Med Chem Res (2012) 21:75–84
DOI 10.1007/s00044-010-9492-1

MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis of new cyclic imides derivatives with potential hypolipidemic activity

Mohamed A. El-Zahabi · Laila M. Gad · Faida H. Bamanie · Zohair Al-Marzooki

Received: 16 November 2009 / Accepted: 28 October 2010 / Published online: 25 November 2010

Abstract Certain new nitrogen-substituted derivatives of cyclic imides phthalimide (a), 1,8-naphthalimide (b), and diphenimide (c), were synthesized aiming to obtain potent hypolipidemic agents. Thus, 2-(*N*-imido) propanoic acids, 2-(*N*-phthalimido)-2-methylpropionic acid, and their ethyl esters were synthesized (Target derivative A). Also their corresponding *N*-substituted-2-(*N*-imido) propionamides and 2-(*N*-phthalimido)-2-methylpropionamides were prepared (Target derivative B). In addition, *N*-phthalimidomethyleneoxy acetate was prepared. Some of the newly prepared compounds were subjected to 3D studies and were found to be superimposed on Clofibrate, which is the first generation of fibrate drugs. The preliminary evaluation of hypolipidemic activity of the newly prepared compounds against triton WR-1339-induced hyperlipidemia in rat showed that several derivatives have demonstrated significant lowering of serum total cholesterol and triglyceride levels at dose of 150 mg/kg/i.p. comparing with Fenofibrate which is one of the second generations of fibrate drugs.

Keywords Synthesis of cyclic imides · Hypolipidemic activity · Antihyperlipidemic activity

M. A. El-Zahabi · L. M. Gad (✉)
Department of Pharmaceutical Chemistry, King Abdulaziz University, 80260, 21589 Jeddah, KSA
e-mail: lgad@kau.edu.sa; gad_laila@yahoo.com

F. H. Bamanie · Z. Al-Marzooki
Department of Clinical Biochemistry, King Abdulaziz University, Jeddah, KSA

Introduction

Hypolipidemic agents or antihyperlipidemic agents are a diverse group of pharmaceuticals that are used in the treatment of hyperlipidemias; some may lower "bad cholesterol" (LDL) more so than others, while others may prudentially increase (HDL) "the good cholesterol". Other studies showed that elevating the high-density lipoprotein (HDL) and lowering the triglyceride levels (TGs) in the serum were accepted measures in treating hyperlipidemias and atherosclerosis (Steinberg *et al*., 1989); (Ginsberg, 1990); (Levine *et al*., 1995); (Larsen and Spilman, 1993).

LDL and VLDL carry cholesterol towards tissues, and elevated levels of these lipoproteins are associated with atheroma formation. HDL, in contrast, carries cholesterol back to the liver and is associated with protection against cardiovascular disease (Miller, 2000).

The efficacy of the hypolipidemic drugs revealed to their effects: (a) decreased cholesterol levels and increased clearance of LDL from the blood stream that is by inhibition of the synthesis of cholesterol, e.g., Statins (Boden, 2000) which are particularly well suited for lowering LDL in people at risk for cardiovascular diseases because of hypercholesterolemia. Or (b) increased HDL and lowered triglyceride level (TGs) , e.g., the first and second generation of Fibrates (Staels *et al*., 1998); (Spieker *et al*., 2000). Niacin and Nicotinamide which are well suited for patient with hypertriglyceridemia (Parsons, 2003). Or (c) inhibit the dietary cholesterol absorption or sequestering the cholesterol-containing bile acids released into the gut and preventing their reabsorption from the gut thus decreasing cholesterol levels in blood plasma. , e.g., Ezetimibe and Bile acid sequestrants (Rossi, 2006). Clinically, the choice of any agent will depend on the patient's cholesterol

profile, cardiovascular risk and the liver and kidney functions of the patient. (Farnier, 1998); (Gavish *et al*., 2000).

Many agents having cyclic imide's functions were generally potent hypolipidemic agents lowering serum cholesterol levels on an average of 35% and serum triglyceride levels on an average of 29% after 16 days dosing at 20 mg/kg/day intrapretonially (i.p.) in mice. (Chapman *et al*., 1984); (Voorstad *et al*., 1985); (Murthy *et al*., 1985); (Hall *et al*., 1986). They possess hypolipidemic activity superior in many cases to Clofibrate (**I**). Design and synthesis of structurally related *N*-substituted cyclic imides; imido-propionic acid and imido-2-methylpropionic acid derivatives was the main objective of the present investigation. Therefore, the design of newly prepared compounds proposed the replacement of the phenoxy ring of the Clofibrate with phthalimido (a), 1,8-naphthalimido (b), diphenimido (c) rings, aiming to obtain potent hypolipidemic agents of high therapeutic index and minimal side effects in comparison with the widely used and commercially available Clofibrate drug (Barakat *et al*., 2000). Overlaying Clofibrate (**I**) as a prototypic compound with some proposed imide's derivatives at the position of the ether's oxygen atom of Clofibrate (**I**) and the imide's nitrogen atom assists our planning. The research design was made by the aid of molecular modeling programs of computer Accelry's softwares.

Research design

The overlay of certain analogs namely, 2-(*N*-phthalimido)-, 2-(*N*-1,8-naphthalimido)-, 2-(*N*-diphenimido)-propionates, and 2-(*N*-phthalimido)-2-methylpropionates with the already known ethyl ester of 2,2-dimethylphenoxyacetic acid; Clofibrate (**I**), as a prototypical compound were made with the aid of computer Accelry's softwares at the Computer laboratory, Faculty of Pharmacy, KAU. These overlays are illustrated in Figs. 1, 2 and 3:

Molecular modeling programs were used to compare the 3D structures of the different cyclic imide's analog, and then overlaying Clofibrate (**I**) as a prototypic compound with some imide's derivatives at the position of the ether's oxygen atom of Clofibrate (**I**) and the imide's nitrogen atom. The software strives to find the best fit in such way that the equivalent centers; the ether oxygen with the cyclic imido nitrogen and the different aromatic rings together. It was found that they are matched up

