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SYNTHESIS OF NOVEL [1-AZIRIDINYL-(HYDROXYIMINO)METHYL]ARENES AND THEIR CYTOTOXIC ACTIVITY

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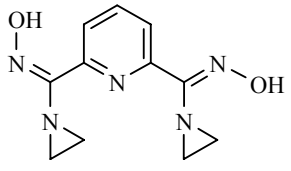
The synthesis has been developed for novel potential anticancer agents whose structures contain an aziridine amidoxime group. The cytotoxic activity of all of the target compounds on different cell lines are given together with the in vitro IC_{50} and LD_{50} values found. The most promising anticancer agents were found to be the methyl 4-[1-aziridinyl(hydroxyimino)methyl]benzoate, 1-aziridinyl(2-naphthyl)-methanone oxime, and 1-aziridinyl(2-quinolyl)methanone oxime.

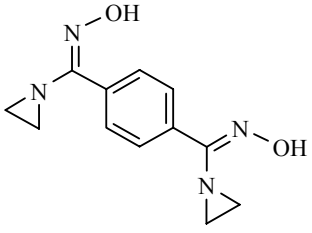
Keywords: aziridine, amidoximes, hydroxyimidoyl chlorides, oximes, cytotoxic activity.

The development of efficient anticancer preparations is a complex problem in contemporary pharmaceutical chemistry [1]. Problems in cancer medication include especially the emergence of resistance of infected cells against new preparations and also the need to discover substances suppressing the reproduction of cancer infected cells without affecting metabolic processes in the host organism cells [2, 3].

Prviously have developed the synthesis of a novel class of cytotoxic agents which contain two functional groups of an amidoxime [4, 5]. There was aziridine-containing amidoxime derivatives due mostly is to their high cytotoxicity and anticancer activity. Selected examples of the most active of these compounds were compounds **1a,b**. However, a limitation of these compounds is the restricted possibility of modification of the



1a



1b

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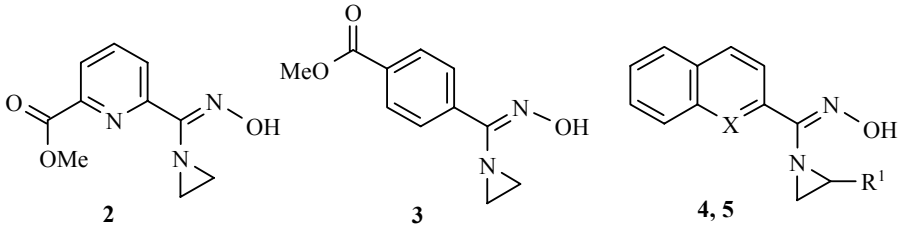
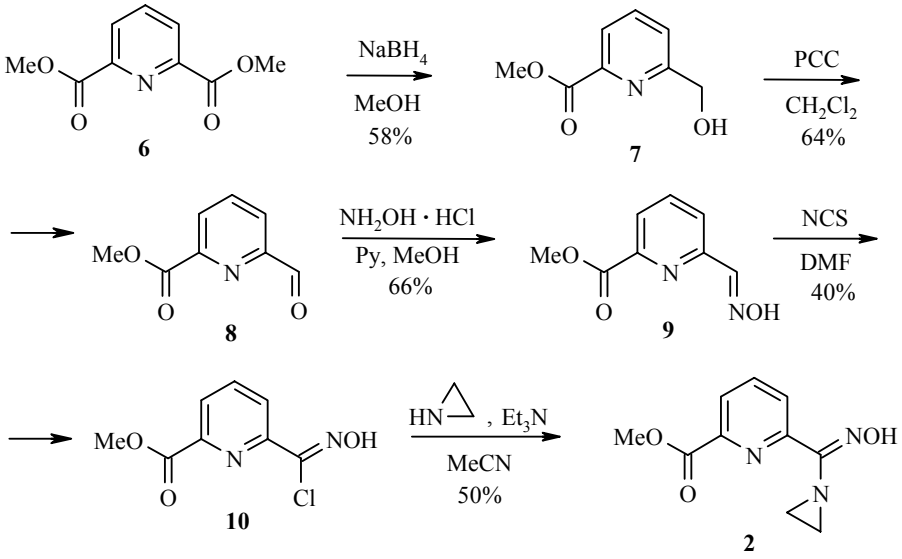
basic structure which hinders the improvement of pharmacokinetic properties of novel compounds. In this connection a search for novel cytotoxic compounds has been carried out. We chose structural analogs of compounds **1a,b** which contain one aziridine amidoxime functional group having the structural formulae **2-5** as synthetic targets (Table 1).



