Designing New 5-Nitroimidazoles: Towards Safer Anti-infectious Agents

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Dedicated to Dr Pascal GEORGE, President of The French Medicinal Chemistry Society (SCT).

I. Pharmacological value of the nitroimidazole moiety

A. Introduction - Majorities

The story of the nitroimidazole moiety from a pharmacological point of view began in 1953 with the study of a strain of *Nocardia mesenterica* from which the 2-nitroimidazole, called Azomycine, was extracted by Japanese researchers Maeda, Osato, Umezawa[1].This compound was studied in 1955 by Nakamura who determined its chemical structure[2] (Fig. **1**).

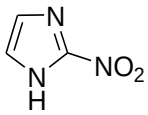


Fig. (1).2-Nitroimidazole (AZOMYCINE®)

In 1956, both Horie [3] and Despois *et al.*[4] separately described the activity of azomycine on certain protozoa, especially *Trichomonas vaginalis*.

Today, the nitroimidazoles include a series of active substances useful in various fields, the position of the nitro group on the imidazole moiety defining their range of activity.2-Nitroimidazoles, especially benznidazole (RADANIL®) (Fig. **2**), are known for their biological activity on *Trypanosoma cruzi*, [5] an agent of Chagas disease, and can also be of value in cancer research [6].

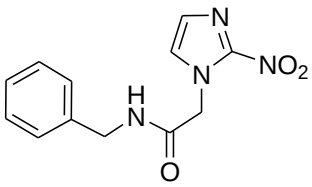


Fig. (2). Benznidazole (RADANIL®)

4-Nitroimidazoles such as azathioprine (IMUREL®) (Fig. **3**), because of their immunosuppressive activity, are generally used to prevent rejection of transplanted organs and to treat autoimmune diseases[7]. They also

showed an activity on the parasite agent of Chagas disease, *Trypanosoma cruzi*, in recent studies performed under the DNDi (Drug for Neglected Diseases initiative)[8].

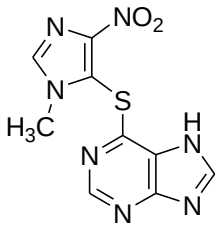
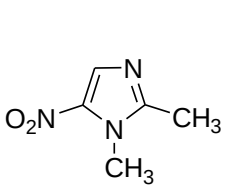
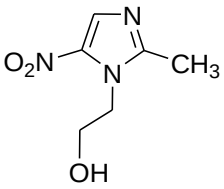


Fig. (3). Azathioprine (IMUREL®)

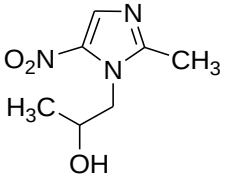
5-Nitroimidazoles are mainly known for their anti-infectious activity[9-13].Today, there are many medical applications for compounds containing the nitroimidazole moiety such as metronidazole (Fig. **4**), which is the compound most widely used.



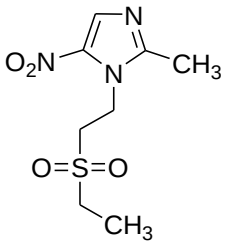
Dimetridazole
(EMTRYL®)



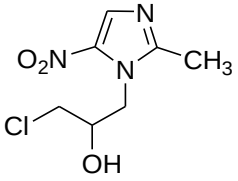
Metronidazole
(FLAGYL®)



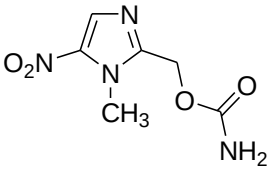
Secnidazole
(SECNOL®)



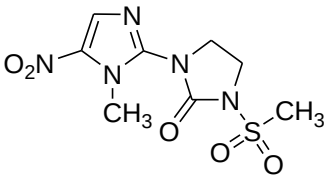
Tinidazole
(FASIGYNE®)



Ornidazole
(TIBERAL®)



Ronidazole
(TRICHOREX®)



Satranidazole
(SATROGYL®)

Fig. (4). Most widely used 5-nitroimidazoles

The 5-nitroimidazole family, which has been the subject of decades of study, offers numerous pharmacological properties that make the compounds presented in the following sections suitable for a wide range of uses.

A.1. Antiparasitic properties

The main target parasites of nitroimidazole compounds are *Entamœba histolytica*, *Giardia intestinalis*, *Balantidium coli* and *Trichomonas vaginalis*[14].*Trichomonas vaginalis*, a flagellate protozoan, is responsible for 30% of non-gonococcal urethritis and for 50% of vaginitis with leukorrhea. The first patent for compounds having an anti-trichomonas activity was filed by the researchers of Rhône-Poulenc [15] in 1957, and the first synthesis of nitroimidazoles resulting from the study of biological activities appeared in 1966[16].These authors

found that 4(5)-nitroimidazole (Fig.**5**)possessed an anti-trichomonas activity close to that of 2-nitroimidazole, but that its toxicity was approximately 10 times weaker.

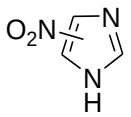


Fig. (5).4(5)-Nitroimidazole

This led to further studies on the 5-nitroimidazole moiety. Indeed, in 1970, Pfizer Inc.[17] demonstrated on the mouse that an electron-withdrawing group like sulfoneat the 1-position strengthened the anti-trichomonas activity in 5-nitroimidazole seriesas reported in tinidazole (Fig.**4**).

Also, Hoffer and Grunberg[18] substituted the 5-nitroimidazole moiety at the 1-position with alkyl chains possessing three carbonsas reported in ornidazole (Fig. **4**). The resulting compounds showed good levels of activity against *Trichomonas vaginalis, Trichomonas fœtus* and *Entamœba histolytica*.

The study on the structure-activity relationship realized by McCowen[19] showed that the presence of an ethylene double bond at the 2-position of the 5-nitromidazole moiety was essential to antiparasitic activity, in particular on *Trypanosoma sp.*, *Entamœba histolytica* and *Trichomonas vaginalis*Fig. (**6**).

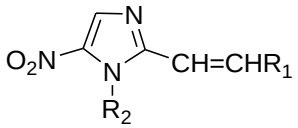


Fig. (6). Ethylene bond at the 2-position

While 5-nitroimidazole moieties have not been proved to have mutagenic activity on the human[20],certain studies revealed their mutagenic activity on prokaryotic cells[21-24].In a study concerning the influence of substituents on the activity and the mutagenicity of 5-nitroimidazoles, Walsh *et al.* demonstrated in 1987 that it was possible to considerably decrease the mutagenicity of these compounds, while conserving a comparable anti-trichomonas activity for ronidazole or metronidazole, the reference molecules, by incorporating substituents at the 4-position, like 2-(1,2-dimethyl-5-nitro-1*H*-imidazol-4-yl)ethanol (Fig. **7**). Indeed, this compound possessed an anti-trichomonas activity (IC_{50} = 10.8 µM) close to those of ronidazole and metronidazole (IC_{50} = 2.33 µM), while showing only 4% of the mutagenicity of metronidazole and 0.28% of the mutagenicity of ronidazole.

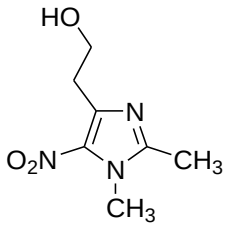
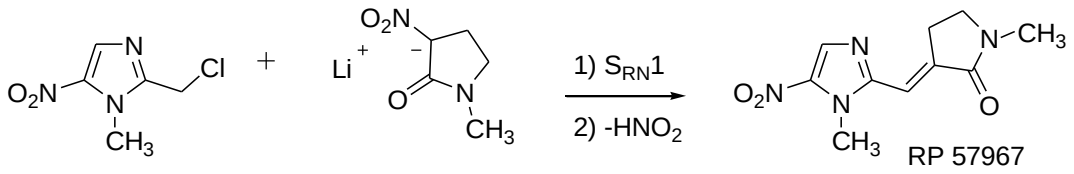


Fig. (7).2-(1,2-Dimethyl-5-nitro-1*H*-imidazol-4-yl)ethanol

Focusing our attention on 5-nitroimidazoles and their reactivity towards $S_{RN}1$,our group was able to synthesize the pyrrolidine derivative RP 57967, which has proved to be particularly active on *Trichomonas vaginalis* and *Entamœba histolytica*[25-27].The 1-methyl-3-[(1-methyl-5-nitro-1*H*-imidazol-2-yl)methylene]pyrrolidin-2-one RP 57967 is very active on anaerobic bacteria, more active than metronidazole and dimetridazole. This molecule was prepared by $S_{RN}1$ reaction of 2-chloromethyl-1-methyl-5-nitro-1*H*-imidazole with 1-methyl-3-nitropyrrolidin-2-one lithium salt, followed by elimination of nitrous acid (Scheme **1**).



Scheme 1. Synthesis of RP 57967 compound

Extending this research focus, the study of 2-cycloheptylidenemethyl-1-methyl-5-nitro-1*H*-imidazole (Fig. **8**)showed a better activity on anaerobic bacteria than metronidazole with an IC_{50} of 0.24 mg/kg on *Clostridium perfringens* as compared to 0.48 mg/kg for metronidazole[28].

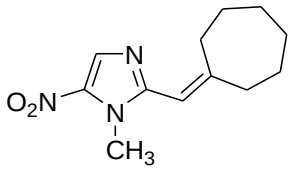


Fig. (8). 2-(Cycloheptylidenemethyl)-1-methyl-5-nitro-1*H*-imidazole

The same study also showed an amœbicidal activity and anti-trichomonas activity of (*E*)-2-(bicyclo[2.2.1]heptan-2-ylidenemethyl)-1-methyl-5-nitro-1*H*-imidazole (Fig. **9**)that was higher than that of metronidazole. Indeed, this product was 4 times as active on *Trichomonas vaginalis* (IC_{50} = 0.5 µg/mL) as metronidazole (IC_{50} = 2 µg/mL), and as active on *Trichomonas fœtus* as metronidazole (the IC_{50} for both molecules being 3 µg/mL).

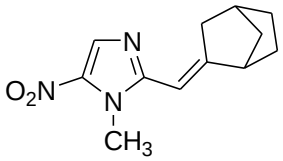


Fig. (9). (*E*)-2-(Bicyclo[2.2.1]heptan-2-ylidenemethyl)-1-methyl-5-nitro-1*H*-imidazole

The 1992 studies of mutagenicity on 48 compounds *via* Ames tests and SOS chromotests showed strong mutagenicity for the tested products, in particular the RP 57967 molecule with an 1-methyl-2-pyrrolydinone-3-ylidenemethyl group at the 2-position, which considerably increased the mutagenicity of the molecule compared to metronidazole[29].

In 2006, our team showed that there was good activity on *Giardia intestinalis* and metronidazole-resistant-*Trichomonas vaginalis* strains by (*E*)-ethyl 2-methyl-3-{4-[2-(1-methyl-5-nitro-1*H*-imidazol-2-yl)vinyl]phenyl}-2-nitropropanoate (Fig. **10**) [30].This product, resulting from an LD-$S_{RN}1$ study (Long Distance – $S_{RN}1$), presented an IC_{50} of 1 µM compared to 50 µM for metronidazole.