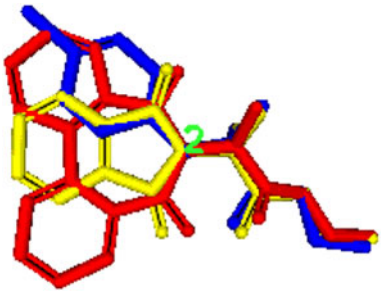
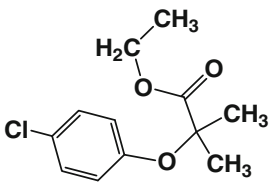


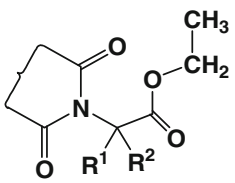
Fig. 1 Overlay of Ethyl 2-(*N*-phthalimido)propionate (IIIa) (*yellow*), and Ethyl-2-(*N*- diphenimido)propionate (IIIc) (*red*), with Clofibrate (**I**) (*blue*); attached at the imido nitrogen of both phthalimido and diphenimido derivatives against the ether oxygen of Clofibrate

Fig. 2 Overlay of Ethyl 2-(*N*-1,8-naphthalimido)propionate (**IIIb**) (*magenta*), with Clofibrate (**I**) (*blue*); attached at the carbonyl carbon of both

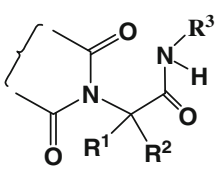
Fig. 3 Overlay of Ethyl 2-(*N*-phthalimido)-2-methylpropionate (**VIa**) (*yellow*), with Clofibrate (**I**) (*blue*) prototypic compound, attached at the carbonyl carbon of both



Clofibrate (I)



Target Derivatives (A)



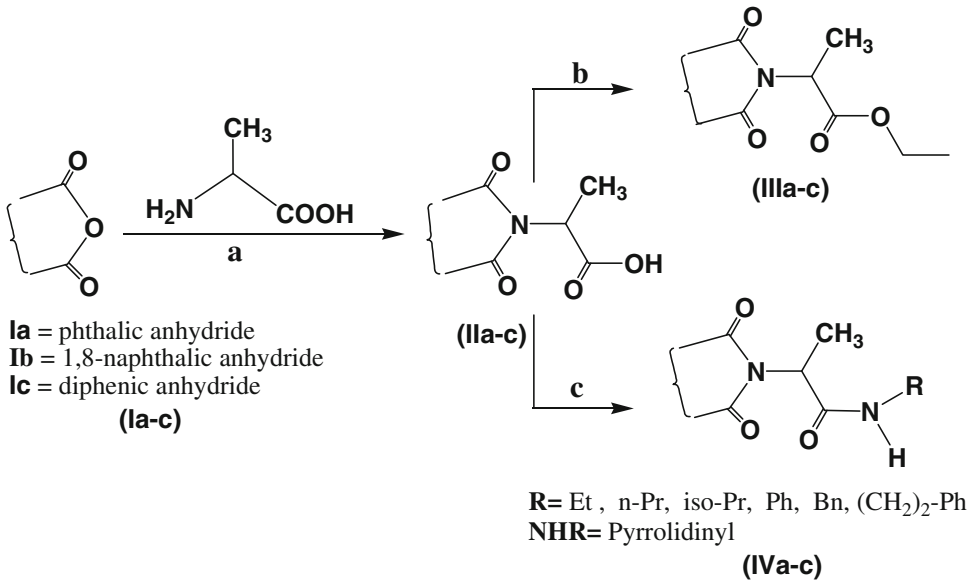
Target Derivatives (B)

resulting in the overlay shown in the previous Figs. 1, 2 and 3.The following points were considered:

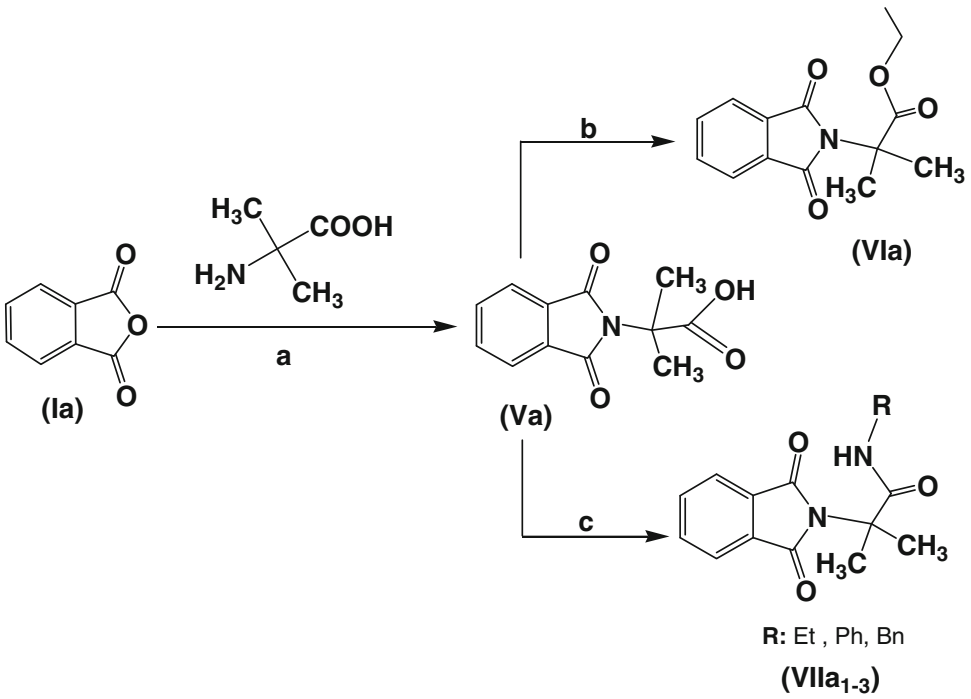
(1) The interatomic distance between ester oxygen and the aromatic ring within the imido compound analogs should be nearly the same as that in the prototypic compound Clofibrate(**I**).
(2) Synthesis of bulky esters or amides of the imido-propionic acids may enhance the hypolipidemic activity by enhancing the lipophilicity of these compounds.

