Synthesis and Prediction of Bioactivity of New Nitroimidazole Derivatives

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Syntheses of 1-propyl derivatives of 2-methyl-5-nitroimidazole (**11**-**17**), containing various azanaphthalene systems attached at 3-position of the propyl group have been described. Due to structural similarity of the derivatives **11**-**17** with metronidazole, an antibacterial and antiprotozoal drug, pharmacological properties of the target compounds were predicted using the PASS program. Polar surface area (PSA) parameter was also applied for estimation of the physical properties of **11**-**17** as drug-like candidates.

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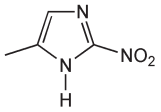
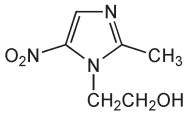
Introduction.

Imidazole and its derivatives, including nitroimidazole, are the compounds that raise continuous interest as biologically active substances [1-4]. The simplest derivative, 2-nitroimidazole (azomycin), is a natural antibiotic with antitrichomonal activity [5]. Antiprotozoal acivity, in particular towards trichomonas and amoebas is shown by *N*-substituted derivatives of imidazole containing nitro group in 2- or 5-position. The most known derivative, 2-(2-methyl-5-nitroimidazolyl)ethanol (Metronidazole, Flagyl®, MetroCream®, Noritrate®, Protostat®), is a synthetic derivative of azomycin. Metronidazole is an antibacterial and antiprotozoal drug, which also has a radiosensitising effect on hypoxic tumor cells. Metronidazole is used in the treatment of various infections, such as amoebiasis, giardiasis, trichomoniasis and leishmaniasis [6,7].



AZOMYCIN



METRONIDAZOLE

This work is a continuation of our research on synthesis of azaheterocyclic compounds and studies of their bioactivity [8-11]. Synthesis of the new metronidazole analogs (**11**-**17**), where the hydroxyethyl group of metronidazole was replaced by a propyl group containing diversified azanaphthalene systems at the chain end, is described. As the azanaphthalene system is present in many therapeutic substances, it can be expected that the new derivatives of 2-methyl-5-nitroimidazole will also show biological activity. The potential bioactivity of **11**-**17** has been evaluated using the PASS program (Prediction of Activity Spectra for Substances) [12-16], while their bioavailability, which is an important feature of bioactive compounds, has been determined on the basis of their physical properties.

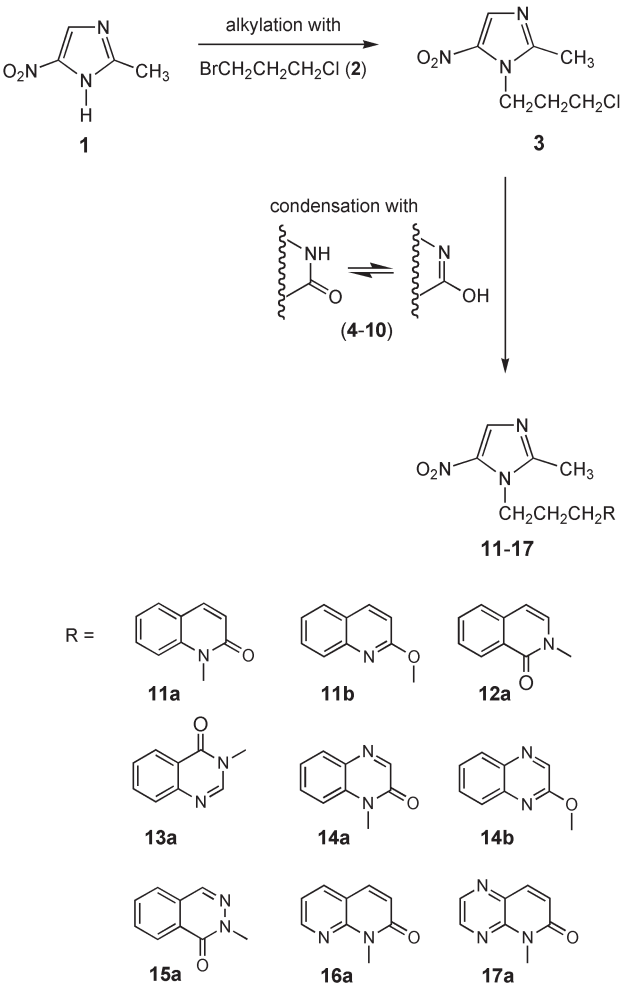
Results and Discussion.

