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Gemfibrozil ester and amide derivatives – synthesis, spectroscopic characterisation and QSPR

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The synthesis and spectroscopic characterisation of various gemfibrozil esters **3** and amides **4** are described. In the first step gemfibrozil was reacted with *N*-1-benzotriazolecarboxylic acid chloride (**1**) yielding gemfibrozil benzotriazolide (**2**). Compound **2** readily reacted with alcohols and amines to form the corresponding esters **3** and amides **4**, potential prodrugs of the well known hypolipaemic drug gemfibrozil. The quantitative structure property relationship (QSPR) was studied in the series of gemfibrozil esters and amides. The following topological descriptors and physicochemical parameters were used: Wiener number (W), connectivity index ($^1\chi^v$), relative molecular mass (M_r), van der Waals volume (V_w) and parameters of lipophilicity (log P and R_M).

1. Introduction

Investigation of lipid regulating agents and their use are constantly progressing since they reduce elevated lipid concentrations, a major risk factor for the development of atherosclerosis and ischaemic heart disease. The first-line treatment for hyperlipidaemia is dietary modification combined with reduction of other risk factors such as smoking, lack of physical exercise and alcohol intake [1]. Lipid regulating agents are used as an adjuvant to these modifications. Gemfibrozil (5-(2,5-dimethylphenoxy)-2,2-dimethylpentanoic acid) is a drug of choice in the treatment of moderate to severe hyperlipoproteinaemia. It reduces triglycerides and very-low-density lipoproteins and increases high-density lipoproteins [2–3]. Gemfibrozil is a clofibrate analogue with a rather short plasma half-life (about 1.5 h), so repeated doses must be given to maintain a therapeutic effect [4]. In order to modify its pharmacokinetics and bioavailability a number of gemfibrozil derivatives such as aliphatic and aromatic esters, benzamides, nicotinic acid and 3-ethoxy, acetoxy or hydroxyl derivatives have been synthesised [5–12]. Some of them have shown hypolipaemic activity in preliminary pharmacological evaluations [5, 8, 10].

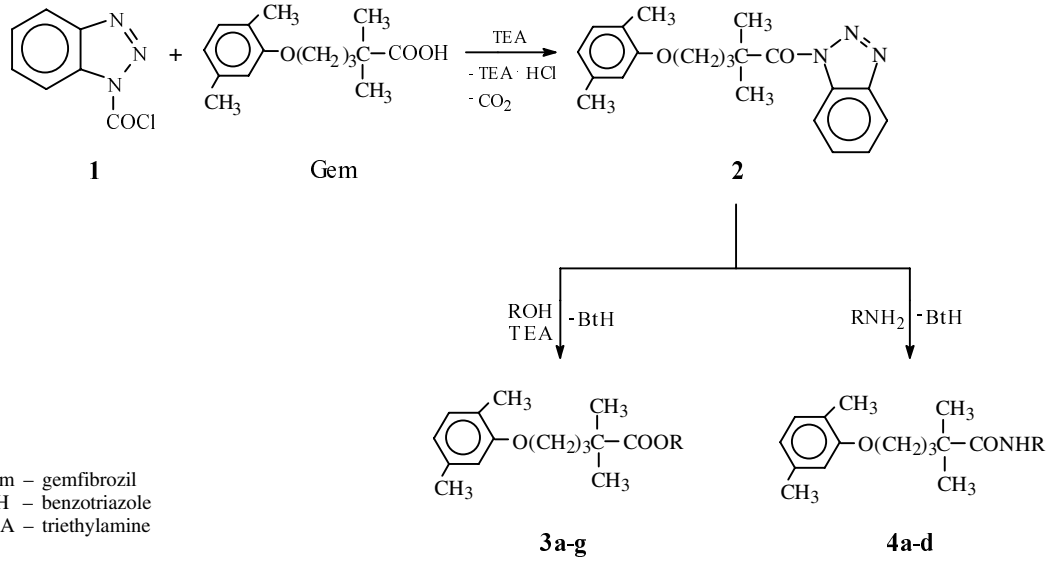
Gemfibrozil and related compounds have also been the subject of several QSAR investigations [13–15]. Craiger et al. studied the effect of structure modifications in gemfibrozil series (different chain spacing between phenoxy and carboxylic group, variations in substituents on the aromatic part and changes in carboxylic moiety) on biological activity [13]. QSAR analyses of a number of hypolipaemic drugs of diverse chemical structures including gemfibrozil and other fibrate analogues, revealed a correlation between molecular connectivity index ($^m\chi_t$) and pharmacological properties [14, 15]. It was demonstrated that this index could be used for the prediction of protein binding, reduction of total cholesterol and LD_{50} in rats, for a group of hypolipaemic drug candidates.

