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Communication

## High Functionalization of 5-Nitro-1*H*-imidazole Derivatives: The TDAE Approach

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**Abstract:** We report herein the synthesis of substituted 2-[4-(1,2-dimethyl-5-nitro-1*H*-imidazol-4-yl)phenyl]-1-arylethanol, ethyl 3-[4-(1,2-dimethyl-5-nitro-1*H*-imidazol-4-yl)phenyl]-2-hydroxypropanoate and 2-[4-(1,2-dimethyl-5-nitro-1*H*-imidazol-4-yl)benzyl]-2-hydroxy-acenaphthylen-1(2*H*)-one from the reactions of 4-[4-(chloromethyl)phenyl]-1,2-dimethyl-5-nitro-1*H*-imidazole with various aromatic carbonyl and  $\alpha$ -carbonyl ester derivatives using tetrakis(dimethylamino)ethylene (TDAE) methodology.

**Keywords:** TDAE; 5-nitro-1*H*-imidazole; arylethanol; carbonyl derivatives

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### 1. Introduction

The 5-nitroimidazole scaffold is well-known for displaying major anti-infectious activities [1–6]. Several 5-nitroimidazole-containing active principles such as metronidazole, secnidazole and ornidazole are commonly used in medicine. These chemotherapeutic agents inhibit the growth of both anaerobic bacteria and some anaerobic protozoa [7]. Nowadays, the most clinically used drug-compounds for the treatment of both infections caused by protozoa such as *Trichomonas vaginalis*, *Entamoeba histolytica*, *Giardia intestinalis* and infections induced by anaerobic bacteria is metronidazole. However, the 5-nitroimidazoles have been found to possess a high mutagenic activity in prokaryotic micro-organisms. A nitroimidazole possessing good pharmacological activities with no

mutagenicity [8] would be of great interest, not only from a safety point of view, but would also provide a basis for further investigations on the mechanism(s) involved in their mutagenicity. Moreover, emergence of metronidazole-resistant *Trichomonas vaginalis* has resulted in decreased success of current therapies [9,10]. These refractory cases are usually treated with higher doses of metronidazole, which leads in turn to an increase in the occurrence of side effects [10,11], so alternative curative therapies are needed.

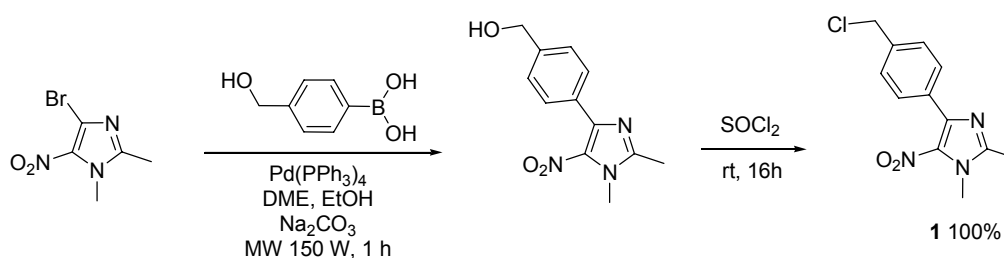
In continuation of our program directed towards the study of electron transfer reactions in heterocyclic series [12-14], we recently investigated  $S_{RN}1$  (unimolecular radical nucleophilic substitution) reactions of 4(5)-[4-(chloromethyl)phenyl]-1,2-dimethyl-5(4)-nitro-1*H*-imidazoles, involving long distance (six bonds) between the electron-withdrawing and leaving groups (LD- $S_{RN}1$ ). The nitronate anions reacted by the substitution at the chloromethyl group and the reaction was very probably mediated by a  $S_{RN}1$  mechanism [15].

Tetrakis(dimethylamino)ethylene (TDAE) is a reducing agent which reacts with halogenated derivatives to generate an anion under mild conditions via two sequential transfers of one electron [16-18]. We have shown that from *o*- or *p*-nitrobenzyl chloride, TDAE could generate a nitrobenzyl carbanion which is able to react with various electrophiles [19]. Since 2003, and using this strategy, we have developed several reactions between nitrobenzylic, heterocyclic or quinonic substrates and a series of carbonylated electrophiles such as aldehydes [19-22], ketones [19-22],  $\alpha$ -ketoesters [23-25],  $\alpha$ -ketolactams [26],  $\alpha$ -diketones [27,28] and diethyl ketomalonate [23-25] leading to the corresponding alcohol adducts. In continuation of our program directed toward the study of electron transfer reactions of bioreductive alkylating agents and the preparation of new and potentially safer nitroimidazoles, we report herein the synthesis of some highly functionalized 5-nitro-1*H*-imidazoles from the reaction of 4-[4-(chloromethyl)phenyl]-1,2-dimethyl-5-nitro-1*H*-imidazole with various aromatic carbonyl and  $\alpha$ -carbonyl ester derivatives using TDAE methodology.

