C. R. Chimie 17 (2014) 1050–1056

Contents lists available at ScienceDirect

Comptes Rendus Chimie

www.sciencedirect.com

Full paper/Mémoire

Synthesis and antibacterial properties of new phenothiazinyl- and phenyl-nitrones

Hermina Iulia Petkes [a], Emese Gál [a], Luiza Găină [a], Mihaela Sabou [b], Cornelia Majdik [a], Luminiţa Silaghi-Dumitrescu [a,*]

[a] Faculty of Chemistry and Chemical Engineering, "Babes-Bolyai" University, Kogalniceanu 1, 400084 Cluj-Napoca, Romania
[b] Faculty of Medicine, "Iuliu Hatieganu", University of Medicine and Pharmacy, Victor Babes 41, 400012 Cluj-Napoca, Romania

ARTICLE INFO

Article history:
Received 28 June 2013
Accepted after revision 16 December 2013
Available online 22 July 2014

Keywords:
Phenothiazinyl-nitrones
Phenyl-nitrones
Antifungal activity
Microwave-assisted synthesis
Fluorescence

ABSTRACT

The synthesis of new phenothiazinyl- and phenyl-nitrones under classical *versus* microwave heating conditions is described. Better yields were obtained under microwave irradiation in the condensation reactions of phenothiazyl-carbaldehyde with hydroxylamine derivatives. The structures of the new phenothiazinyl-nitrones were assigned on the basis of MS, FT–IR and NMR spectra. The new nitrones and some known phenyl-nitrones were screened for their antibacterial and antifungal activity against several *Candida* species, Gram negative bacteria, such as *E. coli*, *Citrobacter* spp, *Morganella* spp, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* (± ESBL), *Proteus* spp, *Acinetobacter* spp and the Gram positive bacterium *Staphylococcus aureus*, with moderate results.

1. Introduction

Phenothiazine, one of the oldest bioactive heterocyclic compounds, is present as major pharmacophore group in many types of drugs in clinical use (tranquillizers [1,2], sedatives, anthelmintic [3,4], anti-inflammatory, antimalarial, antimicrobial, antiparkinsonian [5,6], anticonvulsant [7], antitubercular drugs, etc.), as well as in other biologically active compounds, such as bactericidal products, pesticides [8], compounds with analytical applications (redox indicators and reagents in spectrophotometric determinations) [9,10], high temperature antioxidants for lubricants and dyes [11].

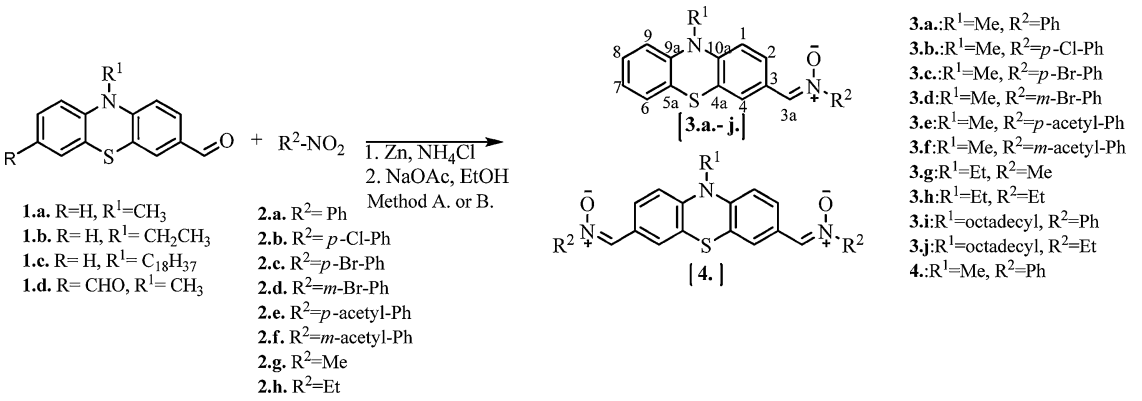
Nitrones are versatile starting materials, with a wide range of applications, including cycloaddition reactions with alkynes, alkenes and α,β-unsaturated aldehydes, to afford carbacephem skeletons [12], isoxazolines [13] and isoxazolidine [14], or generating new carbon–carbon bonds by nucleophilic additions [15]. The interest for the nitrone derivatives is also supported by the antibacterial, antifungal and antiproliferative effects of the above-mentioned classes of organic heterocycles as well as their own antioxidant [16] or antiproliferative properties [17].

The ability of nitrones to trap free radicals and release nitric oxide *in vivo* and *in vitro* is important in the treatment of cerebral ischemia, of neurodegenerative diseases, as well as in the prolongation of lifespan [16,18] – i.e. phenyl-*tert*-butyl-nitrone (PBN or NXY-059) is a free radical scavenger with neuroprotective properties [19].

The most popular method for the preparation of nitrones is the condensation of aldehydes or ketones with N-monosubstituted hydroxylamines [20,21]. The hydroxylamines are generated in *situ* via the reduction of nitro compounds with zinc powder in the presence of weak acids (NH_4Cl or AcOH). Other methods are the direct oxidation of secondary amines to the corresponding nitrones using various metal salts (copper, silver, lead,

* Corresponding author.
E-mail addresses: hermina@chem.ubbcluj.ro (H.I. Petkes), emese@chem.ubbcluj.ro (E. Gál), gluiza@chem.ubbcluj.ro (L. Găină), Sabou.Carmen@umfcluj.ro (M. Sabou), majdik@chem.ubbcluj.ro (C. Majdik), lusi@chem.ubbcluj.ro, luminita.silaghi@gmail.com (L. Silaghi-Dumitrescu).

1631-0748/$ – see front matter © 2013 Académie des sciences. Published by Elsevier Masson SAS. All rights reserved.
http://dx.doi.org/10.1016/j.crci.2013.12.011



Scheme 1. Synthesis of *mono*-phenothiazinyl **3a–3j**, and *di*-phenothiazinyl **4** nitrones. A. MW, 100 °C, 10 min. B. EtOH, 100 °C, 1–6 h.

selenium, mercury, and ruthenium) [22,23] as well as organic oxidants and transition metal complexes (i.e. (salen)Mn(III) [24,25]), the oxidation of imines with *m*-CPBA, dimethyldioxirane (DMD) or the photochemical oxidation ($\lambda = 350$ nm) of aldimines in the presence of O_2 over a TiO_2 suspension [26].

Microwave irradiation is an excellent alternative for a wide range of heterocyclic syntheses, due to its well-known advantages: reaction rate enhancement, reaction time shortage, better yields, lesser solvent usage [27–30]. According to literature data, the improvements achieved under microwave irradiation came from different effects generated by the interaction of electromagnetic waves during the reaction process as compared to the temperature effect [31].