The present paper reports a synthesis and spectroscopic characterisation of gemfibrozil esters and amides. A QSPR study involving their calculated topological indices and physicochemical properties was also carried out.

2. Investigations, results and discussion

A new and convenient method of gemfibrozil esters **3** and amides **4** preparation has been developed. In the first step

Scheme



1 Gem 2

3a-g 4a-d

Gem – gemfibrozil
BtH – benzotriazole
TEA – triethylamine

Table 1: Reaction conditions of synthesis and IR data of esters 3

Compd.	R	Temperature (°C)	Time (h)	Yield (%)	IR (film) ν_{max} (cm^{-1})
3a	CH_3	RT	21	73.9	3047, 2976, 2872, 1728, 1615, 1585, 1509, 1473, 1388, 1264, 1192, 1146, 1131, 1048, 803
3b	CH_3CH_2	RT + reflux	40 + 2.5	39.6	3021, 2954, 2923, 2871, 1732, 1615, 1586, 1509, 1472, 1389, 1310, 1265, 1197, 1147, 1130, 1049, 999, 803
3c	$CH_3(CH_2)_2$	RT + reflux	62 + 6	68.5	3044, 3013, 2970, 2864, 1728, 1615, 1585, 1509, 1472, 1392, 1264, 1192, 1130, 1048, 999, 803
3d	$CH_3(CH_2)_3$	RT + reflux[a]	240 + 26	32.7	3044, 3013, 2959, 2872, 2360, 2339, 1727, 1614, 1585, 1509, 1471, 1414, 1389, 1264, 1047, 946, 803
3e	$CH_3(CH_2)_4$	RT + reflux[a]	34 + 12	53.9	3042, 3021, 2956, 2869, 1728, 1614, 1585, 1509, 1471, 1389, 1264, 1192, 1047, 998, 803
3f	$(CH_3)_2CH$	RT + reflux	192 + 16	37.9	3047, 3024, 2978, 2926, 2864, 1724, 1615, 1586, 1510, 1472, 1414, 1386, 1310, 1265, 1195, 1157, 1108, 1048, 999, 802
3g	$CH_2{=}C(CH_3)CH_2$	RT + reflux[a]	64 + 8	51.0	3083, 3046, 3023, 2925, 2867, 1730, 1659, 1615, 1585, 1509, 1473, 1390, 1310, 1265, 1190, 1130, 1049, 994, 803

[a] 5 ml of toluene was added in the reaction mixture

gemfibrozil was reacted with *N*-1-benzotriazolecarboxylic acid chloride (**1**) giving gemfibrozil benzotriazolide (**2**). The reaction proceeded via a mixed anhydride, which decarboxylated to compound **2**. The benzotriazole activated gemfibrozil **2** readily reacted with nucleophiles such as alcohols and amines giving the corresponding esters **3** and amides **4** (Scheme).