2 **3** **4, 5**

4 X = CH; **5** X = N, R^1 = H, $CONH_2$, CO_2Me

Synthesis of compound **2** was carried out in several steps using dimethyl pyridine-2,6-dicarboxylate **6** as starting material.



PCC = pyridinium chlorochromate, NCS = N-chlorosuccinimide

Sodium borohydride (ether solution, 3 equivalents) was used to achieve the selective reduction of one of the ester groups in the pyridine-2,6-dicarboxylate **6** and a large quantity of methanol was optimum conditions for preparing compound **7** [6]. Aldehyde **8** was prepared from compound **7** using pyridinium chlorochromate as oxidant.

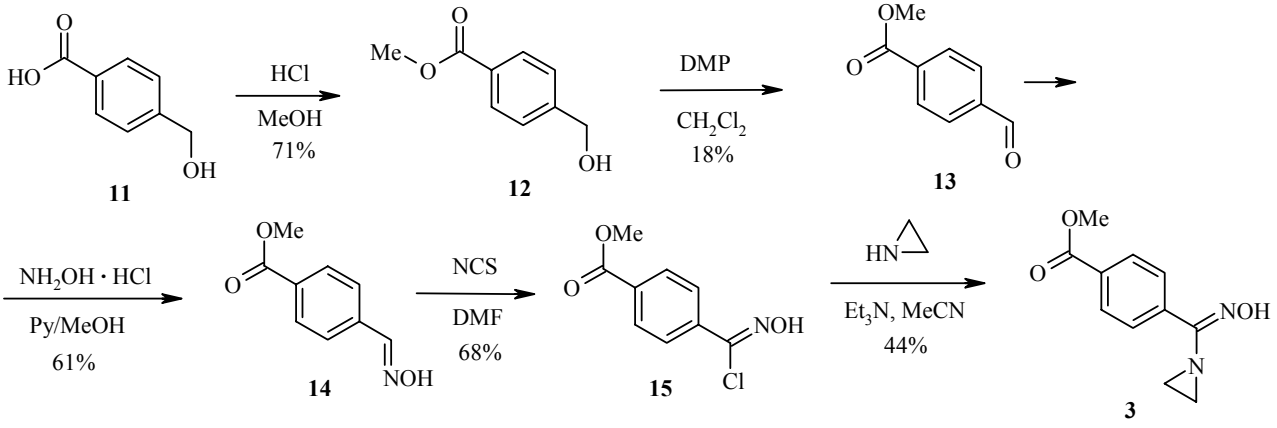
The corresponding oxime **9** was obtained in moderate yield using pyridine as the base. The hydroxyimidoyl chloride **10** was prepared by treating methyl 6-(hydroxyiminomethyl)pyridine-2-carboxylate (**9**) with N-chlorosuccinimide in DMF. The reaction was carried out at temperature sligthly increased to 40ºC. Reaction of hydroxyimidoyl chloride **10** with aziridine gave the final product methyl 6-[1-aziridinyl(hydroxyimino)methyl]pyridine-2-carboxylate (**2**). Formation of side products was also observed due to instability of the aziridine ring.

Hydrolysis of the methyl ester group in compound **2** was unsuccessful, a full degradation of the aziridine ring occurring under these reaction conditions.

