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Antioxidant Activity Evaluation in a Series of Heterocyclic Compounds Derived from 1,8-Diaminonaphthalene

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Abstract

From (2,3-dihydro-1*H*-perimidin-2-yl)-phenyl, the substitution of OH group in *ortho* or *para* position on the phenyl ring, allows us to synthesize the studied compounds. These three compounds have been characterized by conventional spectroscopic methods (NMR and MS). The interest of this work is to review the antioxidant activity of our compounds. The antioxidant activity screening carried out according to FRAP and DPPH methods revealed significant anti-free radical properties for compounds 1 and 2 even at low concentrations. In contrast to the compound 2, compound 3 for which the OH group is substituted in *para* position has the lowest activity in both cases. Therefore the *para* position seems to be the least sensitive position to increase the antioxidant activity of this pharmacophore.

Keywords

Perimidine, Spectrometry, Antioxidant Activity, 2,2-Diphenyl-1-Picrylhydrazyl Method and Ferric Reducing Antioxidant Power Method

1. Introduction

The notion of oxidative stress reflects an imbalance between the production of free radicals and the capacity of antioxidant defense mechanisms to detoxify reactive intermediates to repair the resulting damage. This notion was used for the first time by Sies [1]. Studies have shown that oxidative stress is involved in many diseases as a trigger or associated with complications of their course. It is recognized by many that oxidative stress is the cause of diseases such as cancer, cataracts, acute respiratory distress syndrome, pulmonary edema [2], diabetes, Alzheimer's disease, Parkinson's disease, rheumatism, cardiovascular disease [3], infectious diseases such as AIDS [4] [5], syphilis [6], renal failure [7] [8], malaria and gastric ulcers [9] [10] etc. Taking into account the harmful effects of oxidative stress, the scientific community is looking for new, more effective antioxidant molecules.

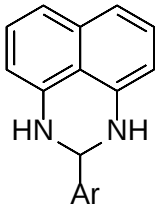
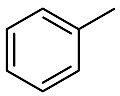
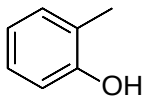
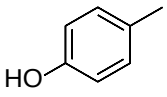
2,3-dihydro-1H-perimidine, are the products resulting from the condensation of primary amines with carbonyl compounds. In addition to their diverse biological activities [11], and their potential to act as antioxidant [12], antimicrobial, antiulcer, antifungal and antitumor agents [13] [14], this products can be a source of molecules with best antioxidant powers. In this work we are interested in structure-activity relationship in a series of 2,3-dihydro-1H-perimidine derived from 1,8-diaminonaphthalene presented in **Table 1**.

2. Material and Methods

2.1. Material

Benzaldehyde, salicylaldehyde, 4-Hydroxybenzaldehyde, and benzene-1,8-diaminonaphtalène were procured from Aldrich and used without further purification. All organic solvents were purchased from Merck and dried before use. Melting points were determined in capillary tube using an MPD Mitamura Riken Kogyo (Japan) electrothermal melting point apparatus and are uncorrected. The 1H NMR spectra were recorded on a Bruker-Avance-300 spectrometer, operating at 300 MHz. The mass spectra were recorded on a TOF LCT Premier (WATERS) Spectrometer coupled to an HPLC Alliance 2695 chain.

Table 1. Structures of 2,3-dihydro-1H-perimidinesynthesized.

	compound	Ar
	1	
	2	
	3	

2.2. Methods

2.2.1. Synthesis of 2-Phenyl-2,3-Dihydro-1H-Perimidine

Benzaldehyde (19.60 mmol) and 1,8-diaminonaphtalène (9.79 mmol) were dissolved in ethanol (50 ml). The mixture was heated at reflux for 07 hours to give a green precipitate. The precipitate obtained was filtered and rinsed in ethanol (Rf: 0.87 in hexane/acetate d'ethyle (2;1), yield: 82%, mp: 206˚C).