Esterification reactions were performed at elevated temperature in the presence of triethylamine (TEA) which accelerated the reactions. Amines, as stronger nucleophiles, react with benzotriazolide **2** more easily, therefore the amidation reactions were performed at room temperature. The following gemfibrozil derivatives were synthesised: methyl (**3a**), ethyl (**3b**), propyl (**3c**), butyl (**3d**), pentyl (**3e**), isopropyl (**3f**) and methallyl (**3g**) esters and benzyl (**4a**), phenylethyl (**4b**), cyclohexyl (**4c**) and 2-hydroxyethyl (**4d**) amides. Spectral analyses of all compounds synthesised were consistent with the assigned structures. The IR spectrum of **2** showed a carbonyl band at 1720 cm^{-1} which is characteristic of reactive *N*-acyl azoles [16]. The carbonyl group in esters had absorption maximum at 1724–1732 cm^{-1} and in amides at 1632–1642 cm^{-1} (amide I) and 1584–1586 cm^{-1} (amide II). Reaction conditions, and physical and IR spectroscopic data for compounds **3** and **4** are given in Tables 1 and 4. ^1H NMR chemical shifts (δ ppm), coupling constants (*J* in Hz) and assignments are given in Tables 2 and 5 and ^{13}C NMR chemical shifts and assignments in Tables 3 and 6. Some of the compounds from series **3**, e.g. the methyl, ethyl and isopropyl esters, have previously been synthesised by other methods and described in the literature without detailed spectroscopic characterisation [6]. That is why their spectroscopic data are reported here together with the data for new compounds.

In the QSPR study, the following topological indices and physicochemical descriptors of gemfibrozil derivatives **3** and **4** were used: Wiener number (W), the first order valence connectivity index ($^1\chi^v$), relative molecular mass (M_r), van der Waals volume (V_w), and parameters of lipophilicity log P and R_M obtained using *f* constants and the TLC retention factor R_f, respectively (Table 7). To determine the relationship between topological indices and physicochemical properties a multiple regression analysis was performed. A significant linear relationship between topological indices (W or $^1\chi^v$) and physicochemical parameters (M_r, V_w, log P or R_M) was obtained for the series of gemfibrozil and its esters ($0.9753 \leq r \leq 0.9990$, $p < 0.05$, $n = 8$, while the experimental parameter of lipophilicity, R_M, correlated well both with the topological indices (W and $^1\chi^v$) and log P only in the homologue series, methyl to pentyl gemfibrozil esters (**3a**–**e**) ($0.9962 \leq r \leq 0.9988$, $p < 0.05$, $n = 5$). QSPR study applied to series comprising both esters and amides, afforded poorer statistic results, as it could be predicted.

3. Experimental

3.1. Apparatus and chemicals

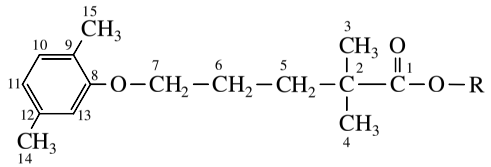
Melting points were determined on a Boëtius Microheating Stage and are uncorrected. IR spectra were recorded on a Perkin Elmer Paragon 500 FT-IR spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Varian Gemini 300 spectrometer, operating at 300 and 75.5 MHz for the ^1H and ^{13}C nucleus, respectively. Samples were measured in $CDCl_3$ or DMSO-d_6 solutions at 20 °C in 5-mm NMR tubes. Chemical shifts, in ppm, are relative to TMS. *J* values (in Hz) are observed through three bonds and are shown in brackets. Elemental analyses were in acceptable range. For TLC Merck silica gel plates Kieselgel 60 F_{254} were used. The following solvent mixtures were used: hexane/acetone (3 : 1) and butanol/water/acetic acid (8 : 1:1). Spots were visualised by short-wave UV light and iodine vapour. Preparative TLC was performed on Merck silica gel plates 2 mm in thickness with hexane/acetone (7 : 1) or chloroform/methanol (19 : 1) as a mobile phase. CC was performed on silica gel (Kemika), 0.063–0.200 mm, with hexane/acetone (1 : 1) as eluent. Gemfibrozil was kindly obtained from Lek. The amines were distilled and dried prior to use. All solvents were of analytical grade purity and dried. *N*-1-Benzotriazolecarboxylic acid chloride (**1**) was synthesised according to the procedure published previously [17]. All computations in the QSPR study were carried out with the statistical programme package Statistica-STAT-SOFT 3.0.