Materials and methods

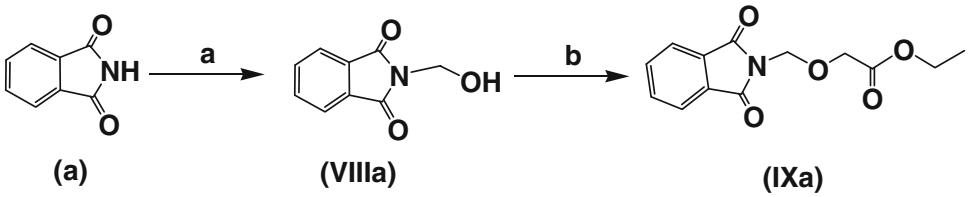
For the preparation of the desired derivatives, Schemes 1, 2, and 3 were adopted.



Scheme 1 Preparation of *N*-imidopropionates (Target derivatives A, **IIIa–c**) and *N*-imidopropionamides (Target derivatives B, **IVa–c**)



Scheme 2 Preparation of *N*-phthalimidomethyopropionate (Target derivatives A, **VIa**) and *N*-Phthalimidomethylpropionamides (Target derivatives B, **VIIa**$_{1-3}$)



Scheme 3 Preparation of Ethyl *N*-phthalimidomethyleneoxyacetate (**IXa**)

Chemistry

2-(*N*-imido)propanoic acids (IIa–c) were prepared—as described in the text—via two steps reaction of the corresponding cyclic anhydride (Ia–c) with L-alanine at first step followed by cyclodehydration using acetic anhydride and a catalytic amount of anhydrous sodium acetate at the second step. Esterification of (IIa–c) with absolute ethanol in the presence of ethylchloroformate and triethyl amine TEA in methylene chloride via a mixed anhydride procedure afforded 2-(*N*-imido)propionate (IIIa–c), while amidation of (IIa–c) using appropriate aliphatic amines and aromatic amines in the presence of ethylchloroformate and TEA and a catalytic amount of dimethylaminopyridine DMAP in methylene chloride yielded series of *N*-substituted-2-(*N*-imido)propionamides (IVa 1–7, IVb1–3 and IVc) Scheme 1.

Furthermore, aminolysis of phthalic anhydride (Ia) with 2-methyl-L-alanine followed by cyclodehydration with acetic anhydride yield 2-(*N*-phthalimido)-2-methylpropionic acid (Va), which was then esterfied to produce ethyl 2-(*N*-phthalimido)-2-methylpropionate (VIa), and also, allowed to react with appropriate primary amines to afford the *N*-substituted-2-(*N*-phthalimido)-2-methylpropionamides ($VIIa_{1-3}$) (Scheme 2)[1].

In addition, *N*-Hydroxymethylphthalimide (VIIIa) was prepared as described in the text and was allowed to react with ethylchlorofomate producing the alkyl ether ester of phthalimide;*N*-(phthalimido)-2-methyleneoxyacetate (IXa) (Scheme 3).[2]

Experimental

Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded on Bruker Advance DP×400 spectrometer using Me_4Si as internal reference and DMSO-d6 or $CDCl_3$ were used as solvent, the chemical shifts were measured in δ ppm: the spectra were carried out at Faculty of Science, King Abdul-Aziz University. Elemental analyses were performed in Perkin Elmer 2400, series II micro-analyzer at Micro-analytical laboratory, Faculty of Science, King Abdul-Aziz University. Melting points were determined with Barnstead electro thermal melting point apparatus and are uncorrected. Chemicals are an Aldrich and Fluka products and are used without further purification. Thin layer chromatography was performed using $CHCl_3/CH_3OH$ (9.5:0.5) or ethyl acetate/cyclohexane (7:3) or (5:5) as eluent.

2-[N-(1,8-naphthalimido)]propionic acid (iib), Scheme 1:

General method (Ossman *et al*., 1991); (El-Helby *et al*., 2003); (El-Zahabi *et al*., 1998): 1,8-Naphthalic anhydride (**Ib**) (19. 8 g, 0.1 mol) and (8.9 g, 0.1 mol) of L-alanine were refluxed in (300) DME for 5 h. The solvent was evaporated under vacuum, and the residue washed with ethanol, air-dried. Acetic anhydride (100 ml) and sodium acetate (2.0 g) were added and heated under reflux for additional 2 h. The reaction mixture was cooled, poured in to ice cold water (500 ml), and the precipitated product was filtered, washed with water, air dried, and crystallized from DMF (Table 1).

Ethyl-2-[N-(1,8-naphthalimido)]propionate (IIIb), Scheme 1:

General method A solution of 2-[*N*-(1,8-naphthalimido)]propionic acid (**IIb**) (2,84 g, 0.01 mol) in CH_2Cl_2 (50 ml), was placed in a flask equipped with two dropping funnels and stirred in ice bath. A solution of triethylamine TEA (1.5 ml, 0.01 mol) in CH_2Cl_2 (5 ml) was placed in one of the dropping funnel, and was added dropwise to the solution of imidopropionic acid while stirring over a period of half an hour in the ice bath, then, ethyl chloroformate (0.12 ml, 0.01 mol) in CH_2Cl_2 (5 ml) was placed in the other dropping funnel, and was added dropwise to the reaction mixture while stirring at room temperature for 1 h. Ethyl alcohol (5 ml) was added dropwise to the reaction mixture while stirring at room temperature for additional 1 h. The prepared ester was extracted with $CHCl_3$ (30 ml),

[1] Reagent and Condition for Schemes 1 and 2: (a) i. DMF/Reflux for 4 h, ii. Ac_2O/reflux for 2 h. (b) i. NEt_3/DMAP/CH_2Cl_2 (−5 to −10°C), ii. ClCOOEt, iii. Et-OH. (c) i. NEt_3/DMAP/CH_2Cl_2 (−5 to −10°C), ii. ClCOOEt, iii. R-NH_2

[2] Reagent and Condition for Scheme 3: (a) HCHO/H_2O Reflux for 2–6 h. (b) /DMF/Na_2CO_3

washed with citric acid (2 ml 10% solution), followed by washing with brine (10 ml), dried over $MgSO_4$. The extract was evaporated under reduced pressure and the obtained solid ester was crystallized from $CHCl_3$/*n*-hexane (Table 2).