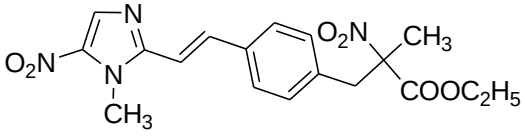


Fig. (10). (*E*)-Ethyl 2-methyl-3-{4-[2-(1-methyl-5-nitro-1*H*-imidazol-2-yl)vinyl]phenyl}-2-nitropropanoate

This study also showed an anti-trichomonas activity for 5 other products whose IC_{50} ranged from 25 to 50 µM (Fig. **11**).

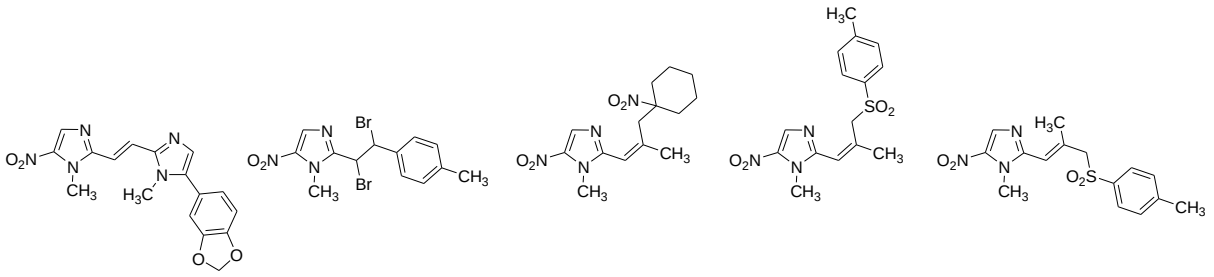


Fig. (11). IC_{50} ranged from 25 to 50 µM in 5-nitroimidazole series

More recently, our team tested the anti-trichomonas activity (TV87 strain), the toxicity on a THP1 human cell strain and the mutagenicity (assay of mutagenicity on *Salmonella typhimurium*) of 24 products substituted by arylsulfonylmethyl groups in 4-position (Fig. **12**).

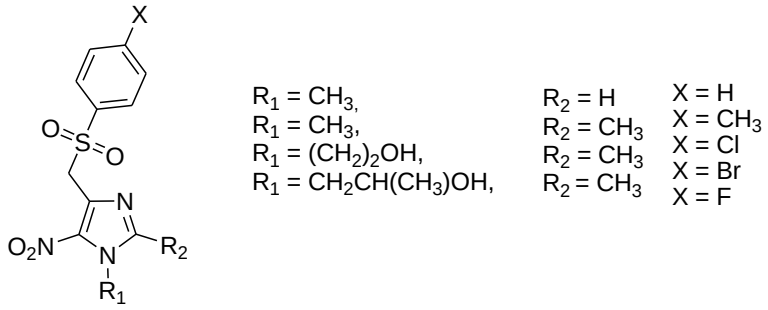


Fig. (12).24 products substituted by arylsulfonylmethyl groups in 4-position

This study showed that the 24 tested molecules presented an anti-trichomonas activity with IC_{50} ranging from 0.044 µM (R_1 = $(CH_2)_2OH$ R_2 = CH_3 X = Cl) to 2.746 µM (metronidazole). In this series of molecules, 21 possessed a higher anti-trichomonas activity than metronidazole, and two possessed a similar activity. Fifteen molecules showed no toxicity on THP1 human cells, and the mutagenicity assay on *Salmonella* showed that the mutagenicity of these products decreased when they were concomitantly substituted by an arylsulfonylmethyl group at the 4-position and by a methyl group at the 2-position. The molecule which proved the most interesting was 2-{4-[(4-chlorophenylsulfonyl)methyl]-2-methyl-5-nitro-1*H*-imidazol-1-yl}ethanol (R_1 = $(CH_2)_2OH$ R_2 = CH_3 X = Cl), with the best IC_{50}, and a specificity index (ratio between the IC_{50} of the human cells and the IC_{50} of the parasites) of 13136[31].

In addition to the anti-trichomonas activity widely exploited within our laboratory, 5-nitroimidazole moieties present antiparasitic activities on other species which are the object of numerous studies. For example, Dunn *et al.* recently studied metronidazole-resistant strains of *Blastocystissp.*, a unicellular protozoan causing intestinal disorders such as diarrhea, nausea, vomiting, constipation, intestinal pains, ranging from moderate to severe[32].These studies examined the mechanism of action as well as the resistance mechanisms of these strains in relation to existing treatments.

Finally, 1-methyl-2-{[4-methylthio)phenoxy]methyl}-5-nitro-1*H*-imidazole, more commonly known under the name of fexinidazole (Fig. **13**), was recently the object of numerous studies on *Trypanosoma bruceigambiense* and *Trypanosoma brucei rhodesiense*[33],leading to phase I studies in 2009 which will soon culminate in phase II/III studies.

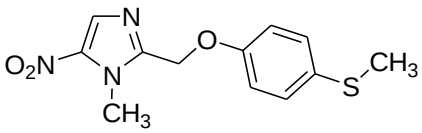


Fig. (13). Fexinidazole

As well as their antiparasitic activity, 5-nitroimidazoles moieties present various biological properties making them useful in a variety of fields.

A.2. Antibacterial properties

5-Nitroimidazole moieties possess original antibacterial activity against anaerobic bacteria[34].They have bactericidal activity against anaerobic Gram-negative bacilli (*Bacteroides*, *Fusobacterium*), anaerobic non-sporulating Gram-positive bacilli such as *Clostridium difficile*, responsible for pseudomembranous colitis and for nosocomial diarrheas in immunocompromised patients or patients under postoperative antibiotic treatment, and against *Gardnerella vaginalis*. The sensitivity of the anaerobic Gram-negative cocci (*Veillonella*) and Gram-positive cocci (*Peptococcus*, *Peptostreptococcus*) is unpredictable, and anaerobic non-sporulating Gram-positive bacilli are naturally resistant (*Actinomyces*, *Propionibacterium*). Used in association, nitroimidazoles are indicated to eradicate *Helicobacter pylori* involved in gastroduodenal ulcers.

A.3. Radiosensitization properties

During radiation therapy, radicals are created from oxygen. Many tumor cells are hypoxic and therefore have reduced sensitivity to radiation. For the treatment by radiotherapy of certain brain tumors in particular, it is useful to decrease hypoxic resistance. 5-Nitroimidazoles simulate oxygen, according to their electron affinity (oxygen effect)[35, 36], allowing normally resistant cells to be recruited to radiation.

A.4. Limitations to use: Resistance to treatment

Little is known about the mechanism of resistance to this type of compound. However, since the activity of 5-nitroimidazoles very probably depends on their reduction by enzymes acting as nitroreductases, such as pyruvate ferredoxin oxidoreductase[35, 36], a decrease in the activity of these enzymes may well explain resistance to these compounds[39].

Thus, Leitsch *et al.* who propose thioredoxin reductase as the principal means of activation of metronidazole, suggest that resistance to these compounds is linked to the activity of this enzyme[40, 41].

Rasoloson *et al.* show that the malic enzyme, present in hydrogenosome, is involved in the reduction of metronidazole and thus in the resistance of the strains concerned[42].

Finally, Pal *et al.* reveal alternative mechanisms of resistance, by means of other nitroreductase enzymes and the production by the treated parasites of nim genes similar to those present in anaerobic bacteria strains such as 5-nitroimidazole-resistant *Bacteroides fragilis*[43].

Some studies also suggest the mechanism of the efflux pump by proteins of the TolC family in bacteria like *Helicobacter pylori*[44].

Given that these molecules have been on the market for a long time, with the emergence of resistance to treatment leading to dose intensification and thus adverse drug reactions, and in view of the inherent mutagenicity of this compound family, we directed our research towards the synthesis of 5-nitroimidazole derivatives with the aim of avoiding these adverse drug reactions and decreasing mutagenicity, while at the same time contributing to a better understanding of their mechanism of action.

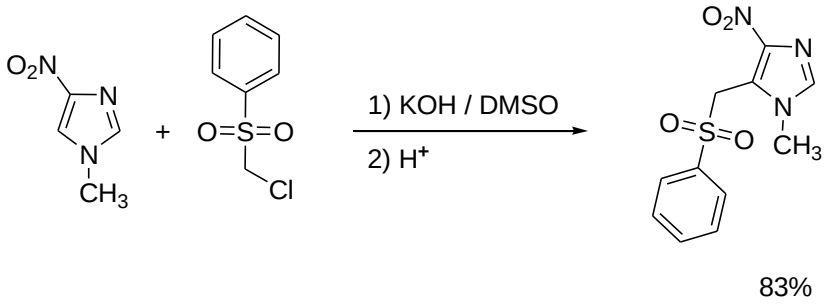
II. Vicarious Nucleophilic Substitution of hydrogen in 5-nitro-imidazole series.

While numerous examples of the VNS reaction are described from benzene and naphthalene derivatives and the nitrogenous analogues (pyridine, quinoline, acridine, and 1,2,4-triazine)[45-47],Makosza showed that

this reaction was also possible with 5-membered nitrated monoheteroaromatic systems such as thiophene, furan or pyrrole[48].

Makosza also showed that the imidazole nucleus was sensitive to the nucleophilic movement of hydrogen according to the VNS reaction scheme, provided that it contains a nitro group as substituent[49]. As in strongly basic medium, nitro-1*H*-imidazoles are converted in corresponding inactive form for nucleophilic additions, successful realization of a VNS reaction requires imidazole derivatives substituted at the 1-position.

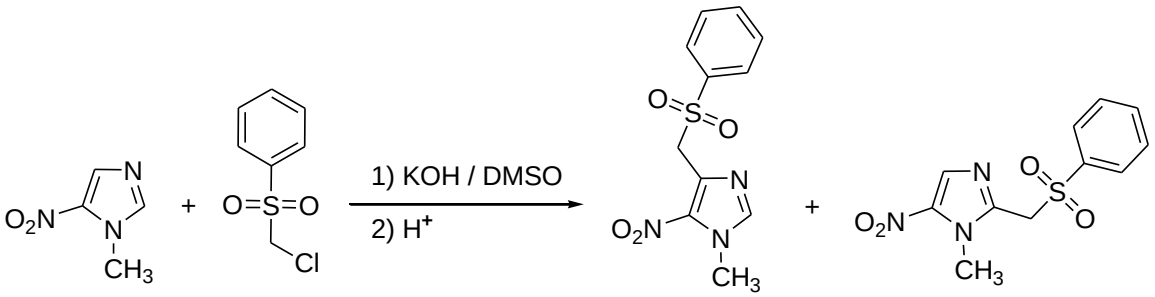
1-Methyl-4-nitro-1*H*-imidazole reacts with chloromethylphenylsulfone in the presence of potassium hydroxide in the DMSO, leading to one single product: 1-methyl-4-nitro-5-phenylsulfonylmethyl-1*H*-imidazole. Only position 5 is then activated by the nitro group (Scheme **2**).



83%

Scheme 2.VNS reactivity between 1-methyl-4-nitro-1*H*-imidazole and chloromethylphenylsulfone.