TABLE 1. Characteristics of Compounds **2-5**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
		C	H	N		
2	$C_{10}H_{11}N_3O_3 \cdot H_2O$	50.68 / 50.21	5.48 / 5.48	17.08 / 17.56	92-96	50
3	$C_{10}H_{12}N_2O_3$	59.85 / 59.99	5.49 / 5.49	12.39 / 12.72	147-151	44
4	$C_{13}H_{12}N_2O \cdot 0.25H_2O$	72.39 / 72.04	5.69 / 5.81	12.83 / 12.92	141-142	14
5a	$C_{12}H_{11}N_3O \cdot 0.2H_2O$	66.34 / 66.47	5.11 / 5.30	19.19 / 19.38	110-112	17
5b	$C_{14}H_{13}N_3O_3$	62.53 / 61.99	4.98 / 4.83	15.01 / 15.49	59-62	36
5c	$C_{13}H_{12}N_4O_2 \cdot 0.2H_2O$	58.64 / 58.86	4.66 / 4.94	20.51 / 21.12	157-159	25

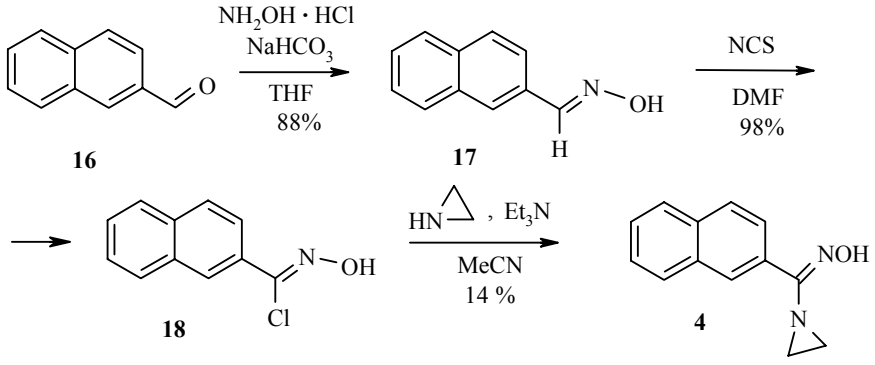
Commercially available 4-hydroxymethylbenzoic acid (**11**) was used as the starting material for the synthesis of **3**. The carboxyl group was first esterified [7] and the product **12** obtained was oxidized by using the Dess-Martin reagent. Further synthesis of compound **3** followed the method reported above for compound **2**.



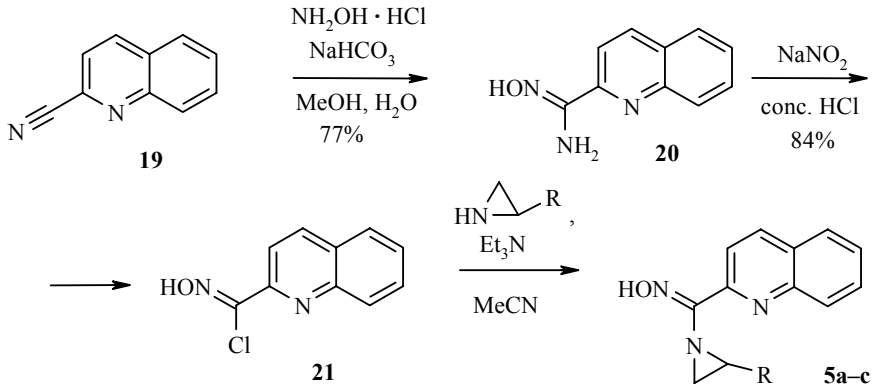
DMP– Dess-Martin reagent

Hydrolysis of the ester group in compound **3** (on attempt to obtain sodium salt) was unsuccessful as in the preceding experiment with ester **2**.

For the preparation of compound **4** the naphthalenecarbaldehyde **16** was treated with hydroxylamine in the presence of sodium bicarbonate in THF solution. Conversion to the hydroxyimidoyl chloride **18** and subsequent reaction with aziridine gave the target compound **4**.