3.2. Chemistry

3.2.1. Synthesis of gemfibrozil benzotriazolide **(2)**

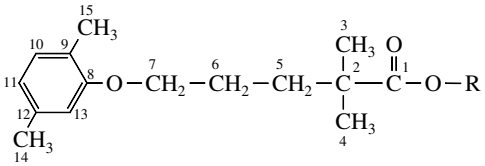
To a solution of gemfibrozil (9.263 g, 0.037 mol) and triethylamine (TEA) (4.048 g, 0.040 mol) in toluene (30 ml) a solution of compound **1** (7.263 g, 0.040 mol) in toluene (35 ml) was added dropwise. The reaction mixture was stirred at room temperature for 2.5 h and extracted three times with water. The organic layer was dried (Na_2SO_4), filtered and evaporated under reduced pressure. The oily product **2** obtained slowly crystallised. Yield: 11.590 g (89.2%). M.p. 50–52 °C. IR (KBr, ν, cm^{-1}): 3108, 3087, 3042, 3022, 2924, 2871, 1721, 1614, 1586, 1509, 1483, 1450, 1414, 1391, 1347, 1309, 1285, 1265, 1157, 1130, 1049, 1005, 951, 899, 804, 753. ^1H NMR ($CDCl_3$), δ, ppm): 8.31 (d, 1 H, $J = 8.2$, H-17); 8.12 (d, 1 H, $J = 8.2$, H-20); 7.65 (t, 1 H, $J = 7.7$, H-18); 7.50 (t, 1 H, $J = 7.7$, H-19); 6.96 (d, 1 H, $J = 7.4$, H-10); 6.61 (d, 1 H, $J = 7.4$, H-11); 6.51 (s, 1 H, H-13); 3.88 (t, 2 H, $J = 6.3$, H-7); 2.38–2.31 (m, 2 H, H-5); 2.25 (s, 3 H, H-15); 2.16 (s, 3 H, H-14); 1.81–1.71 (m, 2 H, H-6); 1.66 (s, 6 H, H-3,4).
$C_{21}H_{25}N_3O_2$

Table 2: ^{1}H NMR data of esters 3 taken in $CDCl_3$ solution, δ (ppm)



