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Design, Synthesis and Biological Activities of Some phthalimides Derivatives

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Aims: To synthesize some phthalimides derivatives and evaluate the compounds for their possible biological properties.
Methods: The substituted phenylisoindoline-1,3-dione were synthesized from the reactions of N-phenyl phthalimide with different substituted aromatic aldehyde. The synthesized compounds were characterized using nuclear magnetic resonance spectroscopic analysis. The Nitric oxide and Ferric reducing antioxidant properties (FRAP) were determined by spectrophochemical method.
Results: The IC_{50} values for all the synthesized compounds were lower than standard, eserine (IC_{50} = 15 ± 2 µg/mL) against Nitric oxide inhibition. Compounds 3 (FRAP = 205±8 µg/ML) and 6 (FRAP = 118±1 µg/ML) were found to exhibit higher FRAP analysis results which were comparable to the results obtained for serine. (FRAP = 202±7 µg/ML).
Conclusion: The considerable activity of the compounds shown by its Nitric oxide and Ferric reducing antioxidant properties (FRAP) makes them good candidates for the development of selective acetylcholinesterase and butyryl cholinesterase inhibitors.

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Keywords: Eserine; chalcones; Nitric oxide; Ferric reducing antioxidant Nitric oxide; Ferric reducing antioxidant properties.

1. INTRODUCTION

Chalcones have aroused the attention of the scientific community, particularly in the last decade due to their diverse pharmacological properties [1]. They serve as precursors for the synthesis of various heterocyclic compounds. Chalcones have been reported to possess anti-inflammatory [2-3] anti-oxidants [4] and anti-malarial [5], antimicrobial [6-8] antibacterial [9], antifungal [10], anticancer [11] antidepressant [12], antiviral. antiangiogenic [13], anti-oxidants, antileishmanial properties. It also inhibits the inducible Nitric Oxide, (NO) synthase expression via a superoxide-dependent mechanism in stimulated mice and secluded the cells against oxidant stress. These interesting biological properties of chalcones are due to the presence of both α, β-unsaturation and an aromatic ring in their structure [14-17].

2. MATERIALS AND METHODS

Melting points were determined with open capillary tube on a Gallenkamp (variable heater) melting point apparatus and were uncorrected. Infrared spectra were recorded as KBr pellets on a Bruker 2000 Spectrometer. The ^{1}H and ^{13}C NMR was run on a Bruker 600 MHz spectrometer (δ in ppm relative to Me_4Si), Mass spectra were taken on a high-resolution ($m/\Delta m$ = 30 000) Thermo Scientific LTQ-Orbitrap Discovery mass spectrometer (San Jose, CA) equipped with an electrospray ionization source at the Department of Chemistry, Portland state University, Portland U.S.A. The purity of the compounds was routinely checked by TLC on silica gel G plates using n-hexane/ethyl acetate (1:1, v/v) solvent system and the developed plates were visualized by UV light. All reagents used were obtained from Sigma–Aldrich Chemical Ltd, except Glacial acetic acid, ethanol, oxalic acid and vanillin which were obtained from BDH Chemical Limited.

2.1 Synthetic Work

Synthesis of 2-(4-acetylphenyl) isoindoline-1,3-dione 1: Phthalic anhydride (5 g), 4-ethoxyaniline (4.0g) in 50 mL glacial acetic acid reacted under reflux for 6 hours. The reaction mixture was poured into crushed ice to obtained 2-(4-acetylphenyl) isoindoline-1,3-dione. IR Spectra (KBr) 3073 cm^{-1} (C-H aromatic), 1736 cm^{-1}(C=O) imide, 1708 cm^{-1} (C=O) imide, 1689 cm^{-1} (C=O) ketone, 1593 cm^{-1} (C=C), 1384 cm^{-1} (C-N) imide.

