Available online at www.sciencedirect.com
SCIENCE DIRECT®
Il Farmaco 58 (2003) 1283–1288
IL FARMACO
www.elsevier.com/locate/farmac

Synthesis and hypolipidemic activity of *N*-substituted phthalimides. Part V☆

Vera L.M. Sena [a], Rajendra M. Srivastava [a,*], Ricardo O. Silva [a], Vera L.M. Lima [b]

[a] *Departamento de Química Fundamental, Universidade Federal de Pernambuco (UFPE), Av. Luis Freire, S/N, Cidade Universitária, CEP 50.740-540 Recife, PE, Brazil*

[b] *Departamento de Bioquímica, Universidade Federal de Pernambuco (UFPE), Av. Prof. Moraes Rego, S/N, Cidade Universitária, CEP 50.670-420 Recife, PE, Brazil*

Received 27 February 2003; accepted 9 June 2003

Abstract

A series of *N*-aryl- or *N*-(1,2,4-triazol-yl)-phthalimides (**4a**–**4i**) have been synthesized starting from phthalic anhydride (**1**) and an appropriate amine (**2a**–**2i**). All compounds presented hypolipidemic activity, but compound **4d** proved to be the most active and reduced plasma cholesterol and triglyceride levels in Swiss white mice significantly.

Keywords: *N*-Arylphthalimides; Hypolipidemic activity; Triglycerides; Cholesterol

1. Introduction

Phthalimide and *N*-substituted phthalimides are an interesting class of compounds because they possess important biological activities [1,2]. For the last two decades, these compounds have also attracted more attention due to their antihyperlipidemic activity, and the research in this area continues. Although there are several drugs, which reduce cholesterol and triglycerides in blood, it is imperative to find still more effective and nontoxic ones. With this idea in view, the present work was undertaken. *N*-substituted phthalimide derivatives were first examined by Chapman Jr et al. [3] in 1979 for their hypolipidemic activity and it was found that *N*-butyl- and *N*-pentylphthalimides were effective in reducing serum cholesterol levels by 46 and 42%, respectively. Two years later, Hall et al. [4] investigated 12 imide analogs and suggested that their ability to lower serum cholesterol should be related to phthalimides' effectiveness to suppress acetyl-CoA synthase activity. In other words, phthalimides are able to inhibit acetyl-CoA carboxylase activity. In 1983, another publication appeared, where 10 *N*-arylphthalimides have been examined and the most potent product, *o*-(*N*-phthalimido)acetophenone, was shown to lower both serum cholesterol and triglyceride levels by 57 and 44% after 16 and 14 days of treatment, respectively [5]. It has also been shown that replacement of one of the oxygen atoms of the carbonyl groups by NH in phthalimide was effective in reducing serum cholesterol (44%); however, the hypotriglyceridemic activity of 3-iminophthalimidine was 15% lower than that of phthalimide itself [6].

Quantitative structure–activity relationships (QSAR) studies have also been carried out for phthalimide and *N*-arylphthalimides, and enhanced hypolipidemic activity has been predicted for certain phthalimides [7,8]. In 1996, Antunes and Srivastava [9] reported the synthesis and semi-empirical molecular orbital calculations of three new phthalimide derivatives, and predicted that these compounds might show antihyperlipidemic activity. Recently, the synthesis and hypolipidemic activity of five *N*-phthalimidomethyl glycosides have been reported from our laboratory [10].

Considering the growing importance of *N*-substituted derivatives of phthalimides, we decided to synthesize seven known *N*-arylphthalimides (**4a**–**4g**) and two new phthalimides (**4h** and **4i**) The structures of latter two

☆ For analgesic effect of *N*-phthalimide derivatives, see Ref. [25].

* Corresponding author.
E-mail address: rms@ufpe.br (R.M. Srivastava).