2.2.2. Synthesis of 2-(2,3-Dihydro-1H-Perimidin-2-yl)Phenol

Salicylaldehyde (18.80 mmol) and 1,8-diaminonaphtalène (9.35 mmol) were dissolved in ether (30 ml). The mixture was stirred at room temperature for three days to give a brown precipitate. The precipitate obtained was filtered and rinsed in ether (Rf: 0.70 in hexane/acetate d'ethyle (2;1) yield: 26.97%, mp: 198.2˚C).

2.2.3. Synthesis of 4-(2,3-Dihydro-1H-Perimidin-2-yl)Phenol

4-Hydroxybenzaldehyde (12.61 mmol) and 1,8-diaminonaphtalène (6.32 mmol) were dissolved in ethanol (50 ml). The mixture was heated at reflux for 05 hours to give amaroonprecipitate. The precipitate obtained was filtered and rinsed in ethanol (Rf: 0.61 in hexane/acetate d'ethyle (2;1), yield: 47.78%, mp > 268˚C).

The general synthesis of the four compounds is shown in **Figure 1**.

2.2.4. Radical scavening Test

1) DPPH (2,2-diphenyl-1-picrylhydrazyl) assay

2,2-diphenyl-1-picrylhydrazyl(DPPH) was one of the first free radicals used to study structure-antioxidant activity relationship of phenolic compounds [15] [16].

Principle

Reduction of the free radical DPPH by an antioxidant can be followed by UV-Visible spectrometry, by measuring the decrease in absorbance at 517 nm caused by the antioxidants [17]. In the presence of free radical traps, purple-colored DPPH was reduced to yellow 2,2-diphenyl-1-picrylhydrazine [18].

****Dosage***

DPPH radical trapping activity was measured according to the protocol described by Lopes-Lutz *et al*. [19] and Athamena *et al*. [20] 100 µL of each methanolic solution of the pure compound at different concentrations (0.0625 - 1 mg/mL) were added to 2.5 mL of the methanolicsolution of DPPH (0.025 g/l). In

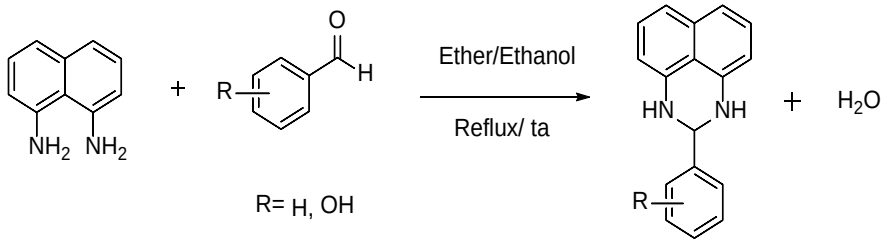


Figure 1. The general synthesis route of compounds 1-3.

parallel, a negative control was prepared by mixing 100 µl of methanol with 2.5 ml of the methanolic solution of DPPH. Absorbance reading was made against a blank prepared for each concentration at 517 nm after 30 minutes of incubation in the dark and at room temperature. The positive control was represented by a solution of a standard antioxidant ascorbic acid, whose absorbance was measured under the same conditions as the samples and for each concentration [21].

The results were expressed in inhibition percentages (I%) of free radical using the following formula.

$$I\% = \left[\left(\text{Abs of con neg} - \text{Abs sample}\right)/\text{Abs of con neg}\right] \times 100$$

I%: Percentage of DPPH inhibition.

Abs Sample: Absorbance of the sample.

Abs of con neg: Absorbance of negative control.

2) FRAP (Ferric Reducing Antioxidant Power) assay

*****Principle***

The process was based on the reduction of a triazine tripyridyl ferric complex to ferrous iron in the presence of antioxidants (test sample). In fact, the sample turns to the blue color followed by colorimetric assay at 593 nm in the presence of antioxidant. The reagent will be prepared as follows.

*****Dosage***

The protocol was based on the method of Benzie *et al.* [22], which had undergone some modifications by Pulido *et al.* [23]. A freshly prepared FRAP solution composed of.

- 25 ml of 300 mM acetate buffer.
- 2.5 ml of 10 mM TPTZ solution in 40 mM HClsolution.
- 2.5 ml of a solution of iron chloride at 20 mM.