When the nitro group occupies the 5-position, as in the case of 1-methyl-5-nitro-1*H*-imidazole, two atoms of carbon are then likely to undergo a nucleophilic attack (carbons C-2 and C-4), potentially leading to either of two products of the VNS reaction. Makosza described the formation of both possible isomers during the VNS reaction between chloromethylphenylsulfone and 1-methyl-5-nitro-1*H*-imidazole, the isomer at the 4-position being always the major product (4-position /2-position = 4.8) (Scheme**3**)[49].



63% 13%

Scheme 3.VNS reactivity between 1-methyl-5-nitro-1*H*-imidazole and chloromethylphenylsulfone.

Finally, Makosza showed that this VNS reaction did not apply to imidazole derivatives without any electron-withdrawing group. Thus, neither 1-methyl-1*H*-imidazole nor 1,2-dimethyl-1*H*-imidazole react through a VNS reaction with chloromethylphenylsulfone, although there are some examples of reactions between halogenated derivatives of imidazoles not carrying an additional withdrawing group and nucleophilic agents*via* an S_NAr mechanism[50].

Having presented the synthesis of five different chloromethylsulfones, we studied their reactivity *via* VNS reactions with the following 5-nitroimidazoles (Fig. **14**):

- 1-methyl-5-nitro-1*H*-imidazole **1**
- 1,2-dimethyl-5-nitro-1*H*-imidazole or dimetridazole **2**

- 2-(2-methyl-5-nitro-1*H*-imidazol-1-yl)ethanol or metronidazole **3**
- 1-(2-methyl-5-nitro-1*H*-imidazol-1-yl)propan-2-ol or secnidazole **4**

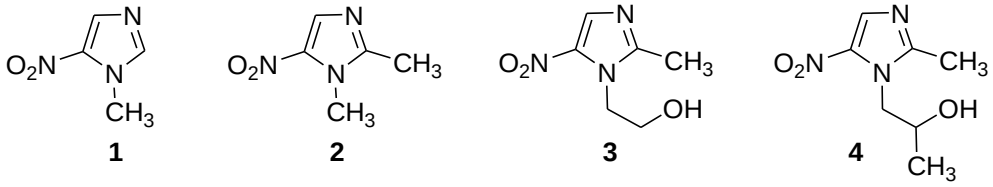


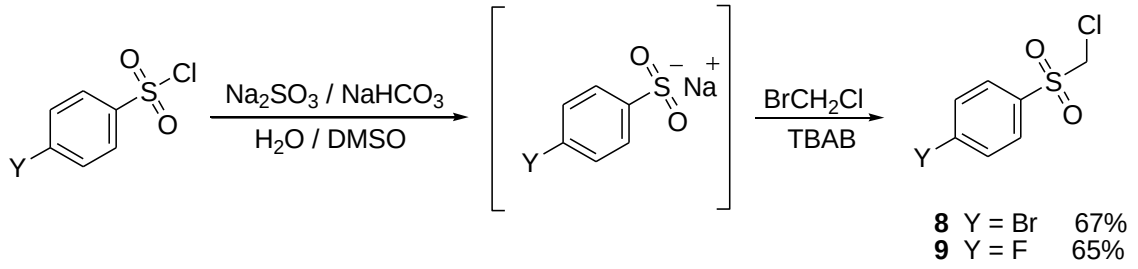
Fig. (14). Starting materials in 5-nitroimidazole series.

II.1. Synthesis of sulfonyl derivatives

To synthesize the precursory chloromethylarylsulfones from VNS reactions, we based our approach on the work of Makosza. From the commercial sodium arylsulfinates, chloromethylarylsulfones **5-7** were obtained by addition of 15 equiv. of bromochloromethane in the DMSO at 58 °C for 6 h[51],with respective yields of 63%, 53% and 47% (Scheme **4**)[52].

Scheme 4. Synthesis of chloromethylarylsulfones **5-7**.

Sodium 4-bromobenzenesulfinate and sodium 4-fluorobenzenesulfinate not being commercially available, we were inspired by the method described by Antane [53] to synthesize 1-bromo-4-chloromethylsulfonylbenzene **8** and 1-fluoro-4-chloromethylsulfonylbenzene **9**. Thus, 4-bromobenzenesulfonyl chloride and 4-fluorobenzenesulfonyl chloride reacted with sodium sulfite and sodium hydrogenocarbonate in a refluxing water-DMSO mixture for 2 h. After obtaining non-isolated sodium intermediate salts, bromochloromethane in excess with tetrabutylammonium bromide in catalytic quantity were added *in situ*, leading after 8 h at 75 °C to 1-bromo-4-(chloromethyl)sulfonylbenzene **8** [52] and 1-fluoro-4-(chloromethyl)sulfonylbenzene **9** in respective yields of 67% and 65% (Scheme **5**).

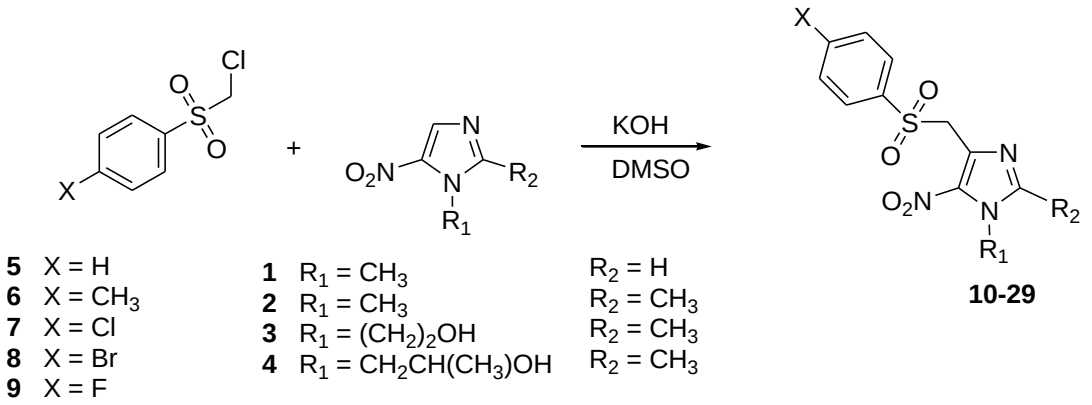


Scheme 5. Synthesis of chloromethylarylsulfones **8-9**.

II.2. Synthesis of 5-nitromidazole derivatives *via* VNS reaction

Following in the footsteps of Makosza, we performed reactions of various imidazoles with chloromethylarylsulfones **5-9** in the presence of 5 equivalents of potassium hydroxide finely crushed in DMSO

for 10 min[54].Thus, we synthesized 20 new compounds (**10-29**) with yields varying from 20 to 69% (Scheme **6**).



Scheme 6. Synthesis of 4-arylsulfonylmethyl derivatives *via* VNS reaction.

The results of these reactions are summarized in Table **1**.

Table 1.Preparation of 1,2-Dialkyl-4-arylsulfonylmethyl-5-nitro-1*H*-imidazoles and 4-Arylsulfonyl-methyl-1-methyl-5-nitro-1*H*-imidazoles[a].

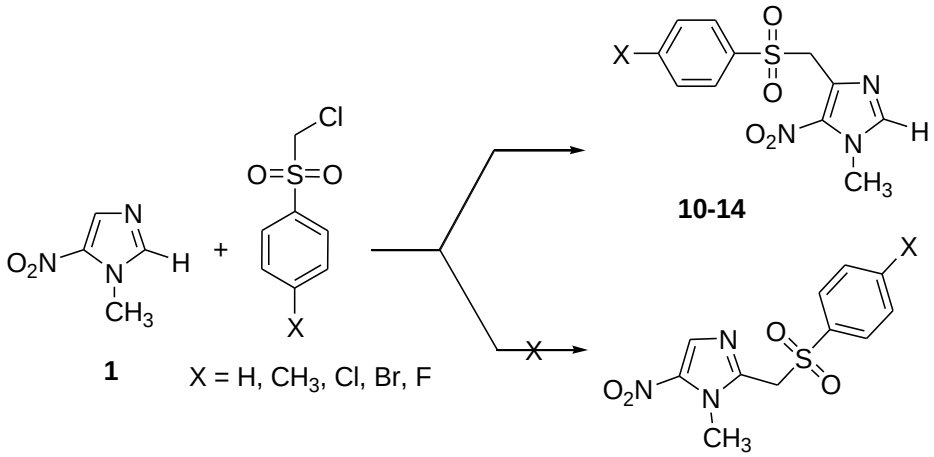
Synthesized compounds *via* VNS			Compound number	Yield (%)[b]
X	R_1	R_2		
H	CH_3	H	**10**	55
CH_3	CH_3	H	**11**	29
Cl	CH_3	H	**12**	42
Br	CH_3	H	**13**	57
F	CH_3	H	**14**	54
H	CH_3	CH_3	**15**	28
CH_3	CH_3	CH_3	**16**	20
Cl	CH_3	CH_3	**17**	49
Br	CH_3	CH_3	**18**	53
F	CH_3	CH_3	**19**	40
H	$(CH_2)_2OH$	CH_3	**20**	24
CH_3	$(CH_2)_2OH$	CH_3	**21**	24

Cl	$(CH_2)_2OH$	CH_3	**22**	41
Br	$(CH_2)_2OH$	CH_3	**23**	51
F	$(CH_2)_2OH$	CH_3	**24**	20
H	$CH_2CH(CH_3)OH$	CH_3	**25**	37
CH_3	$CH_2CH(CH_3)OH$	CH_3	**26**	37
Cl	$CH_2CH(CH_3)OH$	CH_3	**27**	51
Br	$CH_2CH(CH_3)OH$	CH_3	**28**	69
F	$CH_2CH(CH_3)OH$	CH_3	**29**	17

[a] All reactions follow the same procedure: KOH (5 equiv.), 1,2-dialkyl-5-nitro-1*H*-imidazole (1 equiv.) or 1-methyl-5-nitro-1*H*-imidazole (1 equiv.), chloromethylarylsulfone (1 equiv.), DMSO.

[b] Yields are calculated compared with **1, 2, 3** or **4**, on the isolated products by silicagel column chromatography and by recrystallization.

During the reaction between 1-methyl-5-nitro-1*H*-imidazole **1** and chloromethylsulfones **5-9**, we expected to obtain a mixture of substituted compounds at the 2-position and at the 4-position, positions which in theory promote VNS reactions according to the results of Makosza[54].



Scheme 7. Formation of 5-nitroimidazole derivatives in 4-position.

Here, however, only compounds **10-14** substituted at the 4-position were isolated (Scheme **7**), as confirmed by X-ray analysis of 1-methyl-5-nitro-4-phenylsulfonylmethyl-1*H*-imidazole **10**(Fig.**15**). The other structures were assigned by analogy and spectral comparison.