0014-827X/03/$ - see front matter © 2003 Published by Éditions scientifiques et médicales Elsevier SAS.
doi:10.1016/S0014-827X(03)00185-X

compounds are given in Fig. 1. All of them were tested for their hypolipidemic properties because the literature does not record such evaluation of these compounds. Interestingly, the intermediates (**3a**–**3i**) cause hyperlipidemia and increase in animals' body weight [11], whereas phthalimides (**4a**–**4i**) possess hypolipidemic property. This paper, therefore, reports the synthesis and pharmacological tests of these *N*-substituted phthalimides. In fact, one of the compounds, **4d**, presented an excellent and quite promising hypolipidemic activity.

2. Experimental procedures

2.1. General

All compounds were checked for their structures by infrared (IR), UV, and ^{1}H NMR spectroscopy. Melting points were determined on a Tomas-Hoover capillary melting point apparatus and are uncorrected. UV spectra were registered with U-3200 Hitachi spectrophotometer. IR spectra were measured with a Bruker model IF S66 FTIR spectrophotometer using potassium bromide discs. NMR spectra were recorded in $CDCl_3$ (for compounds **4a**–**4g**) or DMSO-d_6 (for compounds **4h** and **4i**) using tetramethylsilane (TMS) as an internal standard, on a Varian Unity Plus 300 MHz spectrophotometer.

2.2. General procedure for the preparation of N-aryl- or N-heterocyclic phthalimides

Compounds **4a**–**4i** have been synthesized by mixing equimolar quantities of phthalic anhydride (**1**; 3.4 mmol) and a suitable substituted amine (**2b**–**2g**; 3.4 mmol), followed by refluxing in nitrobenzene for 45 min. After cooling, the compounds **4b**–**4g** were precipitated by the addition of excess *n*-hexane. Filtration and washing the solid with a small quantity of hexane provided the crude solid, which was crystallized from ethanol to provide pure compound in excellent yield. The compounds **4a**, **4h**, and **4i** in glacial acetic acid were stirred under reflux for 1 h and the solvent in each case was evaporated under reduced pressure to yield the crude product, which was recrystallized from acetone or acetic acid.

2.2.1. 2-Phenylisoindole-1,3-dione (*4a*)

99%, 210 °C (lit. [12]: 205.5–206 °C)—IR (KBr): 3031, 1770, 1711, 1594, 1466, 1452 cm^{-1}. UV (MeOH): λ_{max} 294 and 244 nm. ^{1}H NMR ($CDCl_3$): δ 7.95 (dd, 2H, $J = 3.0$ and $J = 5.4$ Hz, H-4 and H-7), 7.79 (dd, 2H, $J = 3.0$ and $J = 5.4$ Hz, H-5 and H-6), 7.52 (m, 2H, H-5′ and H-3′), 7.47 (m, 2H, H-2′ and H-6′), 7.40 (m, 1H, H-4′) ppm.

2.2.2. 2-(2-Chlorophenyl)-isoindole-1,3-dione (*4b*)

73%, 143–143.6 °C (lit. [13]: 140 °C)—IR (KBr): 1745, 1711, 1588, 1526, 1486, 1469, 1440, 772, 748. UV (MeOH): λ_{max} 288 and 217 nm. ^{1}H NMR ($CDCl_3$): δ 8.00 (dd, 2H, $J = 3.0$ and $J = 5.4$ Hz, H-4 and H-7), 7.83 (dd, 2H, $J = 3.0$ and $J = 5.4$ Hz, H-5 and H-6), 7.58 (m, 1H, H-3′), 7.42–7.48 (m, 2H, H-5′ and H-6′), 7.38 (m, 1H, H-4′) ppm.

2.2.3. 2-(3-Chlorophenyl)-isoindole-1,3-dione (*4c*)

94%, 168.5–169 °C (lit. [14]: 166.8 °C)—IR (KBr): 1721, 1680, 1587, 1550, 1530, 1482, 1433, 774, 735, 684. UV (MeOH): λ_{max} 287 and 218 nm. ^{1}H NMR ($CDCl_3$): δ 7.98 (dd, 2H, $J = 3.0$ and $J = 5.4$ Hz, H-4 and H-7), 7.82 (dd, 2H, $J = 3.0$ and $J = 5.4$ Hz, H-5 and H-6), 7.35–7.41 (m, 3H, H-2′, H-4′ and H-6′), 7.43 (t, 1H, H-5′) ppm.