^{1}H NMR (DMSO-d_6): 7.92(d, 2H, J=7.5,1.5, ArH), 7.85(d, 2H, J=7.5,1.5, ArH), 7.88(t, J=7.5,1.5, ArH), 7.28(d, 2H, J=7.5, 1.5, ArH), 2.50(s, 3H, $COCH_3$). ^{13}C-NMR: 197(C=O), 167(CO-amide), 137, 136,132, 129, 124, 123, 26(CH_3)

Synthesis of 2-(4-(3-(4-hydroxyphenyl) acryloyl) phenyl) isoindoline-1,3-dione 2: 2-(4-acetylphenyl) isoindoline-1,3-dione (1.5 g, 0.00565 mol) was allowed to react with 4-hydroxybenzaldehyde (0.689 g, 0.00565 mol) in 20mL ethanol after which 10 % sodium hydroxide solution was added and the reaction mixture was stirred at room temperature for 48hours.The reaction mixture was poured into distilled water and hydrolyzed with 10 % hydrochloric acid solution to obtain a yellow product (2-(4-(3-(4-hydroxyphenyl) acryloyl) phenyl) isoindoline-1, 3-dione. The product was filtered, recrystallized and then oven-dried.

IR Spectra (KBr): 3469 cm^{-1}(O-H) p-hydroxyl phenol, 3074 cm^{-1} (C-H aromatic), 1735 cm^{-1}(C=O) imide, 1709 cm^{-1} (C=O) imide, 1680 cm^{-1}(C=C) chalcones, 1593 cm^{-1} (C=C), 1384 cm^{-1} (C-N) imide.

^{1}H NMR (DMSO-d_6): 8.06(d, 1H, J=15.1), 7.88(t, 2H, J=7.5, ArH), 7.87(t, J=7.5, ArH), 7.85(d, 2H, J=7.5, ArH), 7.65(d, 2H, J=7.5), 7.36(d, 2H, J=7.5), 7.59(d, 1H, J=15.1). ^{13}C-NMR: 190(C=O), 167(CO-amide), 145(C=C), 132, 131, 124, 121(C=C), 115.

Synthesis of 2-(4-(3-(3-hydroxyphenyl) acryloyl)phenyl)isoindoline-1,3-dione 3: 2-(4-acetylphenyl)isoindoline-1,3-dione(1.5 g, 0.00565 mol) of was allowed to react with 3-hydroxybenzaldehyde (0.689 g, 0.00565 mol) in 20mL ethanol after which 10 % sodium hydroxide solution was added and the reaction mixture was stirred at room temperature for 48hours.The reaction mixture was poured into distilled water and hydrolysed with 10 % hydrochloric acid solution to obtain a yellow product (2-(4-(3-(3-hydroxyphenyl)acryloyl) phenyl)isoindoline-1,3-dione.

IR Spectra (KBr): 3448 cm^{-1}(O-H) m-hydroxyl phenol, 3074 cm^{-1} (C-H aromatic), 1735 cm^{-1}(C=O) imide, 1709 cm^{-1} (C=O) imide, 1680 cm^{-1}

^{1}(C=C) chalcones, 1593 cm^{-1} (C=C), 1384 cm^{-1} (C-N) imide.

^{1}H NMR (DMSO-d_6): 8.06(d, 1H, J=15.1), 7.88(t, 2H, J=7.5, ArH), 7.87(t, J=7.5, ArH), 7.85(d, 2H, J=7.5, ArH), 7.65(d, 2H, J=7.5), 7.36(d, 2H, J=7.5), 7.59(d, 1H, J=15.1). ^{13}C-NMR: 189.7(C=O), 167(CO-amide), 135(C=C), 132, 131, 124, 121(C=C), 117, 115.

Synthesis of 2-(4-(3-(3aH-indol-3yl)acryloyl)phenyl)isoindoline-1,3-dione(compound 4: 2-(4-acetylphenyl)isoindoline-1,3-dione (1.5 g, 0.00565 mol) was allowed to react with Indolecarbaldehyde (2.19 g, 0.015mol) in 20mL ethanol after which 10 % sodium hydroxide solution was added and the reaction mixture was stirred at room temperature for 48hours.The reaction mixture was poured into distilled water and hydrolysed with 10 % hydrochloric acid solution to obtain a yellow product 2-(4-(3-(3ah-indol-3yl)phenyl)isoindoline-1,3-dione.

IR Spectra (KBr): 3221 cm^{-1}(N-H) indole, 3074 cm^{-1} (C-H aromatic), 1735 cm^{-1}(C=O) imide, 1709 cm^{-1} (C=O) imide, 1680 cm^{-1}(C=C) chalcones, 1593 cm^{-1} (C=C), 1384 cm^{-1} (C-N) imide.