The target compounds **5a-c** were synthesized differently to the method reported above. Reaction of the quinolinecarbonitrile **19** with hydroxylamine in the presence of sodium bicarbonate in acetonitrile solution at room temperature gave the N-hydroxyquinoline-2-carboxamidine (**20**) in 77% yield [8].



5 a R = H, **b** R = $C(O)NH_2$, **c** R = CO_2Me

A subsequent diazotization reaction was carried out under quite rigid conditions treating the amidoxime **20** with sodium nitrite in conc. HCl. The hydroxyimidoyl chloride **21** obtained as a result was separated in a pure state. The product was washed with a large quantity of cold water to remove excess hydrochloric acid. Compound **21** served as the starting material for preparation of the target compounds **5a-c** by using aziridine, the amide or methyl ester of aziridine carboxylic acid as reaction components.

The cytotoxic effect (IC_{50}) of the target compounds **2-4, 5a-c** was tested on monolayer cell lines obtained from the ATCC collection (Tables 2 and 3).

The following cell lines were used: 3T3 – mouse embryonic fibroblasts, HT-1080 – human connective tissue fibrosarcoma, MG-22A – mouse hepatoma, MDA-MB-453s (MDA) – human breast adenocarcinoma, estrogen negative, CCRF S-180II (CCL-8) – mouse sarcoma, monolayer, MCF-7 – human adenocarcinoma, estrogen positive, Caco-2 – human intestinal adenocarcinoma, H9C2 – rat cardiomyocytes, HepG2 – human hepatocyte carcinoma, Capan-2 – human pancreatic adenocarcinoma, PANC-1 – human pancreatic carcinoma, and HPAF-II – human pancreatic carcinoma. The MTT and CV tests were used to investigate the IC_{50} cytotoxic effect.

The results of the CV and MTT tests depended on the level of degradation of the membrane structure and/or the degree of suppression of the oxidation-reduction system in the cell. To avoid *in vivo* experiments for determination of the LD_{50} *in vitro* test on the cell line 3T3 was used for calculation the LD_{50} value. Staining was carried out with Neutral Red as reported in the method "Interagency Coordinating Committee on the Validation of Alternative Methods and National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods".

Compound **4** and **5a** were comparable in their efficiency with **1a** and **1b** (for compound **4** the effect is on the Capan-2 line weaker and this may be connected with features of the tumor metabolism). Compound **3** was less effective but also less toxic, its IC_{50} is comparable with known preparation. Compound **2** had little effect and compounds **5b** and **5c** were found to be inactive. Compounds **3, 4, 5a** could be considered as promising.

EXPERIMENTAL

^1H NMR spectra were recorded on a Varian Mercury VX-200 instrument (200 MHz) using DMSO-d_6 as solvent (compounds **2-4, 5a-c, 7-10, 14, 15, 17, 18, 20, 21**) or $CDCl_3$ (compounds **12** ad **13**) with TMS as

TABLE 2. Cytotoxic Activity* of the Target Compounds **2-5** and Compounds **1a,b** in Various Cell Cultures

Compound	IC_{50}, μg/ml	LD_{50}, μg/kg	IC_{50}, μg/ml											
			CV	MTT	CV	MTT	CV	MTT	CV	MTT	CV	MTT	CV	MTT
	3T3		HT-1080		MG22A		MDA		MCF-7		H9C2		Caco-2	
1a	23	371	0.6	0.2	1	0.8	2	1	3	3	1	0.7	5	5
1b	50	517	2	2	2	2	2	2	3	3	3	3	1	1
2	258	1101	41	28	34	34	—	—	—	—	—	—	—	—
3	418	1233	30	20	22	17	8	9	9	11	10	10	10	12
4	79	581	3	2	3	2	5	6	2	2	2	2	4	3
5a	30	384	2	1	2	2	2	2	8	8	2	2	2	5
5b*[2]	268	1139	>100	>100	>100	>100	—	—	—	—	—	—	—	—
5c*[2]	993	1948	>100	>100	>100	>100	—	—	—	—	—	—	—	—

* IC_{50} is the concentration of the compound killing 50% of the cells; LD_{50} is the concentration which kills 50% of animals (in this case LD_{50} is the calculated value from experiments carried out on cells); MTT is 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide (indicating activity of enzymes in living cells); CV is Crystal Violet dye (staining living cell membranes).