2.2.4. 2-(4-Chlorophenyl)-isoindole-1,3-dione (*3d*)

99%, 200.6–201.2 °C (lit. [15]: 201–202 °C)—IR (KBr): 1787, 1712, 1610, 1554, 1495, 1388, 1280, 885, 851, 825. UV (MeOH): λ_{max} 288, 222, and 241 nm. ^{1}H NMR ($CDCl_3$): δ 7.97 (dd, 2H, $J = 3.0$ and $J = 5.4$ Hz, H-4 and H-7), 7.81 (dd, 2H, $J = 3.0$ and $J = 5.4$ Hz, H-5 and H-6), 7.49 (d, 2H, $J = 9$ Hz, H-3′ and H-5′, AA′, and BB′ system), 7.42 (d, 2H, $J = 9.0$ Hz, H-2′ and H-6′, AA′BB′ system) ppm.

2.2.5. 2-(2-Fluorophenyl)-isoindole-1,3-dione (*4e*)

67%, 194–195 °C (lit. [16]: 192–193 °C)—IR (KBr): 1760, 1712, 1680, 1526, 1460, 1423, 1350, 1296, 1260, 988, 754, 727. UV (MeOH): λ_{max} 280 and 222 nm. ^{1}H NMR ($CDCl_3$): δ 7.97 (dd, 2H, $J = 3.0$ and $J = 5.4$ Hz, H-4 and H-7), 7.80 (dd, 2H, $J = 3.0$ and $J = 5.4$ Hz, H-5 and H-6), 7.20–7.50 (m, 4H, H-3′, H-4′, H-5′, and H-6′) ppm.

2.2.6. 2-(3-Fluorophenyl)-isoindole-1,3-dione (*4f*)

89%, 206–207 °C (lit. [16]: 200–201 °C)—IR (KBr): 1768, 1710, 1612, 1590, 1500, 1460, 1409, 1335, 1296, 1172, 981, 774, 728. UV (MeOH): λ_{max} 285 and 222 nm. ^{1}H NMR ($CDCl_3$): δ 7.96 (dd, 2H, $J = 3.0$ and $J = 5.7$ Hz, H-4 and H-7), 7.80 (dd, 2H, $J = 3.0$ and $J = 5.7$ Hz, H-5 and H-6), 7.47 (ddd, 1H, $J_{5',4'} = 8.1$, $J_{5',6'} = 8.1$, and $J_{5',F} = 6.0$ Hz, H-5′), 7.30 (ddd, 1H, $J_{6',5'} = 8.1$, $J_{6',4'} = 0.9$, and $J_{6',2'} = 2.1$ Hz, H-6′), 7.24 (dt, 1H, $J_{2',F} = 9.0$, $J_{2',4'} = 2.4$, and $J_{2',6'} = 2.4$ Hz, H-2′), 7.11 (dddd, 1H, $J_{4',F} = 8.4$, $J_{4',5'} = 8.1$, $J_{4',2'} = 2.4$, and $J_{4',6'} = 0.9$ Hz, H-4′) ppm.

2.2.7. 2-(4-Fluorophenyl)-isoindole-1,3-dione (*4g*)

98%, 180.6–181.2 °C (lit. [17]: 180–181.5 °C)—IR (KBr): 1770, 1680, 1603, 1514, 1467, 1409, 1393, 886, 864, 725. UV (MeOH): λ_{max} 281 and 221 nm. ^{1}H NMR ($CDCl_3$): δ 7.95 (dd, 2H, $J = 3.0$ and $J = 5.4$ Hz, H-4 and H-7), 7.80 (dd, 2H, $J = 3.0$ and $J = 5.4$ Hz, H-5 and

H-6), 7.43 (m, 2H, H-2′ and H-6′), 7.19 (m, 2H, H-3′ and H-5′) ppm.

