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Synthesis, molecular properties prediction and cytotoxic screening of 3-(2-aryl-2-oxoethyl)isobenzofuran-1(3*H*)-ones

Angélica Faleiros da Silva Maia [a], Raoni Pais Siqueira [b], Fabrício Marques de Oliveira [c], Joana Gasperazzo Ferreira [b], Silma Francielle da Silva [a], Clarice Alves Dale Caiuby [a], Leandro Licursi de Oliveira [d], Sérgio Oliveira de Paula [d], Rafael Aparecido Carvalho Souza [e], Silvana Guilardi [e], Gustavo Costa Bressan [b,*], Róbson Ricardo Teixeira [a,*]

[a] Departamento de Química, Universidade Federal de Viçosa, Av. P.H. Rolfs, S/N, Viçosa, MG 36570-900, Brazil
[b] Departmento de Bioquímica e Biologia Molecular, Universidade Federal de Viçosa, Av. P.H. Rolfs, S/N, Viçosa, MG 36570-900, Brazil
[c] Instituto Federal de Minas Gerais (IFMG), Campus Ouro Branco, Rua Afonso Sardinha, 90, Ouro Branco, MG 36420-000, Brazil
[d] Departamento de Biologia Celular, Universidade Federal de Viçosa, Av. P.H. Rolfs, S/N, Viçosa, MG 36570-900, Brazil
[e] Instituto de Química, Universidade Federal de Uberlândia, Av. João Naves de Ávila, 2160-Bloco 1D, Santa Mônica, Uberlândia, MG 39400-902, Brazil

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ABSTRACT

In the present investigation, a collection of nineteen 3-(2-aryl-2-oxoethyl)isobenzofuran-1(3*H*)-ones was synthesized and screened for their cytotoxic activity against a panel of three leukemia cancer cell lines. The compounds were prepared via $ZrOCl_2 \cdot 8H_2O$ catalyzed condensation reactions between phthalaldehydic acid and different acetophenones. The reactions were carried out free of solvent and the isobenzofuran-1(3*H*)-ones were obtained in good yields (80–92%). The identities of the synthesized compounds were confirmed upon IR and NMR (^1H and ^{13}C) spectroscopy as well as high resolution mass spectrometry analyses. Structures of compounds **1**, **4** and **16** were also investigated by X-ray analysis. The synthesized compounds were submitted to in vitro bioassays against HL-60, K562 and NALM6 cancer cell lines using MTT cytotoxicity assay. After 48 h of treatment, twelve derivatives were able to reduce cell viability and presented IC_{50} values equal to or below 20 μmol L^{-1} against at least one of the evaluated lineages. The most active compound corresponded to 3-(3-methylphenyl-2-oxoethyl)isobenzofuran-1(3*H*)-one (**18**) (IC_{50} values obtained for HL-60, K562 and NALM6 were, respectively, 13.5 μmol L^{-1}, 8.83 μmol L^{-1}, and 5.24 μmol L^{-1}). In addition, compound **18** was capable of triggering apoptosis on NALM6 cells. All isobenzofuranones herein evaluated did not present cytotoxicity on peripheral blood mononuclear cells (PBMC), suggesting selective cytotoxic effect on leukemic cells. A computational study allowed prediction of pharmacokinetics and drug-likeness properties of the synthesized compounds. DFT calculations were performed to obtain the energy values of HOMO, LUMO, and dipole moments of isobenzofuranones.

Cancer is a worldwide disease that affects around fourteen million people every year. Moreover, at least eight million of deaths caused by this disease are estimated to occur annually.[1] Hematological malignancies (leukemia or lymphoma) are the fourth most diagnosed cancer in adults (around 9% of the cases), but are responsible for around 50% of the cases in children younger than 15.[2,3] Although several chemotherapeutic regimes have been successfully approached for fighting cancer nowadays, the way on how patients respond to treatments is still a puzzle. Furthermore, most chemotherapies are associated with severe side-effects and cancer resistance, highlighting the necessity of a constant effort toward the development of novel therapies.[4]

Heterocycles play an important role in several branches of chemistry.[5] A myriad of natural products possessing important biological activities are heterocyclic in nature.[6] The vast majority of agrochemicals and pharmaceuticals (approximately more than 70%) bears at least one heterocyclic ring.[7,8] In addition, several dyes (such as malveine), polymers, and luminophores have heterocyclic moieties.

The isobenzofuran-1(3*H*)-ones, also known as phthalides, are a class of heterocycles presenting a benzene ring (I) fused to a γ-lactone one (II) (Fig. 1). During the last decades several natural products containing this structural motif have been isolated and presenting important biological activities.[9] In particular,

* Corresponding authors. Tel.: +55 31 3899 3209; fax: +55 31 3899 3065.
E-mail addresses: gustavo.bressan@ufv.br (G.C. Bressan), robsonr.teixeira@ufv.br (R.R. Teixeira).