*[2] Inactive compound, not tested further.

TABLE 3. Cytotoxic activity of the Target Compounds **2-5** and Compounds **1a,b** on Various Cell Cultures

Compound	IC_{50}, μg/ml											
	CV	MTT	CV	MTT	CV	MTT	CV	MTT	CV	MTT	CV	MTT
	MIA- PaCa-2		Capan-2		PANC-1		HPAF-II		HepG2		CCL8	
1a	2	0.8	6	6	3	4	0.7	0.5	2	2	1.6	2
1b	2	2	2	1	2	2	1	1	3	4	1	1
2	42	37	88	68	33	50	>100	81	—	—	—	—
3	8	8	12	8	14	8	11	9	7	10	10	10
4	2	2	14	12	3	3	2	3	2	2	2	2
5a	2	2	3	3	2	2	2	2	2	3	3	2

internal standard. The course of the reaction and the purity of the product were monitored using TLC on Kieselgel 60 F_{254} plates (Merck) in the system ethyl acetate–hexane in different ratios and vizualized using a UV lamp with 254 nm filter. Column chromatography used Kieselgel silica gel (35-70 and 60-200 μm). Melting points were determined on an Optimelt apparatus and are not corrected.

Methyl 6-Hydroxymethylpyridine-2-carboxylate (7). Dimethyl pyridine-2,6-dicarboxylate (**6)** (1.95 g, 10 mmol) was dissolved in methanol (100 ml), sodium borohydride (1.13 g, 30 mmol) was added, and the reaction mixture was stirred for 1.5 h at room temperature to reach full conversion of the starting material (TLC monitoring). At the end of the reaction the filtrate was evaporated. The obtained residue was treated with cold water (100 ml) and extracted with chloroform (3×50 ml). The extract was washed with water to give 0.97 g (57%) as colorless crystalline product. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.86 (3H, s, OCH_3); 4.61 (2H, d, *J* = 6, $C\underline{H}_2OH$); 5.56 (1H, t, *J* = 6, $CH_2O\underline{H}$); 7.71 (1H, d, *J* = 7.4, 5-CH pyridine); 7.93-8.04 (2H, m, 3,4-CH pyridine).

Methyl 6-Formylpyridine-2-carboxylate (8). Compound **7** (1 g, 6 mmol) was dissolved in dichloromethane (70 ml), pyridinium chlorochromate (1.94 g, 8.98 mmol) was added, and the mixture stirred for 4 h at room temperature (monitored by TLC). The mixture was filtered through Celite and the filtrate evaporated and repeatedly filtered through silica gel. After evaporation, the residue was purified by column chromatography eluting with petroleum ether–ethyl acetate (1:1). Yield 0.63 g (64%). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.94 (3H, s, OCH_3); 8.16 (1H, dd, *J* = 1.4 and *J* = 6.2, 3-CH pyridine); 8.25 (1H, t, *J* = 8, 4-CH pyridine); 8.33 (1H, dd, *J* = 1.4 and *J* = 6.0, 5-CH pyridine); 10.02 (1H, s, CHO).

Methyl 6-(Hydroxyiminomethyl)pyridine-2-carboxylate (9). Compound **8** (250 mg, 1.5 mmol) and hydroxylamine hydrochloride (118 mg, 1.7 mmol) were mixed dry, a mixture of pyridine and methanol (1:1) was added, and the reaction mixture was refluxed to completion of the reaction (TLC monitoring), then was evaporated and residue was suspending in dichloromethane and washed with aqueous sodium bicarbonate solution (10 ml saturated sodium bicarbonate + 40 ml water). The organic layer was separated, dried over sodium sulphate, and evaporated. Product yield 0.236 g (66%). ^{1}H NMR spectrum, δ, ppm: 3.88 (3H, s, OCH_3); 8.02 (3H, s, pyridine); 8.13 (1H, s, C<u>H</u>NOH); 11.87 (1H, s, CHNO<u>H</u>).