2.2.8. 2-[1H-(1,2,4)Triazole-3-yl]-isoindole-1,3-dione (**4h**)

69%, 305–306 °C—IR (KBr): 3392 (>NH), 3063, 2855, 1792, 1770, 1744, 1526, 1492, 1466, 1374, 1353, 1118, 874, 719 cm^{-1}. UV (MeOH): λ_{max} 273, 223, and 205 nm. ^1H NMR (DMSO-d_6): δ 8.68 (s, 1H, H-5′), 8.01 (m, 4H, H-6, H-5, H-4, and H-3) ppm, the NH proton was not visible in the spectrum. It is assumed that the same was present at δ 3.6 ppm along with the protons of the water molecule present in the solvent. Anal. Calc. for $C_{10}H_6N_4O_2$: C, 56.08; H, 2.82; N, 26.16. Found: C, 56.60; H, 3.00; N, 26.08%.

2.2.9. 2-([1,2,4]Triazole-4-yl)-isoindole-1,3-dione (**4i**)

75.4%, 269.7–270.4 °C—IR (KBr): 3107, 1730, 1686, 1560, 1444, 1368, 1346, 1287, 1200, 1173, 1116, 1079, 1052, 879, 704 cm^{-1}. UV (MeOH): λ_{max} 275, 257, and 206 nm. ^1H NMR (DMSO-d_6): δ 8.72 (s, 2H, H-3′, H-5′), 7.78–7.71 (m, 4H, H-7, H-6, H-5, and H-4) ppm. Anal. Calc. for $C_{10}H_6N_4O_2$: C, 56.08; H, 2.82; N, 26.16. Found: C, 56.39; H, 2.70; N, 26.25%.

2.3. Hypolipidemic activity

A suspension of **4a**–**4i** in 1% carboxymethylcellulose (CMC) was administered orally by an intubation needle to Swiss white mice for 16 days at a 20 mg/kg per day dose. This dose was chosen based on the previous experiments with the animals. Blood samples were collected after fasting the animals for 13 h and puncturing their retro-orbital plexus and withdrawing the blood directly into tubes containing a solution (1 mg/ml) of ethylenediaminetetraacetic acid disodium salt (EDTA) before and after 16 days of treatment, and the plasma was separated by centrifugation at 2500 × g for 10 min. The animals were weighed everyday during the treatment. Samples of plasma were used in duplicate to determine the plasma cholesterol and triglyceride levels by using enzymatic assay CHOD-PAP [18], using cholesterol esterase, cholesterol oxidase, and peroxidase contained in Merck test 1.14830.0001 Ecoline 25 reagents (diagnostica-Merck KGaA, Darmstadt, Germany), and GPO-PAP [19], using the enzymes lipase, glycerokinase, glycerol phosphate oxidase, and peroxidase as described in Merck test 1.19706.0001 System Multi-Test, respectively.

3. Results and discussion

3.1. Chemistry

N-Aryl- or *N*-(1,2,4-triazol-yl)-phthalimides (**4a**–**4i**; Scheme 1) were obtained by the reaction of phthalic anhydride (**1**) and an appropriate amine (**2a**–**2i**) following the procedure described earlier [20,21].

The ring opening took place by nucleophilic attack of the amine nitrogen atom on carbonyl carbon of phthalic anhydride with the formation of *N*-substituted phthalamic acids (**3a**–**3i**) as an intermediate which lose water under heating conditions to give products **4a**–**4i** (Scheme 1). The yields were between 69 and 99%.