The present paper aims at describing an efficient microwave synthesis of aromatic and heteroaromatic nitrone derivatives together with their antifungal and antibacterial activities.

2. Results and discussion

The new phenothiazinyl *N*-aryl or *N*-alkyl nitrones **3a–3j**, **4** were synthetized with a modified procedure [16] by condensation reactions of the formyl phenothiazine **1a–d** and hydroxylamines **2a–h** in an ethanol/water mixture (5/1, v/v), with low to good yields (16–84%, Scheme 1).

Hydroxylamines containing electron-withdrawing and electron-donating groups were obtained by reducing the corresponding nitro compounds with ammonium chloride and zinc (powder). A comparison of the reaction conditions and yields after purification by flash chromatography is presented in Table 1. Irrespective of the reaction conditions (classical or microwave-activated process), nitrones **3a–3d** and **4** with electron-withdrawing substituents, such as phenyl, chlorophenyl and bromophenyl, were isolated in low yields: 16 to 35% with classical heating and 28–50% under microwave heating (Table 1). Better yields were obtained for nitrones **3g**, **3h**, **3j** with electron-donating alkyl groups (65–77% with classical heating and 81–84% under microwave heating). The shorter reaction time as well as higher yields obtained under microwave conditions makes this a more advantageous method than the classical synthesis (Table 1).

A notable problem associated with many reactive nitrones is dimerization [32]. In the reactions described in this work, no dimerization product was obtained, but the corresponding imines were formed as byproducts during the reaction as well as the purification by flash chromatography. The new class of phenothyazinyl *N*-substituted nitrones is highly sensitive and decomposes on heating (120–130 °C) without melting.

Our interest in nitrone derivatives is related to their potential antifungal and/or antibacterial properties.

Table 1
The synthesis of phenothiazinyl-nitrones by microwave irradiation and by convection heating.

Entry	Compound	R^1	R^2	Convection heating		Microwave	
				Yield (%)[a]	Reaction time (min)	Yield (%)[a]	Reaction time (min)
1	**3a**	Me	C_6H_5	20	120	37	10
2	**3b**	Me	4-Cl-C_6H_4	16	60	30	10
3	**3c**	Me	4-Br-C_6H_4	21	60	28	10
4	**3d**	Me	3-Br-C_6H_4	35	480	50	10
5	**3e**	Me	4-acetyl-C_6H_4	30	90	44	10
6	**3f**	Me	3-acetyl-C_6H_4	41	60	56	10
7	**3g**	Et	Me	65	75	84	10
8	**3h**	Et	Et	77	75	81	10
9	**3i**	Octadecyl	C_6H_5	52	120	74	10
10	**3j**	Octadecyl	Et	70	75	84	10
11	**4**	Me	C_6H_5	34	60	61	10

[a] Isolated yield after column chromatography.

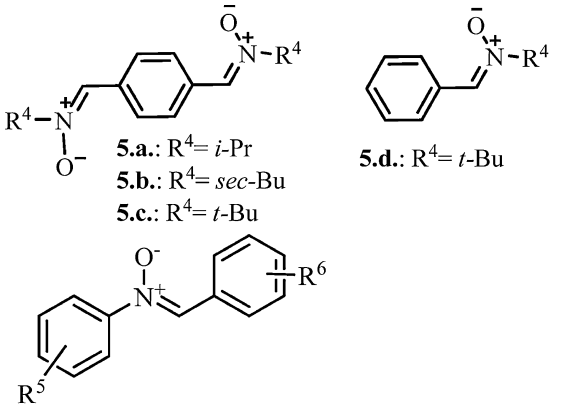
According to our goal, a number of previously reported phenyl-nitrones **5a–d** [33,34], **6a**, **b**, **f** [35] **6d** [36], **6e**, **g**, **h** [37,38], **6m**, **o** [39], **6k** [40], **6j**, **n**, **q** [41,42] was also synthesized (see Fig. 1).

The new phenyl-nitrones **6c**, **6i**, **6l**, **6p** were prepared by the one-pot procedure from the corresponding aromatic amines, nitrobenzene derivatives and zinc powder in acetic acid.

The structures of the newly-synthesized nitrones were confirmed by their ^{1}H NMR, MS and FT–IR spectra. In the ^{1}H NMR spectra, the characteristic signal for the phenothiazinyl-nitrones **3a–j** and **4** is the singlet generated by the imine proton at ~ 7.15 ppm, (value for nitrone **3g**) and 7.79 ppm, for nitrone **4** (see experimental part).

In the UV spectra, the new phenothiazinyl-nitrones **3a–f**, **3i** and **4** present three absorption bands, while the nitrones **3g**, **3h** and **3j** present only two. The intense absorption band at 302–318 nm is due to the π–π^* electronic transition, while the moderate one, in the range 370–400 nm, with the extinction coefficient (ε) between 8×10^3 and 2×10^4, is due to the n–π^* electronic transitions within the phenothiazinyl-imino chromophore. The band around 270 nm is correlated with the presence of the phenyl group. The bathochromic shift of the absorption maxima for compound **4** compared to compound **3a** is due to the presence of the second imine unit. The presence of the molecular ion, the cleavage of the *N*-alkyl bond in the phenothiazine unit and the N–O bond in the nitrone unit are common features of the mass spectra of these new nitrones.

All phenothiazinyl-nitrones display light-blue fluorescence with large Stokes shifts ($\Delta\nu$ = 7076–7888 cm^{-1}) and



6.a.:R^5=H, R^6=*o*-NO$_2$
6.b.:R^5=H, R^6=*m*-NO$_2$
6.c.:R^5=H, R^6=*m*,*p*-diNO$_2$
6.d.:R^5=H, R^6=*p*-Br
6.e.:R^5=H, R^6=*m*,*p*-diMeO
6.f.:R^5=H, R^6=*p*-OMe
6.g.:R^5=H, R^6=*m*-Cl
6.h.:R^5=H, R^6=*p*-Br
6.i.:R^5=*p*-Cl, R^6=*m*-Cl
6.j.:R^5=*p*-Cl, R^6=*p*-Br
6.k.:R^5=*p*-Cl, R^6=*o*-NO$_2$
6.l.:R^5=*p*-Cl, R^6=*m*-OH
6.m.:R^5=*p*-Cl, R^6=*p*-OH
6.n.:R^5=*p*-Cl, R^6=*p*-OMe
6.o.:R^5=*p*-Cl, R^6=*m*,*p*-diMeO
6.p.:R^5=*p*-Br, R^6=*m*-OH
6.q.:R^5=*p*-Br, R^6=*p*-MeO

Fig. 1. Structure of phenyl mono-, and di-nitrones.

Table 2
Optical properties of phenothiazinyl-nitrones.