Syntheses.

The synthesis of the compounds **11**-**17** is shown in Scheme 1.

1-(3-Chloropropyl)-2-methyl-5-nitroimidazole (**3**) was obtained by alkylation of 2-methyl-5-nitroimidazole (**1**)

Scheme 1



with 1-bromo-3-chloropropane (**2**). Next, **3** was condensed with quinolin-2(*1H*)-one (**4**), isoquinolin-1(*2H*)-one (**5**), quinazolin-4(*3H*)-one (**6**), quinoxalin-2(*1H*)-one (**7**), phthalazin-1(*2H*)-one (**8**), 1,8-naphthyridin-2(*1H*)-one (**9**), and pyrido[2,3-*b*]pyrazin-6(*5H*)-one (**10**). Both the alkylation and the condensation reactions were carried out under the same conditions (*i.e.*, at room temperature, in dimethylformamide (DMF) solution and in the presence of K_2CO_3). In all cases, after 48 h of reaction time, *N*-substituted derivatives (**11a**-**17a**) of the heterocyclic amides were obtained with 8% to 82% yields (Table 1).

Low yield of the reaction of **3** with quinolin-2(1*H*)-one (**4**) resulted from low conversion of lactame **4** (50% of unreacted quinolin-2(1*H*)-one (**4**) was recovered), and formation of the *O*-substituted isomer (**11b**), which was isolated from the product mixture in 15% yield. Similarly, the condensation of **3** with quinoxalin-2(*1H*)-one (**7**) led to a mixture of *N*-substituted (**14a**) and *O*-substituted (**14b**) derivatives. The presence of the *N*- and *O*-isomers was confirmed by chromatographic analysis of the product mixtures; these isomers show distinctly different R_F coefficients. Moreover, no characteristic C=O vibrations are observed in the IR spectra of **11b** and **14b**; only the bands corresponding to C-O-C vibrations are present (Table 1).

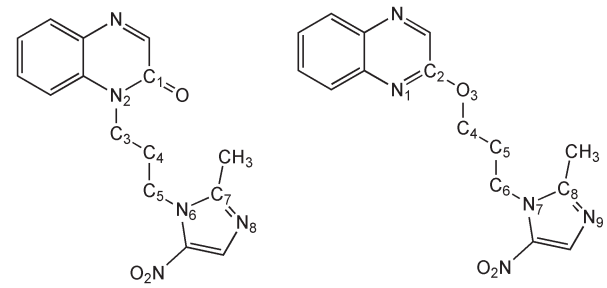
Table 1

Yields of the compounds **11-17** obtained after 48 h condensation of **3** with **4-10**, and their characteristic IR bands.

Compound No.	Yield (%)	Location of stretching vibrations, cm^{-1} $\nu_{C=O}$	ν_{C-O-C}
11a	8	1648	-
11b	15	-	1244 (asym.), 1049 (sym.)
12a	52	1650	-
13a	85	1680	-
14a	35	1657	-
14b	23	-	1222 (asym.), 1034 (sym.)
15a	82	1650	-
16a	78	1658	-
17a	45	1657	-

The proportion of *N*-alkylation versus *O*-alkylation of the cyclic amides is controlled by the equilibrium between their enol and ketone forms. The position of the equilibrium depends not only on the type of amide, but also to a large extent on solvent [17-20].