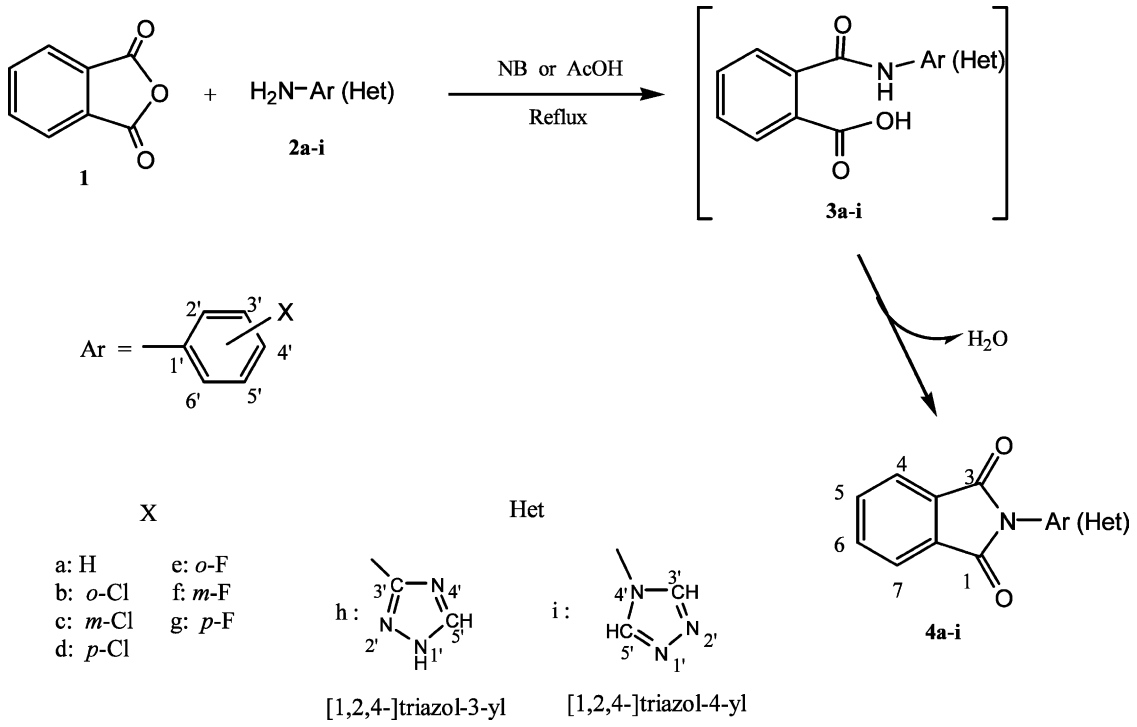
IR spectra of compounds **4a**–**4g** and **4i** did not absorb in the region 3100–3600 cm^{-1} indicating the absence of –OH or –NH groups. The spectra of all compounds showed two strong absorptions around 1777 and 1711 cm^{-1}, the former and the latter absorptions are due to the asymmetric and symmetric stretching vibrations of the carbonyl groups present in the phthalimide ring. Similar absorptions have been reported for *N*-substituted phthalimides [22]. Compound **4h** (Fig. 1) exhibited an absorption characteristic to –NH group at 3392 cm^{-1}, and the absorptions between 1606 and 1527 cm^{-1} which are due C=N and C=C groups.

UV spectra of these compounds exhibited absorptions in two main regions: the low-energy band between 274 and 288 nm ($n \rightarrow \pi^*$) and the high-energy band between 205 and 241 nm corresponding to $\pi \rightarrow \pi^*$ transitions. Such absorptions have been observed for *N*-substituted alkylphthalimides [23].

The chemical shifts of *N*-(*o*-, *m*-, and *p*-chlorophenyl)phthalimides (**4b**–**4d**) have been assigned without any problem. However, it was initially difficult to locate the chemical shifts of the phenyl protons of **4e**–**4g** containing a fluorine atom. We had to carry out several NMR experiments to determine the chemical shifts of the protons in order to make the correct assignments except for the compound **4e** which is still being analyzed. Section 2 provides only the chemical shifts. The detailed NMR studies including J-resolved, irradiation, and C-13 experiments of **4e**–**4g** will be reported elsewhere in the future.

4. Pharmacological evaluations

Although several *N*-arylphthalimides have been evaluated for pharmacological activity [3], none of the present compounds **4a**–**4i** were evaluated for biological activity tests before. The literature [3] reports that *N*-*p*-carboxyphenylphthalimide is quite effective as a hypolipidemic agent causing the reduction of cholesterol and TG by 47 and 42%, respectively.

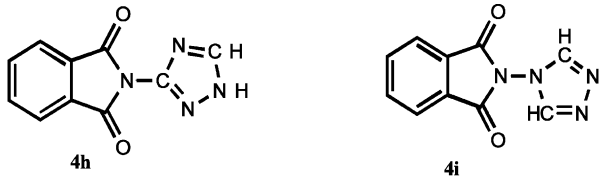


Scheme 1.

