$S_{RN}1$ REACTIONS IN IMIDAZO[1,2-*a*][1,8]NAPHTHYRIDINE SERIES

Patrice Vanelle[1]*, Saïd Ghezali[1], José Maldonado[1], Olivier Chavignon[2], Alain Gueiffier[2], Jean-Claude Teulade[2], and Michel P. Crozet[3]*

[1]Laboratoire de Chimie Organique, Université d'Aix-Marseille 2, Faculté de Pharmacie, 27 Bd J. Moulin, 13385 Marseille Cedex 04, France. [2]Laboratoire de Chimie Organique, CNRS URA 1111, Facultés de Pharmacie, 15 Av Charles Flahaut, 34060 Montpellier Cedex, et 28 Place Henri Dunant, 63001 Clermont-Ferrand Cedex, France. [3]Radicaux Libres et Synthèse, CNRS URA 1412, Université d'Aix-Marseille 3, Faculté des Sciences et Techniques de Saint-Jérôme, BP 562, 13397 Marseille Cedex 20, France

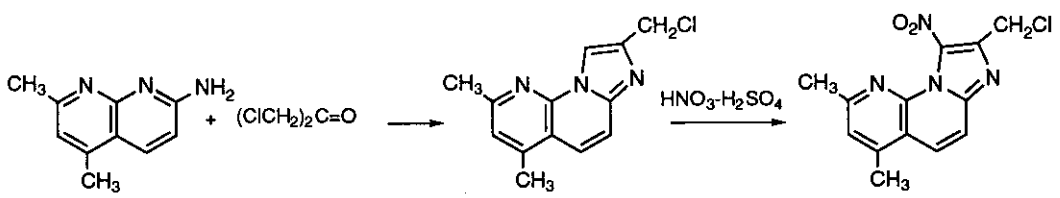
Abstract - 8-Chloromethyl-2,4-dimethyl-9-nitroimidazo[1,2–*a*][1,8]naphthyridine was synthesized as reductive alkylating agent and its reactivity with 2-nitropropane anion was investigated. The $S_{RN}1$ mechanism of the *C*-alkyation was confirmed by the inhibitory effects of *p*-dinitrobenzene, molecular oxygen and TEMPO. Extension of this $S_{RN}1$ reaction to various nitronate anions leads after nitrous acid elimination to a new class of imidazo[1,2-*a*][1,8]naphthyridine derivatives bearing a trisubstituted double bond at the 8-position.

The rare examples of radical anion substitution involving *o*-nitrobenzyl chloride give much less *C*-alkylation of nitronate anions than *p*-nitrobenzyl chloride. The diminished effectiveness of an *o*-nitro group in facilating

electron-transfer substitution is apparently due to steric hindrance to coplanarity in the *ortho* isomer.[1] We have shown that this steric hindrance is dramatically decreased in nitroimidazole series since with these *ortho*-like systems, the yields are much higher and therefore this reaction is of synthetic utility for the preparation of new compounds difficult to obtain by other ways.[2]

Due to the growing interest in tricyclic derivatives of naphthyridine and isosteres known as antibacterial drugs,[3] antianxiety agents,[4] antiallergic compounds,[5] inhibitors of tumor metastasis[6] and antivirals,[6] the search of new reactions to bind functional groups to these structures is very attractive. As a part of our continuing studies on the $S_{RN}1$ reactions of nitroheterocyclic and quinonic alkylating agents[7,8] to prepare potentially bioactive agents involving electron transfer in their modes of action and in order to study the influence of the coplanarity of the electron-acceptor group and of the ring system bearing the leaving group upon these reactions, we have investigated the synthesis of 8-chloromethyl-2,4-dimethyl-9-nitroimidazo[1,2-*a*][1,8]naphthyridine (**2**) and its reactivity with the 2-nitropropane anion (**3a**). Derivative (**2**) was prepared by condensing 5,7-dimethyl-1,8-naphthyridin-2-ylamine with dichloroacetone using Tschitschibabin procedure[9] (58% yield) followed by the nitration of 8-chloromethyl-2,4-dimethylimidazo[1,2-*a*][1,8]naphthyridine (**1**) with HNO_3-H_2SO_4 (94% yield).