In order to find whether the formation of **14a** and **14b** was the result of *N*- and *O*-alkylation of the corresponding tautomeric forms of quinoxalin-2(*1H*)-one (**7**) with **3**, or, the result of rearrangement of the isomers formed, pure **14a** and **14b** were subjected to the same reaction conditions as those used for the condensation (*i.e.* to K_2CO_3 in DMF at room temperature). The reaction progress was monitored by thin layer chromatography. It was found that after 24 h of the reaction time, **14a** did not change, while in the case of **14b** the formation of **14a** was detected. Hence, these data indicate that the formation of **14a** in the reaction of **3** with **7** may result both from direct *N*-alkylation of the amide form of **7** and from rearrangement of the thermodynamically less stable *O*-isomer (**14b**). The formation of the more stable isomer **14a** is consistent with quantum chemical calculations. The heat of formation (ΔH_f) of **14b**, calculated using AM1 parameterization of MOPAC 6 program, equals 78.9 kcal/mol, which is by 3.9 kcal/mol higher than the ΔH_f of **14a**. Figure 1 presents the heat of formation and some details (*i.e.*, torsionals angles) of the final geometry of **14a** and **14b**.

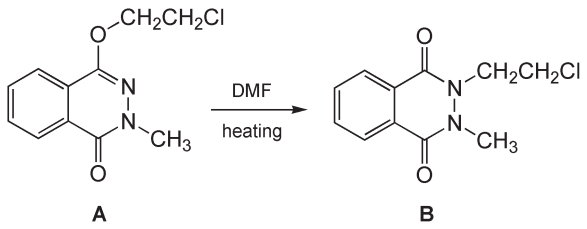


14a; ΔH_f = 75.0 kcal/mol
C_1-N_2-C_3-C_4 = -83.33
N_2-C_3-C_4-C_5 = -179.01
C_3-C_4-C_5-N_6 = -52.88
C_4-C_5-N_6-C_7 = -60.24
C_5-N_6-C_7-N_9 = -175.53

14b; ΔH_f = 78.9 kcal/mol
N_1-C_2-O_3-C_4 = 3.47
C_2-O_3-C_4-C_5 = 178.33
O_3-C_4-C_5-C_6 = 73.15
C_4-C_5-C_6-N_7 = -178.55
C_5-C_6-N_7-C_8 = 98.47
C_6-N_7-C_8-N_9 = -178.68

Figure 1. Heats of formation and selected torsional angles of the final geometry of **14a** and **14b**, calculated using AM1 parameterization of MOPAC 6 program.

The rearrangement of *O*-substituted derivatives of cyclic amides to the corresponding *N*-substituted derivatives was also described by Pring and Swahn [22]. The authors found that 4-(2-chloroethoxy)-2-methylphthalazin-1(*2H*)-one (**A**) (*i.e.*, an *O*-derivative of phthalazinone) isomerized to the thermodynamically more stable *N*-isomer (**B**) upon heating in DMF (Figure 2).



A **B**

Figure 2. Isomerization of 4-(2-chloroethoxy)-2-methylphthalazin-1(*2H*)-one (**A**) into 2-(2-chloroethyl)-2,3-dihydro-3-methylphthalazine-1,4-dione (**B**) [22].

Prediction of Pharmacological Activity.

Keeping in mind that the compounds **11**-**17** contained two pharmocophoric moieties in their structures (*i.e*. imidazole and azanaphthalene rings), we estimated their biological activity spectra by computer prediction. For this purpose we applied the computer program PASS [12], which on the basis of structural formulae of compounds predicts more than 900 pharmacological effects for any drug-like compound. Based on the analysis of structure-activity relationships of a training set consisting of about 52,000 of drugs, drug-candidates and lead compounds, the program PASS estimates probability for a compound to be active (Pa) and inactive (Pi) for each type of activity from the biological activity spectrum. High value of Pa offers a high chance for a compound to show the selected activity in real experiments. On the other hand, low value of Pi is an indicator that the molecule is likely to be inactive in the predicted type of biological activity. The most probable biological activities (Pa) of the compounds **11**-**17,** predicted by PASS, are collected in Table 2. Predicted Pi values for all the activities shown in the Table 2 were less than 3%.