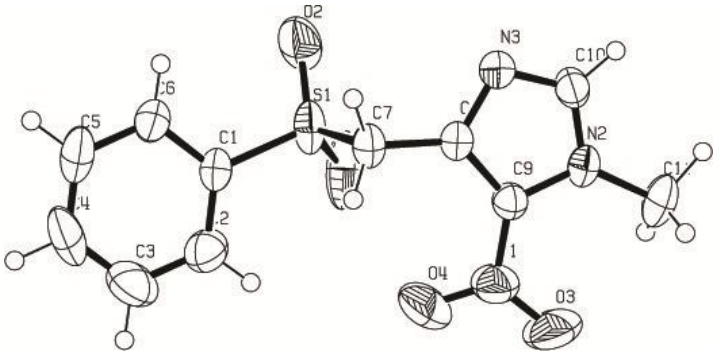


Fig. (15).ORTEP structure of 1-methyl-5-nitro-4-(phenylsulfonylmethyl)-1*H*-imidazole **10**.

II.3. Biological evaluation

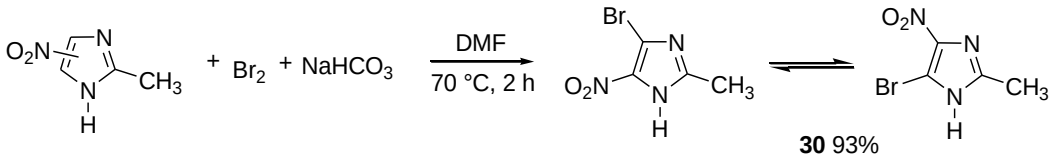
13 of the compounds tested showed a better activity than metronidazole on *Trichomonas vaginalis*, and 5 have an index of selectivity better than those of both reference products: products **10**, **11**, **15**, **22** and **26**. The best result is obtained with compound **22**, which has a remarkable index of selectivity of 13005, compared to 531.95 for metronidazole. This compound possesses an antiparasitic activity 20.4 times greater than that of metronidazole and 4.35 times greater than that of dimetridazole[31].

The incorporation of an arylmethylsulfone substituent at the 4-position of 5-nitroimidazole seems to promote antiparasitic activity.

III. Palladium-catalyzed cross-coupling in 5-nitroimidazole series.

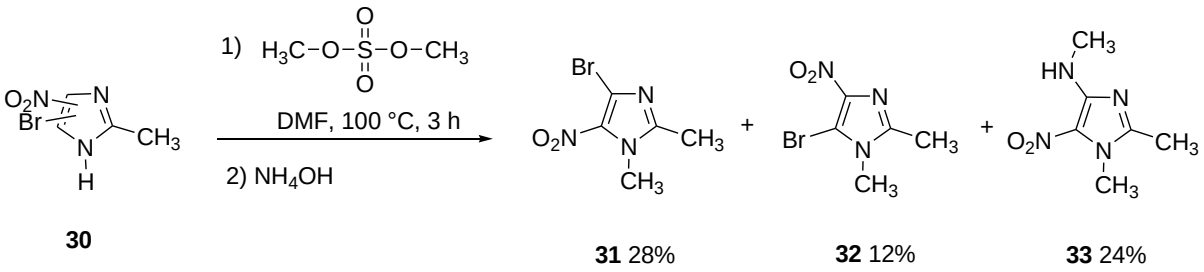
III.A. Suzuki-Miyaura cross-coupling in 4-bromo-1,2-dimethyl-5-nitro-1*H*-imidazole series

We extended our research by focusing on how heating contributes to the Suzuki-Miyaura cross-coupling under microwave irradiation. The required starting material for the Suzuki-Miyaura cross-coupling reaction is 4-bromo-1,2-dimethyl-5-nitro-1*H*-imidazole **31**. Unfortunately, it is impossible to obtain this compound in good yields, directly from the "direct" non-halogenated precursor (dimetridazole or 1,2-dimethyl-5-nitro-1*H*-imidazole). Sunjic *et al.*[55] noted that the reaction of direct bromination of 1-alkyl-2-methyl-5-nitro-1*H*-imidazole is not possible because of the poor reactivity of the 4-position towards the electrophilic substitution reactions. We therefore decided to brominate the 2-methyl-4(5)-nitro-1*H*-imidazole as proposed by Bhujanga Rao *et al.*[56] with the dibrome (1.1 equiv.) in DMF (Scheme **8**).



Scheme 8. Synthesis of 4(5)-bromo-2-methyl-5(4)-nitroimidazole **30**.

4(5)-Bromo-2-methyl-5(4)-nitro-1*H*-imidazole was methylated by dimethylsulfate (DMS), following the procedure proposed by Sunjic *et al.*(Scheme **9**)[53]. Furthermore, during the treatment by ammoniac solution, the product **33** was obtained in 24% yield.

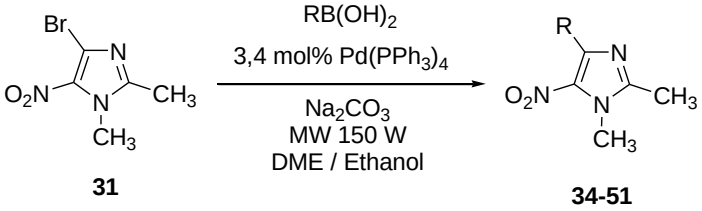


Schema 9. Synthesis of required starting material **31**.

The first Suzuki-Miyaura cross-coupling assay was performed under the following experimental conditions: 10 mol % of $Pd(PPh_3)_4$ (as catalyst), 5 equiv. of Na_2CO_3 (as base), 1.3 equiv. of arylboronic acid derivative and 1 equiv. of tetrabutylammonium bromide (TBAB) in water, under microwave irradiation [57].

Unfortunately, these experimental conditions were not generalizable to 4-bromo-1,2-dimethyl-5-nitro-1*H*-imidazole. Various experimental conditions of cross-coupling reactions were thus tested, to study their influence on reactivity. All the assays were conducted with 4-bromo-1,2-dimethyl-5-nitro-1*H*-imidazole **31** and phenylboronic acid, in a multimode synthesis microwave oven (ETHOS Synth Lab Station) or by the classic heating method.

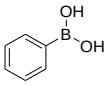
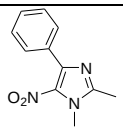
Six reaction parameters were tested (number of equiv. of arylboronic acid, nature of solvent, nature of base, catalyst species, phase transfer agent, heating method). As a result, the best microwave-assisted experimental conditions were defined, allowing the synthesis of 1,2-dimethyl-5-nitro-4-phenyl-1*H*-imidazole **34** in 93% yield in 1 h. To prepare compound **34**, 4-bromo-1,2-dimethyl-5-nitro-1*H*-imidazole **31** and 0.034 equiv. of $Pd(PPh_3)_4$ were dissolved in 1,2-dimethoxyethane (DME) and were mixed for 1 h. A solution of phenylboronic acid in ethanol and 3 equiv. of Na_2CO_3 were added. Finally, the mixture was heated under microwave irradiation (150 W) (Scheme **10**).

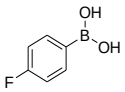
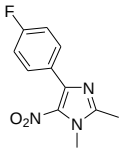
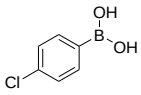
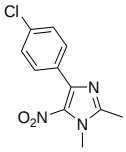
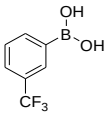
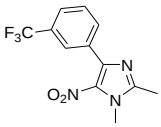
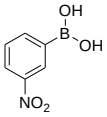
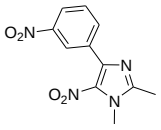
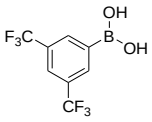
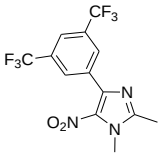
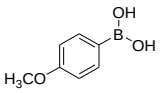
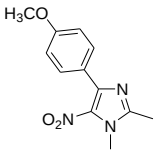
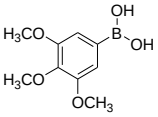
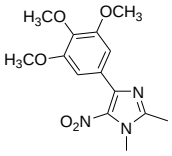
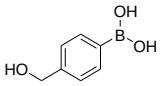
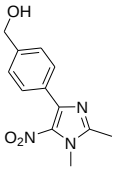
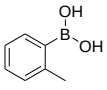
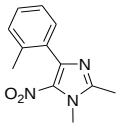


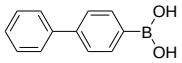
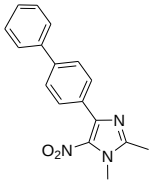
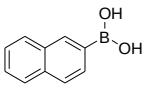
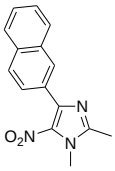
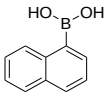
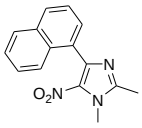
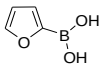
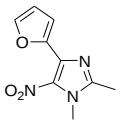
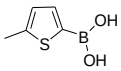
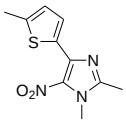
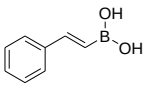
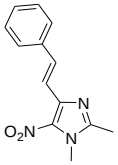
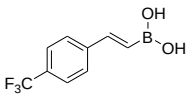
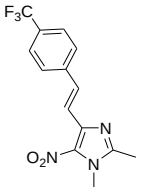
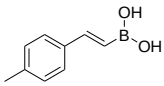
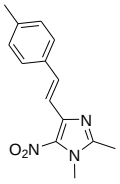
Scheme 10. Microwave-assisted palladium-catalyzed Suzuki-Miyaura cross-coupling reactions of compound **31** with different aryl, heteroaryl ou styrylboronic acids using $Pd(PPh_3)_4$.

To estimate the scope and limitations of this procedure, we performed cross-coupling reactions with 18 variously substituted boronic acid derivatives. The results show that this cross-coupling reaction is applicable to all the aryl, heteroaryl and styrylboronic acids used in our study(Table **2**) [58].

Table 2.Products and Yields of Microwave-Assisted Palladium-Catalyzed Suzuki-Miyaura Cross-Coupling Reactions of Compound 31 with Different Aryl, Heteroaryl orStyrylboronic acids using $Pd(PPh_3)_4$.

Entry	Boronic acid	Product	Compound number	*t* (h)	Yield %
1			**34**	1	93

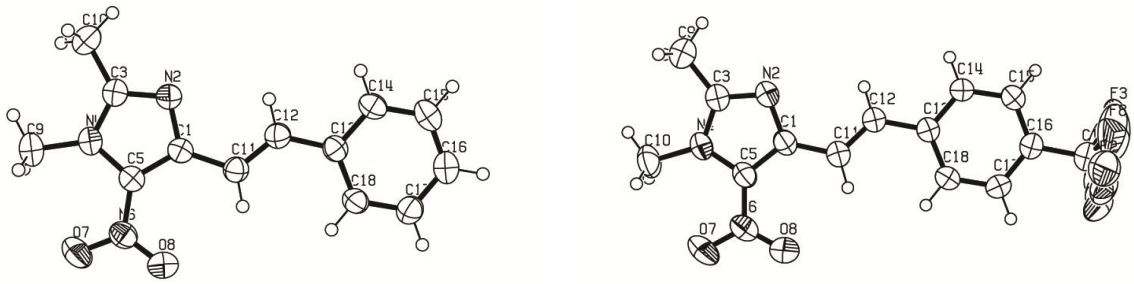
2			**35**	1	93
3			**36**	1	71
4			**37**	1	68
5			**38**	3	80
6			**39**	2	98
7			**40**	1	89
8			**41**	1	91
9			**42**	1	87
10			**43**	1	95

11			**44**	1	78
12			**45**	2	86
13			**46**	2	66
14			**47**	2	87
15			**48**	2	60
16			**49**	1	63
17			**50**	1	95
18			**51**	1	91

Conditions: $Pd(PPh_3)_4$ 3.4 mol%, 4-bromo-1,2-dimethyl-5-nitro-1*H*-imidazole (1 equiv.), arylboronic acid (1.03 equiv.) or heteroarylboronic acid (1.03 equiv.) or (*E*)-styrylboronic acid (1.03 equiv.), Na_2CO_3 (3 equiv.), DME/Ethanol. An initial microwave irradiation of 150 W was used, being increased from ambient temperature to 75 °C and then maintained for time *t*.