Compound	λ_{abs} [nm] (ε mol^{-1}cm^{-1})[a]	λ_{em} [nm]	Stokes shift $\Delta\nu$ [cm^{-1}]	Φ_F[b]
3a	315, 272, 393(9517)	551	7255	7.83
3b	316, 274, 385(8277)	521	7142	5.59
3c	316, 275, 380(10048)	518	7103	5.01
3d	317, 275, 397(9561)	555	7535	5.43
3e	312, 241, 398(8480)	550	7211	7.77
3f	314, 271, 402(9398)	542	7197	8.33
3g	302, 377(14026)	519	7275	3.50
3h	302, 377(21778)	515	7076	4.70
3i	314, 275, 382(14010)	569	7888	1.90
3j	302, 376(22408)	518	7235	4.20
4	318, 419(16280)	554	7595	5.43

[a] UV–Vis measured in CH_2Cl_2.
[b] Quantum yields against perylene standard in cyclohexane.

the quantum yields (Φ_F) between 1.90 for **3i** and 4.7% for **3h**.

The quantum yields were calculated [43] using perylene in cyclohexane as standard, Table 2.

3. Biological assay

The antifungal and antibacterial activities of the new and already reported nitrone derivatives mentioned above were evaluated against several *Candida* species Gram negative bacteria such as *E. coli*, *Citrobacter* spp, *Morganella* spp, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* (± ESBL), *Proteus* spp, *Acinetobacter* spp, and the Gram positive bacterium *Staphylococcus aureus*.

Antifungal and antibacterial activities were investigated in triplicate, by the disk diffusion method at 8 μM nitrone concentration. Low inhibition potentials (diameter of inhibition area 3–5 mm) were recorded with few exceptions, two *Candida* strains (*Candida albicans* and *Candida krusei*), were sensitive to compounds **5a**, **6a** and **6p**, with the diameter of inhibition area at 10–11 mm.

For the phenothiazinyl-nitrones **3a**, **3h** and **4**, the tests were repeated at higher concentration (25 μg/disk), with the same standard fluconazole concentration on the disk. The fluconazole-resistant *Candida* strains involved in these tests were *Candida parapsilosis, famata* and *glabrata* (isolated from blood), and *albicans* and *krusei*, isolated from the urine of patients. For the *C. glabrata* and *C. krusei*, the investigated nitrones did not present inhibition activities. In the case of *C. famata*, compounds **3a** and **4** present minimum inhibition activity (d: 3 mm and 4 mm, respectively). A limited inhibition activity (d: 3 mm) was observed for the phenothiazinyl nitrone **3h** on *C. albicans*. Only the *C. parpsilosis* was sensitive to phenothiazinyl-nitrones, with the inhibition diameter of 6 mm for **3a**, 7 mm for nitrone **3h** and 6 mm for nitrone **4**.

4. Conclusions

In conclusion, a novel class of functionalized phenothiazinyl-nitrones with aromatic and aliphatic chains was synthesized and structurally characterised. Higher yields in a shorter reaction time were obtained under microwave irradiation compared to classical heating. The

new nitrones and some known phenyl-nitrones were screened for their antibacterial and antifungal activity against several *Candida* species and Gram negative or positive bacteria, with moderate results.

5. Experimental

5.1. General information

All reagents and solvents were obtained from commercial sources and were used without purification. Phenyl-nitrones **5a–5d**, **6a–6q** were prepared by the classical synthesis method according to the literature data [29–38].

The infrared spectra were recorded on a Bruker Vector 22 FT–IR spectrometer from 4000 to 600 cm^{-1} using KBr pellets. The NMR spectra were recorded at room temperature on a Bruker Avance instrument ($^1H/^{13}C$: 300 MHz/75 MHz) using deuterated solvents; chemical shifts are reported in ppm relative to TMS, *J* values are given in Hz. For elemental analyses (C, N, H, S), a Thermo Flash 1112 Series elemental analyser was used. Mass spectra were measured on a Shimadzu QP-2010 PLUS GC-MS mass spectrometer (DI, EI-70 eV). The reaction mixtures were irradiated in a CEM Discover LabMate microwave reactor. UV–Vis spectra were recorded in dichloromethane with a PerkinElmer Lambda 35 UV–Vis spectrophotometer; emission spectra were measured in dichloromethane using a PerkinElmer FL 55 fluorescence spectrophotometer. Flash chromatography was performed using silica gel (60 Å, particle size 40–63 μm). The reactions were monitored by thin-layer chromatography (TLC) on aluminium plates precoated with silica gel (60, F_{254}) and visualized by UV light. For the microbial identification, the Vitek 2 bioMerieux system was used.

5.2. Antimicrobial assay

In vitro antifungal and antibacterial activities for the nitrone derivatives were tested according to the disk diffusion method using 5-mm-diameter disk papers [44]. The fungi and bacteria isolated from various body fluids (urine, sputum, wound, blood) were grown [45] onto a Mueller–Hinton culture medium by incubation at 37 °C for 48 h. After identification, according the CLSI standards [46], each colony was suspended in 5 mL of a sterile saline solution. The turbidity of the inoculum was adjusted to McFarland Turbidity Standard No. 0.5, and the inoculums were added to different Petri plates filled with a Mueller–Hinton culture medium, or Mueller–Hinton and methylene blue culture medium for *Candida* spp. strains. The five sterile filter paper disks were aseptically placed on the inoculated plate, at equal distance from each other. On each plate, the paper disks were impregnated aseptically by pipetting with DMSO (10 μL, the solvent was used as a reference) or with each one of the investigated compounds **3a–j**, **6a–q** (10 μL, 8 mM solution in DMSO). Agar plates were incubated at 37 °C for 24 h, 48 h and 72 h, respectively, and the diameter of the inhibition area was measured. Tests were performed in triplicate.

5.3. General experimental procedures for the synthesis of phenothiazinyl-nitrones

5.3.1. Preparation of hydroxylamines

The nitro derivative (1 mmol) disolved in ethanol (5 mL), ammonium chloride (0.053 g, 1 mmol) and water (1 mL) were mixed under stirring and cooled on an ice bath to 5 °C, after which zinc dust (0.13 g, 2 mmol) was added slowly. The suspension thus obtained was used without further purification.

5.3.1.1. Method A: microwave-assisted synthesis. In a 10-mL microwave reaction vessel equipped with a stirrer and a cap, the corresponding hydroxylamine solution (1 mmol) and sodium acetate (0.123 g, 1.5 mmol) were added to the corresponding phenothiazine derivative (1 mmol). The reaction mixture was subjected to microwave irradiation using a power level of 100 W at 100 °C for 10 min. After cooling, the mixture was diluted with water and dichloromethane, filtered and the residue washed with the organic solvent. The organic layer was separated, dried on anhydrous sodium sulphate and filtered. The solvent was removed under vacuum and the residue was purified by flash column chromatography on silica with various eluent systems.