^{1}H NMR (DMSO-d_6): 8.05(d, 1H, J=15.1), 7.87(t, 2H, J=7.5, ArH), 7.85(t, J=7.5, ArH), 7.84(d, 2H, J=7.5, ArH), 7.66(d, 2H, J=7.5), 7.38(d, 2H, J=7.5), 7.19(t, 1H, J=15.1), 7.14(d, 1H, J=7.5), 6.93(t, 1H, J=7.5). ^{13}C-NMR: 192(C=O), 169(CO-amide), 145(C=C), 137, 133, 132, 127(C=C), 124, 111.

Synthesis of 2-(4-(3-(4-chlorophenyl) acryloyl) phenyl) isoindoline-1,3-dione 5: 2-(4-acetylphenyl) isoindoline-1,3-dione (1.5 g, 0.00565 mol) was allowed to react with 4-chlorobenzaldehyde (1.12 g, 0.00795mol) in 20mL ethanol after which 10 % sodium hydroxide solution was added and the reaction mixture was stirred at room temperature for 48hours.The reaction mixture was poured into distilled water and hydrolyzed with 10 % hydrochloric acid solution to obtain a yellow product 2-(4-(3-(4-chlorophenyl) acryloyl) phenyl) isoindoline-1,3-dione 5

IR Spectra (KBr): 3074 cm^{-1} (C-H aromatic), 1735 cm^{-1}(C=O) imide, 1709 cm^{-1} (C=O) imide, 1680 cm^{-1}(C=C) chalcones, 1593 cm^{-1} (C=C), 1384 cm^{-1} (C-N) imide, 1091 cm^{-1} (C-Cl)

^{1}H NMR (DMSO-d_6): 8.03(d, 1H, J=15.1), 7.88(t, 2H, J=7.5, ArH), 7.87(t, J=7.5, ArH), 7.85(d, 2H, J=7.5, ArH), 7.68(d, 2H, J=7.5), 7.59(d, 2H, J=15), 7.44(d, 1H, J=7.5), 7.36(d, 2H, J=7.5. ^{13}C-NMR: 188(C=O), 165(CO-amide), 145(C=C), 133, 132, 131, 128, 121(C=C), 117, 115.

Synthesis of 2-(4-(3-(3-methoxyphenyl) acryloyl) phenyl) isoindoline-1,3-dione 6: 2-(4-acetylphenyl) isoindoline-1,3-dione (1.53g, 0.00577mol) was allowed to react with m-methoxybenzaldehyde (0.785 g, 0.00577mol) in 20mL ethanol after which 10% sodium hydroxide was stirred at room temperature for 48hours.The mixture was poured into distilled water and hydrolyzed with 10% hydrochloric acid solution to obtain a red product, 2-(4-(3-(3-methoxyphenyl) acryloyl) phenyl) isoindoline-1,3-dione

IR Spectra (KBr): 3074 cm^{-1} (C-H aromatic), 1735 cm^{-1}(C=O) imide, 1709 cm^{-1} (C=O) imide, 1680 cm^{-1}(C=C) chalcones, 1593 cm^{-1} (C=C), 1384 cm^{-1} (C-N) imide, 1234 cm^{-1} C-O-C) methoxy, 1126 cm^{-1} (C-O-C) methoxy.

^{1}H NMR (DMSO-d_6): 8.05(d, 1H, J=15.1), 7.88(t, 2H, J=7.5, ArH), 7.87(t, J=7.5, ArH), 7.85(d, 2H, J=7.5, ArH), 7.68(d, 2H, J=7.5), 7.59(d, 2H, J=15), 7.44(d, 1H, J=7.5), 7.36(d, 2H, J=7.5, 7.16(s, 1H), 3.83(s, 3H(CO-CH_3) ^{13}C-NMR: 188(C=O), 160(CO-amide), 145(C=C), 133, 132, 131, 128, 121(C=C), 117, 115, 55(CO-CH_3)