H atom	R							
	$-\overset{16}{H}$	$-\overset{16}{CH_3}$	$-\overset{16}{CH_2}-\overset{17}{CH_3}$	$-\overset{16}{CH_2}-\overset{17}{CH_2}-\overset{18}{CH_3}$	$-\overset{16}{CH_2}-\overset{17}{CH_2}-\overset{18}{CH_2}-\overset{19}{CH_3}$	$-\overset{16}{CH_2}-\overset{17}{CH_2}-\overset{18}{CH_2}-\overset{19}{CH_2}-\overset{20}{CH_3}$	$-\overset{16}{CH}(\overset{17}{CH_3})(\overset{18}{CH_3})$	$-\overset{16}{CH_2}-\overset{17}{C}(\overset{19}{CH_3})=\overset{18}{CH_2}$
	Gem	**3a**	**3b**	**3c**	**3d**	**3e**	**3f**	**3g**
H-3, 4	1.25 s 6H	1.21 s 6H	1.24 s 6H	1.22 s 6H	1.21 s 6H	1.22 s 6H	1.24 s 6H	1.25 s 6H
H-5, 6	1.84–1.73 m 4H	1.71 s 4H	1.75 s 4H	1.73–1.72 m 4H	1.72 s 4H	1.73–1.72 m 4H	1.74–1.73 m 4H	1.75 s 4H
H-7	3.92 t 2H (5.6)	3.89 s 2H	3.94 t 2H (4.9)	3.91 t 2H (4.6)	3.91 s 2H	3.91 t 2H (5.1)	3.96 t 2H (5.3)	3.91 s 2H
H-10	6.99 d 1H (7.4)	6.69 d 1H (7.4)	7.03 d 1H (7.4)	6.99 d 1H (7.4)	6.99 d 1H (7.4)	6.99 d 1H (7.4)	7.02 d 1H (7.4)	6.99 d 1H (7.4)
H-11	6.65 d 1H (7.4)	6.64 d 1H (7.4)	6.68 d 1H (7.4)	6.65 d 1H (7.4)	6.65 d 1H (7.4)	6.62 d 1H (7.4)	6.67 d 1H (7.4)	6.65 d 1H (7.4)
H-13	6.60 s 1H	6.59 s 1H	6.63 s 1H	6.60 s 1H	6.60 s 1H	6.60 s 1H	6.63 s 1H	6.60 s 1H
H-14	2.17 s 3H	2.17 s 3H	2.20 s 3H	2.17 s 3H	2.17 s 3H	2.17 s 3H	2.20 s 3H	2.17 s 3H
H-15	2.30 s 3H	2.29 s 3H	2.33 s 3H	2.30 s 3H	2.30 s 3H	2.30 s 3H	2.33 s 3H	2.30 s 3H
H-16	≈12 weak and broad signal	3.65 s 3H	4.12 q 2H (7.2)	4.02 t 2H (6.5)	4.06 t 2H (6.5)	4.05 t 2H (6.7)	5.10–4.99 m 1H	4.49 s 2H
H-17			1.27 t 3H (7.2)	1.64 q 2H (7. 4)	1.65–1.56 m 2H	1.67–1.57 m 2H	1.26 d 6H (6.4)	4.98 and 4.91 2s 2H
H-18				0.94 t 3H (7.4)	1.44–1.32 m 2H	1.35–1.32 m 4H		
H-19					0.93 t 3H (7.3)			1.75 s 3H
H-20						0.90 t 3H (6.8)		

Table 3: ^{13}C NMR data of esters 3 taken in $CDCl_3$ solution, δ (ppm)



C atom	R							
	−H	$-\overset{16}{C}H_3$	$-\overset{16}{C}H_2-\overset{17}{C}H_3$	$-\overset{16}{C}H_2-\overset{17}{C}H_2-\overset{18}{C}H_3$	$-\overset{16}{C}H_2-\overset{17}{C}H_2-\overset{18}{C}H_2-\overset{19}{C}H_3$	$-\overset{16}{C}H_2-\overset{17}{C}H_2-\overset{18}{C}H_2-\overset{19}{C}H_2-\overset{20}{C}H_3$	$-\overset{16}{\underset{\displaystyle\overset{17}{CH_3}}{\underset{\displaystyle\overset{18}{CH_3}}{CH}}}$	$-\overset{16}{C}H_2-\overset{17}{\underset{\displaystyle\overset{19}{CH_3}}{C}}=\overset{18}{C}H_2$
	Gem	**3a**	**3b**	**3c**	**3d**	**3e**	**3f**	**3g**
C-1	184.94	178.82	177.84	177.90	177.86	177.85	177.30	177.46
C-2	41.79	41.81	41.73	41.89	41.81	41.82	41.65	41.99
C-3, 4	24.74	24.88	24.91	24.95	24.91	24.91	24.88	24.95
C-5	36.66	36.84	36.87	36.93	36.87	36.87	36.86	36.93
C-6	24.91	24.88	24.99	24.99	24.98	36.87	24.99	24.98
C-7	67.73	67.60	67.75	67.98	67.70	67.74	67.81	67.75
C-8	156.94	156.88	156.94	156.96	156.91	156.91	156.96	156.94
C-9	123.54	123.40	123.50	123.51	123.45	123.50	123.51	123.53
C-10	130.26	130.17	130.22	130.23	130.18	130.18	130.22	130.25
C-11	120.65	120.54	120.59	120.60	120.54	120.56	120.57	120.62
C-12	136.43	136.30	136.38	136.40	136.32	136.34	136.38	136.40
C-13	111.85	111.75	111.82	111.84	111.76	111.78	111.82	111.84
C-14	15.53	15.44	15.48	15.50	15.45	15.45	15.50	15.51
C-15	21.19	21.08	21.14	21.16	21.11	21.09	21.13	21.16
C-16		51.43	60.12	65.80	64.01	64.31	67.17	67.46
C-17			13.96	21.79	30.41	28.05	21.48	140.10
C-18				10.19	18.90	22.02	21.48	112.52
C-19					13.41	27.85		19.26
C-20						13.67		