5.3.1.2. Method B: classical synthesis. Hydroxylamine was synthesized as described above. To the hydroxylamine suspension (1 mmol), the corresponding phenothiazine derivative (1 mmol) and sodium acetate (0.123 g, 1.5 mmol) were added; the reaction mixture was stirred at 100 °C for 1–6 h. After cooling, the mixture was worked up as described before for microwave-assisted synthesis.

Synthetic procedures for each phenothiazinyl-nitrones and copies of ^1H NMR, ^{13}C NMR are included as Supplementary material (S) and are available on the website of this journal.

5.3.2. (Z)-N-((10-methyl-10H-phenothiazin-3-yl)methylene)aniline oxide 3a

Yellowish–green solid; yield 37% (0.12 g) was obtained by microwave-assisted heating, and 20% (0.06 g) by convective heating. Decomposition: 121 °C without melting. IR (KBr) ν_{max}/cm^{-1} 3015, 1550, 679; MS (70 eV), *m/z* (%): 332 (100, $[M]^+$), 317 (18); ^1H NMR ($CDCl_3$) δ 3.41 (s, 3H, N–CH_3), 6.86–6.81 (m, 2H, H_1, H_9), 6.95 (t, 1H, H_7, $J_{H_7-H_6} = 7.9$, $J_{H_7-H_8} = 7.4$), 7.13 (d, 1H, H_6, $J_{H_7-H_6} = 7.9$), 7.19 (t, 1H, H_8, $J_{H_7-H_8} = 7.4$, $J_{H_8-H_9} = 8.9$), 7.49–7.44 (m, 3H, H_c, H_d), 7.75 (d, 2H, H_b, $J_{H_b-H_c} = 7.5$), 7.78 (s, 1H, H_{3a}), 8.18 (d, 1H, H_4, $J_{H_2-H_4} = 1.7$), 8.26 (d, 1H, H_2, $J_{H_1-H_2} = 7.8$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.9, 144.7, 133.6, 133.6, 129.81, 129.3, 129.2, 127.7, 127.6, 127.3, 125.4, 123.4, 123.2, 121.7, 114.5, 113.9, 35.7; anal. calcd. for $C_{20}H_{16}N_2OS$: C, 72.26; H, 4.85; N, 8.43; S, 9.65; O, 4.81; found: C, 72.36; H, 4.89; N, 8.40; S, 9.58.

5.3.3. (Z)-4-chloro-N-((10-methyl-10H-phenothiazin-3-yl)methylene)aniline oxide 3b

Yellowish–green solid; yield 30% (0.11 g) was obtained by microwave-assisted heating, and 16% (0.05 g) by convective heating. Decomposition: 115 °C without melting.

IR (KBr) ν_{max}/cm^{-1} 2894, 1611, 812, 734; MS (70 eV, EI), *m/z* (%): 366 (100, $[M]^+$), 351 (32), 350 (21); ^1H NMR ($CDCl_3$) δ 3.42 (s, 3H, N–CH_3), 6.87–6.82 (m, 2H, H_1, H_9), 6.96 (t, 1H, H7, $J_{H_7-H_6} = 7.5$, $J_{H_7-H_8} = 7.4$), 7.18–7.12 (m, 2H, H_6, H_8), 7.43 (d, 2H, H_b, $J_{H_b-H_c} = 8.8$), 7.72 (d, 2H, H_c, $J_{H_b-H_c} = 8.8$), 7.76 (s, 1H, H_{3a}), 8.16 (d, 1H, H_4, $J_{H_2-H_4} = 1.4$), 8.25 (d, 1H, H_2, $J_{H_1-H_2} = 8.4$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.2, 153.1, 148.3, 146.7, 134.2, 133.2, 131.7, 129.3, 127.6, 125.6, 124.9, 122.6, 120.0, 120.1, 119.9, 118.5, 117.3; anal. calcd. for $C_{20}H_{15}ClN_2OS$: C, 65.48; H, 4.12; N, 7.64; S, 8.74; O, 4.36; found: C, 65.47; H, 4.14; N, 7.63; S, 8.73.

5.3.4. (Z)-4-bromo-N-((10-methyl-10H-phenothiazin-3-yl)methylene)aniline oxide 3c

Yellowish–green solid; yield 28% (0.11 g) was obtained by microwave-assisted heating, and 21%, (0.08 g) by convective heating. Decomposition: 125–127 °C without melting. IR (KBr) ν_{max}/cm^{-1} 3124, 1542, 757, 593; MS (70 eV), *m/z* (%): 410 (100, $[M]^+$), 412 (96), 394 (27), 396 (23); ^1H NMR ($CDCl_3$) δ 3.41 (s, 3H, N–CH_3), 6.86–6.82 (m, 2H, H_1, H_9), 6.96 (t, 1H, H_7, $J_{H_7-H_6} = 7.4$, $J_{H_7-H_8} = 7.4$), 7.21–7.11 (m, 4H, H_6, H_8, H_b), 7.60 (d, 2H, Hc, $J_{H_b-H_c} = 8.5$), 7.76 (s, 1H, H_{3a}), 8.16 (d, 1H, H_4, $J_{H_2-H_4} = 1.7$), 8.23 (d, 1H, H_2, $J_{H_1-H_2} = 8.6$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.1, 144.6, 133.7, 132.3, 129.4, 129.2, 128.3, 127.7, 127.4, 125.4, 123.2, 114.6, 113.9; anal. calcd. for $C_{20}H_{15}BrN_2OS$: C, 58.40; H, 3.68; N, 6.81; S, 7.80; O, 3.89; found: C, 58.42; H, 3.70; N, 6.82; S, 7.84.

5.3.5. (Z)-3-bromo-N-((10-methyl-10H-phenothiazin-3-yl)methylene)aniline oxide 3d

Yellowish–green solid; yield 50% (0.21 g) was obtained by microwave-assisted heating, and 35% (0.14 g) by convective heating. Decomposition: 127 °C without melting. IR (cm^{-1}, KBr) ν_{max} 3155, 1608, 762, 593; MS (70 eV), *m/z* (%): 410 (100, $[M]^+$), 412 (98), 394 (31), 396 (26); ^1H NMR ($CDCl_3$) δ 3.41 (s, 3H, N–CH_3), 6.85–6.82 (m, 2H, H_1, H_9), 6.97 (t, 1H, H_7, $J_{H_7-H_6} = 7.5$, $J_{H_7-H_8} = 7.4$), 7.15 (d, 1H, H_6, $J_{H_7-H_6} = 7.0$), 7.19 (t, 1H, H_8, $J_{H_7-H_8} = 7.4$, $J_{H_8-H_9} = 8.0$), 7.33 (t, 1H, H_e, $J_{H_e-H_d} = 8.1$, $J_{H_e-H_f} = 8.0$), 7.76 (d, 1H, H_f, $J_{H_e-H_f} = 8.0$), 7.71 (d, 1H, H_d, $J_{H_e-H_d} = 8.1$), 7.77 (s, 1H, H_{3a}), 7.96 (d, 1H, H_b, $J_{H_b-H_f} = 1.7$), 8.19 (d, 1H, H_4, $J_{H_2-H_4} = 1.6$), 8.24 (d, 1H, H_2, $J_{H_1-H_2} = 7$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.3, 148, 144.5, 133.8, 132.7, 130.5, 129.4, 127.7, 127.6, 127.3, 125, 124.9, 123.3, 123.2, 122.8, 122.7, 120.2, 114.5, 113.8, 35.6; anal. calcd. for $C_{20}H_{15}BrN_2OS$: C, 58.40; H, 3.68; N, 6.81; S, 7.80; O, 3.89; found: C, 58.45; H, 3.73; N, 6.78; S, 7.89.

