-Methyl-4H-2-imidazo[4,5-b]pyridineacetamide oxime (**12**)
2-(2-Imidazo[4,5-b]pyridine)propaneamide oxime (**26**)

To a solution of nitrile **7** or **22** (0.003 mol) in CH_3OH (5 ml) a freshly prepared aqueous solution of $NH_2OH \cdot HCl$ (0.003 mol) and Na_2CO_3 (0.003 mol) was added and the mixture was refluxed for 30 min. After cooling the precipitated solid was filtered off and recrystallized (Table).

2-(α-Cyano-β-arylvinyl)imidazo[4,5-b]pyridines **1-3, 14-17**

To 0.01 mol of a nitrile **29**[2], **30**[3], **31**[1], or **7** in anhydrous C_2H_5OH (10 ml), 0.01 mol of the appropriate aldehyde and 0.5 ml of piperidine were added. Then the mixture was refluxed for 1-2 h. After cooling the precipitate was filtered off and recrystallized. IR spectra of the compounds **1-3** and **14-17** displayed the signal due to C≡N group in the 2210 cm^{-1} region (Table).

2-(α-Carbothioamide-β-arylvinyl)imidazo[4,5-b]pyridines **4, 5, 6**
2-(2-Imidazo[4,5-b]pyridine)propanethioamide (**27**)

To a solution of a nitrile **1, 2, 3,** or **22** (0.01 mol) in pyridine or C_2H_5OH (**1, 22**), $N(C_2H_5)_3$ (0.1 mol) was added and the mixture was saturated with H_2S for 1-4 h and then left to stand at room temp. for 3 days. The precipitate was filtered off and purified by recrystallization (Table).

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