Under these experimental conditions we synthesized, by reaction with (*E*)-styrylboronic acid, (*E*)-4-(trifluoromethyl)styrylboronic acid and (*E*)-4-methylstyrylboronic acid, compounds **49**-**51** in good yields (Table **2**, entries 16-18). This method constitutes a valuable alternative to the Heck reaction. Indeed, to the best of our knowledge, there is only one description in the literature of the Heck reaction on 4-bromo-1,2-dimethyl-5-nitro-

1*H*-imidazole**31**. Furthermore, the reaction is 100% stereoselective. X-ray structure analysis of a crystal of compounds **49** and **50** confirmed the presence of *E*-isomer alone (Fig.**16**).



49 **50**

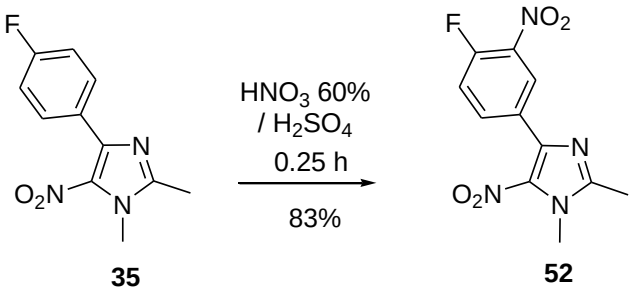
Fig.(16). ORTEP structures of (*E*)-1,2-dimethyl-5-nitro-4-styryl-1*H*-imidazole (**49**) and (*E*)-1,2-dimethyl-5-nitro-4-[4-(trifluoromethyl)styryl]-1*H*-imidazole (**50**).

III.B. Palladium-catalyzed *O*-arylation in 4-(4-fluoro-3-nitrophenyl)-1,2-dimethyl-5-nitro-1*H*-imidazole series

During the course of our research on the chemistry of new safer antiprotozoal [59] agents in 5-nitroimidazole series[25, 27, 28, 30-32, 39, 52, 60-64], we observed what appeared to be palladium-catalyzed *O*-arylation of an aryl fluoride.

The development of mild conditions for the synthesis of diaryl ethers has attracted considerable attention, mainly due to their biological activity[64-71].Reactions used to generate aryl ethers appear in the literature, e.g. the Cu-promoted arylation of alcohol derivatives with phenylboronic acids known as Chan-Lam coupling[72-74],the Cu-mediated Ullmann condensation[75-78] of phenols with aryl halides and the Buchwald's palladium-catalyzed C-O coupling[79-82] of phenols with aryl halides. However, to the best of our knowledge, no example of diaryl ether synthesis using arylboronic acid and aryl halides under the catalytic effects of palladium species has ever been described.

The required starting material was obtained by nitration using a mixture of HNO_3 60%/H_2SO_4 of compound **35** (Scheme **11**).

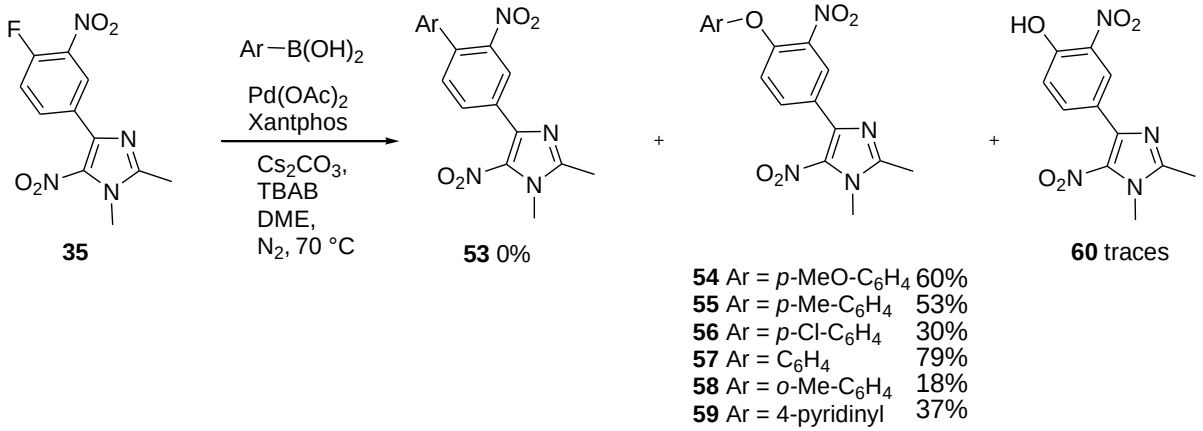


35 **52**

Scheme 11. Preparation of starting material **52**.

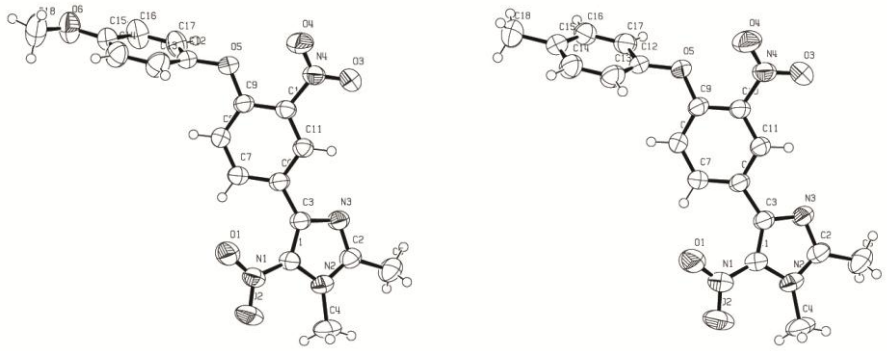
Compound **52**, reacted with 4-methoxyphenylboronic acid in classical Suzuki-Miyaura reaction conditions using $Pd(OAc)_2$/xantphos catalyst, Cs_2CO_3 under inert atmosphere in DME at 70 °C in the presence of tetrabutylammonium bromide (TBAB), gave unexpected methoxyphenoxy derivative **54** in 60% yield, and traces of nitrophenol derivative **60** instead of the expected C-C coupled derivative **53**. Adding 10 equiv. of water to the same reaction medium afforded compound **54** in similar yields (51% *vs* 60% without addition of water).

Thus, the formation of compound **60** could result from an S_NAr reaction between compound **35** and either carbonate or hydroxide anion as oxygen sources. Then, this reactivity was confirmed with other boronic acids, giving *O*-arylated compounds **55**-**59** in 30 to 79% yields (Scheme **12**).



Scheme 12. Reaction of **35** and boronic acids.

X-Ray spectroscopyof **54** and **55** (Fig.**17**) and HRMS spectrum of these four compounds confirmed the C-O bond formation.



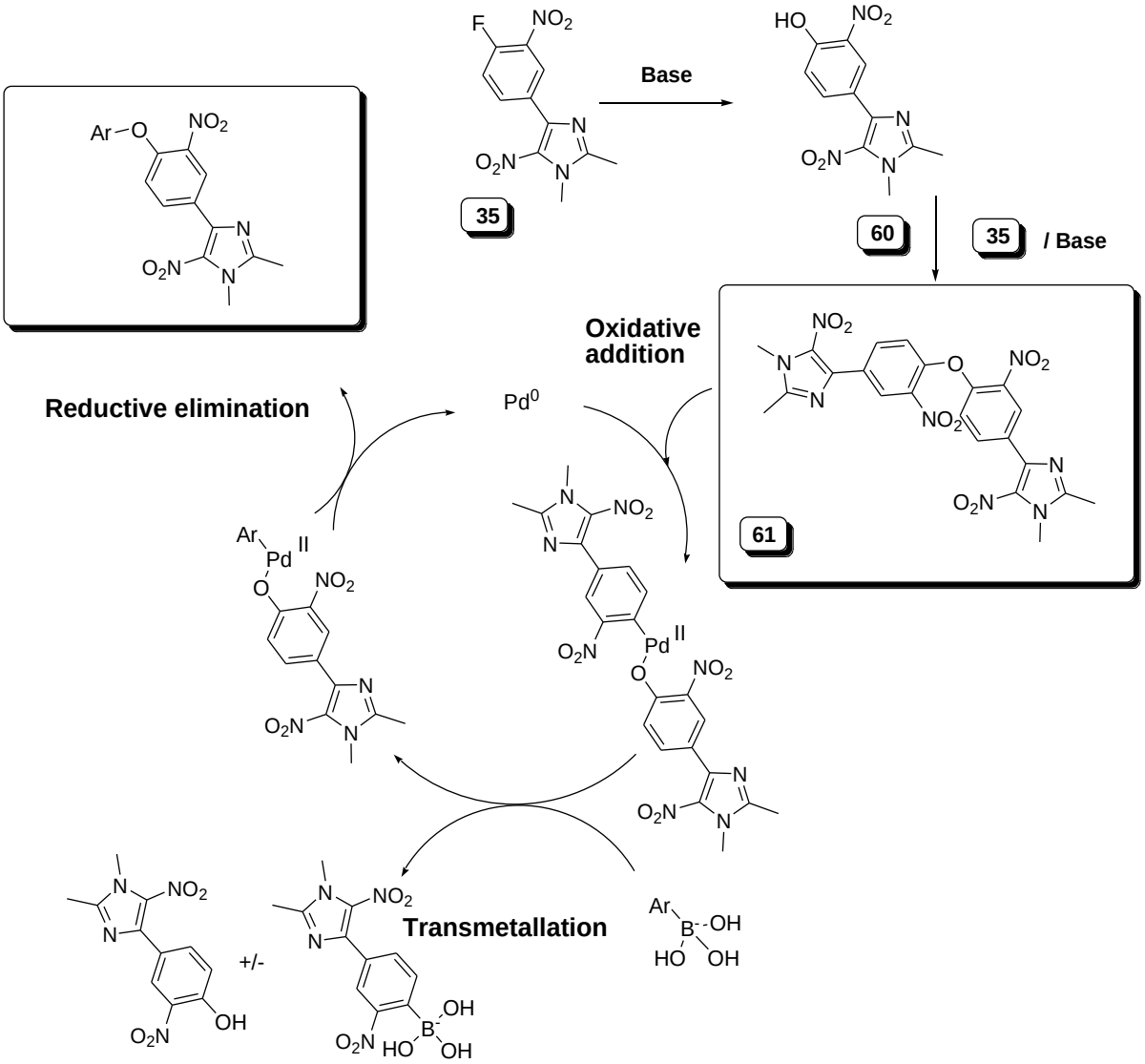
54 **55**

Fig.(17). Ortep drawings of **54** and **55**.