5.3.6. (Z)-4-acetyl-N-((10-methyl-10H-phenothiazin-3-yl)methylene)aniline oxide 3e

Orange-red solid; yield 44% (0.16 g) was obtained by microwave-assisted heating, and 30% (0.10 g) by convective heating. Decomposition: 123 °C without melting. IR (KBr) ν_{max}/cm^{-1} 2986, 1721, 1573, 589MS (70 eV), *m/z* (%): 374 (100, $[M]^+$), 359 (42), 358 (37); ^1H NMR ($CDCl_3$) δ 2.62 (s, 3H, CH_3), 3.38 (s, 3H, N–CH_3), 6.82–6.79 (m, 2H, H_1, H_9), 6.94 (t, 1H, H_7, $J_{H_7-H_6} = 7.0$, $J_{H_7-H_8} = 7.6$), 7.11 (d, 1H, H_6, $J_{H_7-H_6} = 7.6$), 7.11 (t, 1H, H_8, $J_{H_7-H_6} = 7.6$), 7.85 (d, 2H, H_b, $J_{H_b-H_c} = 8.6$), 7.84 (s, 1H, H_{3a}), 8.01 (d, 2H, $J_{H_c-H_b} = 8.6$), 8.19 (d, 1H, H_4, $J_{H_2-H_4} = 1.6$), 8.23 (d, 1H, H_2, $J_{H_1-H_2} = 8.3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.8, 151.5, 148.2, 144.4, 137.7, 134.3, 129.6, 129.4, 127.7, 127.7, 127.3, 124.8, 123.3, 122.7, 121.7, 114.6 113.8, 35.6, 26.8; anal. calcd. for $C_{22}H_{18}N_2O_2S$: C, 70.57; H, 4.85; N, 7.48; S, 8.56; O, 8.55; found: C, 70.59; H, 4.87; N, 7.47; S, 7.57.

5.3.7. (Z)-3-acetyl-N-((10-methyl-10H-phenothiazin-3-yl)methylene)aniline oxide 3f

Orange-red solid; yield 56% (0.21 g) was obtained by microwave-assisted heating, and 41% (0.14 g) by convective heating. Decomposition: 123–126 °C without melting. IR (KBr) ν_{max}/cm^{-1} 3086, 1811, 1636, 593; MS (70 eV), *m/z* (%): 347 (100, $[M]^+$), 359 (32), 358 (22); ^1H NMR ($CDCl_3$) δ 2.65 (s, 3H, CH_3), 3.40 (s, 3H, N–CH_3), 6.85–6.80 (m, 2H, H_1, H_9), 6.95 (t, 1H, H_7, $J_{H_7-H_6} = 7.5$, $J_{H_7-H_8} = 7.4$), 7.12 (d, 1H, H_6, $J_{H_7-H_6} = 7.5$), 7.17 (t, 1H, H_8, $J_{H_7-H_8} = 7.4$, $J_{H_8-H_9} = 8.0$), 7.57 (t, 1H, H_e, $J_{H_e-H_d} = 7.8$, $J_{H_e-H_f} = 8.0$), 7.86 (s, 1H, H_{3a}), 8.02–7.98 (m, 2H, H_d, H_f), 8.25–8.22 (m, 2H, H_b, H_2), 8.32 (d, 1H, H_4, $J_{H_1-H_2} = 1.6$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.9, 170.4, 149, 148.1, 144.5, 137.9, 133.9, 129.7, 129.5, 129.4, 127.7, 127.3, 126, 124.9, 123.4, 123.3, 122.8, 121.1, 114.5, 113.8; anal. calcd. for $C_{22}H_{18}N_2O_2S$: C, 70.57; H, 4.85; N, 7.48; S, 8.56; O, 8.55; found: C, 70.56; H, 4.80; N, 7.50; S, 8.59.

5.3.8. (Z)-N-((10-ethyl-10H-phenothiazin-3-yl)methylene)methanamine oxide 3g

Green oil; yield 84% (0.22 g) was obtained by microwave irradiation, and 65% (0.17 g) by convective heating. Decomposition: 126 °C without melting. IR (KBr) ν_{max}/cm^{-1} 2874, 1645, 1468, 670; MS (70 eV), *m/z* (%): 284 (100, $[M]^+$), 269 (62), 268 (45); ^1H NMR ($CDCl_3$) δ 1.33 (t, 3H, CH_3, $J_{CH_2-CH_3} = 14$), 3.75 (s, 3H, CH_3), 3.84 (q, 2H, CH_2, $J_{CH_2-CH_3} = 14$), 6.80–6.74 (m, 2H, H_1, H_9), 6.85 (t, 1H, H_7, $J_{H_7-H_6} = 7.0$, $J_{H_7-H_8} = 7.6$), 7.02 (d, 1H, H_6, $J_{H_7-H_6} = 7.0$), 7.08 (t, 1H, H_8, $J_{H_7-H_8} = 7.6$, $J_{H_8-H_9} = 7.8$), 7.15 (s, 1H, H_{3a}), 7.91 (d, 1H, H_4, $J_{H_2-H_4} = 1.7$), 7.98 (d, 1H, H_2, $J_{H_1-H_2} = 8.1$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.3, 143.6, 134.4, 128.2, 127.4, 127.3, 127.1, 124.7, 123.5, 123.4, 122.8, 115.1, 114.3, 53.9, 42, 12.8; anal. calcd. for $C_{16}H_{16}N_2OS$: C, 67.58; H, 5.67; N, 9.85; S, 11.28; O, 5.63; found: C, 67.23; H, 5.62; N, 9.8050; S, 11.09.