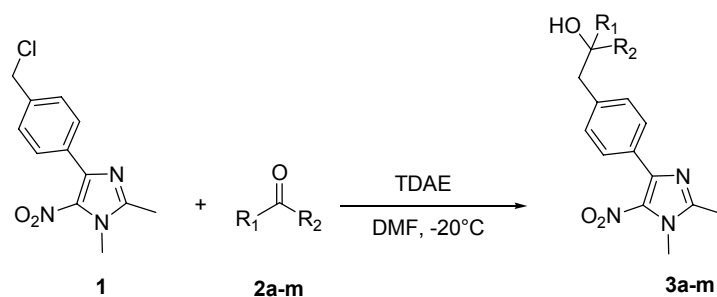
## 2. Results and Discussion

4-[4-(Chloromethyl)phenyl]-1,2-dimethyl-5-nitro-1*H*-imidazole (**1**) was prepared from the previously described [4-(1,2-dimethyl-5-nitro-1*H*-imidazol-4-yl)phenyl]methanol [29], according to a classical chlorination reaction with  $SOCl_2$  [20] (Scheme 1).

**Scheme 1.** Preparation of 4-[4-(chloromethyl)phenyl]-1,2-dimethyl-5-nitro-1*H*-imidazole (**1**).



The reaction of **1** with 3 equivalents of various aromatic aldehydes **2a-j** in the presence of TDAE at  $-20$  °C for 1 h, followed by 24 h at rt (Scheme 2), led to the corresponding alcohol derivatives **3a-j** in moderate to good yields (24–78%) as shown in Table 1.

**Scheme 2.** Reaction of **1** with various carbonyl compounds using TDAE strategy.**Table 1.** Products' yields from the reaction of **1** with various carbonyl compounds using TDAE strategy.

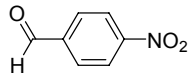
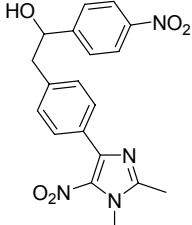
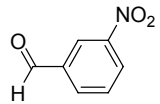
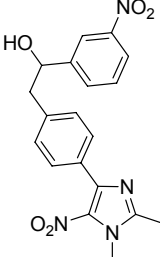
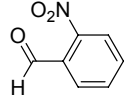
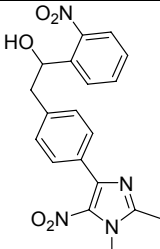
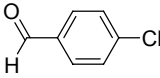
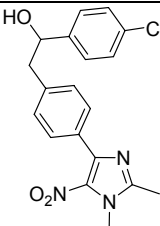
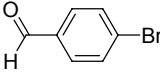
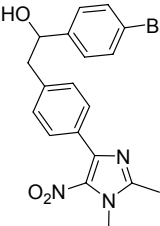
Carbonyl compound	Product <sup>a</sup>	Product number	Yield (%) <sup>b</sup>
 <b>2a</b>	 <b>3a</b>	<b>3a</b>	69
 <b>2b</b>	 <b>3b</b>	<b>3b</b>	46
 <b>2c</b>	 <b>3c</b>	<b>3c</b>	37
 <b>2d</b>	 <b>3d</b>	<b>3d</b>	24
 <b>2e</b>	 <b>3e</b>	<b>3e</b>	60

Table 1. Cont.

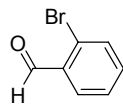
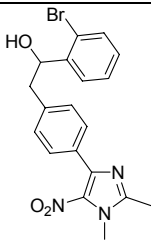
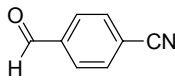
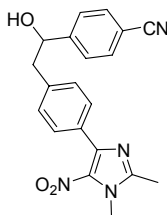
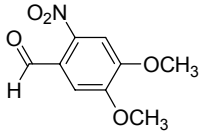
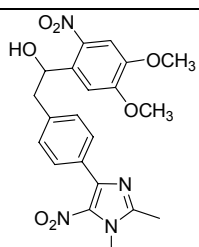
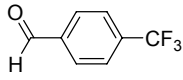
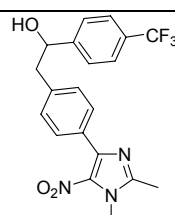
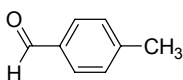
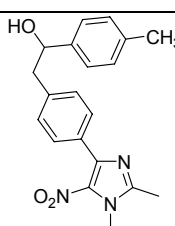
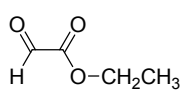
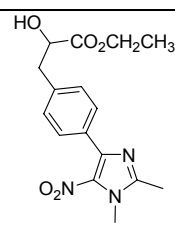
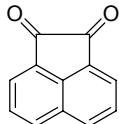
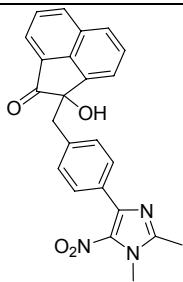
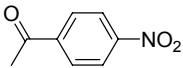
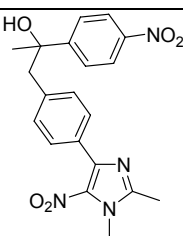
Carbonyl compound	Product <sup>a</sup>	Product number	Yield (%) <sup>b</sup>
<p><b>2f</b></p> 		<b>3f</b>	68
<p><b>2g</b></p> 		<b>3g</b>	78
<p><b>2h</b></p> 		<b>3h</b>	30
<p><b>2i</b></p> 		<b>3i</b>	45
<p><b>2j</b></p> 		<b>3j</b>	25
<p><b>2k</b></p> 		<b>3k</b>	42
<p><b>2l</b></p> 		<b>3l</b>	45

Table 1. Cont.