The mixture was incubated at 37˚C for the duration of the experiment. The test consisted of mixing in glass hemolysis tubes 100 µl of extract diluted with 300 µl of distilled water and then with 3000 µl of working solution maintained at 37˚C. The absorbance was measured at 593 nm after incubating the reaction in a water bath thermostated at 37˚C in the dark for exactly 30 minutes. The calibration line was derived from the absorbance read for the trolox solution range (0.0312 to 1 mg/mL) used as antioxidant reference. The concentration in mg/mL of trolox equivalent per gram of dry matter was calculated based on the regression line of the trolox sampling curve.

3. Results and Discussion

3.1. MS Study

The mass spectra (HR-ESI-MS) of the title compounds showed peaks corresponding to the molecular ions at m/z 263 $[M + H]^+$, that allowed to propose $C_{17}H_{14}N_2$ empirical formula for compounds 2 and 3. Concerning compounds 1 the peak at m/z 247 $[M + H]^+$, was conform to propose $C_{17}H_{14}N_2$ empirical formula.

3.2. ^{1}H NMR and ^{13}C NMR Spectroscopy

^{1}H NMR and ^{13}C NMR spectral data in deuterated CDCl3 solution of the synthesized compounds are given in Table 2. The resonance of protons had been assigned on the basis of their integration and multiplicity pattern [24]. The ^{1}H NMR spectra exhibited multi-signals at 3.51; 3.50; 3.36 ppm respectively for compounds 1, 2 and 3, attributed to protons was bonded to azote atoms CH-N-. The singulet at 5.80; 5.75; 5.29 ppm for compounds 1, 2 and 3, attributed to perimidine cyclic protons CH-, respectively. The multi-signals within the 8.19 - 6.47 ppm range are assigned to the aromatic protons of the three rings.

The signals at 60.97; 61.46; 76.6 ppm attributed to carbon are bonded both to two azote atoms and to phenyl group.

The 1H-NMR spectral data of the perimidines synthesized were in accord with the proposed structures.

3.3. Anti-Radical Activity by DPPH Method

Statistical analysis in this study gave the results recorded in Table 3. Analysis of Table 3 showed that all the compounds studied had antioxidant properties. We also observed a significant difference ($P < 0.001$) between inhibition percentages when switching from one compound to another. Inhibition percentage determination indicated 89,212 ± 0.462; 87,687 ± 1019; 73,574 ± 3025; 43,598 ± 7743, respectively for Trolox, compounds 2, 1 and 3. Like FRAP method, DPPH assays showed that the antioxidant activities were ranked one more time in Trolox > 2 > 1 > 3 decreasing order. For molecules 1 and 3, we obtained relatively lower inhibition values than Trolox, but with a non-negligible inhibition effect.

Table 2. ^{1}H NMR data[a-c] and ^{13}C NMR data of compounds.

compounds	Molecular formula	N-H m	C-H s	C_6-H m	N-C-H
1	$C_{17}H_{14}N_2$	3.51 (2H)	5.80 (1H)	8.08 - 6.47 (11H)	60.97
2	$C_{17}H_{14}N_2O$	3.50 (2H)	5.75 (1H)	8.24 - 6.48 (10H)	61.46
3	$C_{17}H_{14}N_2O$	3.36 (2H)	5.29 (1H)	8.19 - 6.64 (10H)	76.6

[a]Multiplicity is given as s = singlet, m = multi-signals; [b]Chemical shits in ppm; [c]Integration: number of protons in brackets.

Table 3. Inhibition percentage values by DPPH method.

Compounds	Means of inhibition % + standard deviation
3	43.598 ± 7.743
2	73.574 ± 3.025
1	87.687 ± 1.019
TROLOX	89.212 ± 0.462
F	167.602
P	<0.001

Statistically, compound 2 had the same antiradical effect as Trolox. Compound 3 was the one that weakest inhibited DPPH even at low concentrations, as shown by the histogram below (Figure 2).