Compounds **4a**–**4i**, when tested for activity in Swiss white mice using 20 mg/kg per day, presented the reduction of plasma cholesterol and TG levels (Table 1). According to the literature [5], compound **4a** decreased cholesterol level by 43% after 16 days, whereas the triglycerides presented a reduction of 39% after 14 days. Our experiments show a lower diminution of cholesterol, but higher decrease in triglyceride levels (see Table 1). Among compounds tested, only *N*-(4-chlorophenyl)phthalimide (**4d**) presented significant hypolipidemic activity ($P < 0.05$), characterized by 63 and 47% decrease in cholesterol and TG levels, respectively (Table 1).

Although compounds **4b** and **4c** are less effective in diminishing plasma cholesterol levels (11 and 22%, respectively), they are much better in reducing TG (39 and 21%, respectively). Compounds containing fluorine atom in the phenyl ring, **4e**–**4g**, have also been found to reduce TG levels in plasma by 37, 38, and 50%, respectively. Phthalimides *N*-[3-chlorophenyl]phthalimide (**4c**) and *N*-[3-fluorophenyl]phthalimide (**4f**) are similar in decreasing cholesterol concentration (22 and 20%, respectively). When a comparison of the biological activity of *p*-chloro and *p*-fluoro substituents in phenyl ring of compounds **4d** and **4g** was made, the *p*-chloro substituent proved to be approximately twice as effective as *p*-fluoro substituent. In fact, *N*-*o*-chloro- and *N*-*o*-fluorophenylphthalimides presented only little effects in terms of diminishing the cholesterol levels. When *N*-aryl groups of phthalimide was replaced by triazoles, the activity of compound **4g** was found to lower the serum cholesterol content by 40%, whereas **4i** was 50% less effective as hypocholesterolemic agent.

Under similar conditions as used for our compounds, we tested pravastatin (drug used commercially) and observed a 36% reduction in the cholesterol levels (3.3 ± 0.1 mmol/l before the treatment and 2.1 ± 0.05 mmol/l after the treatment, significant for $P < 0.001$). The animals also presented a reduction of 42% (0.89 ± 0.2 mmol/l before the treatment and 0.52 ± 0.09 mmol/l after the treatment) in TG levels being significant for $P < 0.001$. This is interesting because two of our compounds,



2-[1*H*-(1,2,4)Triazol-3-yl]-isoindole-1,3-diona 2-[1,2,4]Triazol-4-yl-isoindole-1,3-diona

Fig. 1. Structures of compounds **4h** and **4i**.

Table 1
Effects of *N*-substituted phthalimides on mice plasma cholesterol and triglycerides levels

	Cholesterol (mmol/l)			Triglycerides (mmol/l)		
Comp.	Before	After	Reduction (%)	Before	After	Reduction (%)
4a	2.73±0.61	1.83±0.23 [a]	33	1.52±0.41	0.75±0.12 [a]	51
4b	2.10±0.55	1.86±0.50	11	1.14±0.43	0.69±0.18 [a]	40
4c	2.49±0.53	1.94±0.52	22	1.70±0.44	1.35±0.57 [a]	21
4d	3.18±1.32	1.19±0.65	63	1.54±0.46	0.81±0.37 [b]	47
4e	2.56±0.63	2.41±0.34	6	1.45±0.51	0.91±0.21	37
4f	2.01±0.63	1.60±0.30 [a]	24	0.78±0.33	0.48±0.14 [a]	39
4g	2.85±0.31	2.13±0.23	25	1.53±0.42	0.77±0.23 [a]	50
4h	3.13±0.56	1.87±0.37	40	1.88±0.10	1.60±0.03 [a]	15
4i	2.77±0.28	2.24±0.21 [a]	19	1.80±0.14	1.59±0.12	12
CMC [c]	2.04±0.31	2.09±0.23	3 [d]	1.01±0.31	0.98±0.15	2

Values represent the mean±S.D. for six animals in each group.
[a] Significant difference $P < 0.05$.
[b] Significant difference $P < 0.005$.
[c] Neither cholesterol nor triglycerides showed any significant reduction in their blood plasma.
[d] In fact, the cholesterol level increased slightly.