Scheme 1



1 **2**

The chloride (**2**) reacts with **3a** under conditions conducive to $S_{RN}1$ reaction (nitrogen atmosphere, photostimulation) and various experimental conditions reported in the Table I are studied for establishing the nature of this mechanism.

Table I

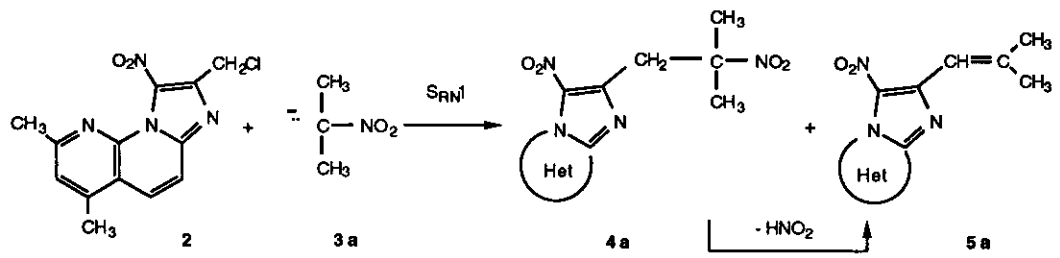
Influence of experimental conditions in the reaction of **2** with **3a**

Entry[a]	Mol. equiv. of **3a**	Solvent	Scavenger (Mol. equiv.)	**4a**	**5a** % Yield[b]
1	1	DMF	-	34	20
2	2	DMF	-	31	65
3	2	DMF	$CuCl_2$ (6×10^{-6})	29	63
4	2	DMF	$CuCl_2$ (1.2×10^{-4})	31	63
5	1	CH_2Cl_2/H_2O	-	traces	25
6	2	CH_2Cl_2/H_2O	-	32	46
7	3	CH_2Cl_2/H_2O	-	29	58
8	4	CH_2Cl_2/H_2O	-	26	65
9	3	CH_2Cl_2/H_2O	dark	traces	48
10	3	CH_2Cl_2/H_2O	dark, O_2 (bubbling)	0	0
11	3	CH_2Cl_2/H_2O	TEMPO (0.1)	0	0
12	3	CH_2Cl_2/H_2O	*p*-$NO_2C_6H_4NO_2$ (1)	29	32

[a]All reactions were irradiated at room temperature during 24 h under nitrogen with fluorescent lamps (2 x 60 W) by using one equivalent of imidazonaphthyridine derivative (**2**). [b]% yield relative to the chloride (**2**).

The results of Table I show that **2** reacts with **3a** to give the *C*-alkylation product (**4a**) which undergoes under these conditions incomplete elimination of nitrous acid to give 2,4-dimethyl-8-(2-methylpropenyl)-9-nitro-imidazo[1,2-*a*][1,8]naphthyridine (**5a**) as illustrated by Scheme 2. The nitrous acid elimination is favoured by using a large excess of nitronate anion as shown the study of the donor/acceptor ratio. The fact that *C*-alkylation product is isolated in these reactions even with an excess of anion indicates that the protons of the methylene group are less acidic than these of other imidazole derivatives or a steric effect of *o*-nitro group. The best *C*-alkylation yield is obtained when 2 equivalents of 2-nitropropane anion are used in DMF under Kornblum conditions.[10] The phase transfer conditions of Norris[11] (40% tetrabutylammonium hydroxide in water and dichloromethane) gave lower yield as already observed in other series[7] and a larger excess of anion must be used to obtain similar yields.