Carbonyl compound	Product <sup>a</sup>	Product number	Yield (%) <sup>b</sup>
<b>2m<sup>c</sup></b> 		<b>3m</b>	64

<sup>a</sup> All the reactions are performed using 3 equivalents of carbonyl compounds **2a-l**, 1 equivalent of chloride **1** and 1 equivalent of TDAE in anhydrous DMF stirred at  $-20\text{ }^{\circ}\text{C}$  for 1 h and then warmed up to rt for 24 h. <sup>b</sup> % Yield relative to chloride **1**. <sup>c</sup> The reaction is performed using 3 equivalents of carbonyl compounds **2m**, 1 equivalent of chloride **1** and 1 equivalent of TDAE in anhydrous DMF stirred at  $-20\text{ }^{\circ}\text{C}$  for 1 h and then warmed up to  $80\text{ }^{\circ}\text{C}$  for 24 h.

High yields were obtained with *p*-nitrobenzaldehyde (**2a**), *o*-bromobenzaldehyde (**2f**) and *p*-cyanobenzaldehyde (**2g**), whereas *p*-chlorobenzaldehyde (**2d**), *p*-methylbenzaldehyde (**2j**) and 6-nitroveratraldehyde (**2h**) produced low yields. In summary, the difference of yields seems explained by the electronic effects, whereby the electron-withdrawing groups furnished the best yields, the electron-donating groups furnished the lowest yields and the halogen groups led to varied yields. The different yields with halobenzaldehydes could be explained by some purification problems encountered with the compound **3d**. With nitrobenzaldehydes, steric hindrance could explain the difference between the *o*- and *m*-nitrobenzaldehyde (37% versus 46%). Moreover, after the reaction with aromatic aldehydes, we have investigated the reaction of **1** with  $\alpha$ -keto-ester derivatives such as ethyl glyoxylate (**2k**), with an  $\alpha$ -diketone such as acenaphthenedione (**2l**) and with a ketone like *p*-nitroacetophenone (**2m**). The reaction of **1** in the presence of TDAE with these electrophiles furnished the corresponding hydroxyl derivatives **3k-m** in moderate to good yields (42–64%), as shown in Table 1. As observed in the *p*-nitrobenzyl series [19], due to its poor reactivity, *p*-nitroacetophenone (**2l**) needed heating for 24 h at  $80\text{ }^{\circ}\text{C}$  to drive the reaction to completion.

### 3. Experimental

Melting points were determined on Büchi B-540 and are uncorrected. Elemental analyses were carried out at the Spectropole, Faculté des Sciences et Techniques de Saint-Jérôme. Both  $^1\text{H}$ - and  $^{13}\text{C}$ -NMR spectra were determined on Bruker ARX 200 spectrometer. The  $^1\text{H}$  chemical shifts were reported as parts per million downfield from tetramethylsilane ( $\text{Me}_4\text{Si}$ ), and the  $^{13}\text{C}$  chemical shifts were referenced to the solvent peak of  $\text{CDCl}_3$  (76.9 ppm). The following adsorbent was used for column chromatography: silica gel 60 (Merck, 230–400 mesh). Thin-layer chromatography was performed with silica gel Merck 60F-254 (0.25 mm layer thickness).

*4-[4-(Chloromethyl)phenyl]-1,2-dimethyl-5-nitro-1H-imidazole (1)*: This compound was prepared from [4-(1,2-dimethyl-5-nitro-1H-imidazol-4-yl)phenyl]methanol [29], according to a classical chlorination reaction with  $\text{SOCl}_2$  [20]. Yellow solid; mp  $120\text{ }^{\circ}\text{C}$  (isopropyl alcohol);  $^1\text{H}$ -NMR ( $\text{CDCl}_3$ )  $\delta$ : 2.51 (s, 3H,  $\text{CH}_3$ ), 3.90 (s, 3H,  $\text{CH}_3$ ), 4.62 (s, 2H,  $\text{CH}_2$ ), 7.45 (d,  $J = 8.1\text{ Hz}$ , 2H, 2xCH), 7.76 (d,

$J = 8.1$  Hz, 2H, 2xCH);  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 14.0 ( $\text{CH}_3$ ), 34.2 ( $\text{CH}_3$ ), 45.8 ( $\text{CH}_2$ ), 128.2 (2xCH), 129.9 (2xCH), 131.6 (C), 138.6 (C), 142.5 (C), 148.3 (C). The C-nitro was not observed in this experiment; Anal. Calcd for  $\text{C}_{12}\text{H}_{12}\text{N}_3\text{O}_2\text{Cl}$ : C, 54.25; H, 4.55; N, 15.82. Found: C, 54.31; H, 4.61; N, 15.97.