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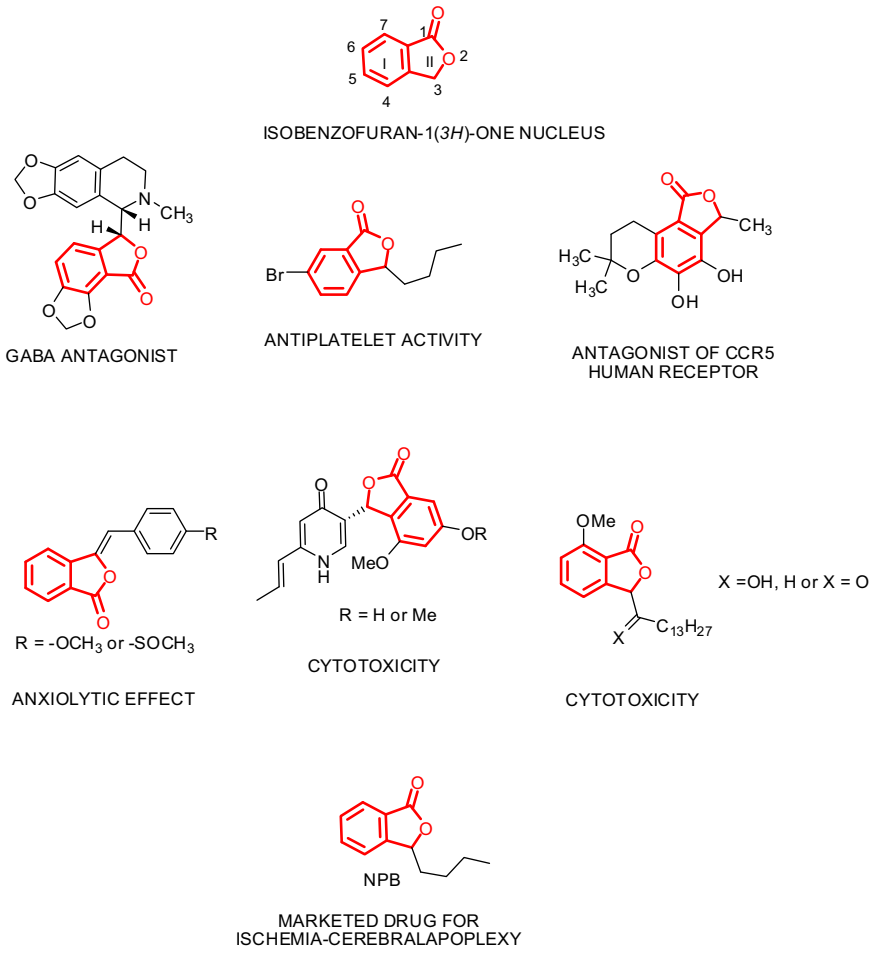


Figure 1. Structures of some C-3 functionalized isobenzofuran-1(3*H*)-ones and their associated biological properties.

phthalides functionalized at C-3 position (Fig. 1) display useful medicinal properties.[10–15] It stands out the success story of 3-butylisobenzofuran-1(3*H*)-one (also known as *n*-butylphthalide, NBP, Fig. 1), a compound which nowadays has been used clinically as antiplatelet drug for ischemia-cerebralapoplexy.[16,17] This example illustrates the potential utility of isobenzofuranone scaffold for pharmaceutical purposes.

In addition to their broad spectrum of biological activities, the phthalides are also valuable synthetic building blocks.[18,19]

We have been involved in the search of bioactive compounds that can be useful for the treatment of leukemia[20] as well as in the synthesis and biological evaluation of C-3 functionalized isobenzofuran-1(3*H*)-ones. Our investigations have demonstrated phytotoxic[21] along with cytotoxic effects of phthalides containing aromatic and alicyclic groups attached to C-3 position of the isobenzofuranone nucleus.[22] Concerning their cytotoxic effects, these phthalides were evaluated against K562 and U937 leukemia cell lines. It was found that two compounds (Fig. 2) displayed superior cytotoxic effects against K562 cell line compared to etoposide (VP-16) used as positive control in the biological assays.[22]

These results prompted us to investigate further chemical modifications at C-3 position of isobenzofuranone nucleus in order to afford derivatives endowed with cytotoxic effects. We describe in this paper the synthesis of nineteen 3-(2-aryl-2-oxoethyl)isobenzofuran-1(3*H*)-ones. Their cytotoxic activity was evaluated against the cancer cell lines HL-60 (acute myelogenous leukemia), K562 (chronic myelogenous leukemia) and NALM6 (B cell acute lymphoblastic leukemia). The effect of the most active compound,

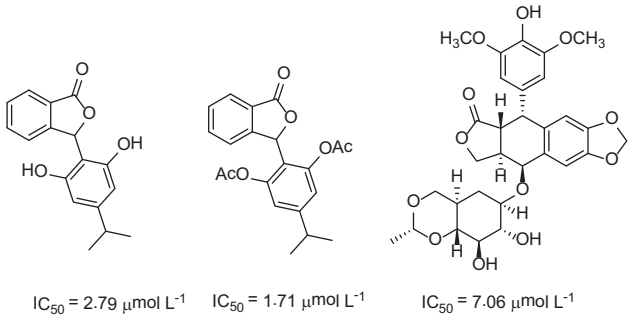
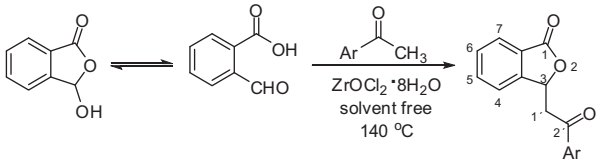


Figure 2. Results from previous isobenzofuranone screening against K562 cell line compared to etoposide (VP-16) [From Ref. 22].