viz. **4a** and **4h**, produced similar results as that of pravastatin. The literature also reports that *N*-phthalimidobutan-3-one reduces serum cholesterol level by 37% in 16 days [3]. There are other phthalimides which decrease this level still higher [5]. When we compare the results of compound **4d** with the results of pravastatin, we verified that compound **4d** presented antihypercholesterolemic activity (reduction of 63% in the cholesterol level) superior to pravastatin (36% reduction). However, this same compound presented hypotriglyceridemic activity (47% of reduction) similar to pravastatin (42%). Thus, it is clear that *para*-substituted *N*-phenyl- and *N*-(1,2,4)-triazole-3-yl-phthalimides are better in lowering the plasma cholesterol and TG levels. Our results clearly indicate the superiority of **4d** over the commercially available drug. Although it has not been proven experimentally, it is possible that the alterations found in the plasmatic TG levels can be due to the interference of those drugs in the enzymes that regulate the synthesis de novo of TG. Lamb et al. [24] demonstrated that a positive correlation exists among the inhibition in the activity of the enzyme regulators (glycerol-3-phosphate acyltransferase and phosphatidase phosphohydrolase) and the decrease in the levels of TG in the serum. Similar observation was found by Chapman and coworkers [4] for saccharin and phthalimide. It is interesting to note that changes in phenyl substitution of *N*-phenylphthalimide affect hypolipidemic activity.

4.1. Statistic

The results are expressed as the mean±standard error and they were evaluated statistically using the paired Student's *t*-test and $P < 0.05$ as the criterion of statistical significance.

Acknowledgements

We thank Brazilian National Research Council (CNPq) and Pernambuco State Foundation for Science and Technology (FACEPE) for financial support.

References

[1] L.M. Lima, P. Castro, A.L. Machado, C.A.M. Fraga, C. Lugnier, V.L.G. Moraes, E.J. Barreiro, Bioorg. Med. Chem. 10 (2002) 3067–3073.
[2] A. Orzeszko, B. Kaminska, G. Orzesko, J. Starosciak, Synthesis and antimicrobial activity of new adamantine derivatives. II, Farmaco 55 (2000) 619–623.
[3] J.M. Chapman, Jr., G.H. Cocolas, I.H. Hall, Hypolipidemic activity of phthalimide derivatives. 1. *N*-substituted phthalimide derivatives, J. Med. Chem. 22 (1979) 1399–1402.
[4] I.H. Hall, J.M. Chapman, Jr., G.H. Cocolas, Effects of imide analogs on enzymes required for cholesterol and fatty acid synthesis, J. Pharm. Sci. 70 (1981) 321–328.
[5] J.M. Chapman, Jr., P.J. Voorstad, G.H. Cocolas, I.H. Hall, Hypolipidemic activity of phthalimide derivatives. 2. *N*-Phenylphthalimide and derivatives, J. Med. Chem. 26 (1983) 237–243.
[6] A.R. Murthy, O.T. Wong, D.J. Reynolds, I.H. Hall, Synthesis and hypolipidemic activity of 3-imino-1-oxoisoindolines in rodents, Pharm. Res. 4 (1987) 21–27.
[7] M.N. Ramos, B.d.B. Neto, Eletronic structure and hypolipidemic activity of phthalimide and related compounds: a QSAR study, J. Comput. Chem. 11 (1990) 572–596.
[8] M.D.C. Neto, W.C.P. Filho, B.B. Neto, The hypolipidemic activity of *N*-phenylphthalimide derivatives: a QSAR study, J. Braz. Chem. Soc. 4 (1993) 139–142.
[9] R. Antunes, R.M. Srivastava, A new series of *N*-(3-phenyl-1,2,4-oxadiazol-5-yl)alkylphthalimides. I, Heterocycl. Commun. 2 (1996) 247–250.
[10] R.M. Srivastava, F.J.S. Oliveira, L.P. Silva, J.R. de Freitas Filho, S.P. Oliveira, V.L.M. Lima, Synthesis and hypolipidemic activity of *N*-phthalimidomethyl tetra-*O*-acyl-α-D-mannopyranosides, Carbohydr. Res. 332 (2001) 335–340.