Synthesis of 2-(4-(3-(2-hydroxy-4-methoxyphenyl) acryloyl) phenyl) isoindoline-1,3-dione 7: 2-(4-acetylphenyl) isoindoline-1,3-dione (1.53g, 0.00577mol) was reacted with o-vanillin (0.975g, 0.00641mol) (0.785g,0.00577mol) in 20mL ethanol after which 10% sodium hydroxide was stirred at room temperature for 48hours.The mixture was poured into distilled water and hydrolyzed with 10% hydrochloric acid solution to obtain a red product 2-(4-(3-(2-hydroxy-4-methoxyphenyl)acryloyl)phenyl)isoindoline-1,3-dione 7

IR Spectra (KBr): 3460 cm^{-1} (O-H) phenolic, 3074 cm^{-1} (C-H aromatic), 1735 cm^{-1}(C=O) imide, 1709 cm^{-1} (C=O) imide, 1680 cm^{-1}(C=C) chalcones, 1593 cm^{-1} (C=C), 1384 cm^{-1} (C-N) imide, 1233 cm^{-1} C-O-C) methoxy, 1124 cm^{-1} (C-O-C) methoxy.

^{1}H NMR (DMSO-d_6): 8.33(d, 1H, J=15.1), 7.99(d, 1H), 7.88(t, 2H, J=7.5, ArH), 7.87(t, J=7.5, ArH), 7.85(d, 2H, J=7.5, ArH), 7.68(d, 2H, J=7.5),

7.42(d, 2H, J=15), 7.44(d, 1H, J=7.5), 7.36(d, 2H, J=7.5, 3.43(s, 3H(CO-CH_3). ^{13}C-NMR: 189(C=O), 168(CO-amide), 146(C=C), 133, 132, 131, 128, 121(C=C), 117, 115, 55(CO-CH_3)

2.2 Biological Assays

2.2.1 Nitric oxide procedure

Serial dilutions (**6 concentrations)** of synthesized compounds was prepared and also serial dilutions (**7 concentrations)** of standard (**ascorbic acid**) was prepared, 100 µl of each synthesized compound concentration in triplicates was dispensed in a microplate and 100 µl sodium nitroprusside (2.5mM) in phosphate buffer saline was incubated under illumination for 150minute. This was followed by addition of 50µl of 1% sulphanilamide in 5% phosphoric acid was added and incubated in the dark for 10min., followed by addition of 50µl 0.1% NED (N-1-napthylethylenediamine dihydrochloride). The absorbance of the chromophore formed was measured at 546nm. The percentage inhibition of nitric oxide radical formation was calculated as expressed below

$$I\% = [(A_{blank}-A_{sample})/A_{blank}] \times 100$$

Where A_{blank} is the absorbance of the control reaction (containing all reagents except the test compound), and A_{sample} is the absorbance of the test compound. Sample concentration providing 50% inhibition (IC_{50}) was calculated from the graph plotting inhibition percentage against compound's concentrations.

2.2.2 FRAP protocol

The FRAP assay uses antioxidants as reductants in a redox-linked colorimetric method with absorbance measured with a spectrophotometer.

Procedure: A 300mmol/L acetate buffer of pH 3.6, 10mmol/L 2, 4, 6-tri-(2-pyridyl)-1, 3, 5-triazine and 20mmol/L $FeCl_3.6H_2O$ were mixed together in the ratio of 10:1:1 respectively, to give the working FRAP reagent. A 50µl of the synthesized compounds at 0.1mg/ml and 50µl of standard solutions of ascorbic acid (20, 40, 60, 80, 100 µg/ml) was added to 1ml of FRAP reagent. Absorbance measurement was taken at 593nm exactly 10 minutes after mixing against reagent blank containing 50µl of distilled water. The reducing power was expressed as equivalent concentration (EC) which is defined as the concentration of antioxidant that gave a ferric reducing ability equivalent to that of the ascorbic acid standard.

3. RESULTS AND DISCUSSION

3.1 Chemistry

The respective chalcones was synthesized by reacting 2-(4-acetylphenyl)isoindoline with hydroxybenzaldehyde, m-hydroxybenzaldehyde, indole carbaldehyde, 4-chlorobenzaldehyde, m-methoxybenzaldehyde and o-vanillin respectively in the presence of NaOH as a catalyst and ethanol as a solvent using the method described by (17).