Table 2

Probabilities of biological activity (Pa) of the compounds **11**-**17**

Activity Type	Compound								
	11a	**11b**	**12a**	**13a**	**14a**	**14b**	**15a**	**16a**	**17a**
Antiprotozoal	0.835	0.849	0.875	0.825	0.842	0.847	0.813	0.838	0.840
Antileishmanial	0.684	0.662	0.619	0.621	0.699	0.660	0.643	0.666	0.717
Antitrichomonal	0.699	0.680	0.877	0.644	0.713	0.703	0.707	0.723	0.713
Antiamebic	0.669	0.652	0.651	0.636	0.691	0.674	0.654	0.686	0.677
Radiosensitizer	0.655	0.651	0.650	0.636	0.677	0.656	0.624	0.653	0.675

The data in Table 2 indicate that all of the compounds studied exhibit high probability of antiprotozoal activity reaching 81-88%. The probability of antileishmanial activity of **11**-**17** is in the range 62-72%, which is close to that of antitrichomonal and antiamebic activities, except for **12a**. Moreover, the PASS predictions suggest that the compounds **11**-**17** should be able to act as radiosensitizers.

The biological activity of **11**-**17** within a selected activity group practically does not depend on the type of amide and depends only slightly on the amide substitution. In fact, the predicted by PASS pharmacological activities of **11**-**17** are the same as the activities found for metronidazole. Hence it can be concluded that the new derivatives of 2-methyl-5-nitroimidazole (**11**-**17**) do not change the activity profile characteristic for metronidazole and no other significant pharmacological properties show up.

Prediction of Bioavailability.

One of the features the bioactive compounds should have is their bioavailability defined as the ability of the compound to pass through biological membranes [23,24]. The parameter of organic molecules that strongly correlates with membrane permeability is their polar surface area (PSA) [24,25]. The upper limit of PSA for good oral absorption is ~ 140-150 Å^2, while the upper PSA threshold for blood-brain barrier penetration is ~ 90 Å^2 [24,25].

The PSA is defined as the sum of Van-der-Waals surface areas of polar atoms (*i.e*., oxygen and nitrogen) in a molecule [26,27]. The calculation of PSA in a classical way requires special software to generate 3D structures of molecules, which makes the prediction process time consuming [28].

Recently, fast algorithms for PSA calculation that do not need a 3D structure have been developed by Ertl *et al*. [25]. The method, called "topological PSA" (TPSA), provides results which are practically identical with the 3D PSA. The correlation coefficient between the 3D PSA and the fragment-based TPSA is 0.99 for over 34,000 molecules from the World Drug Index [25]. The TPSA algorithm does not require any computationally demanding steps, because it is based on identification and summation of tabulated surface contributions of polar fragments in the molecule. The PSA parameters of the targeted compounds, calculated by the use of TPSA methodology, are 85.6 Å^2 for **11a** and **12a**, and 85.8 Å^2 for **11b**; 98.5 Å^2 for **13a**-**16a**, and 98.7 and 114.4 Å^2 for **14b** and **17a** respectively. In Figure 3 example values of atomic contributions of polar atoms, used for PSA calculation of the compound **11a**, are shown.

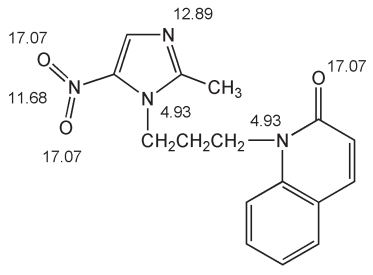


Figure 3. Atomic contribution (Å^2) of polar atoms in **11a**, taken to its PSA calculation.