The histogram revealed in detail the antioxidant power of this series of compounds. In the concentration range localized between 1 and 0.0312 mg/ml, the inhibition percentage values of compound 2 are comparable to Trolox one. At 0.5 mg/ml, compound 2 showed an antiradical activity greater than the reference molecule. whatever the concentration, 2,3-dihydro-1H-perimidine compound, substitued by the hydroxyde group in *para* position on benzylic nuclei seem to be unfavorable to improve the biological activity. Whereas, *ortho* position appeared to be the site most sensitive to increase the antioxidant activity of this pharmacophore. For this class of molecule, it is the first time, to our knowledge, that, such important antioxidant properties were observed.

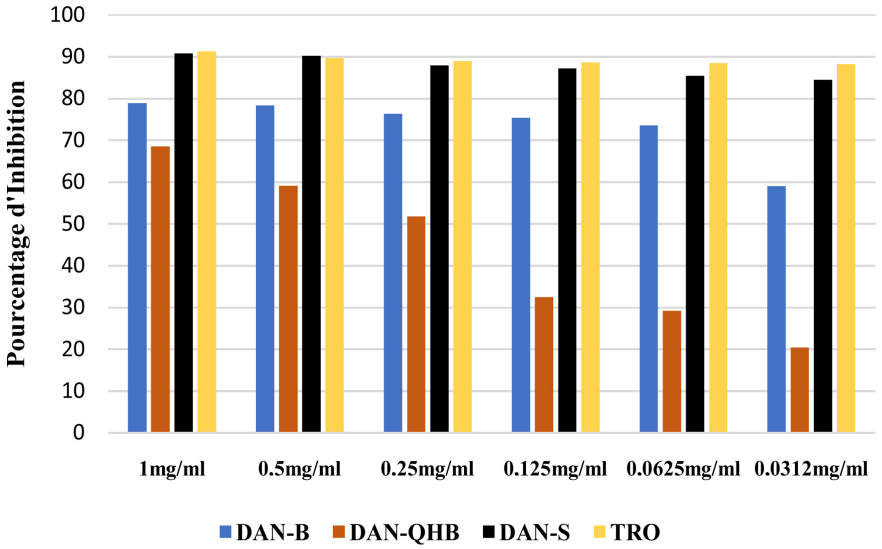


Figure 2. Antioxidant activity by DPPH method at 1 to 0.0312 mg/mL.

3.4. Ferric Reducing Antioxidant Power (FRAP) Assay

The results of the ferric reduction antioxidant power, expressed in mg/mL Trolox equivalent, obtained from a calibration straight line at different concentrations, are presented in Table 4.

Table 4. Antioxidant power of ferric reduction of pure compounds.

Compounds	Means of inhibition % + standard deviation
3	0.07946658 ± 0.03925419
1	0.09285675 ± 0.04448092
2	0.09700133 ± 0.04513959
Fisher value F	20.618
P value	<0.001

According to FRAP method, in this series, antioxidant activities are ranked in as follow decreasing order: 1 > 2 > 3.

These results revealed that the compounds 1 and 2 with FRAP values respectively of 0.09700133 ± 0.04513959 and 0.09285675 ± 0.04448092, are the most active compared to compound 3 ($P < 0.001$). It is deduced that the no-substituted compound 1 is the very most active of them. Compound 3 with its FRAP value of 0.07946658 ± 0.03925419 is the least active of them. The compound 3 meanwhile, has mean antioxidant activity. From the compound 1, introduction of a hydroxide group in this structure sensibly decreased the antioxidant activity. Therefore, *para* position on the benzylidene nuclei seemed to be the least sensitive position which is not promotes biological activity.

4. Conclusion

Antioxidant screening carried out according to FRAP and DPPH methods revealed important antiradical properties for compounds 1 and 2. This study also revealed that the antioxidant activities were arranged in decreasing order: 2 > 1 > 3 for DPPH and 1 > 2 > 3 for FRAP. Ortho-substituted compound 2 in the case of DPPH and no-substituted in FRAP case are the most active, exhibited a much higher antioxidant activity even at low concentrations. With their excellent antioxidant activity, compounds 2 and 1 are proven to become good candidate for the development of a new class of 2,3-dihydro-1H-perimidine profile antioxidant compounds.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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