[11] V.L.M. Sena, R.M. Srivastava, S.P. Oliveira, V.L.M. Lima, Microwave-assisted synthesis of *N*-arylphthalamic acids with hyperlipidemic activity, Bioorg. Med. Chem. Lett. 11 (2001) 2671–2674.
[12] M.S. Khajavi, F. Nikpour, M. Hajihadi, Microwave irradiation promoted reactions of anhydrides with isocyanates. Preparation of *N*-substituted phthalimides, J. Chem. Res. (S) (1996) 96–97.
[13] A.M. Khalil, I.I. Abdelgawad, M.H. El-Metwally, Synthesis of 2-aryl and 2-alkylthio-4-phthalyl-2-thiazolin-5-ones and their reactions with aromatic amines, Indian J. Chem. 51 (1977) 1029–1031.
[14] A.F.M. Fahmy, N.F. Aly, M.H. Arief, Phathalimides: part II—synthesis and reactions of *N*-(arylcarbamoyloxy)phthalimides, Indian J. Chem. 16B (1978) 697–701.
[15] A.F.M. Fahmy, N.F. Aly, M.O. Orabi, Phthalimides. III. Ammonolysis, hydrazinolysis, pyrolysis and action of Grignard reagents on phthalimide derivatives, Bull. Chem. Soc. Jpn. 51 (1978) 2148–2152.
[16] G. Pagani, A.J. Buruffine, P. Borgana, G. Carcialanza, Acidi ftalamici variamente *N*-sostituiti, Farmaco 23 (1968) 448–457.
[17] K. Suzuki, E.K. Weisburger, J.H. Weisburger, Derivatives of 3-fluorofluorene by the Pschorr synthesis, J. Org. Chem. 26 (1961) 2239–2273.
[18] C.C. Allain, L.S. Poon, C.S. Chan, W. Richmond, P.C. Fu, Enzymatic determination of serum cholesterol, Clin. Chem. 20 (1974) 470–475.
[19] M.W. McGrowan, J.D. Artiss, D.R. Strandberg, B. Zak, A peroxidase-coupled method for the colorimetric determination of serum triglycerides, Clin. Chem. 29 (1983) 538–542.
[20] J. Demnitz, B.D.A Monteiro, N.R. Mozart, R.M. Srivastava, Synthesis and mass spectral studies of *N*-arylphthalimides, Heterocycl. Commun. 3 (1997) 115–122.
[21] M.R. Kanyonyo, J.H. Poupaert, P. Levêque, A. Gozzo, K. Van derpoorten, D.M. Lambert, O. Diouf, J. Vamecq, Reaction of aryl isothiocyanates with phthalic acid derivatives, Bull. Soc. Chim. Belg. 105 (1996) 55–56.
[22] C. Fayat, A. Foucaud, Fréquences ét intensités des bands d'absorption infrarouge des vibrations de valence des carbonyls. II. *N*-phénylphthalimides. Problènie de la résonance de Fermi, Bull. Soc. Chim. France 5 (1970) 4501–4505.
[23] J. Gawronski, F. Kazmierczak, K. Gawronska, U. Rychlewska, B. Nordén, A. Holmén, Excited states of the phthalimide chromophore and their exciton couplings: a tool for stereochemical assignments, J. Am. Chem. Soc. 120 (1998) 2083–12091.
[24] R.G. Lamb, S.D. Wyrick, C. Piantadosi, Hypolipidemic activity of in vitro inhibitors of hepatic and intestinal *sn*-glycerol-3-phosphate acyltransferase and phosphatidate phosphohydrolase, Atherosclerosis 27 (1977) 147–154.
[25] R. Antunes, H. Batista, R.M. Srivastava, G. Thomas, C.C. Araújo, R.L. Longo, H. Magalhães, M.B.C. Leão, A.C. Pavão, Synthesis, characterization and interaction mechanism of new oxadiazolo-phthalimides as peripheral analgesics. IV, J. Mol. Struct., in press.