Scheme 2

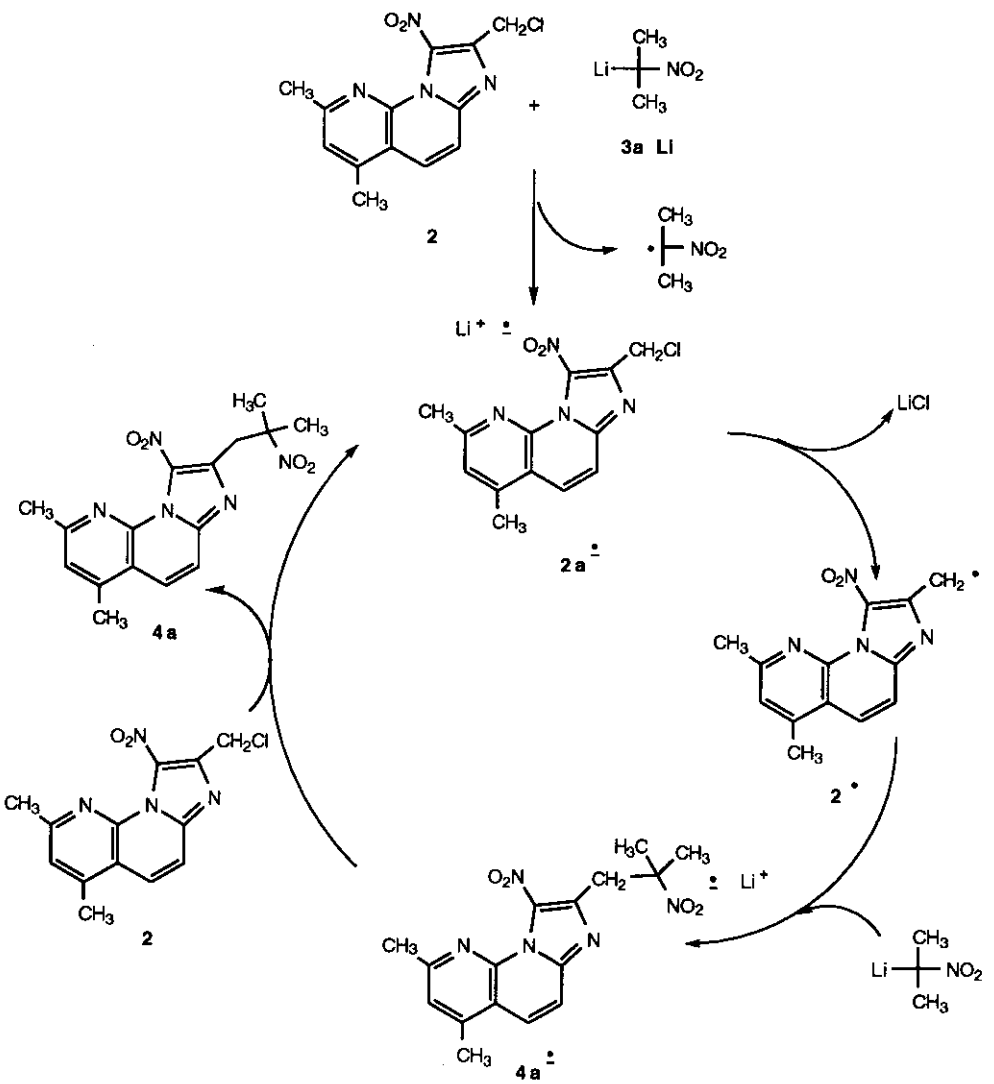


The $S_{RN}1$ mechanism is confirmed by inhibition studies.[12] Under the experimental conditions of Entry 7, the use of *p*-dinitrobenzene gives little inhibition (Entry 12). This observation suggests that **2** and **4a** have a reduction potential similar to that of *p*-dinitrobenzene and then the formation of their radical anion can compete with single electron transfer to *p*-dinitrobenzene. In the same way, the reaction carried out in the dark (Entry 9) shows lower yield, the *C*-alkylation yield decreasing from 87% to 48%, which indicates a spontaneous electron transfer process from **3a** to the substrate and also demonstrates the catalytic effect of light on electron transfer.[13] The addition of oxygen in the dark (Entry 10) or catalytic amount of 2,2,6,6-tetramethyl-1,4-piperidinyl *N*-oxide (TEMPO) (Entry 11) shows complete inhibition clearly indicating the radical chain nature of this process as required for a $S_{RN}1$ reaction. In these experimental conditions, the aldehyde derivative resulting from the competitive *O*-alkylation is not isolated from the reaction mixture as observed for other nitroimidazolealdehydes. However, there is no inhibition by $CuCl_2$ (Entries 3 and 4) as observed in imidazo[1,2-*a*]pyridine series,[2,19] and this result can be explained by the formation of complexes with these nitrogen heterocycles and cupric salt which may change the concentration and the properties of the scavenger.

The reaction between 8-chloromethyl-2,4-dimethylimidazo[1,2-*a*][1,8]naphthyridine (**1**) and the 2-nitropropane salt (**3a**) under the experimental conditions of Entries 2 and 7, has been unsuccessful and neither the *C*-alkylation nor the *O*-alkylation products have been extracted from the reaction mixture, indicating the necessity of the presence of the electron-withdrawing nitro group for $S_{RN}1$ *C*-alkylation.