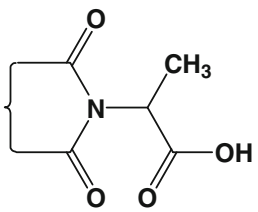
N-Substituted-2-[N-(1,8-naphthalimido)]propionamides (IVb 1-3), Scheme 1

General method The previous procedure used for the preparation of ester derivatives was adopted for the formation of *N*-substituted-2-[*N*-(1.8-naphthalimido)]propionamides, and instead of addition of ethyl alcohol, an equivent amount of the appropriate amine (0.012 mol) was added, and the reaction mixture was stirred, and refluxed gently for 2 h. The appropriate amines that are used for the preparation of *N*-substituted amides are ethyl amine, *n*-propyl amine, isopropyl amine, aniline, benzyl amine, and phenethyl amine, and pyrrolidine (Table 3).

2-(N-Phthalimido)-2-methylpropionic acid (Va), Scheme 2

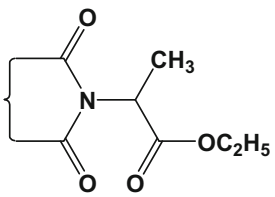
A mixture of phthalic anhydride (**Ia**) (7.4 g, 0.05 mol), and 2-methyl-L-alanine (5.15 g, 0.05 mol), and DMF (80 ml) was stirred under reflux for 4 h. The DMF was then removed under vacuum, and the residue was dissolved in acetic anhydride (60 ml). The reaction mixture was stirred under reflux for 2 h., then cooled, poured in to ice cold water (200 ml) and the precipitated product was filtered, washed with water, air dried and crystallized from ethanol, $\mathbf{C_{12}H_{14}NO_3}$ (M.Wt. 233.22), mp 155–157°C in 35% yield.

Table 1 Physicochemical properties of 2-(N-imido)propanoic acids (IIa–c):



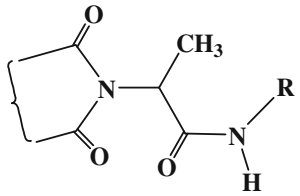
Serial no.	Amide moiety	Mol. formula (mol. wt)	Cryst.solvent yield %	M.p °C	1H NMR DMSO-d6
IIa	Phthalimido	$C_{11}H_9NO_4$ (219.19)	$CHCl_3$/ C_2H_5OH (70)	163–165	(IIa) δ: 1.58–1.59 (d, 3H, CH3), 4.80–4.85 (q, 1H, CH), 7.91 (s, 4H, Ar–H).
IIb	1,8-Naphthalimido	$C_{15}H_{11}NO_4$ (269.25)	DMF (63)	226–228	(IIb) δ: 1.58–1.59 (d, 3H, CH3), 5.62–5.65 (q, 1H, CH), 7.92–7.96 (t, 2H, Ar–H), 8.51–8.53 (d, 2H, Ar–H), 8.56–8.58 (d, 2H, Ar–H).
IIc	Diphenimido	$C_{17}H_{13}NO_4$ (295.29)	2-propanol (43)	191–193	

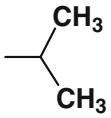
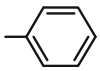
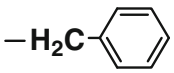
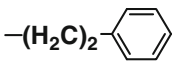
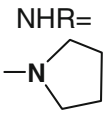
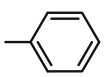
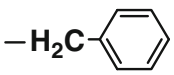
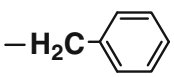
Table 2 Physicochemical properties of ethyl 2-(N-imido)propionates (IIIa–c):



Serial no.	Amide moiety	Mol. formula (mol. wt)	Cryst. solvent yield %	M.p °C	Microanalysis		
						Calc.	Fd.
IIIa	Phthalimido	$C_{13}H_{13}NO_4$ (247.25)	$CHCl_3/C_2H_5OH$ (78)	61–62	C	63.15	62.43
					H	5.30	6.24
					N	5.67	6.28
IIIb	1,8-Naphthalimido	$C_{17}H_{15}NO_4$ (279.31)	Ethyl acetate (73)	109–111	C	68.68	68.47
					H	5.09	5.74
					N	4.71	5.43
IIIc	Diphenimido	$C_{19}H_{17}NO_4$ (323.34)	CH2Cl2 (65)	90–92	C	70.58	70.59
					H	5.30	5.16
					N	4.33	4.17

Table 3 Physicochemical properties of *N*-substituted-2-(*N*-imido)propionamides (IVa–c):



Serial no.	Substituent	Mol. formula (mol. wt)	Cryst. solvent yield %	M.p °C	Microanalysis		
						Calc.	Fd.
IVa-1	$-CH_2-CH_3$	$C_{13}H_{14}N_2O_3$ (246.26)	C_2H_5OH (78)	143–145	C	63.40	63.43
					H	5.73	6.22
					N	11.38	11.52
IVa-2	$-CH_2CH_2CH_3$	$C_{14}H_{16}N_2O_3$ (260.29)	C_2H_5OH (71)	136–138	C	64.60	64.45
					H	6.20	6.70
					N	10.76	10.72
IVa-3		$C_{14}H_{16}N_2O_3$ (260.29)	C_2H_5OH (68)	167–168	C	64.60	65.01
					H	6.20	6.71
					N	10.76	10.84
IVa-4		$C_{17}H_{14}N_2O_3$ (294.30)	C_2H_5OH (73)	163 –164	C	69.38	68.83
					H	4.79	4.10
					N	9.52	9.47
IVa-5		$C_{18}H_{16}N_2O_3$ (308.33)	C_2H_5OH (83)	142–144	C	70.12	69.37
					H	5.23	5.96
					N	9.09	9.14
IVa-6		$C_{19}H_{18}N_2O_3$ (322.13)	C_2H_5OH (75)	178–180	C	70.79	70.65
					H	5.63	5.21
					N	8.69	8.73
IVa-7		$C_{15}H_{16}N_2O_3$ (272. 3)	C_2H_5OH (66)	148–149	C	66.16	65.52
					H	5.92	5.95
					N	10.29	10.32
IVb-1	$-CH_2-CH_3$	$C_{17}H_{16}N_2O_3$ (296.32)	CH_2C_{l2} (82)	212–214	C	68.91	68.47
					H	5.44	5.74
					N	9.45	9.12
IVb-2		$C_{21}H_{18}N_2O_3$ (344.36)	CH_2C_{l2} (84) (76)	222–223	C	73.24	72.65
					H	4.68	5.25
					N	8.13	8.57
IVb-3		$C_{22}H_{18}N_2O_3$ (358.39)	CH_2C_{l2} (87)	249–251	C	73.73	73.13
					H	5.06	5.67
					N	7.82	8.18
IVc		$C_{24}H_{20}N_2O_3$ (384.43)	C_2H_5OH (35)	145–147	C	74.98	73.51
					H	5.24	5.24
					N	7.29	7.12