Since palladium-catalyzed *O*-arylation had never been described with arylboronic acids and electron-deficient aryl fluorides, additional experiments were performed to further clarify the mechanism of the C-O bond formation. Palladium catalysis, boron species, oxidation conditions were investigated.

We hypothesized that a possible mechanism for the *O*-arylation could be *via* the intermediate **61** after palladium oxidative addition and cross-coupling with arylboronic acids, even though, to the best of our knowledge, no such palladium addition had ever been described.

In order to propose a mechanism, supposing the *in situ* formation of compound **61**, we realized a special assay using the same reaction conditions and 1 equiv. of compound **60**. Thus, with *p*-chlorophenylboronic acid, the desired product **56** was formed in 30% yield. In order to confirm the proposed mechanism, compound **61** was synthesized by reaction with aryl fluoride derivative **35** and nitrophenol derivative **60** under base-mediated conditions.Then, compound **61** was tested with 4-methoxyphenylboronic acid under the above experimental conditions. After 48 h, a conversion of **61** in *O*-arylated compound **54** (39%), nitrophenol **60** (60%) and *C*-arylated compound **53** (traces) was observed, suggesting the mechanism depicted in scheme **13**.



Scheme 13. Proposed mechanism of C-O bond formation.

This work was the first example of a palladium-catalyzed C-O bond formed from a reaction between an activated phenylfluoride derivative and aryl or heteroaryl boronic acids[83].

III.C. Sonogashira cross-coupling reactions in 4-bromo-1,2-dimethyl-5-nitro-1*H*-imidazole series

In continuation of our research program centered on the design and synthesis of novel molecules, we focused our work on the synthesis and the evaluation of some heterocyclic compounds displaying diverse biological activities[84-88].We report in this section the preparation of 5-nitroimidazoles bearing alkynyl derivatives at the 4-position to widen anti-infectious pharmacomodulation in 5-nitroimidazole series. Furthermore, the 4-alkynylimidazole scaffold can be found in glutamate receptor antagonist molecules used for the treatment of central nervous system diseases (Alzheimer, Parkinson, Huntington's chorea, ...)[89-91].4-Alkynyl-5-nitroimidazoles are also useful as substrates in organic synthesis. As Michael acceptors, they may react *via* the attack of nucleophilic species[92-94],particularly of azide [95], and could not only constitute good candidate substrates for Huisgen cycloaddition, but also provide molecules able to react through electron transfer reactions like $S_{RN}1$ [96] and TDAE-assisted methodology [97].

Although the Sonogashira reaction has proved to be extremely versatile, being used extensively in natural products[98-105] and heterocyclic synthesis[106, 107], only a few examples of Sonogashira cross-coupling reactions in 4-bromoimidazole series are reported in the literature[108-111].Moreover, to the best of our knowledge, only one example of a Sonogashira reaction performed on a nitrated imidazole ring was described[89].Unfortunately, under these conditions it was not possible to perform the Sonogashira cross-coupling between 4-bromo-1,2-dimethyl-5-nitro-1*H*-imidazole (**31**) and propargylic alcohol, so a more general method providing easy access to 4-alkynyl-5-nitroimidazoles was investigated.

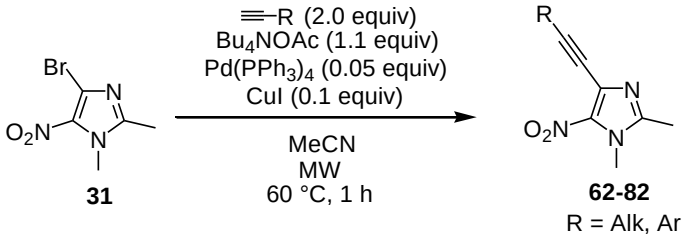
The required starting material for the Sonogashira cross-coupling reaction is the 4-bromo-1,2-dimethyl-5-nitro-1*H*-imidazole **31** which was prepared in 22% overall yield (cf. III.A. section).

Basing ourselves on the reportedSonogashira reactions[89, 108-117],we tested different cross-coupling reaction conditions, focusing on 5 parameters: catalyst, co-catalyst, base, solvent, heating method.

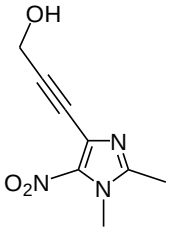
As a result, optimized microwave-assisted experimental conditions were established and led to the synthesis of 3-(1,2-dimethyl-5-nitro-1*H*-imidazol-4-yl)prop-2-yn-1-ol **62** in 93% yield in 1 h[118].The best experimental conditions were found to be $Pd(PPh_3)_4$ (0.05 equiv.); CuI (0.1 equiv.); propargylic alcohol (2.0 equiv.) and Bu_4NOAc (1.1 equiv.) in MeCN under microwave irradiation (60 °C) for 1 h. $PdCl_2(PPh_3)_2$ as palladium source and DMF as solvent gave similar results. Using Et_3N as base led to cross-coupling in only a moderate yield (40%). Currently, the reasons for the beneficial effect of Bu_4NOAc in these reactions are not clear. Undoubtedly, Bu_4NOAc acts as a mild base to deprotonate the most acidic hydrogen in the alkyne, but according to Urgaonkar[117] the acetate anion in combination with a bulky cation could also play a crucial role by providing a naked more reactive acetate anion or by stabilizing the oxidative addition adduct $ArPd^{(II)}X$.

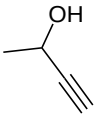
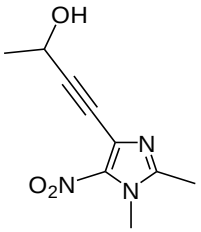
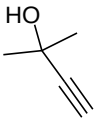
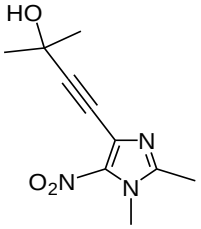
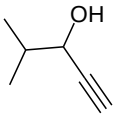
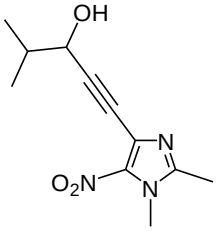
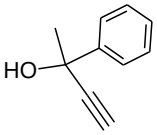
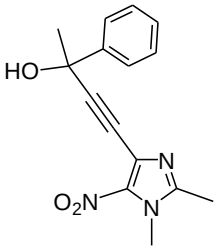
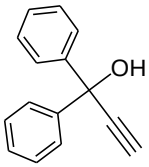
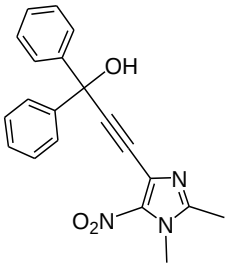
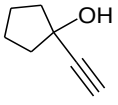
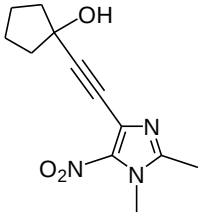
To evaluate the scope and the limitations of this procedure, we performed coupling reactions with 24 variously substituted terminal alkynes (Table **3**).

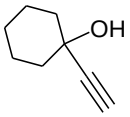
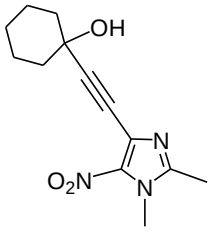
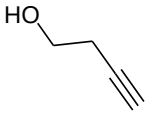
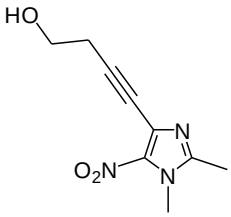
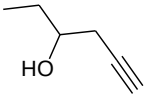
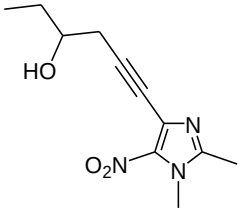
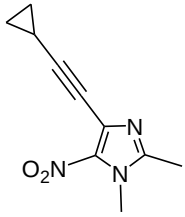
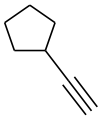
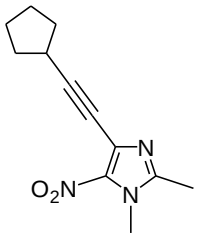
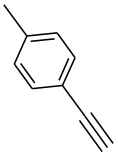
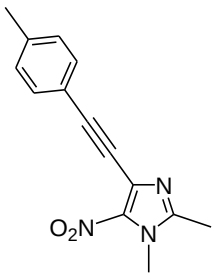
Table 3. Microwave-Mediated Sonogashira Coupling Reactions of Imidazole 31 with Alkyl- or Phenyl-Acetylene[a].

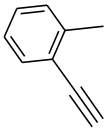
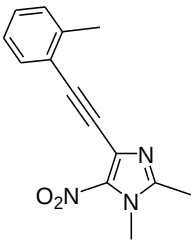
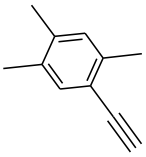
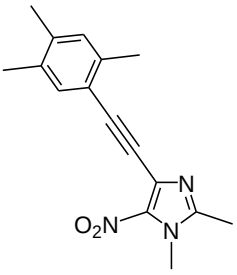
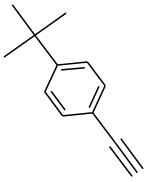
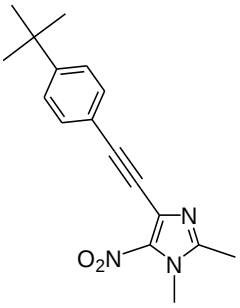
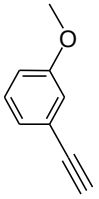
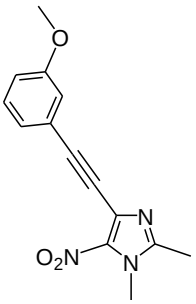
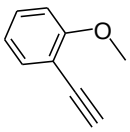
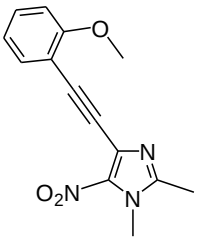


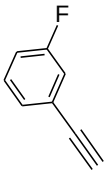
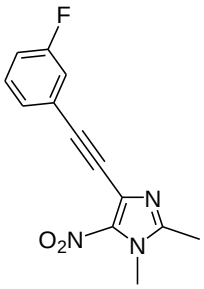
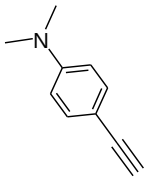
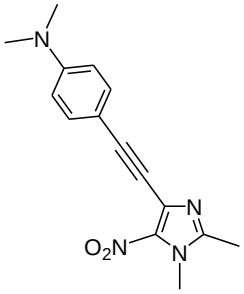
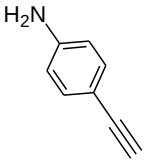
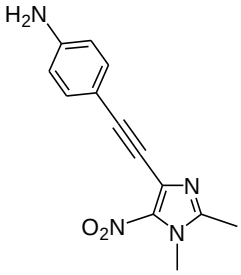
31 **62-82**
R = Alk, Ar

Entry	Alkyne	Product	Compound Number	Yield (%)
1			**62**	93

2			**63**	87
3			**64**	72
4			**65**	52
5			**66**	80
6			**67**	84
7			**68**	98

8			**69**	98
9			**70**	87
10			**71**	79
11			**72**	54
12			**73**	72
13			**74**	98

14			**75**	78
15			**76**	93
16			**77**	80
17			**78**	94
18			**79**	75

19			**80**	70
20			**81**	40
21			**82**	98

[a]Conditions: $Pd(PPh_3)_4$ (0.05 equiv.); CuI (0.1 equiv.); alkyne (2.0 equiv.) and Bu_4NOAc (1.1 equiv.) in MeCN under microwave irradiation (60 °C).