From the results of these classical inhibition experiments, we conclude that an $S_{RN}1$ mechanism is the most probable for the *C*-alkylation of 8-chloromethyl-2,4-dimethyl-9-nitroimidazo[1,2–*a*][1,8]naphthyridine (**2**), as shown in Scheme 3.

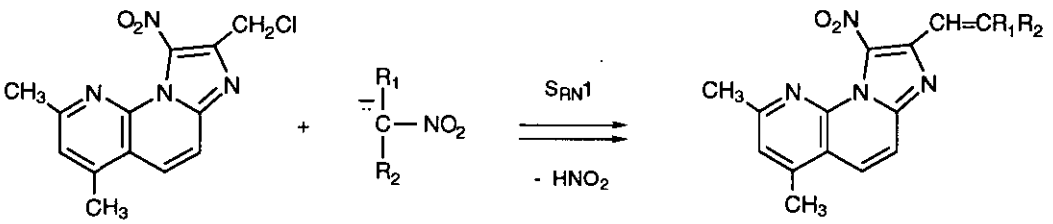
Scheme 3



As the nitroheterocycle (**5a**) shows potential pharmacological activity,[14] the reaction of 8-chloromethyl-2,4-

dimethyl-9-nitroimidazo[1,2–*a*][1,8]naphthyridine (**2**) and 2-nitropropane salts has been extended to various nitronate anions. The precursors of the nitronate anions (**3b-g**) are commercially available or obtained by oxidation of the corresponding primary amines by *m*-chloroperbenzoic acid.[15] By using the experimental conditions of Entry 2, we obtained new 2,4-dimethyl-8-alkylidenemethyl-9-nitroimidazo[1,2-*a*][1,8] naphthyridine derivatives (**5b-g**) in good yields (59-97 %) as shown in the Scheme 4.

Scheme 4



2 **3 b-g** **5 b-g**

R_1-R_2 = $(CH_2)_4$, $(CH_2)_5$, $(CH_2)_6$, $(CH_2)_7$, $(CH_2)_{11}$,

In these reactions, only the ethylenic derivative was isolated. Such a difference in the elimination of nitrous acid between tertiary nitroalkane and nitrocycloalkanes has been already observed[16] and is apparently due to steric hindrance. This behavior should be related to internal strain of ring systems and basicity of cyclic nitronate anions.[17]

In conclusion, these results show that 8-chloromethyl-2,4-dimethyl-9-nitroimidazo[1,2–*a*][1,8] naphthyridine (**2**) is an other *ortho*-like system which is able to react with nitronate anions in good yields to give *C*-alkylation by $S_{RN}1$ mechanism. This reaction is followed by a base-mediated nitrous acid elimination leading to new 2,4-dimethyl-8-alkylidenemethyl-9-nitroimidazo[1,2-*a*][1,8] naphthyridines (**5**) bearing a trisubstituted double bond at the 8-position.