*General Procedure for the Reaction of Chloride 1 and Aromatic Carbonyl Derivatives 2a-m Using TDAE*

A solution of 4-[4-(chloromethyl)phenyl]-1,2-dimethyl-5-nitro-1H-imidazole (**1**, 0.15 g, 0.56 mmol, 1 equiv.) in anhydrous DMF (6 mL) and the corresponding carbonyl derivative **2a-m** (1.68 mmol, 3 equiv.) were placed under nitrogen at  $-20$  °C in a two-necked flask equipped with a silica-gel drying tube and a nitrogen inlet. The solution was stirred and kept at this temperature for 30 min and then the TDAE (0.11 g, 0.56 mmol, 1 equiv.) was added dropwise via a syringe. The solution was vigorously stirred at  $-20$  °C for 1 h and then warmed up to room temperature for 24 h [heating for 24 h at 80 °C in the case of *p*-nitroacetophenone (**2m**)]. After this time TLC analysis ( $\text{CH}_2\text{Cl}_2/\text{EtOAc}$  (7/3) as eluent) clearly showed that **1** was totally consumed. The orange-red turbid solution was filtered and rinsed with toluene. The organic layer was washed with  $\text{H}_2\text{O}$  ( $3 \times 40$  mL) and dried over  $\text{MgSO}_4$ . Evaporation of the solvent left an orange viscous liquid as crude product. Purification by silica gel chromatography [ $\text{CH}_2\text{Cl}_2/\text{EtOAc}$  (7:3)] gave the corresponding aryethanol or  $\alpha$ -hydroxyester derivatives.

*2-[4-(1,2-Dimethyl-5-nitro-1H-imidazol-4-yl)phenyl]-1-(4-nitrophenyl)ethanol (3a)*: Beige solid; mp 200 °C (isopropyl alcohol);  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 2.60 (s, 3H,  $\text{CH}_3$ ), 3.02–3.10 (m, 2H,  $\text{CH}_2$ ), 3.95 (s, 3H,  $\text{CH}_3$ ), 5.04 (dd,  $J = 5.3$  Hz et  $J = 7.9$  Hz, 1H, CH), 7.26 (d,  $J = 8.0$  Hz, 2H, 2xCH), 7.52 (d,  $J = 8.7$  Hz, 2H, 2xCH), 7.73 (d,  $J = 8.0$  Hz, 2H, 2xCH), 8.20 (d,  $J = 8.7$  Hz, 2H, 2xCH);  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 13.9 ( $\text{CH}_3$ ), 34.1 ( $\text{CH}_3$ ), 45.1 ( $\text{CH}_2$ ), 72.7 (CH), 123.3 (2xCH), 127.3 (2xCH), 128.9 (2xCH), 129.3 (2xCH), 129.9 (C), 139.7 (C), 142.3 (C), 146.6 (C), 149.2 (C), 153.7 (C). The C-nitro was not observed in this experiment; Anal. Calcd for  $\text{C}_{19}\text{H}_{18}\text{N}_4\text{O}_5$ : C, 59.68; H, 4.74; N, 14.65. Found: C, 59.68; H, 4.92; N, 14.41.

*2-[4-(1,2-Dimethyl-5-nitro-1H-imidazol-4-yl)phenyl]-1-(3-nitrophenyl)ethanol (3b)*: Yellow solid; mp 225 °C (ethyl alcohol);  $^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 2.45 (s, 3H,  $\text{CH}_3$ ), 2.94–2.99 (m, 2H,  $\text{CH}_2$ ), 3.81 (s, 3H,  $\text{CH}_3$ ), 4.96–5.04 (m, 1H, CH), 5.67–5.69 (m, 1H, OH), 7.27 (d,  $J = 8.2$  Hz, 2H, 2xCH), 7.58 (d,  $J = 8.2$  Hz, 2H, 2xCH), 7.64 (s, 1H, CH), 7.79 (d,  $J = 7.7$  Hz, 1H, CH), 8.09 (d,  $J = 8.2$  Hz, 1H, CH), 8.22 (s, 1H, CH);  $^{13}\text{C-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 13.9 ( $\text{CH}_3$ ), 34.1 ( $\text{CH}_3$ ), 45.2 ( $\text{CH}_2$ ), 72.5 (CH), 120.7 (CH), 121.9 (CH), 128.9 (2xCH), 129.3 (2xCH), 129.6 (CH), 130.1 (C), 132.9 (CH), 134.6 (C), 139.8 (C), 142.4 (C), 147.8 (C), 148.2 (C), 149.2 (C); Anal. Calcd for  $\text{C}_{19}\text{H}_{18}\text{N}_4\text{O}_5$ : C, 59.68; H, 4.74; N, 14.65. Found: C, 59.25; H, 4.78; N, 14.36.