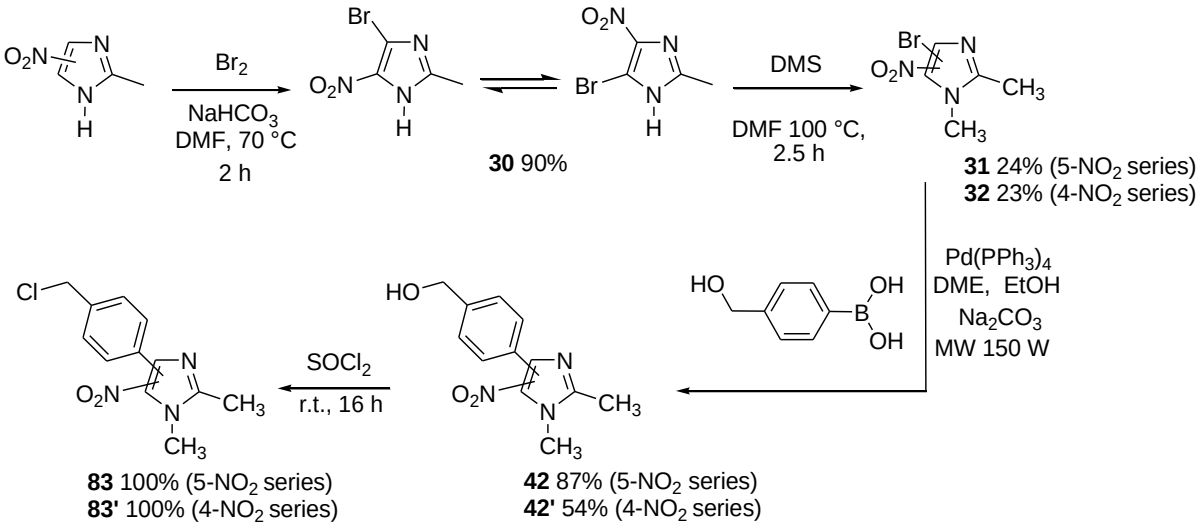
Despite numerous trials, no combination of the previous parameters was successful for 3 terminal alkynes: 1-phenylprop-2-yn-1-ol, prop-2-ynylbenzene and phenyl(prop-2-ynyl)sulfane.

IV. Synthesis of novel nitroimidazoles *via* electron transfer reactions

IV.A. Long-Distance $S_{RN}1$ (LD-$S_{RN}1$) in 5-nitroimidazole series

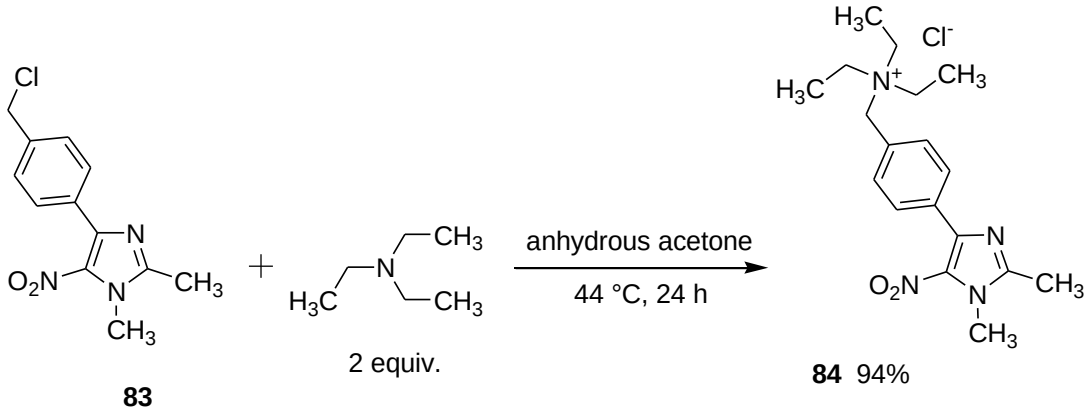
To increase our knowledge of the reactivity of LD-$S_{RN}1$ and its limitations in 5-nitroimidazole series, and within the framework of our research on the preparation of new potentially less toxic nitroimidazoles (less cytotoxic and less mutagenic), we prepared 4(5)-[4-(chloromethyl)phenyl]-1,2-dimethyl-5(4)-nitro-1*H*-imidazoles and studied their reactivities with different nucleophiles in $S_{RN}1$ experimental conditions (LD-$S_{RN}1$) in order to determine the reactivity of both isomers.

4-[4-(Chloromethyl)phenyl]-1,2-dimethyl-5-nitro-1*H*-imidazole, which appeared to be a good candidate to study LD-$S_{RN}1$ reactivity, was obtained by bromination of 2-methyl-4(5)-nitro-1*H*-imidazole by action of dibrome in DMF, methylation by dimethylsulfate, Suzuki-Miyaura cross-coupling reaction [58] and chlorination by thionyl chloride (Scheme **14**) [64].



Scheme 14. Preparation of alkylating agents **83** and **83'**.

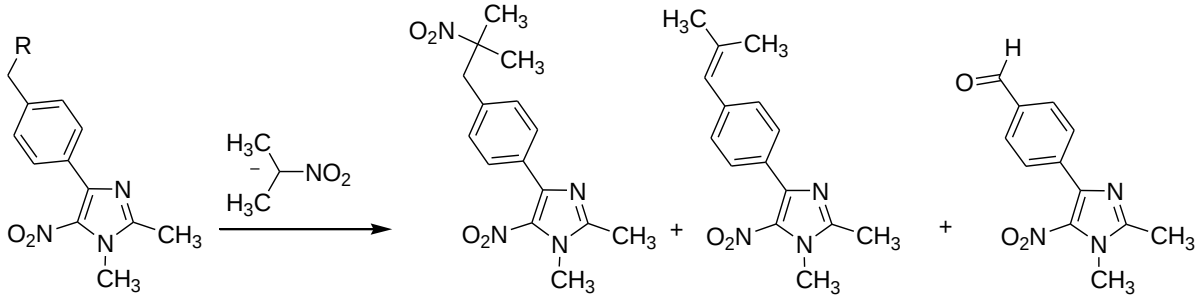
Furthermore, as ammonium chlorides are known to be poor leaving groups in S_N2 reactions[119-126],we decided to synthesize and to study the reactivity of *N*-[4-(1,2-dimethyl-5-nitro-1*H*-imidazol-4-yl)benzyl]-*N*,*N*-diethylethanaminium chloride **84** which was prepared in 94% yield from 4-[4-(chloromethyl)phenyl]-1,2-dimethyl-5-nitro-1*H*-imidazole **83** with two equiv. of triethylamine in anhydrous acetone at 44 °C for 24 h (Scheme **15**).



Scheme 15. Preparation of alkylating agent **84**.

The first result shows that compound **83** reacts with the 2-nitropropane anion to give compound **87** alone, resulting from an *O*-alkylation following an S_N2 mechanism in good yields under the classic $S_{RN}1$ conditions described by Kornblum (65% in DMSO and 72% in DMF) at room temperature. Various $S_{RN}1$ experimental conditions were then tested, to study their influence on the reactivity. Under classic heating (heating by oil bath) in DMSO at 170 °C, a mixture of expected products from *C*-alkylation **85** (36%) and **86** (43%), resulting consecutively from *C*-alkylation following an $S_{RN}1$ mechanism and then *via* a base-promoted nitrous acid elimination, was obtained. In DMF at 140 °C, the reaction led to compounds **85** (57%) and **87** (12%), but without any trace of compound **86**. Indeed, DMSO should solvate counterions in 2-nitropropane anion sodium salt better than DMF, inducing higher base strength in the 2-nitropropane anion[127].

Table 4.LD-S_{RN}1 reactivity with 2-nitropropane anion and compounds 83 and 84.



83 R = Cl
84 R = $(Et)_3N^+Cl^-$

85 **86** **87**

Entry	Product	Equiv. Anion	Solvent	T (h)	Conditions	**85** (%)	**86** (%)	**87** (%)
1	83	6	DMF	0.5	N_2, darkness, rt	-	-	73
2	83	6	DMF	0.5	N_2, hν,rt	-	-	72
3	83	6	DMF	0.5	N_2, darkness, 140 °C	56	-	-
4	83	6	DMF	0.5	140 °C	57	-	12
5	**83**	**6**	**DMF**	**0.5**	**MW 140 °C**	60	10	22
6	83	3	DMSO	0.5	N_2, hν, rt	-	-	62
7	83	6	DMSO	0.5	N_2, darkness, 170 °C	28	33	traces
8	83	6	DMSO	0.5	170 °C	36	43	-
9	**83**	**6**	**DMSO**	**0.5**	**MW 170 °C**	-	60	-
10	84	3	DMSO	48	N_2, hν, rt	-	-	22
11	**84**	**6**	**DMF**	**0.5**	**MW 140 °C**	44	32	-

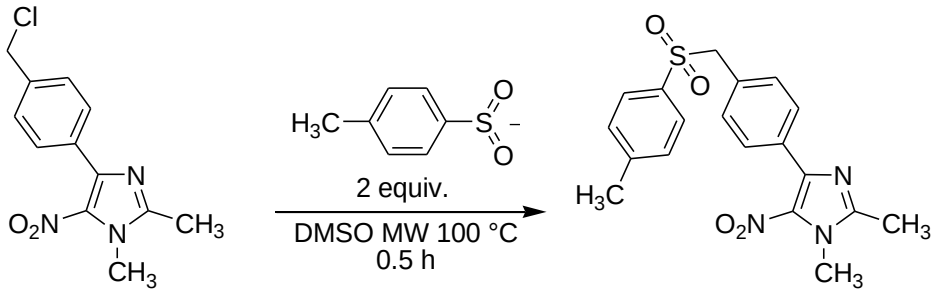
On the basis of these encouraging results and previous studies[128-133], we decided to estimate the influence that microwave irradiation might have on the LD-S_{RN}1 reaction. The best microwave-assisted experimental conditions were defined and led in DMF to a mixture of compounds **85**(60%), **86** (10%) and **87** (22%)(Table **4**, entry 5) [63]. In DMSO, these conditions led to the formation of compound **86**in 60% yield (Entry 9). Thus, no "special effect" (non-thermal effect) resulting from the microwave irradiation was observed and only the thermal effect seems to influence the main mechanism (from S_N2 to $S_{RN}1$). Furthermore, no trace of aldehyde appeared to be formed. Therefore, these results suggest that both substrates **83** and **84** form *C*-alkylated products by an $S_{RN}1$ mechanism. To confirm this mechanism by single electron transfer, reactions of inhibition were performed by adding to the reaction mixture catalytic quantities (10 mol%) of cupric chloride ($CuCl_2$) or 2,2,6,6-tetramethyl-1-piperidinyloxyle (TEMPO), inhibitors usually used in mechanistic studies to prove $S_{RN}1$ mechanisms. Reaction times for the reactions of inhibition are identical to those of Table **4**, entry 5 without inhibitors.