Preparation of Compounds 10, 15, 18 (General Method). N-Chlorosuccinimide (1.20 mmol) was added to a solution of the starting oxime (1 mmol) in DMF (5 ml). The reaction mixture was stirred for 2 h at room temperature and then held for 1 h at 40ºC (for the synthesis of compound **18** the temperature was raised to 80ºC). The mixture was cooled and water with ice (50 ml) was added. After cooling, the precipitate was filtered and thoroughly washed with cold water.

Compound 10. Yield 55%. ^{1}H NMR spectrum, δ, ppm: 3.91 (3H, s, OCH_3); 8.08-8.12 (3H, m, pyridine).

Compound 15. Yield 68%. ^{1}H NMR spectrum, δ, ppm: 3.87 (3H, s, OCH_3); 7.99 (4H, dd, *J* = 8.8 and *J* = 1.3, C_6H_5).

Compound 18. Yield 98%. ^{1}H NMR spectrum, δ, ppm: 7.60 (2H, m, $C_{10}H_7$); 8.06 (5H, m, $C_{10}H_7$); 8.35 (1H, s, 1-CH $C_{10}H_7$); 12.53 (1H, s, NOH).

Methyl 4-Hydroxymethylbenzoate (12). 4-Hydroxymethylbenzoic acid (**11)** (1.09 g, 6.57 mmol) was dissolved in methanol (30 ml), acidified with HCl (3 ml), and refluxed for 4 h. After cooling, the reaction mixture was neutralized with triethylamine (TEA) to pH 7 and evaporated. The residue obtained was dissolved in dichloromethane (20 ml) and washed with a 5% aqueous solution of sodium bicarbonate (2×20 ml). The organic layer was separated, dried over sodium sulphate, and evaporated. Yield 782 mg (72%). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.11 (1H, br. s, OH); 3.85 (3H, s, OCH_3); 4.67 (2H, s, CH_2); 7.37 (2H, d, *J* = 8, 2,6-CH Ph); 7.95 (2H, d, *J* = 8, 3,5-CH Ph).

Methyl Formylbenzoate (13). The Dess-Martin reagent (0.54 ml, 1.7 mmol) was added to a solution of compound **12** (0.264 g, 1.6 mmol) in dichloromethane (10 ml), the reaction mixture was stirred at room temperature for 12 h, extracted with ether. The organic layer was washed with a saturated solution of sodium bicarbonate and separated. The aqueous layer was repeatedly extracted with ether. The extracts were

combined, washed with saturated sodium chloride solution, and dried over sodium sulphate. Evaporation gave the product which was purified by column chromatography using ethyl acetate–petroleum ether (1:4) as eluent. Yield 49 mg (18%). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.96 (3H, s, OCH_3); 7.96 (2H, d, *J* = 8, 2,6-CH Ph); 8.18 (2H, d, *J* = 8, 3,5-CH Ph); 10.09 (1H, s, COH).

Methyl 4-(Hydroxyiminomethyl)benzoate (14) was prepared by the method reported above for compound **9**. Yield 61%. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.85 (3H, s, OCH_3); 7.73 (2H, d, *J* = 8.8, 2,6-CH Ph); 7.97 (2H, d, *J* = 8.2, 3,5-CH Ph); 8.22 (1H, s, CHNOH); 11.87 (1H, s, NOH).