*2-[4-(1,2-Dimethyl-5-nitro-1H-imidazol-4-yl)phenyl]-1-(2-nitrophenyl)ethanol (3c)*: Orange solid; mp 216 °C (ethyl alcohol);  $^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 2.45 (s, 3H,  $\text{CH}_3$ ), 2.80 (dd,  $J = 8.1$  Hz et  $J = 13.0$  Hz, 1H,  $\text{CH}_2$ ), 3.04 (dd,  $J = 8.1$  Hz and  $J = 13.0$  Hz, 1H,  $\text{CH}_2$ ), 3.82 (s, 3H,  $\text{CH}_3$ ), 5.25 (m, 1H, CH), 5.66 (d,  $J = 4.9$  Hz, 1H, OH), 7.31 (d,  $J = 8.1$  Hz, 2H, 2xCH), 7.53 (t,  $J = 8.1$  Hz, 1H, CH), 7.63 (d,

$J = 8.1$  Hz, 2H, 2xCH), 7.75 (t,  $J = 8.1$  Hz, 1H, CH), 7.86 (d,  $J = 8.1$  Hz, 1H, CH), 7.94 (d,  $J = 8.1$  Hz, 1H, CH);  $^{13}\text{C-NMR}$  (DMSO- $d_6$ )  $\delta$ : 14.0 (CH<sub>3</sub>), 34.1 (CH<sub>3</sub>), 44.7 (CH<sub>2</sub>), 69.2 (CH), 124.0 (CH), 128.4 (CH), 128.5 (CH), 129.1 (4xCH), 130.2 (C), 133.6 (CH), 134.7 (C), 140.2 (C), 140.8 (C), 142.5 (C), 147.5 (C), 149.3 (C); Anal. Calcd for C<sub>19</sub>H<sub>18</sub>N<sub>4</sub>O<sub>5</sub>: C, 59.68; H, 4.74; N, 14.65. Found: C, 58.83; H, 4.82; N, 14.01.

*1-(4-Chlorophenyl)-2-[4-(1,2-dimethyl-5-nitro-1H-imidazol-4-yl)phenyl]ethanol (3d)*: Pink solid; mp 199 °C (isopropyl alcohol);  $^1\text{H-NMR}$  (DMSO- $d_6$ ): 2.45 (s, 3H, CH<sub>3</sub>), 2.90 (d,  $J = 6.6$  Hz, 2H, CH<sub>2</sub>), 3.81 (s, 3H, CH<sub>3</sub>), 4.77–4.85 (m, 1H, CH), 5.44 (d,  $J = 4.8$  Hz, 1H, OH), 7.23 (d,  $J = 8.1$  Hz, 2H, 2xCH), 7.35 (bs, 4H, 4xCH), 7.57 (d,  $J = 8.1$  Hz, 2H, 2xCH);  $^{13}\text{C-NMR}$  (DMSO- $d_6$ )  $\delta$ : 13.9 (CH<sub>3</sub>), 34.1 (CH<sub>3</sub>), 45.4 (CH<sub>2</sub>), 72.9 (CH), 128.0 (4xCH), 128.9 (2xCH), 129.2 (2xCH), 130.0 (C), 131.3 (C), 134.6 (C), 140.2 (C), 142.5 (C), 144.8 (C), 149.3 (C); Anal. Calcd for C<sub>19</sub>H<sub>18</sub>ClN<sub>3</sub>O<sub>3</sub>: C, 61.38; H, 4.88; N, 11.30. Found: C, 60.85; H, 4.94; N, 11.03.

*1-(4-Bromophenyl)-2-[4-(1,2-dimethyl-5-nitro-1H-imidazol-4-yl)phenyl]ethanol (3e)*: White solid; mp 211 °C (isopropyl alcohol);  $^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$ : 2.45 (s, 3H, CH<sub>3</sub>), 2.90 (d,  $J = 6.5$  Hz, 2H, CH<sub>2</sub>), 3.81 (s, 3H, CH<sub>3</sub>), 4.80 (q,  $J = 5.3$  Hz, 1H, CH), 5.42 (d,  $J = 4.8$  Hz, 1H, OH), 7.23 (d,  $J = 8.2$  Hz, 2H, 2xCH), 7.29 (d,  $J = 8.4$  Hz, 2H, 2xCH), 7.49 (d,  $J = 8.4$  Hz, 2H, 2xCH), 7.57 (d,  $J = 8.2$  Hz, 2H, 2xCH);  $^{13}\text{C-NMR}$  (DMSO- $d_6$ )  $\delta$ : 13.9 (CH<sub>3</sub>), 34.1 (CH<sub>3</sub>), 45.3 (CH<sub>2</sub>), 72.9 (CH), 119.8 (C), 128.4 (2xCH), 128.9 (2xCH), 129.2 (2xCH), 130.0 (C), 130.9 (2xCH), 134.6 (C), 140.2 (C), 142.5 (C), 145.2 (C), 149.3 (C); Anal. Calcd for C<sub>19</sub>H<sub>18</sub>BrN<sub>3</sub>O<sub>3</sub>: C, 54.82; H, 4.36; N, 10.09. Found: C, 54.78; H, 4.42; N, 9.97.