Comparison of the PSA values of the compounds **11**-**17** and metronidazole (PSA = 83.9 Å^2) with the upper limit of PSA for compounds with good blood-brain barrier penetration (PSA ~ 90 Å^2) indicate that all of the compounds studied should have poor blood-brain barrier permeability. On the other hand, the PSA values much lower than 140 Å^2 indicate that the compounds **11**-**17** and metronidazole should show good oral absorbtivity. Very close PSA value of metronidazole to that of **11a**-**b** and **12a**, indicate very close bioavailability of these compounds. In conclusion it has to be pointed out that all the compounds **11**-**17** are good candidates for study as drug-like, orally administered, agents.

EXPERIMENTAL

Melting points were determined on a Böetius melting point apparatus and are uncorrected. Elemental analyses were performed on a Perkin-Elmer 2400 analyzer located in the Regional Laboratory of Jagiellonian University, and the results are within ± 0.4% of the calculated values. IR spectra were recorded on a Bio-Rad FTS – 175C spectrophotometer in KBr pellets. ^{1}H NMR spectra were taken on a Tesla 487C (80 MHz) spectrometer in $CDCl_3$ solution, using TMS as an internal standard; the chemical shifts are given in ppm (δ); and, the coupling constants are taken from the expanded spectra. Mass spectra (EI) were recorded with a Varian – MAT 112 spectrometer at 70 eV. The reactions and the product purification were monitored by TLC on silica-gel plates (Merck 60F_{254}) using chloroform/methanol (95:5) mixture as eluent. For column chromatography, silica gel (Merck) was used. Starting materials, solvents, and reagents were purchased from commercial sources (Aldrich and Merck) and were used without further purification, except for DMF, which was purified by distillation shortly before use. The semiempirical AM1 calculations (full geometry optimization at the gradient norm < 0.1 kcal/Å(radian)) were done using MOPAC 6.0 (QCPE) program.

The cyclic amides **4**-**10** were prepared according to the literature data: quinolin-2(1*H*)-one (**4**) [29], isoquinolin-1(2*H*)-one (**5**) [30], quinazolin-4(3*H*)-one (**6**) [31], quinoxalin-2(1*H*)-one (**7**) [32], phthalazin-1(2*H*)-one (**8**) [33], 1,8-naphthyridin-2(1*H*)-one (**9**) [34], and pyrido[2,3-*b*]pyrazin-6(5*H*)-one (**10**) [35].

Synthesis of 1-(3-Chloropropyl)-2-methyl-5-nitroimidazole (**3**).

A mixture of 22.8 g (0.18 mol) of 2-methyl-5-nitroimidazole (**1**), 31.5 g (0.20 mol) of 1-bromo-3-chloropropane (**2**) and 38.6 g (0.28 mol) of anhydrous potassium carbonate in 200 mL of dimethylformamide was stirred at room temperature for 48 hours. After evaporation of the solvent almost to dryness, 100 mL of acetone was added to the residue and the precipitate was filtered off. The acetone solution was poured into 200 mL of water, and the mixture was extracted with chloroform. Evaporation of chloroform gave brown, semisolid product. The row material was recrystallized from 2-propanol to yield 18.5 g (60%) of 1-(3-chloropropyl)-2-methyl-5-nitroimidazole (**3**) with mp 65-67 °C, ^{1}H nmr: δ 2.31 (m, 2H, $CH_2CH_2CH_2$), 2.48 (s, 3H, CH_3), 3.55 (t, 2H, CH_2-Cl, J = 5.7 Hz), 4.15 (t, 2H, CH_2-N-imidazole, J = 7.1 Hz,), 7.71 ppm (s, 1H, imidazole 4-H).

Anal. Calcd. for $C_7H_{10}ClN_3O_2$: C, 41.29; H, 4.95; N, 20.64. Found: C, 41.18; H, 5.20; N, 20.82.