2-Naphthalenecarbaldehyde Oxime (17). Aqueous sodium bicarbonate solution (3 ml) was added to a solution of compound **16** (312 mg, 2 mmol) in THF (7 ml). After 10 min hydroxylamine hydrochloride (278 mg, 4 mmol) was added. The reaction mixture was held for 12 h at room temperature, extraction was carried out with ethyl acetate, extract dried over sodium sulphate and evaporated. Column chromatography of the mixture obtained gave compound **17** (eluent petroleum ether–ethyl acetate, 1:2). Yield 88%. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.57 (2H, m, $C_{10}H_7$); 7.82 (1H, d, *J* = 8.8, H-4 $C_{10}H_7$); 7.91 (3H, m, $C_{10}H_7$); 8.00 (1H, s, H-1 $C_{10}H_7$); 8.29 (1H, s, CHNOH); 11.34 (1H, s, NOH).

N-Hydroxyquinoline-2-carboxamidine (20). Hydroxylamine hydrochloride (139 mg, 2 mmol) was dissolved in methanol (15 ml), cooled in an ice bath, and an aqueous solution of sodium bicarbonate (168 mg, 2 mmol/5 ml of water) was added with stirring at room temperature for 30 min. Freshly prepared hydroxylamine solution was added to a solution of the 3-quinolinecarbonitrile (**19)** (308 mg, 2 mmol) in methanol (15 ml). The reaction mixture was stirred at room temperature for 1.5 h and then for 1.5 h at 40-50ºC. The precipitate formed was filtered off and washed with a large amount of water. Yield 77%. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 5.99 (2H, br. s, NH_2); 7.62 (1H, dt, *J* = 1.6 and *J* = 7.2, 6-CH quinoline); 7.79 (1H, dt, *J* = 1.4 and 7.2, 7-CH quinoline); 8.01 (3H, dd, *J* = 4.2 and *J* = 7.8, quinoline); 8.33 (1H, d, *J* = 8.6, 8-CH quinoline); 10.21 (1H, s, NOH).

Quinoline-2-carboximidoyl Chloride (21). A solution of compound **20** (280 mg, 1.5 mmol) in conc. HCl (5 ml) was cooled to 0-5ºC, an aqueous solution of sodium nitrite (332 mg, 4 mmol/1 ml water) was added and stirred for 1 h at 0-4ºC and then at room temperature for 12 h. The precipitate formed was filtered off and dried *in vacuo*. Yield of product 0.26 g (84%). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.68 (1H, t, *J* = 7.4, 6-CH quinoline); 7.83 (1H, t, *J* = 7.6, 7-CH quinoline); 8.05 (3H, dd, *J* = 6.4 and *J* = 9.4, quinoline); 8.44 (1H, d, *J* = 8.6, 8-CH quinoline); 10.23 (1H, s, NOH).

Preparation of Target Compounds 2-5 (General Method). A mixture of TEA and aziridine in acetonitrile was cooled to 0ºC. A suspension of the hydroxyimidoyl chloride in acetonitrile was added (2 ml of solvent for 0.5 mmol of starting material, the reaction being carried out in an inert atmosphere) and the reaction mixture was held for 30 min at the low temperature and then at room temperature until the reaction was complete (TLC monitoring). In some cases a precipitate of triethylamine hydrochloride was formed and this was filtered off. The filtrate was evaporated and the tarry residue was triturated with ether using a glass rod. The precipitated material was filtered off and washed on the filter with a small amount of ether.

Methyl 6-[1-Aziridinyl(hydroxyimino)methyl]pyridine-2-carboxylate (2) was prepared from TEA (0.29 ml, 2.1 mmol), aziridine (0.08 ml, 1.6 mmol), and the starting product **10** (113 mg, 0.53 mmol). Yield of compound **2** 70 mg (50%). ^{1}H NMR spectrum, δ, ppm: 2.24 (4H, s, CH_2 aziridine); 3.90 (3H, s, OCH_3); 8.0 (3H, m, CH pyridine); 10.79 (1H, s, NOH).