5.3.9. (Z)-N-((10-ethyl-10H-phenothiazin-3-yl)ethylene)methanamine oxide 3h

Green solid; yield 81% (0.23 g) was obtained by microwave irradiation, and 77% (0.18 g) by convective heating. Decomposition: 127 °C without melting. IR (KBr) ν_{max}/cm^{-1} 3019, 1501, 1468, 751; MS (70 eV), *m/z* (%): 298 (100, $[M]^+$), 283 (58), 282 (39); 269 (13); ^1H NMR ($CDCl_3$) δ 1.39 (t, 3H, CH_3, $J_{CH_2-CH_3} = 14.5$), 1.52 (t, 3H, CH_3, $J_{CH_2-CH_3} = 13.9$), 3.95–3.86 (quin, 4H, CH_2), 6.81 (d, 1H, H_9, $J_{H_8-H_9} = 7.0$), 6.82 (d, 1H, H_1, $J_{H_1-H_2} = 7.5$), 6.90 (t, 1H, H_7, $J_{H_7-H_6} = 7.6$, $J_{H_7-H_8} = 7.4$), 7.07 (d, 1H, H_6, $J_{H_7-H_6} = 7.6$), 7.11 (t, 1H, H_8, $J_{H_7-H_8} = 7.4$, $J_{H_8-H_9} = 7.0$), 7.24 (s, 1H, H_{3a}), 7.99 (d, 1H, H_4, $J_{H_2-H_4} = 1.2$), 8.05 (d, 1H, H_2, $J_{H_1-H_2} = 7.9$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.1, 143.5, 132.7, 128.2, 127.2, 127.1, 127, 124.7, 123.4, 123.2, 122.7, 115, 114.2, 61.3, 41.8, 13.4, 12.6; anal. calcd. for $C_{17}H_{18}N_2OS$: C, 68.42; H, 6.08; N, 9.39; S, 10.5; O, 5.36; found: C, 68.42; H, 6.03; N, 9.35; S, 10.09.

5.3.10. (Z)-N-((10-octadecyl-10H-phenothiazin-3-yl)methylene)aniline oxide **3i**

Green solid; yield 74% (0.42 g) was obtained by microwave irradiation, and 52% (0.29 g) by convective heating. Decomposition: 121–124 °C without melting. IR (KBr) ν_{max}/cm^{-1} 2919, 1457, 756; MS (70 eV), *m/z* (%): 570 (74, $[M]^+$), 554 (23), 499 (39), 485 (82), 387 (27), 359 (18), 345 (32); ^1H NMR ($CDCl_3$) δ 0.88 (t, 3H, δCH_3, $J_{CH_2-CH_3} = 12.3J$), 1.26 (s, 30H, CH_2), 1.79 (q, 2H, βCH_2, $J_{CH_2-CH_2} = 13.4$), 3.95–3.86 (quin, 4H, CH_2, $J_{CH_2-CH_2} = 13.1$), 3.83 (t, 2H, αCH_2, $J_{CH_2-CH_2} = 13.8$), 6.85–6.83 (m, 2H, H_1, H_9), 6.90 (t, 1H, H_7, $J_{H_7-H_6} = 7.4$, $J_{H_7-H_8} = 7.4$), 7.15–7.06 (m, 2H, H_6, H_8), 7.43–7.41 (m, 3H, H_c, H_d), 7.76–7.72 (m, 3H, H_{3a}, H_b), 7.13(d, 1H, H_4, $J_{H_2-H_4} = 1.2$), 8.25 (d, 1H, H_2, $J_{H_1-H_2} = 8.6$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.8 8, 147,1, 143.9, 133.5, 129.6, 129.1, 128.8, 127.7, 127.4, 127.3, 125, 124.2, 123.9, 122.9, 121.5, 115.5, 114.7, 47.7, 31.9, 29.7, 29.5, 29.4, 29.2, 26.8, 26.7, 22.7, 14.1; anal. calcd. for $C_{37}H_{50}N_2OS$: C, 77.85; H, 8.83; N, 4.91; S, 5.62; O, 2.80; found: C, 77.84; H, 8.89; N, 4.97; S, 5.67.

5.3.11. (N)-N-((10-octedecyl-10H-phenothiazin-3-yl)ethylene)methanamine oxide **3j**

Yellowish–green solid, yield 84% (0.43 g) was obtained by microwave irradiation, and 70% (0.36 g) by convective heating. Decomposition: 125 °C without melting. IR (KBr) ν_{max}/cm^{-1} 3102, 1576, 834; MS (70 eV), *m/z* (%): 522 (100, $[M]^+$), 507 (26), 506 (41), 451 (21), 395 (56), 311 (100); ^1H NMR ($CDCl_3$) δ 0.87 (t, 3H, δCH_3, $J_{CH_2-CH_3} = 12.6$), 1.25 (s, 30H, CH_2), 1.77 (q, 2H, βCH_2, $J_{CH_2-CH_2} = 13.3$), 3.90 (q, 2H, CH_2, $J_{CH_2-CH_2} = 13.3$, 6.84–6.80 (m, 2H, H_1, H_9), 6.89 (t, 1H, H_7, $J_{H_7-H_6} = 6.8$, $J_{H_7-H_8} = 7.4$), 7.07 (d, 1H, H_6, $J_{H_7-H_6} = 6.8$), 7.12 (t, 1H, H_8, $J_{H_7-H_8} = 7.4$), 7.23 (s, 1H, H_{3a}), 7.95 (d, 1H, H_4, $J_{H_2-H_4} = 1.8$), 8.10 (d, 1H, H_2, $J_{H_1-H_2} = 6.8$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.6, 144.2, 132.7, 128.1, 127.4), 127.3, 127.2, 124.9, 124.3, 124.1, 122.8, 115.5, 114.7, 61.5, 47.6, 29.7, 29.75, 29.6 29.4, 29.3, 26.9, 26.7, 22.7, 14.2, 13.6; anal. cald. for $C_{33}H_{50}N_2OS$: C, 75.81; H, 9.64; N, 5.36; S, 6.13; O, 3.06; found: C, 75.83; H, 9.65; N, 5.33; S, 6.19; anal. calcd. for $C_{33}H_{50}N_2OS$: C, 75.81; H, 9.64; N, 5.36; S, 6.13; O, 3.06; found: C, 75.83; H, 9.65; N, 5.33; S, 6.19.

5.3.12. (N,N′Z,N,N′Z)-N,N′-(10-methyl-10H-phenothiazine-3,7-diyl)bis(methan-1-yl-1-ylidene) dianiline oxide **4**

Green solid; yield 61% (0.27 g) was obtained by microwave irradiation, and 34% (0.15 g) by convective heating. Decomposition: 128 °C without melting. IR (KBr) ν_{max}/cm^{-1} 2916, 1442, 624; MS (70 eV), *m/z* (%): 451 (100, $[M]^+$), 436 (24), 435 (39); ^1H NMR ($CDCl_3$) δ 3.42 (s, 3H, N–CH_3), 6.85–6.82 (m, 2H, H_1, H_9), 7.49–7.42 (m, 6H, H_c, H_d), 7.76–7.73 (m, 4H, H_b), 7.79 (s, 1H, H_{3a}), 7.16(d, 2H, H_4, H_6, $J_{H_2-H_4} = 1.6$), 8.27 (d, 2H, H_2, H_6, $J_{H_1-H_2} = 8.6$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.9, 145.5, 133.4, 129.9, 129.2, 129.2, 127.6, 125.9, 122.9, 121.7, 114.2, 35. 9; anal. calcd. for $C_{33}H_{50}N_2OS$: C, 71.82; H, 4.69; N, 9.31; S, 7.10; O, 7.09; found: C, 71.82; H, 4.71; N, 9.31; S, 7.12.