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EXPERIMENTAL

The ^{1}H-nmr spectra were recorded on a Bruker AC 200 MHz spectrometer. Chemical shifts are reported in δ units (ppm) relative to internal TMS. Melting points were determined on a Büchi apparatus and are uncorrected. Thin layer chromatography was performed on precoated aluminium oxide 60 F-254 plates (0.25 mm; E. Merck). Elemental analyses were performed by the Elemental Analysis Center, Faculty of Sciences of St Jérôme, Aix-Marseille University, France.

8-Chloromethyl-2,4-dimethylimidazo[1,2-*a*][1,8]naphthyridine (1).

To 1.76 g (10 mmol) of 5,7-dimethyl-1,8-naphthyridin-2-ylamine dissolved in 100 ml of chloroform was added with stirring 2.54 g (20 mmol) of dichloroacetone and 1.7 g (20 mmol) of sodium bicarbonate. After 24 h refluxing, the mixture was filtered, washed with two portions of 100 ml of water, dried over $MgSO_4$ and evaporated. The residue was purified by chromatography on alumina column eluted with dichloromethane. Recrystallization from methanol gave 1.43 g (58%) as pale yellow needles. mp 195 °C. ^{1}H-Nmr ($CDCl_3$) δ 2.63 (s, 3H); 2.67 (s, 3H); 4.83 (s, 2H); 7.13 (s, 1H); 7.61 (AB, J = 9.5 Hz, 2H); 8.48 (s, 1H). Anal. Calcd for $C_{13}H_{12}N_3Cl$: C, 63.55; H, 4.92; N, 17.10; Cl, 14.43. Found: C, 63.60; H, 4.89; N, 17.21; Cl, 14.40.

8-Chloromethyl-2,4-dimethyl-9-nitroimidazo[1,2-*a*][1,8]naphthyridine (2).

To a cooled (-10 °C) and stirred solution of **1** (1.43 g; 5.85 mmol) in 10 ml of sulfuric acid, 1.6 ml of nitric acid (d = 1.38) was added dropwise. The reaction mixture was stirred at room temperature for 3 h and was poured into water. The solid was collected by filtration and purified by recrystallization from methanol to give 1.36 g (94 %) of yellow needles. mp 148-149 °C. ^{1}H-Nmr($CDCl_3$) δ 2.65 (s, 3H); 2.71 (s, 3H); 4.92 (s, 2H); 7.26 (s, 1H); 7.78 (AB, J = 9.5 Hz, 2H). Anal. Calcd for $C_{13}H_{11}N_4O_2Cl$: C, 53.71; H, 3.81; N, 19.27; Cl, 12.2.

Found: C, 53.79; H, 3.88; N, 19.34; Cl, 12.40.

The lithium salts of 2-nitropropane (**3a**)[18] and nitrocycloalkanes(**3b-g**)[19] were prepared as previously described.

General procedure for $S_{RN}1$ reactions

* Kornblum conditions (Entry 2)

To a solution of 0.40 g (1.38 mmol) of 8-chloromethyl-2,4-dimethyl-9-nitroimidazo[1,2-*a*][1,8]naphthyridine (**2**) in 20 ml of dry DMF, 0.26 g (2.76 mmol) of lithium salt of 2-nitropropane was added under nitrogen and under anhydrous conditions, the solution turning red. The reaction mixture was then irradiated with two 60 W fluorescent lamps from a distance of 10 cm. After stirring at room temperature for 24 h, the reaction mixture was poured into water (200 ml). The aqueous solution was extracted with benzene (3 x 40 ml) and ether (1 x 40 ml). The organic extracts were washed with water (3 x 100 ml), dried over $MgSO_4$ and evaporated under reduced pressure. Purification by chromatography on alumina column eluting with dichloromethane gave :