Methyl 4-[1-Aziridinyl(hydroxyimino)methyl]benzoate (3). TEA (0.28 ml, 2 mmol), aziridine (0.08 ml, 1.6 mmol), and the starting product **15** (106 mg, 0.5 mmol) were stirred at room temperature for 1 h. Yield of compound **3** 48 mg (44%). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.21 (4H, s, CH_2 aziridine); 3.86 (3H, s, OCH_3); 7.80 (2H, d, *J* = 8.6, CH Ph); 7.97 (2H, d, *J* = 8.6, CH Ph); 10.71 (1H, s, NOH).

1-Aziridinyl(2-naphthyl)methanone Oxime (4). TEA (0.56 ml, 4 mmol), aziridine (0.15 ml, 3 mmol), and the starting product **18** (210 mg, 1 mmol) were stirred for 1.5 h at room temperature. Yield of compound **4** 30 mg (14%). ^{1}H NMR spectrum, δ, ppm: 2.27 (4H, s, CH_2 aziridine); 7.54 (2H, m, $C_{10}H_7$); 7.90 (4H, m, $C_{10}H_7$); 8.21 (1H, s, 1-CH $C_{10}H_7$); 10.54 (1H, s, NOH).

1-Aziridinyl(2-quinolyl)methanone Oxime (5a) TEA (0.56 ml, 4 mmol), aziridine (0.15 ml, 3 mmol), and starting product **21** (207 mg, 1 mmol) were stirred at room temperature for 1 h. Yield of compound **5a** 37 mg (17%). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.31 (4H, s, CH_2 aziridine); 7.67 (1H, t, *J* = 6.4, 6-CH quinoline); 7.78 (1H, t, *J* = 6.4, 7-CH quinoline); 8.00 (3H, m, quinoline); 8.32 (1H, d, *J* = 8.8, 8-CH quinoline); 10.89 (1H, s, NOH).

1-[Hydroxyimino(2-quinolyl)methyl]aziridine-2-carboxamide (5b). TEA (0.44 ml, 3.2 mmol), aziridinecarboxamide (206 mg, 2.4 mmol), and the starting product **21** (150 mg, 0.8 mmol) were stirred at room temperature for 1.5 h. The product was filtered off, washed with ethyl acetate, and dried *in vacuo*. Yield of compound **5b** 40 mg (25%). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.50 (2H, CH_2 aziridine, proton signal situated under the solvent signal); 3.02 (1H, dd, *J* = 3.6 and *J* = 1.5, CH aziridine); 7.09 (2H, s, NH_2); 7.58 (1H, s, CH quinoline); 7.64 (1H, t, *J* = 6.6, CH quinoline); 7.95 (3H, m, CH quinoline); 8.28 (1H, d, *J* = 8.8, 8-CH quinoline); 10.94 (1H, s, NOH).

Methyl 1-[Hydroxyimino(2-quinolyl)methyl]aziridine-2-carboxylate (5c) TEA (0.56 ml, 3.2 mmol), methyl aziridine carboxylate (300 mg, 3 mmol) and the starting product **21** (190 mg, 1.0 mmol) wered stirred for 3 h at room temperature. After evaporation, the oily product was purified by column chromatography eluting with a mixture of ethyl acetate and petroleum ether (1:1). Yield of compound **5c** 100 mg (36%). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.67 (1H, d, *J* = 3.4, CH aziridine); 2.73 (1H, d, *J* = 6, CH aziridine); 3.23 (1H, proton signal partly situated under the D_2O signal, CH aziridine); 3.61 (3H, s, OCH_3); 7.62 (1H, t, *J* = 6.6, CH quinoline); 7.78 (1H, dt, *J* = 1.4 and *J* = 8, CH quinoline); 7.94 (3H, dd, *J* = 4.2 and *J* = 4.2, CH quinoline); 8.32 (1H, d, *J* = 8.8, 8-CH quinoline); 11.07 (1H, s, NOH).

Biological Screening. The cytotoxic properties of the target compounds *in vitro* were determined on 96 well panels using the vital dyes MTT and CV in accordance with methods [9, 10] validated [11].

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