Table 5.Inhibition Reactions with 2-Nitropropane Anion[a].

Entry	Inhibitor (0.1 equiv)	**85** (%)	**86** (%)	**87** (%)
1	-	60	10	22
2	$CuCl_2$	25	14	22
3	TEMPO	8	10	27

[a] All reactions were performed using 1 equiv. of **83**, 6 equiv. of 2-nitropropane anion in DMF under microwave irradiations at 140 °C, for 0.5 h.

Formation of compound **85** was observed to be inhibited with TEMPO and $CuCl_2$. The effects of the classic inhibitors in the reaction between compound **83** and the 2-nitropropane anion are proof of an $S_{RN}1$ mechanism for this *C*-alkylation reaction. To extend the reaction to other nucleophiles, we studied anions centered on the sulfur atom(Scheme **16**). The reaction between sodium 4-methylbenzenesulfinate and substrate **83** in DMSO at 100 °C under microwave irradiation led to *S*-alkylated compound **88** in good yields (79%).



83 **88** 79%

Scheme 16. Reactivity of **83** with sodium 4-methylbenzenesulfinate.

In order to identify the main mechanism of this reaction, the reactivity of the latter was studied by adding an inhibitor (Table **6**, entries 2 and 3).

Table 6.Inhibition Reaction with Sodium 4-Methylbenzenesulfinate[a].

Entry	Inhibitor (0.1 equiv.)	**44** (%)
1	-	79
2	$CuCl_2$	55
3	TEMPO	46

[a]All reactions were performed using 1 equiv. of **83**, 2 equiv. of sodium 4-methylbenzene-sulfinate in DMSO under microwave irradiation at 100 °C, for 0.5 h.

The decrease in the reaction rate is less significant than with the 2-nitropropane anion and indicates that the reaction may follow a combination of S_N2 and $S_{RN}1$ mechanisms.

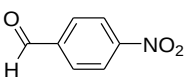
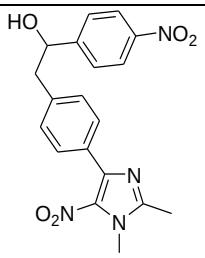
IV.B. Tetrakis(dimethylamino)ethylene (TDAE) methodology in 5-nitroimidazole series

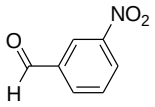
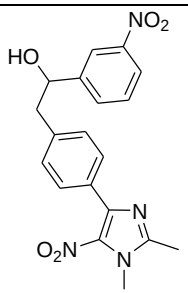
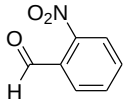
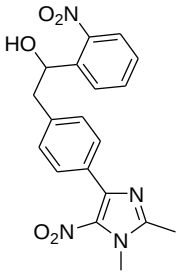
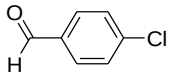
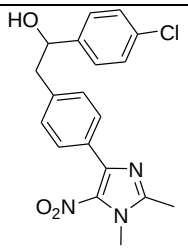
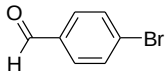
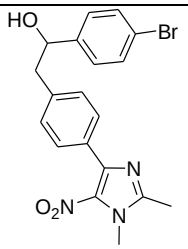
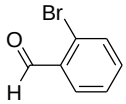
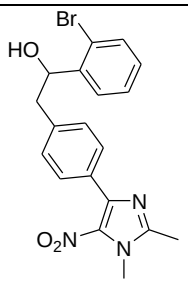
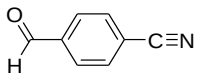
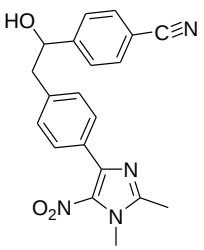
Tetrakis(dimethylamino)ethylene (TDAE) is a reducing agent which reacts with halogenated derivatives to generate an anion in soft conditions by means of two sequential transfers of one electron[134-136].We showed that from *o*- or *p*-nitrobenzyl chlorides, TDAE was able to generate a nitrobenzylic carbanion capable of reacting with various electrophiles[137].Since 2003 and by means of this strategy, we have developed several reactions between nitrobenzylic substrates, heterocyclic or quinonic and carbonylated electrophile series such as aldehydes [137-140], ketones [137-140], α-ketoesters [141-143], α-ketolactames [144], α-diketones [145, 146] and diethyl ketomalonate [141-143], leading to adducts of the corresponding alcohol. In line with our program on the study of electron transfer reactions of bioreducible alkylating agents and the preparation of new nitroimidazoles with biological potential, we synthesized new highly functionalized 5-nitro-1*H*-imidazoles from 4-[4-(chloromethyl)phenyl]-1,2-dimethyl-5-nitro-1*H*-imidazole **83** and various carbonylated aromatic derivatives or α-carbonylated-ester by using the TDAE methodology. The reaction of compound **83** with 3 equiv. of diverse aromatic aldehydes **89a-j** in the presence of TDAE, at -20 °C for 1 h, followed by 24 h at room temperature (Scheme **17**), led to the corresponding derived alcohols **90a-j** in moderate to good yields (24-78%) (Table **7**)[64].

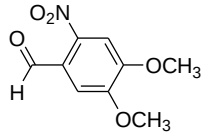
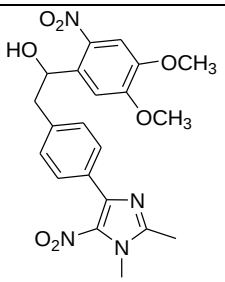
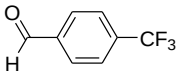
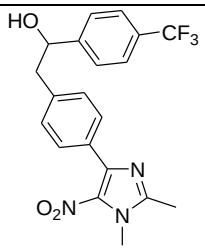
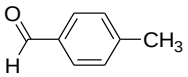
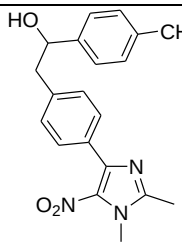
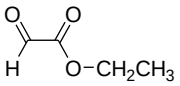
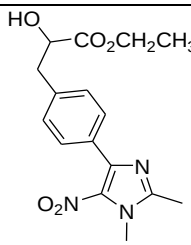
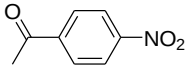
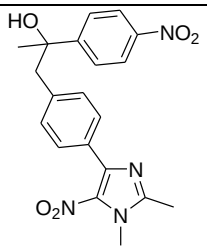
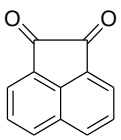
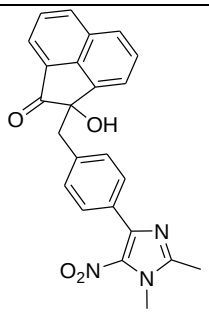
83 **89a-m** **90a-m**

Scheme 17. Reaction of compound **83** with various carbonylated compounds using TDAE methodology.

Table 7.Products and Yields of the Reaction of 83 with Various Carbonylated Compounds Using TDAE Methodology[a].

Entry	Carbonylated compound	Product	Compound number	T (h)	Yield (%)[b]
89a			**90a**	2	69

89b			**90b**	2	46
89c			**90c**	2	37
89d			**90d**	2	24
89e			**90e**	2	60
89f			**90f**	2	68
89g			**90g**	2	78

89h			**90h**	2	30
89i			**90i**	2	45
89j			**90j**	2	25
89k			**90k**	2	42
89l			**90l**	24[c]	45
89m			**90m**	2	64

[a] All reactions were performed using 3 equiv. ofcarbonylated compound **89 a-l,** 1 equiv. of chloride derivative **83** and 1 equiv. of TDAE in anhydrous DMF stirred at -20 °C for 1 h and then warmed up to rt for 24 h. [b] Yield relative to chloride **83**. [c] The reaction was performed using 3 equiv. of carbonyl compounds **89m**, 1 equiv. of

chloride **83** and 1 equiv. of TDAE in anhydrous DMF stirred at -20 °C for 1 h and then warmed up to 80 °C for 24 h.

High yields were obtained with *p*-nitrobenzaldehyde (**89a**), *o*-bromobenzaldehyde (**89f**) and *p*-cyanobenzaldehyde (**89g**), whereas *p*-chlorobenzaldehyde (**89d**), *p*-methylbenzaldehyde (**89j**) and 6-nitroveratraldehyde (**89h**) produced low yields. This difference in yields could be explained by electronic effects: compounds bearing withdrawing groups gave the best yields, whereas those bearing electron-donating groups led to the lowest yields, while in the presence of halogen atoms, yields were variable. With compound **90d**, the low yield obtained is likely to result from purification problems. With nitrobenzaldehydes derivatives, steric hindrances could explain the difference between *o*-and *m*-nitrobenzaldehyde (37% *vs* 46%). We also studied the reaction between compound **83** and α-ketoester derivatives as ethyl glyoxylate (**89k**), α-diketone derivatives such as acenaphtenedione (**89m**) and ketones such as *p*-acetophenone (**89l**) and we obtained corresponding hydroxylated derivatives **90k-m** in moderate to good yields (42-64%)(Table **7**). Just as in *p*-nitrobenzylic series, because of its low reactivity, the use of *p*-acetophenone (**89l**) required heating for 24 h at 80 °C to lead to the end of the reaction.

CONCLUSION

The 5-nitroimidazoles continue to be the drugs of choice for treating parasitic and bacterial infections, in spite of the mutagenicity and development of resistance observed with metronidazole. In our attempts to develop new molecules which might offer advantages in clinical use over the well-established metronidazole, we have explored new strategies of synthesis: VNS reaction, palladium-catalyzed cross-coupling reactions (Suzuki-Miyaura, *O*-arylation of an aryl fluoride, Sonogashira) and electron transfer reactions (LD-$S_{RN}1$, TDAE methodology). These new 5-nitroimidazoles hold promise for the development of drugs that can meet the principal challenge to obtain a reasonable degree of activity (in particular against metronidazole-resistant strains) and an absence of mutagenicity.

CONFLICT OF INTEREST

The authors confirm that the article content has no conflict of interest.

ACKNOWLEDGEMENTS

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KEYWORDS

Anti-infectious agents;Electron transfer reactions; 5-Nitroimidazole; Palladium-catalyzed reactions, VNS reaction.

ABSTRACT

5-Nitroimidazoles are drugs having both antiprotozoal and antibacterial activity, but show mutagenicity and development of resistance observed particularly with metronidazole. For the development of new potentially safer derivatives, we investigated new strategies of synthesis: such as Vicarious Nucleophilic Substitution of hydrogen (VNS), palladium-catalyzed cross-coupling reactions (Suzuki-Miyaura, Sonogashira…) and electron transfer reactions (Unimolecular Radical Nucleophilic Substitution ($S_{RN}1$), TDAE methodology) applied in 5-nitroimidazole series.

GRAPHICAL ABSTRACT