2,4-Dimethyl-8-(2-methylpropenyl)-9-nitroimidazo[1,2-*a*][1,8]naphthyridine (5a). 0.26 g (65%). R_f 0.93 (dichloromethane), yellow solid, mp 133 °C (methanol). ^{1}H-Nmr($CDCl_3$)δ 1.96 (d, J = 1.0 Hz, 3H); 2.26 (d, J = 1.0 Hz, 3H); 2.56 (s, 3H); 2.59 (s, 3H); 6.54 (t, J = 1.3 Hz, 1H); 7.12 (s, 1H); 7.63 (AB, J = 9.5 Hz, 2H). Anal. Calcd for $C_{16}H_{16}N_4O_2$: C, 55.97; H, 4.99; N, 20.40. Found: C, 55.94; H, 4.92; N, 20.51.

2,4-Dimethyl-8-(2-methyl-2-nitropropyl)-9-nitroimidazo[1,2-*a*][1,8]naphthyridine (4a). 0.15 g (31%). R_f 0.79 (dichloromethane), yellow solid, mp 178 °C (methanol). ^{1}H-Nmr($CDCl_3$)δ 1.67 (s, 6H); 2.57 (s, 3H); 2.61 (s, 3H); 3.58 (s, 2H); 7.16 (s, 1H); 7.65 (AB, J = 9.5 Hz, 2H). Anal. Calcd for $C_{16}H_{17}N_5O_4$: C, 64.86; H, 5.44; N, 18.91. Found: C, 64.94; H, 5.47; N, 18.89.

* Norris conditions (Entry 7)

Under nitrogen atmosphere, an aqueous solution of 40% tetrabutylammonium hydroxide in water (0.26 g, 4.14

mmol) was reacted with 2-nitropropane (0.37 g, 4.14 mmol) for 1 h. A solution of 8-chloromethyl-2,4-dimethyl-9-nitroimidazo[1,2–*a*][1,8]naphthyridine (**2**) (0.40 g, 1.38 mmol) in 20 ml of dichloromethane was added and the mixture was stirred for 24 h under nitrogen and irradiation with fluorescent lamps. The organic layer was separated and the aqueous layer was extracted with three portions of dichloromethane (20 ml). The combined organic layers were removed under reduced pressure. The obtained residue was dissolved in 40 ml of benzene, washed twice with 40 ml of water, dried over $MgSO_4$ and evaporated. The purification already described gave **4a** (0.14 g, 28%) and **5a** (0.24 g, 58%).

Inhibition studies with *p*-dinitrobenzene, cupric chloride and TEMPO were carried out by adding the required amount of *p*-dinitrobenzene, cupric chloride and TEMPO to the reaction mixture immediately prior to the chloride. The study in the dark was obtained by wrapping the flask in aluminium foil. Inhibition study with oxygen was carried out by replacing nitrogen gas by oxygen gas. The results of these respective studies are shown in Table I.

Extension to other nitronate anions was performed by using the procedure of Entry 2.

8-Cyclopentylidenemethyl-2,4-dimethyl-9-nitroimidazo[1,2-*a*][1,8]naphthyridine (5b). 96% yield, yellow solid, mp 205 °C (methanol). ^{1}H-Nmr($CDCl_3$)δ 1.80 (m, 4H); 2.60 (t, J = 6.5 Hz, 2H); 2.64 (s, 3H); 2.67 (s, 3H); 2.97 (t, J = 6.5 Hz, 2H); 6.84 (s, 1H); 7.19 (s, 1H); 7.74 (AB, J = 9.5 Hz, 2H). Anal. Calcd for $C_{18}H_{18}N_4O_2$: C, 67.07; H, 5.63; N, 17.38. Found: C, 67.24; H, 5.79; N, 17.20.