3.2.2. Synthesis of series **3**

A solution of **2** (0.351, 0.001 mol) and TEA (0.405 g, 0.004 mol) in the corresponding alcohol (5–10 ml) or alcohol/toluene mixture was stirred at room temperature or refluxed until the starting compound **2** disappeared (TLC control). The reaction mixture was evaporated under reduced pressure and chromatographed on a preparative TLC plate (mobile phase: hexane/acetone 7 : 1). The oil products **3a**–**g** were separated as pure compounds.

The detailed reaction conditions and analytical data for **3** are given in Tables 1–3.

3.2.3. Synthesis of series **4**

Method A: A solution of **2** (0.250 g, 0.0007 mol) in toluene (10 ml) was added dropwise to a solution of 0.005 mol of the corresponding amine in toluene (10 ml). The reaction mixture was stirred for 2.5–3 h at room temperature, extracted several times with dilute HCl (to remove benzotriazole and excess amine) and then with water. The organic layer was dried (sodium sulphate), filtered and evaporated under reduced pressure. The crude product obtained was recrystallised from ethanol (**4a** and **4c**) or chromatographed on a preparative TLC plate (mobile phase: chloroform/methanol 19 : 1) (**4b**).

Method B: A solution of **2** (0.250 g, 0.0007 mol) in acetonitrile (5 ml) was added dropwise to a solution of ethanolamine (0.128 g, 0.0021 mol) in acetonitrile (1 ml). The reaction mixture was stirred for 1.5 h at room temperature and evaporated under reduced pressure. The crude residue obtained was washed with water. CC with hexane/acetone (1 : 1) as the eluent yielded the pure compound **4d**.

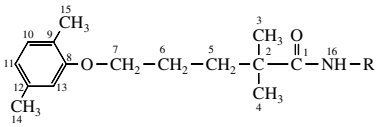
The reaction conditions and analytical data for compounds **4** are given in Tables 4–6.

Table 4: Reaction conditions of synthesis and IR data of amides 4

Compd.	R	Solvent	Time (h)	Yield (%)	M.p. (°C)	IR (KBr) ν_{max} (cm^{-1})
4a	$C_6H_5CH_2$	toluene	3	30.6	119–122	3339, 3034, 2963, 2928, 2870, 1642, 1584, 1537, 1510, 1457, 1416, 1396, 1363, 1263, 1224, 1158, 1130, 1088, 1033, 1016, 937, 858, 807, 733, 693, 587, 513
4b	$C_6H_5CH_2CH_2$	toluene	3	28.2	oil	3350, 3027, 2952, 2925, 2867, 1639, 1586, 1530, 1510, 1476, 1455, 1414, 1391, 1366, 1285, 1265, 1226, 1157, 1130, 1041, 1000, 844, 804, 748, 700[a]
4c	C_6H_{11}	toluene	2.5	71.4	88–91	3317, 3256, 3044, 2972, 2935, 2855, 1632, 1586, 1536, 1511, 1475, 1454, 1413, 1394, 1302, 1268, 1218, 1157, 1130, 1094, 1049, 996, 889, 866, 802, 664, 586
4d	$HOCH_2CH_2$	acetonitrile	1.5	67.3	93–96	3310, 2953, 2924, 2853, 1634, 1585, 1545, 1512, 1482, 1454, 1399, 1365, 1288, 1260, 1227, 1212, 1157, 1133, 1038, 998, 947, 902, 820, 756, 706, 613, 591, 540

[a] film

Table 5: ^{1}H NMR data of amides 4 taken in $CDCl_3$[a] or DMSO-d_6[b] solution, δ (ppm)