***^{1}H NMR of (Va), DMSO-d6, δ*:** 1.72 (s, 6H, $2CH_3$), 7.83 (s, 4H, Ar–H), 12.7–13.0 (brs, 1H, COOH).

N-(2-Hydroxymethyl)phthalimide (VIIIa), Scheme 3

Phthalimide (a) (10.2 g) (5.2 ml) formalin, and (35 ml) water refluxed until clear, filtered while hot, and the filtrate cooled yielded 11.2 g. of ***N*-(2-Hydroxymethyl)-phthalimide (VIIIa)** $\mathbf{C_9H_7NO_3}$ (M.Wt. 177.16) mp 138–41°C (recorded mp 140–145°C) (Winstead *et al.,* 1955).

Ethyl N-(phthalimido)-2-methyleneoxyacetate (IXa), Scheme 3

Equimolar quantities (0.01 mol) of ethyl cloroacetate was mixed with anhydrous Na_2CO_3 (1.06 g, 0.01 mol) in DMF (50 ml). *N*-(2-Hydroxymethyl)-phthalimide (**VIIIa**) (0.01 mol) was added, and the mixture was heated under reflux on a boiling water bath for 1 h., then cooled, and poured in to ice-cold water (200 ml) and stirred well for 30 min. The solid obtained was filtered, washed with water, dried, and crystallized from ethanol, yielded **Ethyl *N*-(phthalimido)-2-methyleneoxyacetate** (**IXa**) in 74% yield, $\mathbf{C_{13}H_{13}NO_5}$ (M.Wt. 263.25) mp 107–109°C. ***^{1}HNMR* of (IXa) *DMSO-d6, δ*:** 1.18–1.22 (t, 3H, CH_3), 4.13–4.18 (q, 2H, CH_2–CH_3), 4.45 (s, 2H, CH_2–COO), 6.06 (s, 2H, N–CH_2-O), 7.82–7.95 (m, 4H, Ar–H).

Calculated analysis **C** 59.31**; H** 4.98**; N** 5.32%

Found analysis **C** 58.83**; H** 5.46**; N** 5.43%

^{1}H NMR of (IIIa–c), DMSO-d6

- (**IIIa**) ***δ*:** 1.13–1.17 (t, 3H, CH_2–CH_3), 1.56–1.58 (d, 3H, N–CH-CH_3), 3.9–4.1 (q, 2H, CH_2-CH_3), 4.9–5.1 (q, 1H, CH–CH_3), 7.92 (brs, 4H, Ar–H).
- (**IIIb**) ***δ*:** 1.16–1.19 (t, 3H, CH_2–CH_3), 1.61 -1.63 (d, 3H, N–CH-CH_3), 4.15–4.19 (q, 2H, CH_2-CH_3), 5.71–5.73 (q, 1H, CH), 7.94–7.98 (t, 2H, Ar–H), 8.53–8.55 (d, 2H, Ar–H), 8.58–8.59 (d, 2H, Ar–H).
- (**IIIc**) **$CDCl_3$, *δ*:** 1.23–1.15 (t, 3H, CH_2–CH_3), 1.66–1.62 (d, 3H, CH–CH_3), 4.25–4.10 (q, 2H, –CH_2–CH_3), 5.59–5.53 (q, 1H, –CH–CH_3), 7.89–7.48 (m, 8H, Ar–H).

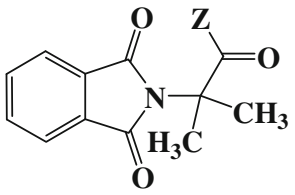
^{1}H NMR of (IVa 1–7, IVb 1–3 and IVc), DMSO-d6