*1-(2-Bromophenyl)-2-[4-(1,2-dimethyl-5-nitro-1H-imidazol-4-yl)phenyl]ethanol (3f)*: Yellow solid; mp 228 °C (isopropyl alcohol);  $^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$ : 2.45 (s, 3H, CH<sub>3</sub>), 2.59 (dd,  $J = 9.0$  Hz et  $J = 13.7$  Hz, 1H, CH<sub>2</sub>), 2.98 (dd,  $J = 9.0$  Hz and  $J = 13.7$  Hz, 1H, CH<sub>2</sub>), 3.82 (s, 3H, CH<sub>3</sub>), 5.00–5.09 (m, 1H, CH), 5.56 (d,  $J = 4.9$  Hz, 1H, OH), 7.20 (t,  $J = 7.7$  Hz, 1H, CH), 7.32 (d,  $J = 8.0$  Hz, 2H, 2xCH), 7.41 (t,  $J = 7.7$  Hz, 1H, CH), 7.56 (s, 1H, CH), 7.62 (d,  $J = 8.0$  Hz, 3H, 3xCH);  $^{13}\text{C-NMR}$  (DMSO- $d_6$ )  $\delta$ : 13.9 (CH<sub>3</sub>), 34.1 (CH<sub>3</sub>), 43.9 (CH<sub>2</sub>), 72.6 (CH), 121.3 (C), 127.9 (CH), 128.0 (CH), 129.0 (5xCH), 130.1 (C), 132.3 (CH), 134.7 (C), 140.4 (C), 142.5 (C), 144.7 (C), 149.3 (C); Anal. Calcd for C<sub>19</sub>H<sub>18</sub>BrN<sub>3</sub>O<sub>3</sub>: C, 54.82; H, 4.36; N, 10.09. Found: C, 54.70; H, 4.44; N, 9.95.

*4-{2-[4-(1,2-Dimethyl-5-nitro-1H-imidazol-4-yl)phenyl]-1-hydroxyethyl}benzonitrile (3g)*: Yellow solid; mp 208 °C (isopropyl alcohol);  $^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$ : 2.45 (s, 3H, CH<sub>3</sub>), 2.91–2.92 (m, 2H, CH<sub>2</sub>), 3.81 (s, 3H, CH<sub>3</sub>), 4.87–4.96 (m, 1H, CH), 5.60 (d,  $J = 4.9$  Hz, 1H, OH), 7.24 (d,  $J = 8.1$  Hz, 2H, 2xCH), 7.56 (t,  $J = 8.1$  Hz, 4H, 4xCH), 7.77 (d,  $J = 8.1$  Hz, 2H, 2xCH);  $^{13}\text{C-NMR}$  (DMSO- $d_6$ )  $\delta$ : 13.9 (CH<sub>3</sub>), 34.1 (CH<sub>3</sub>), 45.1 (CH<sub>2</sub>), 73.0 (CH), 109.6 (C), 119.2 (C), 127.1 (2xCH), 128.9 (2xCH), 129.2 (2xCH), 130.1 (C), 132.1 (2xCH), 134.6 (C), 139.8 (C), 142.5 (C), 149.3 (C), 151.6 (C); Anal. Calcd for C<sub>20</sub>H<sub>18</sub>N<sub>4</sub>O<sub>3</sub>: C, 66.29; H, 5.01; N, 15.46. Found: C, 66.17; H, 5.07; N, 15.22.

*1-(4,5-Dimethoxy-2-nitrophenyl)-2-[4-(1,2-dimethyl-5-nitro-1H-imidazol-4-yl)phenyl]ethanol (3h)*: Black solid; mp 234 °C (acetonitrile);  $^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$ : 2.46 (s, 3H, CH<sub>3</sub>), 2.81 (dd,  $J = 7.9$  Hz et  $J = 13.4$  Hz, 1H, CH<sub>2</sub>), 3.05 (dd,  $J = 2.1$  Hz and  $J = 13.4$  Hz, 1H, CH<sub>2</sub>), 3.83 (s, 3H, CH<sub>3</sub>), 3.84 (s, 3H,



CH<sub>3</sub>), 3.86 (s, 3H, CH<sub>3</sub>), 5.37–5.45 (m, 1H, CH), 5.61 (d,  $J = 4.9$  Hz, 1H, OH), 7.29–7.34 (m, 3H, 3xCH), 7.59–7.65 (m, 3H, 3xCH); <sup>13</sup>C-NMR (DMSO-d<sub>6</sub>)  $\delta$ : 14.0 (CH<sub>3</sub>), 34.1 (CH<sub>3</sub>), 44.5 (CH<sub>2</sub>), 56.2 (2xCH<sub>3</sub>), 69.1 (CH), 107.5 (CH), 109.9 (CH), 129.0 (2xCH), 129.2 (2xCH), 130.2 (C), 134.7 (C), 136.8 (C), 139.1 (C), 140.3 (C), 142.6 (C), 147.4 (C), 149.3 (C), 153.3 (C); Anal. Calcd for C<sub>21</sub>H<sub>22</sub>N<sub>4</sub>O<sub>7</sub>: C, 57.01; H, 5.01; N, 12.66. Found: C, 56.81; H, 4.95; N, 12.50.