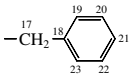
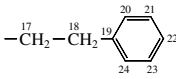
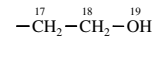
H atom	R			
				
	4a[a]	**4b**[b]	**4c**[b]	**4d**[b]
H-3, 4	1.24 s 6H	1.03 s 6H	1.08 s 6H	1.10 s 6H
H-5, 6	1.73 s 4H	1.49 s 4H	1.59 s 4H	1.58 s 4H
H-7	3.90 t 2H (5.4)	3.84 s 2H	3.89 s 2H	3.87 s 2H
H-10	6.99 d 1H (7.4)	7.07 d 1H (7.5)	6.96 d 1H (7.5)	6.97 d 1H (7.5)
H-11	6.65 d 1H (7.4)	6.62 d 1H (7.5)	6.61 d 1H (7.5)	6.62 d 1H (7.5)
H-13	6.60 s 1H	6.68 s 1H	6.66 s 1H	6.69 s 1H
H-14	2.14 s 3H	2.10 s 3H	2.08 s 3H	2.09 s 3H
H-15	2.30 s 3H	2.25 s 3H	2.23 s 3H	2.25 s 3H
H-16	5.99 s 1H	7.56 t 1H (4.9)	7.07 d 1H (7.8)	7.43 t 1H (5.4)
H-17	4.44 d 2H (5.4)	3.33–3.27 m 2H	3.60 d 1H	3.17–3.11 m 2H
H-18		2.72 t 2H (7.3)		3.41–3.35 m 2H
H-19	7.34–7.24 m 5H		1.69–1.13 2m 10 H	4.64 t 1H (5.5)
H-20				
H-21				
H-22		7.30–7.15 2m 5H		
H-23				
H-24				

Table 6: ^{13}C NMR data of amides 4 taken in $CDCl_3$[a] or DMSO-d_6[b] solution, δ (ppm)

C atom	**4a**[a]	**4b**[b]	**4c**[b]	**4d**[b]
C-1	177.33	176.68	175.74	177.01
C-2	41.70	41.18	41.06	41.22
C-3, 4	25.31	25.38	25.07	25.36
C-5	37.33	37.05	37.11	37.08
C-6	24.87	24.65	24.70	24.68
C-7	67.72	67.83	67.85	67.84
C-8	156.88	156.81	156.79	156.81
C-9	123.40	122.72	122.76	122.70
C-10	130.22	130.28	130.28	130.27
C-11	120.65	120.69	120.70	120.69
C-12	136.44	136.28	136.26	136.28
C-13	111.93	112.21	112.24	112.23
C-14	15.53	15.61	15.63	15.60
C-15	21.14	21.10	21.09	21.08
C-17	43.41	40.52	47.87	41.78
C-18	138.55	35.28	32.47	60.05
C-19	128.65	139.86	25.42	
C-20	127.60	128.88	25.42	
C-21	127.60	128.47	25.42	
C-22	127.60	126.19	32.47	
C-23	128.65	128.47		
C-24		128.88		

Table 7: Topological and physicochemical descriptors used in QSPR study of compounds 3 and 4

Compd.	Formula	W	$^1\chi^v$	M_r	V_w ($cm^3\ mol^{-1}$)	log P	R_M
Gem	$C_{15}H_{22}O_3$	803	6.262	250.32	152.69	4.642	0.212
3a	$C_{16}H_{24}O_3$	927	6.651	264.34	161.82	5.006	−0.454
3b	$C_{17}H_{26}O_3$	1070	7.238	278.37	172.05	5.536	−0.501
3c	$C_{18}H_{28}O_3$	1233	7.738	292.39	182.28	6.066	−0.575
3d	$C_{19}H_{30}O_3$	1417	8.238	306.42	192.51	6.596	−0.630
3e	$C_{20}H_{32}O_3$	1623	8.738	320.45	202.74	7.126	−0.689
3f	$C_{18}H_{28}O_3$	1215	7.633	292.39	182.27	5.943	−0.602
3g	$C_{19}H_{28}O_3$	1419	7.738	304.41	189.00	6.471	−0.575
4a	$C_{21}H_{29}NO_2$	2071	8.553	327.46	208.80	5.302	0.176
4b	$C_{23}H_{31}NO_2$	2348	9.053	353.50	264.87	5.832	0.176
4c	$C_{21}H_{33}NO_2$	1739	9.183	331.49	209.53	5.771	0
4d	$C_{17}H_{27}NO_3$	1233	7.105	293.40	181.23	2.455	0.907
4e[a]	$C_{17}H_{28}N_2O_2$	1233	7.197	292.42	183.73	2.518	