Some physical properties of the synthesized compounds: The results of some physical properties of the synthesized compounds as shown in Table 1 gave percentage yield of the synthesized compounds ranged between 66.30% - 72.12%. The melting point ranged between 155 and 238^{0}C.

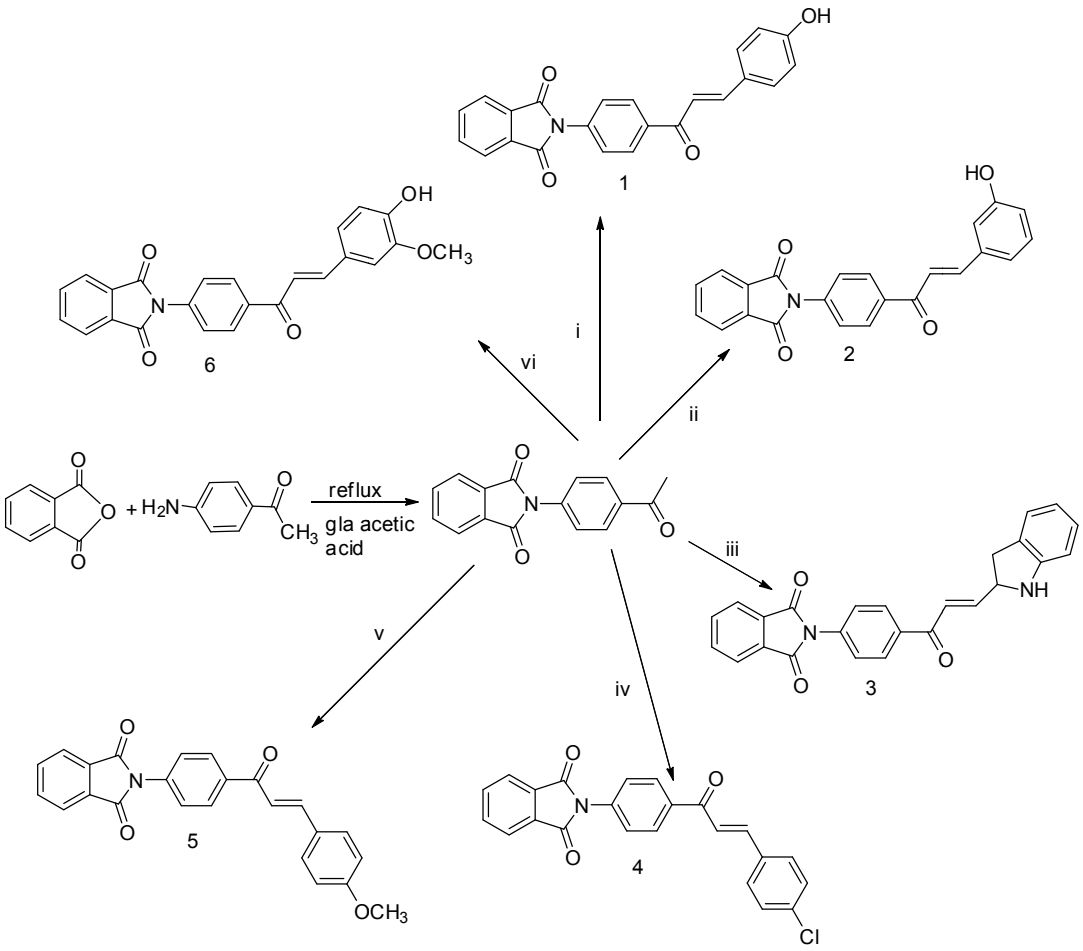
3.2 Biology

3.2.1 Nitric Oxide activity

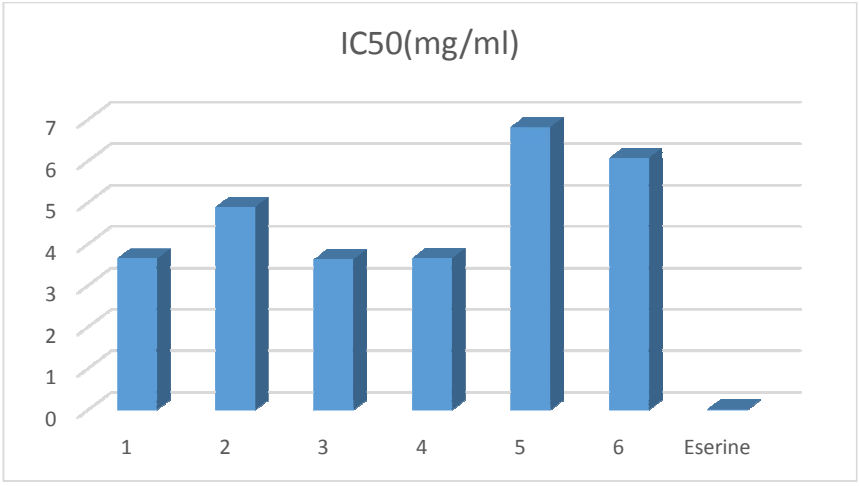
The results obtained ranged from 2.75±0.01 to 6.82±0.01 (Table 1). The best Nitric Oxide inhibitory activity was exhibited by compound **1** (2.75±0.01) when compared with the rest of the compounds. The activity of the compounds was lower when compared with the standard Eserine.

3.2.2 FRAP analysis

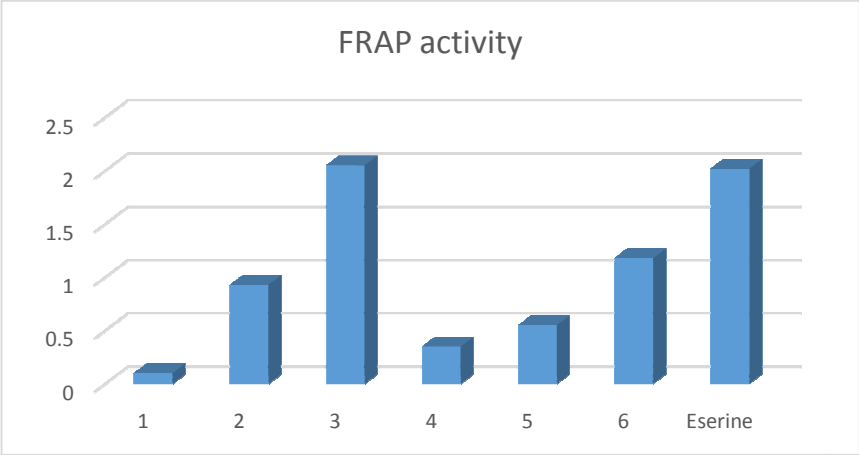
The results showed that the activity ranged from 0.35±0.04 to 2.05±0.08. (Table 2). Compound **3** has the best activity due to the highest value the order of the increase in the activity is shown to be 3>6>2>5>4>1.



i) 4-hydroxy benzaldehyde in ethanolic NaOH ii) i) 3-hydroxy benzaldehyde in ethanolic NaOH
iii) indole-2-carbaldelhyde in ethanolic NaOH iv) 4-chloro benzaldehyde in ethanolic NaOH
v i) 3-methoxy benzaldehyde in ethanolic NaOH vi) i) o-valline in ethanolic NaOH



The IC_{50} of Nitric Oxide plotting compounds against the concentration



The results of FRAP activity of the Chalcones

Table 1. Result of IC50values for nitric oxide activity of the Chalcones

COMPOUNDS	IC50(mg/ml)
1	2.75±0.01
2	4.89±0.01
3	3.63±0.2
4	3.66±0.6
5	6.82±0.01
6	6.07±0.03
Eserine	0.015±0.02

Table 2. Results for FRAP activity of the Chalcones

COMPOUNDS	AVERAGE (mg/SAM/g)
1	0.10±0.02
2	0.93±0.01
3	2.05±0.08
4	0.35 ±0.04
5	0.55 ±0.01
6	1.18 ± 0.01
Eserine	2.02±0.07

Eserine = physostigmine sulfate salt

4. CONCLUSION

It can be concluded that the synthesis of compounds 1-6 was successful and the workup stage was environmentally friendly. The bioactivities of all synthesized chalcones analogues 1-6 were tested in vitro by using the standard antibacterial activity protocol. It was observed that this study identifies a new class of potential antibacterial compounds that could be developed into drugs.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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