General Procedure for the Reaction of **3** with the Cyclic Amides **4**-**10**.

A mixture of 6.4 mmol of **3**, 6.4 mmol of the respective cyclic amide **4**-**10**, 19.1 mmol of anhydrous potassium carbonate, and a few crystals (~ 0.01 g) of potassium iodide in 15-20 mL of dimethylformamide was stirred with magnetic stirrer at room temperature for 48 hours. Next, the reaction mixture was poured into 100-150 mL of water, and, the precipitate was either collected by filtration or extracted with chloroform. The crude products **12a**, **13a** and **15a**-**17a**, were purified by crystallization. The mixtures of **11a** with **11b** and **14a** with **14b** were separated by column chromatography, using chloroform:methanol (95:5) as eluent, and then recrystallized. The yields of **11a**, **11b**, **12a**, **13a**, **14a**, **14b**, and **15a**-**17a** were collected in the Table 1.

1-[3-(2-Methyl-5-nitro-1*H*-imidazol-1-yl)propyl]quinolin-2(1*H*)-one (**11a**).

This compound was obtained as colorless needles (methyl alcohol), mp 225-226,5 °C; ^{1}H nmr: δ 2.19-2.44 (m, 2H, $CH_2CH_2CH_2$), 2.42 (s, 3H, CH_3), 4.09 (t, 2H, CH_2-N-imidazole), 4.45 (t, 2H, CH_2-N-quinolinone), 6.71 (d, 1H, quinolinone 3-H), 7.44-7.70 (m, 4H, quinolinone 5-8-H), 7.74 (d,1H, quinolinone 4-H), 7.82 ppm (s, 1H, imidazole 4-H), $J_{3,4}$ = 9.7 Hz; ms: m/z (%) 312 (M^+, 9); R_F 0.22 (chloroform:methanol 95:5).

Anal. Calcd. for $C_{16}H_{16}N_4O_3$: C, 61.53; H, 5.16; N, 17.94. Found: C, 61.18; H, 5.27; N, 17.82.

2-[3-(2-Methyl-5-nitro-1*H*-imidazol-1-yl)propoxy]quinoline (**11b**).

This compound was obtained as colorless plates (methyl alcohol), mp 147-149 °C; ^{1}H nmr: δ 2.24-2.48 (m, 2H, $CH_2CH_2CH_2$), 2.44 (s, 3H, CH_3), 4.13 (t, 2H, CH_2-N-imidazole), 4.56 (t, 2H, CH_2-N-quinoline), 6.87 (d,1H, quinoline 3-H), 7.44-8.00 (m, 4H, quinoline 5-8-H), 7.83 (s, 1H, imidazole 4-H), 8.02 ppm (d,1H, quinoline 4-H), $J_{3,4}$ = 9,4 Hz; ms: m/z (%) 312 (M^+, 11); R_F 0.40 (chloroform:methanol 95:5).

Anal. Calcd. for $C_{16}H_{16}N_4O_3$: C, 61.53; H, 5.16; N, 17.94. Found: C, 61.45; H, 5.18; N, 18.08.

2-[3-(2-Methyl-5-nitro-1*H*-imidazol-1-yl)propyl]isoquinolin-1(2*H*)-one (**12a**).

This compound was obtained as colorless needles (methyl alcohol), mp 182-184 °C; ^{1}H nmr: δ 2.12-2.50 (m, 2H, $CH_2CH_2CH_2$), 2.41 (s, 3H, CH_3), 4.03 (t, 2H, CH_2-N-isoquinolinone), 4.11 (t, 2H, CH_2-N-imidazole), 6.55 (d, 1H, isoquinolinone 4-H), 7.01 (d,1H, isoquinolinone 3-H), 7.44-8.47 (m, 4H, isoquinolinone 5-8-H), 7.84 ppm (s, 1H, imidazole 4-H); $J_{3,4}$ = 7.3 Hz; ms: m/z (%) 312 (M^+, 4).