*2-[4-(1,2-Dimethyl-5-nitro-1H-imidazol-4-yl)phenyl]-1-[4-(trifluoromethyl)phenyl]ethanol (3i)*: Yellow solid; mp 195 °C (isopropyl alcohol); <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$ : 2.51 (s, 3H, CH<sub>3</sub>), 3.01–3.06 (m, 2H, CH<sub>2</sub>), 3.91 (s, 3H, CH<sub>3</sub>), 4.96 (dd,  $J = 5.5$  Hz and  $J = 7.8$  Hz, 1H, CH), 7.24 (d,  $J = 7.8$  Hz, 2H, 2xCH), 7.46 (d,  $J = 8.2$  Hz, 2H, 2xCH), 7.60 (d,  $J = 8.2$  Hz, 2H, 2xCH), 7.70 (d,  $J = 8.2$  Hz, 2H, 2xCH); <sup>13</sup>C-NMR (CDCl<sub>3</sub>)  $\delta$ : 13.9 (CH<sub>3</sub>), 34.1 (CH<sub>3</sub>), 45.3 (CH<sub>2</sub>), 73.0 (CH), 124.6 (q,  $J = 272$  Hz, C), 124.9 (q,  $J = 3.5$  Hz, CH), 125.0 (CH), 126.9 (2xCH), 127.6 (q,  $J = 31.5$  Hz, C), 129.0 (2xCH), 129.2 (2xCH), 130.0 (C), 134.7 (C), 140.1 (C), 142.5 (C), 149.3 (C), 150.6 (C); Anal. Calcd for C<sub>20</sub>H<sub>18</sub>F<sub>3</sub>N<sub>3</sub>O<sub>3</sub>: C, 59.26; H, 4.48; N, 10.37. Found: C, 59.26; H, 4.81; N, 10.30.

*2-[4-(1,2-Dimethyl-5-nitro-1H-imidazol-4-yl)phenyl]-1-p-tolyethanol (3j)*: Yellow solid; mp 155 °C (isopropyl alcohol); <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$ : 2.16 (bs, 1H, OH), 2.34 (s, 3H, CH<sub>3</sub>), 2.50 (s, 3H, CH<sub>3</sub>), 3.05 (d,  $J = 6.7$  Hz, 2H, CH<sub>2</sub>), 3.89 (s, 3H, CH<sub>3</sub>), 4.88 (t,  $J = 6.7$  Hz, 1H, CH), 7.14 (d,  $J = 8.0$  Hz, 2H, 2xCH), 7.25 (d,  $J = 8.0$  Hz, 4H, 4xCH), 7.69 (d,  $J = 8.0$  Hz, 2H, 2xCH); <sup>13</sup>C-NMR (CDCl<sub>3</sub>)  $\delta$ : 14.1 (CH<sub>3</sub>), 21.1 (CH<sub>3</sub>), 34.1 (CH<sub>3</sub>), 45.9 (CH<sub>2</sub>), 75.0 (CH), 125.8 (2xCH), 129.1 (2xCH), 129.2 (2xCH), 129.6 (2xCH), 130.0 (C), 134.7 (C), 137.2 (C), 139.7 (C), 140.8 (C), 143.5 (C), 148.3 (C); Anal. Calcd for C<sub>20</sub>H<sub>21</sub>N<sub>3</sub>O<sub>3</sub>: C, 68.36; H, 6.02; N, 11.96. Found: C, 68.36; H, 6.16; N, 11.90.

*Ethyl 3-[4-(1,2-dimethyl-5-nitro-1H-imidazol-4-yl)phenyl]-2-hydroxypropanoate (3k)*: Yellow solid; mp 99 °C (isopropyl alcohol); <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$ : 1.28 (t,  $J = 7.1$  Hz, 3H, CH<sub>3</sub>), 2.55 (s, 3H, CH<sub>3</sub>), 3.02 (dd,  $J = 6.7$  Hz and  $J = 13.9$  Hz, 1H, CH<sub>2</sub>), 3.17 (dd,  $J = 4.6$  Hz and  $J = 13.9$  Hz, 1H, CH<sub>2</sub>), 3.91 (s, 3H, CH<sub>3</sub>), 4.22 (q,  $J = 7.1$  Hz, 2H, CH<sub>2</sub>), 4.46 (dd,  $J = 4.6$  Hz and  $J = 6.7$  Hz, 1H, CH), 7.31 (d,  $J = 7.9$  Hz, 2H, 2xCH), 7.72 (d,  $J = 8.2$  Hz, 2H, 2xCH); <sup>13</sup>C-NMR (CDCl<sub>3</sub>)  $\delta$ : 14.2 (CH<sub>3</sub>), 34.5 (CH<sub>3</sub>), 40.4 (CH<sub>2</sub>), 61.9 (CH<sub>2</sub>), 70.9 (CH<sub>3</sub>), 77.2 (CH), 126.8 (C), 129.6 (2xCH), 129.8 (2xCH), 134.1 (C), 139.4 (C), 139.8 (C), 147.7 (C), 173.9 (C); Anal. Calcd for C<sub>16</sub>H<sub>19</sub>N<sub>3</sub>O<sub>5</sub>: C, 57.65; H, 5.75; N, 12.61. Found: C, 57.74; H, 5.87; N, 12.65.