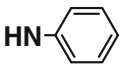
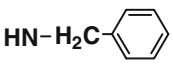
- (**IVa-1**) ***δ*:** 1.05–1.08 (t, 3H, CH_2–CH_3), 1.61–1.63 (d, 3H, N–CH-CH_3), 3.16–3.20 (pented, 2H, CH_2–CH_3), 4.74–4.82 (q, 1H, N–CH–CH_3), 7.95 (brs, 4H, Ar–H), 8.15–8.25 (broad, 1H, NH).
- (**IVa-2**) ***δ*:** 0.77–0.81 (t, 3H, CH_3), 1.33–1.42 (septet, 2H, CH_2), 1.52–1.54 (d, 3H, CH_3), 2.95–3.06 (m, 2H, CH_2), 4.66–4.71 (q, 1H, CH), 7.84–7.89 (m, 4H, Ar–H), 8.01–8.03 (broad, 1H, NH).
- **(IVa-3) *δ*:** 0.99–1.01 (d, 3H, CH_3), 1.03–1.04 (d, 3H, CH_3), 1.51–1.53 (d, 3H, CH_3), 3.86–3.91 (septet, 1H, CH $(CH_3)_2$), 4.63–4.69 (q, 1H, CH), 7.81–7.89 (m, 4H, Ar–H).
- **(IVa-4) *δ*:** 1.60–1.62 (d, 3H, CH_3), 4.91–4.96 (q, 1H, CH), 7.04–7.07(t, 1H, Ar–H), 7.27–7.31 (t, 2H, Ar–H), 7.53–7.55 (d, 2H, Ar–H), 7.86–7.93 (m, 4H, Ar–H), 9.89 (s, 1H, NH).
- **(IVa-5) *δ*:** 1.59–1.61 (d, 3H, CH_3), 4.29–4.31 (d, 2H, CH_2), 4.79–4.84 (q, 1H, CH), 7.20–7.33 (m, 5H, Ar–H), 7.84–7.91 (m, 4H, Ar–H), 8.61–8.64 (t, 1H, NH).
- **(IVa-6) *δ*:** 1.53–1.54 (d, 3H, CH_3), 2.63–2.72 (m, 2H, CH_2), 3.22–3.27 (q, 2H, CH_2), 4.67–4.72 (q, 1H, CH), 7.17–7.29 (m, 5H, Ar–H), 7.85–7.91 (m, 4H, Ar–H), 8.17–8.18 (t, 1H, NH).
- **(IVa-7) *δ*:** 1.54–1.55 (d, 3H, CH_3), 1.64–1.76 (m, 2H, CH_2), 1.77–1.84 (m, 2H, CH_2), 3.14–3.92 (q, 1H, CH), 3.24–3.34 (m, 2H, CH_2), 3.38–3.42 (m, 1H, CH), 4.94–4.98 (q, 1H, CH), 7.86 (s, 4H, Ar–H).
- **(IVb-1) *δ*:** 1.02–1.06 (t, 3H, CH_3), 1.60–1.61 (d, 3H, CH_3), 3.1–3.2 (q, 2H, CH_2), 5.50–5.60 (q, 1H, CH), 7.95–8.0 (t, 2H, Arom.-H), 8.0–8.15 (broad t-like, 1H, NH), 8.53–8.55 (d, 2H, Ar–H), 8.56–8.58 (d, 2H, Ar–H).
- **(IVb-2) *δ*:** 1.81–1.85 (d, 3H, CH_3), 5.88–5.93 (q, 1H, CH), 7.07–7.10 (t, 1H, Ar–H), 7.28–7.31 (t-like, 2H, Ar–H), 7.51–7.53 (d, 2H, Ar–H), 7.57 (broad, 1H, NH), 7.75–7.79 (d, 2H, Ar–H), 8.24–8.26 (d, 2H, Ar–H), 8.61–8.63 (d, 2H, Ar–H).
- **(IVb-3) *δ*:** 1.75–1.77 (d, 3H, CH_3), 4.50–4.61 (dd, 2H, CH_2), 5.78–5.83 (q, 1H, CH), 6.06 (broad, 1H, NH), 7.32–7.35 (brs, 5H, Ar–H), 7.76–7.79 (t, 2H, Ar–H), 8.23–8.25 (d, 2H, Ar–H), 8.61–8.63 (d, 2H, Ar–H).
- **(IVc) *δ*:** 1.61–1.63 (d, 3H, CH_3), 4.30–4.33 (t, 2H, CH_2), 5.44–5.45 (q, 1H, CH), 7.23–7.25 (t, 1H, Ar–H), 7.29–7.35 (m, 4H, Ar–H), 7.57–7.60 (t, 2H, Ar–H), 7.69–7.71 (d, 2H, Ar–H), 7.73–7.76 (t, 2H, Ar–H), 7.80–7.81 (d, 2H, Ar–H), 8.38–8.40 (t, broad, 1H, NH) (Table 4).

^{1}H NMR of (VIIa-2, 3), DMSO-d6

- **(VIIa-2) *δ*:** 1.76 (s, 6H, 2 CH_3), 7.02–7.05 (t, 1H, Ar–H), 7.26–7.29 (t, 2H, Ar–H), 7.52–7.53 (d, 2H, Ar–H), 7.85 (s, 4H, Ar–H), 9.71 (brs, 1H, NH).
- **(VIIa-3) *δ*:** 1.73 (s, 6H, 2 CH_3), 4.258–4.269 (d, 2H, CH_2), 7.20–7.24 (q, 3H, Ar–H), 7.26–7.31 (t-like 2H, Ar–H), 7.83 (s, 4H, Ar–H), 8.49–8.51 (t-like, broad, 1H, NH).

Table 4 Physicochemical properties of Ethyl ester of 2-(*N*-phthalimido)-2-methylpropionic acid (VIa) and its *N*-substituted-2-(*N*-phthalimido)-2-methylpropionamides (VIIa1–3):



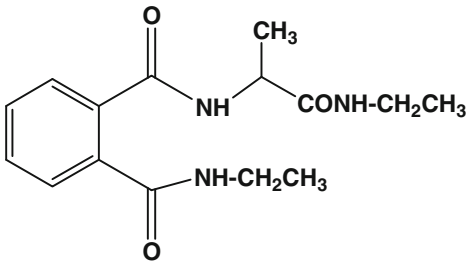
Serial no.	Z	Mol. formula (mol. wt)	Cryst. solvent yield %	M.p °C	Microanalysis		
						Calc.	Fd.
VIa	OC_2H_5	$C_{14}H_{15}NO_4$ (261.27)	C_2H_5OH (72)	83–85	C	64.36	63.89
					H	5.79	5.39
					N	5.36	4.96
VII1	$NH–C_2H_5$	$C_{14}H_{16}N_2O_3$ (260.29)	C_2H_5OH (55)	114–116	C	64.60	64.72
					H	6.20	5.44
					N	10.76	9.84
VII2		$C_{18}H_{16}N_2O_3$ (308.33)	C_2H_5OH (50)	199–201	C	70.12	69.98
					H	5.23	4.34
					N	9.09	9.06
VII3		$C_{19}H_{18}N_2O_3$ (322.36)	C_2H_5OH (65)	142–144	C	70.79	69.75
					H	5.63	6.13
					N	8.69	8.49

- **Unexpected phthalamic acid derivative (Xa)** was obtained while performing the amidation of 2-(*N*-phthalimido)propionic acid (IIa) with excess ethylamine (Scheme1), and its structure was confirmed by both spectral and elemental analyses, **$C_{15}H_{21}N_3O_3$** (M.Wt. 291.35), mp 157–157°C.

^{1}HNMR spectrum of ***N^1*-Ethyl,*N^2*-(*N*-ethyl-2-methylacetamido)phthalic dicarboxamide (Xa), DMSO-d_6, δ:** 1.062–1.263 (m- 6H, 2 CH_3), 1.28–1.29 (d, 3H, CH_3), 3.09–3.15 (q, 1H, CH of CH_2), 3.21–3.27 (q, 1H, CH of CH_2), 4.25–4.29 (pentet, 1H, CH), 7.41–7.57 (m, 4H, Arom-H), 8.02–8.04 (t, 1H, NH), 8.53–8.55 (d, 2H, 2NH).