Anal. Calcd. for $C_{16}H_{16}N_4O_3$: C, 61.53; H, 5.16; N, 17.94. Found: C, 61.40; H, 5.13; N, 17.58.

3-[3-(2-Methyl-5-nitro-1*H*-imidazol-1-yl)propyl]quinazolin-4(3*H*)-one (**13a**).

This compound was obtained as colorless plates (acetonitrile), mp 252-254 °C; ^{1}H nmr: δ 2.29-2,38 (m, 2H, $CH_2CH_2CH_2$), 2.45 (s, 3H, CH_3), 4.10 (t, 2H, CH_2-N-imidazole), 4.07 (t, 2H, CH_2-N-quinazolinone), 7.53-8.33 (m, 4H, quinazolinone 5-8-H), 7.84 (s,1H, imidazole 4-H), 8.00 ppm (s,1H, quinazolinone 2-H); ms: m/z (%) 313 (M^+, 45).

Anal. Calcd. for $C_{15}H_{15}N_5O_3$: C, 57.50; H, 4.83; N, 22.35. Found: C, 57.31; H, 4.83; N, 22.41.

1-[3-(2-Methyl-5-nitro-1*H*-imidazol-1-yl)propyl]quinoxalin-2(1*H*)-one (**14a**).

This compound was obtained as colorless needles (acetonitrile), mp 248-250 °C; ^{1}H nmr: δ 2.21-2.49 (m, 2H, $CH_2CH_2CH_2$), 2.43 (s, 3H, CH_3), 4.12 (t, 2H, CH_2-N-imidazole), 4.40 (t, 2H, CH_2-N-quinoxalinone), 7.40-8.10 (m, 4H, quinoxalinone 5-8-H), 7.84 (s, 1H, imidazole 4-H), 8.33 ppm (s,1H, quinoxalinone 3-H); ms: m/z (%) 313 (M^+, 29); R_F 0.23 (chloroform:methanol 95:5).

Anal. Calcd. for $C_{15}H_{15}N_5O_3$: C, 57.50; H, 4.83; N, 22.35. Found: C, 57.29; H, 4.80; N, 22.34.

2-[3-(2-Methyl-5-nitro-1*H*-imidazol-1-yl)propoxy]quinoxaline (**14b**).

This compound was obtained as colorless needles (1-propanol), mp 157-159 °C; ^{1}H nmr: δ 2.22-2.55 (m, 2H, $CH_2CH_2H_2$), 2.46 (s, 3H, CH_3), 4.19 (t, 2H, CH_2-N-imidazole), 4.56 (t, 2H, CH_2-N-quinoxaline), 7.59-8.17 (m, 4H, quinoxaline 5-8-H), 7.83 (s, 1H, imidazole 4-H), 8.54 ppm (s, 1H, quinoxaline 3-H); ms: m/z (%) 313 (M^+, 27); R_F 0.31 (chloroform: methanol 95:5).

Anal. Calcd. for $C_{15}H_{15}N_5O_3$: C, 57.50; H, 4.83; N, 22.35. Found: C, 57.40; H, 4.80; N, 22.37.

2-[3-(2-Methyl-5-nitro-1*H*-imidazol-1-yl)propyl]phthalazin-1(2*H*)-one (**15a**).

This compound was obtained as colorless needles (ethyl alcohol), mp 190-193 °C; ^{1}H nmr: δ 2.22-2.53 (m, 2H, $CH_2CH_2CH_2$), 2.44 (s, 3H, CH_3), 4.06 (t, 2H, CH_2-N-imidazole), 4.36 (t, 2H, CH_2-N-phthalazinone), 7.66-8.42 (m, 4H, phthalazinone 5-8-H), 7.85 (s, 1H, imidazole 4-H), 8.20 ppm (s,1H, phthalazinone 4-H); ms: m/z (%) 313 (M^+, 24).