[a] gemfibrozil 2-aminoethyl amide previously synthesised [25]

3.3. QSPR study

Wiener number, W, a topological index which appears to be a convenient measure of the compactness of the molecule is based on a distance matrix and is defined as the half-sum of all the elements of the distance matrix D:

$$W = \frac{1}{2}\sum_{k=1}^{N}\sum_{l=1}^{N}(D)_{kl}$$

where D_{kl} represents off-diagonal elements of D, the sum of the least distances between the observed vertex and all other vertices present in the graph; a single bond is counted as one, a double bond as two, and a triple bond as three distances [18–20].

The first order valence connectivity index, $^1\chi^v$, is defined as

$$^1\chi^v = \sum_{\text{edges}}[\delta(i)\,\delta(j)]^{-1/2}$$

where δ(i) and δ(j) are weights (valence delta values) of vertices (atoms) *i* and *j* making up the $i-j$ edge (bond) in a vertex-weighted graph (heteroatomic system) G_{vw} [21–22]. Valence delta values are given by

$$\delta(i) = (Z_i^v - H_i)/(Z_i - Z_i^v - 1)$$

where Z_i^v stands for the number of valence electrons in the atom *i*, Z is its atomic number, and H_i is the number of hydrogen atoms attached to *i*.

Van der Waals volume, V_w ($cm^3\ mol^{-1}$), was obtained by summing van der Waals group increments for each group contained in the molecular structure [23]. The following group increments were used: 13.67 ($-CH_3$), 23.90 ($-C_2H_5$), 34.13 ($-C_3H_7$), 34.12 ($-CH(CH_3)_2$), 10.23 ($-CH_2-$), 30.67 ($-C(CH_3)_2-$), 11.94 ($=CH_2$), 5.01 (=C<), 8.06 (=CH− ar.) and 5.54 (=CR− al., ar.), 45.84 ($-C_6H_5$), 11.70 (>CO al.), 15.2 (−O−CO− al., ar.), 8.04 (−OH al., ar.), 3.7 (−O− al.), 3.2 (−O− ar.), 6.78 (>CH−), 8.47 (=CH−), 8.08 (−NH−), 10.54 ($-NH_2$) and 56.8 ($-cy-C_6H_{11}$).

A lipophilic parameter log P was obtained using hidrophobic fragment constants *f* (Rekker's constant) [23, 24]. It is defined by the following equation:

$$\log P = \Sigma\, a_n f_n$$

where *f* represents a lipophilic contribution of the structure fragment to the total lipophilicity, and *a* is a factor which defines an appearance of each fragment in chemical structure. The following *f* constants were used: 1.431 ($-C_6H_3$), 0.702 ($-CH_3$), -0.433 (−O− ar.), 0.530 ($-CH_2-$), 0.200 (>C<), −0.954 (−COOH), −1.292 (−COO− al.), 0.235 (−CH<), 0.935 (>C=CH_2), −2.71 (−CONH−), 1.886 ($-C_6H_5$), −1.491 (−OH al.) and −1.428 ($-NH_2$ al.).

A lipophilic parameter R_M is expressed as

$$R_M = \log\,(1/R_f - 1)$$

where R_f is the retention factor obtained by TLC.

The calculated topological descriptors and physicochemical parameters are given in Table 7.

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