*2-[4-(1,2-Dimethyl-5-nitro-1H-imidazol-4-yl)benzyl]-2-hydroxyacenaphthylen-1(2H)-one (3l)*: Yellow solid; mp 211 °C (isopropyl alcohol); <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>)  $\delta$ : 2.41 (s, 3H, CH<sub>3</sub>), 3.17 (d,  $J = 13.2$  Hz, 1H, CH<sub>2</sub>), 3.41 (d,  $J = 13.2$  Hz, 1H, CH<sub>2</sub>), 3.77 (s, 3H, CH<sub>3</sub>), 6.99 (d,  $J = 7.5$  Hz, 2H, 2xCH), 7.12 (bs, 1H, OH), 7.33–7.40 (m, 3H, 3xCH), 7.63–7.77 (m, 2H, 2xCH), 7.84 (d,  $J = 8.4$  Hz, 1H, CH), 7.94 (d,  $J = 7.0$  Hz, 1H, CH), 8.19 (d,  $J = 8.1$  Hz, 1H, CH); <sup>13</sup>C-NMR (DMSO-d<sub>6</sub>)  $\delta$ : 13.7 (CH<sub>3</sub>), 34.2 (CH<sub>3</sub>), 42.9 (CH<sub>2</sub>), 79.8 (C), 121.3 (2xCH), 125.1 (CH), 128.5 (2xCH), 128.7 (2xCH), 129.9 (CH), 130.0 (2xCH), 130.2 (C), 131.0 (C), 132.0 (C), 134.6 (C), 137.0 (C), 140.4 (C), 140.8 (C), 141.7 (C), 149.1 (C), 205.3 (C); Anal. Calcd for C<sub>24</sub>H<sub>19</sub>N<sub>3</sub>O<sub>4</sub>: C, 69.72; H, 4.63; N, 10.16. Found: C, 69.41; H, 4.73; N, 10.13.

1-[4-(1,2-Dimethyl-5-nitro-1*H*-imidazol-4-yl)phenyl]-2-(4-nitrophenyl)propan-2-ol (**3m**): Orange solid; mp 179 °C (acetonitrile); <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.60 (s, 3H, CH<sub>3</sub>), 2.51 (s, 3H, CH<sub>3</sub>), 3.12 (dd, *J* = 13.2 Hz and *J* = 18.3 Hz, 2H, CH<sub>2</sub>), 3.90 (s, 3H, CH<sub>3</sub>), 7.06 (d, *J* = 8.3 Hz, 2H, 2xCH), 7.57 (d, *J* = 9.0 Hz, 2H, 2xCH), 7.63 (d, *J* = 8.3 Hz, 2H, 2xCH), 8.16 (d, *J* = 9.0 Hz, 2H, 2xCH); <sup>13</sup>C-NMR (CDCl<sub>3</sub>) δ: 14.0 (CH<sub>3</sub>), 29.4 (CH<sub>3</sub>), 34.1 (CH<sub>3</sub>), 50.0 (CH<sub>2</sub>), 74.4 (C), 123.3 (2xCH), 126.1 (2xCH), 129.4 (2xCH), 130.2 (2xCH), 130.4 (C), 134.7 (C), 137.2 (C), 142.9 (C), 146.7 (C), 148.3 (C), 154.8 (C); Anal. Calcd for C<sub>20</sub>H<sub>20</sub>N<sub>4</sub>O<sub>5</sub>: C, 60.60; H, 5.09; N, 14.13. Found: C, 60.60; H, 5.15; N, 13.97.

#### 4. Conclusions

We have reported the synthesis of substituted 2-[4-(1,2-dimethyl-5-nitro-1*H*-imidazol-4-yl)phenyl]-1-arylethanol, ethyl 3-[4-(1,2-dimethyl-5-nitro-1*H*-imidazol-4-yl)phenyl]-2-hydroxypropanoate and 2-[4-(1,2-dimethyl-5-nitro-1*H*-imidazol-4-yl)benzyl]-2-hydroxy-acenaphthylene-1(2*H*)-one from the reaction of 4-[4-(chloromethyl)phenyl]-1,2-dimethyl-5-nitro-1*H*-imidazole with various aromatic carbonyl and α-carbonyl ester derivatives using TDAE methodology. We have shown a new application of TDAE methodology in a heterocyclic series. The pharmacological evaluation, against metronidazole-resistant lines of *Blastocystis sp.*, of all synthesized compounds is under active investigation.

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#### Conflict of Interest

The authors declare no conflict of interest.

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*Sample Availability:* Samples of the compounds **3a-m** are available from the authors.

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