5.3.13. (Z)-N-benzylidene-3,4-dinitroaniline oxide **6c**

Light brown solid, yield 85% (0.24 g), mp 120–121 °C. MS (70 eV), *m/z* (%): 287 (100, $[M]^+$), 271 (65); ^1H NMR ($CDCl_3$) δ 7.55–7.53 (m, 3H, H_3, H_4, H_5), 7.80–7.77 (m, 2H, H_2, H_6), 8.55 (dd, 1H, H_f, $J_{H_f-H_e} = 8.5$, $J_{H_f-H_b} = 2.3$), 8.73 (s, 1H, CH), 8.90 (d, 1H, H_b), 9.71(d, 1H, H_e, $J_{H_f-H_e} = 8.5$), ^{13}C NMR (75 MHz, $CDCl_3$) δ 120.5, 121.8, 126.7, 127.8, 129.5, 129.7, 130.2, 131,4; anal. calcd. for $C_{13}H_9N_3O5$: C, 54.36; H, 3.16; N, 14.63; O, 27.85; found: C, 454.27; H, 3.20; N, 14.58.

5.3.14. (Z)-3-chloro-N-(4-chlorobenzylidene)aniline oxide **6i**

Beige solid, yield 75% (0.19 g); mp 105–106 °C. MS (70 eV), *m/z* (%): 265/267/269 (30/7/3, $[M]^+$), 249 (100); ^1H NMR ($CDCl_3$) δ 7.51–7.40 (mt, 3H, H_1, H_2, H_d), 7.75 (d, 2H, H_3, H_6, $J_{H_3-H_2} = 8$), 7.90 (s, 1H, CH), 8.17 (t, 1H, H_c, $J_{H_c-H_b} = 8$, $J_{H_c-H_d} = 8$), 8.26 (d, 1H, H_b, $J_{H_c-H_b} = 8$), 8.55 (s, 1H, H_f); ^{13}C NMR (75 MHz, $CDCl_3$) δ 123.0, 127.1, 127.2, 128.5, 128.9, 129, 129.5, 129.9, 131.1, 131.9,133.2, 134.8, 136.1; anal. calcd. for $C_{13}H_9Cl_2NO$: C, 58.67; H, 3.41; Cl, 26.64; N, 5.26; O 6.01; found: C, 58.72; H, 3.48; N, 5.18.

5.3.15. (Z)-N-(4-chlorobenzylidene)-3-hydroxyaniline oxide **6l**

Off-white solid, yield 83% (0.2 g); mp 195–196 °C. MS (70 eV), *m/z* (%): 247/249 (70/21, $[M]^+$), 230/232 (100); ^1H NMR (DMSO-d_6) δ 6.90 (dd, 1H, H_d, $J_{H_d-H_e} = 8.9$, $J_{H_d-H_f} = 1.7$), 7.29 (t, 1H, H_e, $J_{H_d-H_e} = 8.9$, $J_{H_f-H_e} = 7.8$), 7.60 (d, 2H, H_2, H_6, $J_{H_2-H_3} = 8.8$), 7.71 (d, 1H, H_f,, $J_{H_f-H_e} = 7.8$), 7.95 (d, 2H, H_3, H_5, $J_{H_2-H_3} = 8.8$), 8.16 (s, 1H, CH), 8.43 (s, 1H, H_b), 9.68 (broad s, 1H, OH); ^{13}C NMR (75 MHz, DMSO) δ 114.8, 118.2, 120.7, 123.4, 129.0, 129.5, 131.9, 134.1, 134.2, 147.2, 157.2; anal. calcd. for $C_{13}H_{10}ClNO_2$: C, 63.04; H, 4.07; Cl, 14.31; N, 5.66; O, 12.92; found: C, 63.12; H, 4.10; N, 5.62.

5.3.16. (Z)-N-(4-bromobenzylidene)-3-hydroxyaniline oxide **6p**

Beige solid, yield 80% (0.23 g); mp 188–190 °C. MS (70 eV), *m/z* (%): 291/293 (100, $[M]^+$), 275/277 (85); ^1H NMR (DMSO-d_6) δ 6.91 (dd, 1H, H_d, $J_{H_d-H_e} = 8.6$, $J_{H_d-H_f} = 1.7$), 7.29 (t, 1H, H_e, $J_{H_d-H_e} = 8.6$, $J_{H_f-H_e} = 7.9$), 7.75–7.69 (m, 3H, H_2, H_6, H_f), 7.89 (d, 2H, H_3, H_5, $J_{H_2-H_3} = 8.9$), 8.15 (s, 1H, CH), 8.44 (s, 1H, H_b), 9.68 (broad s, 1H, OH); ^{13}C NMR (75 MHz, DMSO) δ 115, 118.2, 120, 120.7, 122.8, 123.7, 129.5, 131.2, 131.9, 134.1, 147.6, 157.3; anal. calcd. for $C_{13}H_{10}NO_2$: C, 53.45; H, 3.45; Br, 27.35; N, 4.79; O, 10.95; found: C, 53.50; H, 3.49; N, 4.82.

Acknowledgments

Financial support from the Romanian Ministry of Education, Research Youth and Sports (Grant ID PCCE 140/2008), as well as from the Sectorial Operational Programs for Human Resources Development 2007–2013, co-financed by the European Social Fund, under the project No. POSDRU/107/1.5/S/76841 with the title "Modern Doctoral Studies: Internationalization and Interdisciplinarity" is gratefully acknowledged.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.crci.2013.12.011.