Anal. Calcd. for $C_{15}H_{15}N_5O_3$: C, 57.50; H, 4.83; N, 22.35. Found: C, 57.15; H, 4.82; N, 22.27.

1-[3-(2-Methyl-5-nitro-1*H*-imidazol-1-yl)propyl]-1,8-naphthyridin-2(1*H*)-one (**16a**).

This compound was obtained as colorless plates (methyl alcohol), mp 201-204 °C; ^{1}H nmr: δ 2.25-2.51 (m, 2H, $CH_2CH_2CH_2$), 2.42 (s, 3H, CH_3), 4.06 (t, 2H, CH_2-N-imidazole), 4.65 (t, 2H, CH_2-N-1,8-naphthyridone), 6.75 (d, 1H, 1,8-naphthyridone 3-H), 7.22 (t, 1H, 1,8-naphthyridone 6-H), 7.68 (d,1H,1,8-naphthyridone 4-H), 7.92 (dd, 1H, 1,8-naphthyridone 5-H), 8.62 ppm (dd, 1H, 1,8-naphthyridone 7-H); $J_{3,4}$ = 9,5 Hz, $J_{5,6}$ = 7.8 Hz, $J_{6,7}$ = 4.6 Hz, $J_{5,7}$ = 1.8 Hz; ms: m/z (%) 313 (M^+, 8).

Anal. Calcd. for $C_{15}H_{15}N_5O_3$: C, 57.50; H, 4.83; N, 22.35. Found: C, 57.37; H, 4.89; N, 22.22.

5-[3-(2-Methyl-5-nitro-1*H*-imidazol-1-yl)propyl]pyrido[2,3-*b*]-pyrazin-6(5*H*)-one (**17a**).

This compound was obtained as colorless needles (2-propanol), mp 205-206 °C; ^{1}H nmr: δ 2.22-2.53 (m, 2H, $CH_2CH_2CH_2$), 2.44 (s, 3H, CH_3), 4.07 (t, 2H, CH_2-N-imidazole), 4.56 (t, 2H, CH_2-N-pyridopyrazinone), 7.00 (d, 1H, pyridopyrazinone 3-H), 7.92 (s, 1H, imidazole 4-H), 7.95 (d,1H, pyridopyrazinone 4-H), 8.55 ppm (s, 2H, pyridopyrazinone 6,7-H); $J_{3,4}$ = 9,8 Hz; ms: m/z (%) 314 (M^+, 14).

Anal. Calcd. for $C_{14}H_{14}N_6O_3$: C, 53.50; H, 4.49; N, 26.74. Found: C, 53.34; H, 4.47; N, 22.35.

Isomerization Experiments.

The isomerization reactions of **14a** and **14b** in dimethylformamide in the presence of potassium carbonate were followed by means of TLC, using chloroform:methanol (95:5) as eluent. The component spots were visualized under a short-wave ultraviolet lamp.

1-[3-(2-methyl-5-nitro-1*H*-imidazol-1-yl)propyl]quinoxalin-2(1*H*)-one (**14a**).

Compound **14a** (0.31 g, 1 mmol) and 0.28 g (2 mmol) of potassium carbonate in 4 mL of dimethylformamide was stirred at room temperature for 24 h. Only one spot, that due to the starting material (R_F 0.23) was observed; no other product appeared.

2-[3-(2-methyl-5-nitro-1*H*-imidazol-1-yl)propoxy]quinoxaline (**14b**).

Compound **14b** (0.31g, 1 mmol) and 0.28 g (2 mmol) of potassium carbonate in 4 mL of dimethylformamide was stirred at room temperature. A distinct spot on the TLC plate, corresponding to the compound **14a** (R_F 0.23), appeared after 24 hours. Prolongation of the reaction time increased the intensity of the spot corresponding to **14a** compared to that of the starting compound **14b** (R_F 0.31).

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