Calculated analysis **C** 61.84**; H** 7.27**; N** 14.42%

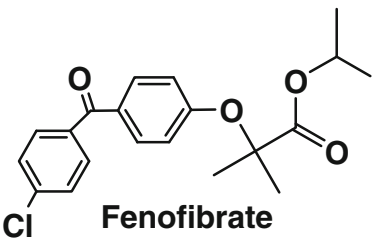
Found analysis **C** 68.83**; H** 6.59**; N** 14.26%.



(Xa)

Hypolipidemic activity

The pharmacological screening for the antihyperlipidemic activity of selected imido derivatives as performed against Triton WR-1339-induced hyperlipidemia in rats following the procedure reported by Kuroda *et al*. (1977) with some modifications and using Fenofibrate drug as reference standard.



Fenofibrate

Thus, antihyperlipidemic activity of 17 compounds including Target derivative (a): *N*-imidopropionate (IIIa,b), *N*-phthalimidomethyl-propionate (VIa), and *N*-(Ethoxycarbonyl-methoxymethyl)phthalimides (IXa); and Target derivative (b): *N*-imidopropionimide (IVa 1–7, IVb 1–3 and IVc) and *N*-phthalimidomethyl-prpionimide (VIIa) and compound *N^1*-Ethyl,*N^2*-(*N*-ethyl-2-methylacetamido) phthalic dicarboxamide (Xa) were performed.

Materials and apparatus

Fenofibrate (Sigma) was used as a reference antihyperlipidemic drug available in the market. Triton WR-1339 (Tyloxapol, Sigma) was used to induce the suitable hyperlipidemia within 24 h by intraperitoneal injection (i.p.) at a dose of 300 mg/kg rat body weight. Male albino Wister rats (5–6 week-old, 150–190 g body weight) were used as experimental animals. Carboxymethylcellulose sodium (CMC–Na, Sigma, 1% in normal saline) was used as a suspending agent. The tested compounds and the reference drug were suspended in carboxymethylcellulose sodium solution (1% in normal saline). Fenofibrate and tested compounds suspension were given orally to rats by Gavage at a dose of 150 mg/kg 2 h before the injection of triton. Triton was dissolved in normal saline to give 10% solution.

Procedure: (Kuroda *et al*., 1977)

Male albino Wister rats were arranged in 20 group (100 animals/20 = 5 in each group). Animals in the first group were injected with saline and kept as a normal control group. Hyperlipidemia in rats was induced in the other groups (19 groups) by i.p. injection of triton. The second group was used as hyperlipidemic (HL) control rats. Animals in the third group were orally dosed with 150 mg/kg Fenofibrate and kept as a reference group. At the same time, the remaining groups (17 groups) were orally given the tested compounds at a dose level of 150 mg/kg body weight. 2 h later, rats in groups from the second group to the 20 group (19 group) were injected by triton in the given dose, and once they injected by triton they were deprived from food but were allowed free on excess of drinking water ad libitum over the next 24 h. After 24 h, blood samples were withdrawn from the rat's orbital sinus and serum was separated. Total cholesterol (TC), and Total triacyl glycerol (triglyceride, TG), HDL, and LDL levels were determined using automated analyzer RXL-MAX1.

Discussion of pharmacological screening

- Fenofibrate, as reference standard, induced slightly but non-significant decrease in serum levels of TC (23%), and TG (20%). However, it slightly increase the HDL (11.7%) and but this unexpected increase of effect in LDL (13%) may be due to that Fenofibrate was used in a single dose only that was not sufficient to provide the expected effect.
- The biaryl imides (**IVb, IVc**), the substituted amide derivatives of 1,8-naphthalimidopropionamdes (**IVb 1–3**) and benzyl-*N*-diphenimidopropionamide **(IVc)** show the potent antihyperlipidemic activity and they significantly increased the serum levels of HDL 246–29.3%, protective therapeutic effects against CHD. The tested compounds showed a little effect on the LDL serum levels, since the induced reduction ranged from 37 to 4.5%.

This potent antihyperlipidemic activity of 1,8-naphthalimido, diphenimido derivatives seems to be due to the good efficacy of their binding to the fatty acid receptor sites, which are responsible for regulating the modulation of lipoproteins. These receptors may require larger imide's nucleus or cyclic imide's derivatives containing relatively bulky *N*-substituent for modulation of the receptor activity. Phthalimide without such bulky imido nitrogen substitution may bind to the receptor less efficaciously.

- While none of the tested N-phthalimidopropinimide derivatives were as potent as the parent compound phthalimide **(a)** in hypolipidemic activity, but, in contrary, the pharmacological screening showed that all derivatives, **(IVa 1–3 and 5–7)** except **(IVa-4)**, induced unexpected hyperlipidemia by elevating both TC and TG serum levels; they also induced significant elevation in the LDL serum levels ranging from 87.6 to 35.5%. The worse effect of these compounds is that they are capable of inducing serious reduction in the HDL serum levels. However, we still unable to explain such experimental evidence which needs more extensive research. Compound *N*-phenyl-*N*-(phthalimido) propionimide **(IVa-4)** induced slight lowering effect but not significant reduction (<24% reduction in both TC and TG). The authors are still unable to explain such experimental evidence which needs more extensive research.
- The open structure of phthalimidopropionimide **(Xa)** to give the dicarboxamide derivative induces significant lowering effects −48.6%, and −46.5% in TC and TG respectively, which is better than the cyclic structure **(IV-a)** and reference standard Fenofibrate.

Results

The comparative study of the antihyperlipidemic activities **(SAR)** of the *N*-substituted-phthalimide and other *N*-substituted-imides based on the obtained results of the pharmacological screening were limited to three areas:

(i) Changes in the structure of phthalimides: involving the imide's ring system by the replacement of the phenyl group of phthalimide with the aromatic system of naphthalimide (comp. IIIb, IVb1–3), or diphenimide (comp. IVc), led to a potent significant

antihyperlipidemic effect. Compound (IIIb) has shown three folds decrease in TC, TG and LDL and over 20 folds that of fenofibrate HDL. Conversely, the corresponding five membered Phthalimido propionate (IIIa) did not show any significant lowering of anyone of the lipid parameters (TC, TG or LDL).