9-Cyclohexylidenemethyl-2,4-dimethyl-9-nitroimidazo[1,2-*a*][1,8]naphthyridine (5c). 97% yield, yellow solid, mp 174 °C (methanol). ^{1}H-Nmr($CDCl_3$) δ 1.64 (m, 6H); 2.35 (t, J = 6 Hz, 2H); 2.60 (s, 3H); 2.63 (s, 3H); 2.99 (t, J = 6.5 Hz, 2H); 6.51 (s, 1H); 7.16 (s, 1H); 7.66 (AB, J = 9.5 Hz, 2H). Anal. Calcd for $C_{19}H_{20}N_4O_2$: C, 67.84; H, 5.99; N, 16,65. Found: C, 67.54; H, 6.15; N, 16.60.

8-Cycloheptylidenemethyl-2,4-dimethyl-9-nitroimidazo[1,2-*a*][1,8]naphthyridine (5d). 73% yield, yellow solid, mp 151°C (methanol). ^{1}H-Nmr($CDCl_3$)δ 1.52 (m, 4H); 1.67 (m, 4H); 2.47 (t, J = 6.2 Hz,

2H); 2.56 (s, 3H); 2.60 (s, 3H); 3.00 (t, J = 6.2 Hz, 2H); 6.56 (s, 1H); 7.12 (s, 1H); 7.66 (AB, J = 9.5 Hz, 2H). Anal. Calcd for $C_{20}H_{22}N_4O_2$: C, 68.55; H, 6.33; N, 15.99. Found: C, 68.50; H, 6.46; N, 15.88.

8-Cyclooctylidenemethyl-2,4-dimethyl-9-nitroimidazo[1,2-*a*][1,8]naphthyridine (5e). 59% yield, yellow solid, mp 158 °C (methanol). ^{1}H-Nmr($CDCl_3$)δ 1.52 (m, 6H); 1.83 (m, 4H); 2.47 (t, J = 6.2 Hz, 2H); 2.63 (s, 3H); 2.67 (s, 3H); 3.00 (t, J = 6.2 Hz, 2H); 6.68 (s, 1H); 7.26 (s, 1H); 7.71 (AB, J = 9.5 Hz, 2H). Anal. Calcd for $C_{21}H_{24}N_4O_2$: C, 69.21; H, 6.64; N, 15.37. Found: C, 69,14; H, 6.70; N, 15.57.

8-Cyclododecylidenemethyl-2,4-dimethyl-9-nitroimidazo[1,2-*a*][1,8]naphthyridine (5f). 64% yield, yellow solid, mp 154 °C (methanol). ^{1}H-Nmr($CDCl_3$)δ 1.23-1.45 (m, 14H); 1.62-1.78 (m, 4H); 2.32 (t, J = 6.8 Hz, 2H); 2.61 (s, 3H); 2.65 (s, 3H); 2.90 (t, J = 6.8 Hz, 2H); 6.63 (s, 1H); 7.17 (s, 1H); 7.68 (AB, J = 9.5 Hz, 2H). Anal. Calcd for $C_{25}H_{32}N_4O_2$: C, 71.40; H, 7.67; N, 13.32. Found: C, 71.44; H, 7.87; N, 13.30.

8-Bicyclo[2.2.1]hept-2-ylidenemethyl-2,4-dimethyl-9-nitroimidazo[1,2-*a*][1,8]naphthyridine (5g). 89% yield, yellow solid, mp 134 °C (methanol). ^{1}H-Nmr($CDCl_3$)δ 1.21-1.87 (m, 6H); 2.54 (br s, 1H); 2.63 (s, 3H); 2.66 (s, 3H); 2.70 (m, 2H); 2.98 (br s, 1H); 6.82 (s, 1H); 7.18 (s, 1H); 7.70 (AB, J = 9.5 Hz, 2H). Anal. Calcd for $C_{20}H_{20}N_4O_2$: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.74; H, 5.89; N, 16.10.

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