References

[1] R. Hazard, E. Corteggiani, A. Cornec, C.R. Soc. Biol. 143 (1950) 906.
[2] Y. Kase, T. Yuizonto, Chem. Pharm. Bull. 7 (1959) 378.
[3] L.E. Swanson, D.A. Porter, J.W. Connelly, J. Am. Vet. Med. Assoc. 96 (1940) 704.
[4] H.A. Oelbers, Arznein. Forsch. 5 (II) (1951) 139.
[5] V.G. Longo, D. Bovet, Pharm. Sci. Technol. Today 4 (1950) 515.
[6] J. Mahaux, K.K. Kowalewski, J. Mahaux, K.K. Kowalewski, Arch Int. Pharmacodyn. Ther. 80 (1949) 464.
[7] A. Balestrieri, Arch. Int. Pharmacodyn. Ther. 100 (1955) 361.
[8] F.L. Campbell, W.N. Sullivan, L.E. Smith, H.L. Haller, J. Econ. Entomol. 27 (1934) 1176.
[9] Phenothiazines and 1,4-benzothiazines, R.R. Gupta (Ed.), Chemical and Biomedical Aspects in Bioactive Molecules, Vol. 4, Elsevier, Amsterdam, 1988.
[10] G. Taurand, Phenothiazine and Derivatives. Ullmann's Encyclopaedia of Industrial Chemistry, Wiley-VCH Verlag, Weinheim, Germany, 2005, p. 601.
[11] D. Chasan, E. Ng, J. Tribol. 5 (2010) 220.
[12] B. Grzeszczyk, K. Polawska, Y.M. Shaker, S. Stecko, A. Mames, M. Woznic, M. Chmielewski, B. Furman, Tetrahedron 68 (2012) 10633.
[13] B. Chakraborty, G.P. Luitel, Tetrahedron Lett. 54 (2013) 765.
[14] S.S. Chow, M. Nevalainen, C.A. Evans, C.W. Johannes, Tetrahedron Lett. 48 (2007) 277.
[15] C. Liu, H. Kang, R.H. Wightman, S. Jiang, Tetrahedron Lett. 54 (2013) 1192.
[16] A. Samadi, E. Soriano, J. Revuelta, C. Valderas, M. Chioua, I. Garrido, B. Bartolome, I. Tomassolli, L. Ismaili, L. Gonzalez-Lafuente, M. Villarroya, A.G. Garcia, M.J. Oset-Gasque, J. Marco-Contelles, Bioorg. Med. Chem. 19 (2011) 951.
[17] M. Buchlovic, Z. Kriz, C. Hofr, M. Potacek, Bioorg. Med. Chem. 21 (2013) 1078.
[18] R.A. Floyd, K. Hensley, M.J. Forster, J.A. Kelleher-Andersson, P.L. Wood, Mech. Ageing Dev. 123 (2002) 1021.
[19] M.R. Macleod, B. van der Worp, E.S. Sena, D.W. Howells, U. Dirhagl, G.A. Donnan, Stroke 39 (2008) 2824.
[20] S.R. Sandler, W. Karo, Organic Functional Group Preparations, Vol. 3, Ed. Sec. Ac. Press, San Diego, 1989, p. 351.
[21] H. Valizadeh, L. Dinparast, Heteroat. Chem. 20 (2009) 177.
[22] S. Cicchi, M. Marradi, A. Goti, A. Brandi, Tetrahedron Lett. 42 (2001) 6503.
[23] S. Yamazaki, Bull. Chem. Soc. Jpn. 70 (1997) 877.
[24] S. Cicchi, F. Cardona, A. Brandi, M. Corsi, A. Goti, Tetrahedron Lett. 40 (1999) 1989.
[25] G. Barabella, S. Bruekker, G. Pitacco, E. Valentin, Tetrahedron 40 (1984) 2441.
[26] H. Feuer (Ed.), Nitrile oxides, Nitrones, and Nitronates in Organic Synthesis, Novel Strategies in Synthesis, Sec. Wiley & Sons, Inc, Hoboken, New Jersey, 2008.
[27] G.N. Zbancioc, T. Huhn, U. Groth, C. Deleanu, I.I. Mangalagiu, Tetrahedron 66 (2010) 4298.
[28] G. Zbancioc, V. Bejan, M. Risca, C. Moldoveanu, I.I. Mangalagiu, Molecules 14 (2009) 403.
[29] V. Bejan, D. Mantu, I.I. Mangalagiu, Ultrasonics Sonochem. 19 (2012) 999.
[30] D. Obermayer, T.N. Glasnov, C.O. Kappe, J. Org. Chem. 76 (2011) 6657.
[31] A. Loupy (Ed.), 2nd ed., Microwave in organic synthesis, Vol. 1, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, 2006.
[32] C. Chavarría, D.I. Perez, C. Pérez, J.A. Morales Garcia, S. Alonso-Gil, A. Pérez-Castillo, C. Gil, J.M. Souza, W. Porcal, Eur. J. Med. Chem. 58 (2012) 44.
[33] R. Huie, W.R. Cherry, J. Org. Chem. 50 (1985) 1531.
[34] S. Kim, G.V.M. de, A. Vilela, J. Bouajila, A.G. Dias, F.Z.G.A. Cyrino, E. Bouskela, P.R.R. Costa, F. Nepveu, Bioorg. Med. Chem. 15 (2007) 3572.
[35] L. Reyes, S. Corona, G. Arroyo, F. Delgado, R. Miranda, Int. J. Mol. Sci. 11 (2010) 2576.
[36] C. Venkatachalapathy, M. Thirumalaikumar, S. Muthusubramanian, K.P. Tani, S. Sivasubramanian, Synth. Commun. 27 (1997) 4041.
[37] Y. Bai, J. Fang, J. Ren, Z. Wang, Chem. Eur. J. 15 (2009) 8975.
[38] A.M. Lobo, S. Prarhakar, H.S. Rzepa, A.C. Skapski, M.R. Tavares, D.A. Widdwson, Tetrahedron 39 (1983) 3833.
[39] H. F. Campbell, Lansdale; Norman J Satora, Roslyn; George H. Douglas A61U 31/275, US Patent, 1979.
[40] H. Valizadeh, Heteroat. Chem. 21 (2010) 78.
[41] B. Hu, J. Zhu, S. Xing, J. Fang, D. Du, Z. Wang, Chem. Eur. J. 15 (2009) 324.
[42] R.L. Atienza, H.S. Roth, K.A. Scheidt, Chem. Sci. 2 (2011) 1772.
[43] S. Fery-Forgues, D. Lavabre, J. Chem. Educ. 76 (1999) 1260.
[44] A.W. Bauer, M.M. Kirby, J.C. Sherris, M. Truck, Am. J. Clin. Pathol. 45 (1966) 493.
[45] M. Cuenca-Estrella, P.E. Verweij, M.C. Arendrup, S. Arikan-Akdagli, J. Bille, J.P. Donnelly, H.E. Jensen, C. Lass-Florl, M.D. Richardson, M. Akova, M. Bassetti, T. Calandra, E. Castagnola, O.A. Cornely, J. Garbino, A.H. Groll, R. Herbrecht, W.W. Hope, B.J. Kullberg, O. Lortholary, W. Meersseman, G. Petrikkos, E. Roilides, C. Viscoli, A.J. Ullmann, Clin. Microbiol. Infect. 18 (2012) 9.
[46] A.A. Bedair, A.M. Darwazeh, M.M. Al-Aboosi, Oral Surg. Oral Med. Oral Pathol. Oral Radiol. 114 (2012) 610.