(ii) *N*-Substitution of phthalimide with 2,2-dimethyl acetic acid moiety: (ethyl N-phthalimidomethylpropionate comp. (VIa) have regained the activity for the phthalimido ring and showed appreciable decrease of TC, TG, and LDL with parallel increase in HDL. Meanwhile, its corresponding phthalimido amides (VIIa) have demonstrated good lowering of TC and TG and have shown the maximum decrease of LDL (among all tested compounds) with good increase in HDL. This could be explained in terms of increasing steric bulk, and lipophilicity on the phthalimido nitrogen-afforded compounds proved to have significant hypolipidemic activity.

(iii) *N*-Substitution of imide's nitrogen of phthalimide with four atom side chain— one of them is oxygen (alkyl ether ester) proven to have significant antihyperlipidemic effect such as comp.(IXa), has shown a similar decrease of TC and TG similar to that of (VIa) with over 15-fold increase of HDL.

Acknowledgments A part of this was supported by funds from *Institute of Research and Consultation,* King Abdul-Aziz University, Ministry of Higher Education, Jeddah, Kingdom of Saudi Arabia. Therefore, the authors would like to express our special thanks and profound appreciation to all members in the institute. Deepest thank to Dr. Salah A. Ghareib, Professor of Pharmacology and toxicology, Pharmacology and Toxicology Department, Faculty of Pharmacy, King AbdulaAziz University, Jeddah, Kingdom of Saudi Arabia, for carrying out the pharmacological screening of the antihyperlipidemic activity of the prepared compounds.

References

Barakat SES, El-Zahabi MA, Radwan MF (2000) Synthesis and hypolipidemic activity of some new dibenz[c, e]azepine derivatives. Saudi Pharm J 8(2–3):110–115

Boden WE (2000) High-density lipoprotein cholesterol as an independent risk factor in cardiovascular disease: assessing the data from Framingham to the Veterans Affairs high-density lipoprotein intervention trial. Am J Cardiol 86:19L–22L Abstract-MEDLINE

Chapman JM, Wyrick SD, Maguire JH, Cocolas GH, Hall IH (1984) Hypolipidemic agents of phthalimide derivatives 6. Effect of aromatic vs. non-aromatic imides. J Pharm Res 6:267–269

El-Helby AA, El-Zahabi MA, Radwan MF (2003) Synthesis and anticonvulsant activity of some new *N*-substituted-1, 8-naphthalimides. Egypt J Biomed Sci 11:13–22

El-Zahabi MA, Ibrahim MK, Abdel-Rahman AA, El Zahabi HSA (1998) Synthesis and anticonvulsant activity of some new novel 4,4′-dibromo-dibenz [c, e]-Azepin-5,7-(6H)diones. Egypt J Pharm Sci 39(4–6):475–486

Farnier M (1998) Cerivastatin in the treatment of mixed hyperlipidemia: the RIGHT study. The cerivastatin study group. Cerivastatin gemfibrozil hyperlipidemia treatment. Am J Cardiol 82:47J–51J

Gavish D, Leibovitz E, Shapira I, Rubinstein A (2000) Bezafibrate and simvastatin combination therapy for diabetic dyslipidaemia: efficacy and safety. J Intern Med 247:563–569

Ginsberg HN (1990) Lipoprotein physiology and its relationship to atherogenesis. Endocrinal Metab Clin Nort Am 19:211–222

Hall IH, Murthy ARK, Wyrick SD (1986) Hypolipidemic activity of 6-substituted 6,7-dihydro-5h-dibenz[c, e]azepine and the effects of 6,7-dihydro-5h-dibenz[c, e]azepine on lipid metabolism of rodents. J Pharm Sci 75(6):622–626

Kuroda M, Tanzawa K, Tsujita Y, Endo A (1977) Mechanism for elevation of hepatic cholesterol level in triton WR-1339-induced hyperlipidemia. Biochim Biophys Acta 489:119–125

Larsen SD, Spilman CH (1993) New potential therapies for the treatment of atherosclerosis. Ann Rep Med Chem 28:217–225

Levine GN, Keaney JF Jr, Vita JA (1995) Cholesterol reduction in cardiovascular disease, clinical benefits and possible mechanism. N Engl J Med 332:215

Miller M (2000) Differentiating the effects of raising low levels of high-density lipoprotein cholesterol versus lowering normal triglycerides: further insights from the veteran's affairs high-density lipoprotein intervention trial. Am J Cardiol 86:23–27

Murthy AR, Wyrick SD, Voorstad PJ, Hall IH (1985) Hypolipidemic Activity of N-substituted diphenimides in rodents. Euro J Med Chem 20(6):547–550

Ossman AE, Ossman AN, Khalifa M, El-Zahaby MA (1991) Synthesis of dibenz[c, e]azepine-5, 7-Dione derivatives. Egypt J Chem 34(1):51–64

Parsons WB (2003) Cholesterol control without diet! The niacin solution 2nd edn, updated. Lilac Press, Buena Vista, CO. ISBN 0-9662568-7-5

Rossi S (ed) (2006) Australian medicines handbook. ISBN 0-9757919-2-3

Spieker LE, Noll G, Hannak M, Luscher TF (2000) Efficacy and tolerability of fluvastatin and bezafibrate in patients with hyperlipidemia and persistently high triglyceride levels. J Cardiovasc Pharmacol 35:361–365

Staels B, Dallongeville J, Auwerz J, Schoonjans K, Leitersdorf E, Fruchart J (1998) Mechanism of action of fibrates on lipid and lipoprotein metabolism. Circulation 98(19):2088–2093

Steinberg D, Parthasarathy S, Carew TE, Khoo JC, Witztum JL (1989) Beyond cholesterol, modification of low density lipoprotein that increases its atherogenesis. J Am Med Assoc 320:915–924

Voorstad PJ, Chapman JM, Cocolas GH, Wyrick SD, Hall IH (1985) Comparison of the hypolipidemic activity of cyclic vs. acyclic imides. J Med Chem 28:9–12

Winstead MB, Heine HW (1955) N-(Arylaminomethyl)phthalimides. J Am Chem Society 7:1913–1914