3-(3-methylphenyl-2-oxoethyl)isobenzofuran-1(3*H*)-one (**18**), on triggering cell death events was also assessed by flow cytometry assays. In silico drug like properties of the evaluated compounds were determined and the results are also discussed.

The 3-(2-aryl-2-oxoethyl)isobenzofuran-1(3*H*)-ones **1**–**19** (Fig. 3) were synthesized via condensation reactions between phthalaldehydic acid and different acetophenones [18].[23] The reactions were carried out free of solvent and catalyzed by $ZrOCl_2{\cdot}8H_2O$ a versatile catalyst that has been involved in several synthetically useful transformations.[24–27] The compounds were obtained in good yields (80–92%) after purification by column chromatography followed by recrystallization.[28]



1-19

Compound	Ar	Reaction Time (hours)	Yield (%)
1	Phenyl	3	91
2	2-hydroxy phenyl	4	80
3	3-hydroxy phenyl	4	89
4	4-hydroxy phenyl	4	81
5	2-nitro phenyl	3.5	88
6	3-nitro phenyl	3	89
7	4-nitro phenyl	3	89
8	2-bromo phenyl	3	90
9	3-bromo phenyl	3	91
10	4-bromo phenyl	3	91
11	2-fluoro phenyl	3	89
12	3-fluoro phenyl	3	92
13	4-fluoro phenyl	3	90
14	2-methoxy phenyl	3.5	80
15	3-methoxy phenyl	3	92
16	4-methoxy phenyl	2	89
17	2-methyl phenyl	3	90
18	3-methyl phenyl	3	91
19	4-methyl phenyl	3	90

Figure 3. Synthesis of isobenzofuranones **1**–**19**.

The identities of compounds **1**–**19** were confirmed upon IR, NMR (^{1}H and ^{13}C) as well as mass spectrometry analyses.[28] The IR spectra of **1**–**19** exhibited strong diagnostic IR absorptions in the 1747–1785 cm^{-1} range (for —COO— stretching) and in the 1639–1691 cm^{-1} range (for —CO— stretching) concordant with carbonyl stretching frequencies. Diagnostic bands for other functional groups (such as —NO_2 and —OH) were also noticed. The ^{13}C NMR spectrum analyses also confirmed the presence of the carbonyl groups in the structure of phthalides **1**–**19**. In the ^{1}H NMR spectra, the diastereotopics —CH_2CO— hydrogens were observed as a pair of doublet of doublets. The molecular formulas of the compounds were confirmed upon high resolution mass spectrometry analyses.[28]

We were able to obtain good crystals of compounds **1**, **4** and **16** which allowed their structures to be investigated by X-ray diffraction.[29] Concerning compound **16**, its crystallographic data is presented in Table 1. The molecular structure of this compound with anisotropic displacement ellipsoids (30% probability) and numbering scheme is shown in Figure 4. Selected bond lengths, bond angles and torsion angles are summarized in Table 2.

Compound **16** crystallizes in the monoclinic space group $P2_1/n$. In the crystal structure of **16** there is one C—H···O intra molecular interaction involving the O3 atom. Inversion dimmers are linked by pairs of C7—H7···O1 interactions generate R_2^2 (10) ring motifs,[30] which are connected by two C—H···O intermolecular interactions forming ribbons along *b* axis. Furthermore, two C—H···π

Table 1
Crystallographic data and details for compound **16**

Compound **16**	
Empirical formula	$C_{17}H_{14}O_4$
Formula weight (g mol^{-1})	282.28
Temperature (K)	100(2)
Crystal system	Monoclinic
Space group	$P2_1/n$
Unit cell dimensions (Å,°)	
a	5.0961(1)
b	11.2354(2)
c	23.6337(6)
β	92.543(1)
Volume (Å^3), *Z*	1351.86(5), 4
Calculated density (g cm^{-3})	1.387
μ (mm^{-1})	0.099
F(000)	592
Crystal size (mm)	0.461 × 0.114 × 0.108
θ range (°)	0.41–27.1
Limiting indices	−6,6; −14,14; 0,30
Reflections collected	16676
Independent reflections	2330 [$R_{(int)}$ = 0.051]
Goof	1.119
Data/restraints/parameters	2330/0/190
R indices [$I > 2\sigma(I)$]	*R* = 0.0415, *wR* = 0.1162
R indices (all data)	*R* = 0.0581, *wR* = 0.1441
Largest diff. peak and hole (e A^{-3})	0.343 and −0.310

$R = \Sigma(||F_0| - |F_c||)/\Sigma|F_0|$; $wR = [\Sigma w(|F_0^2| - |F_c^2|)/\Sigma w|F_0^2|^2]^{1/2}$.

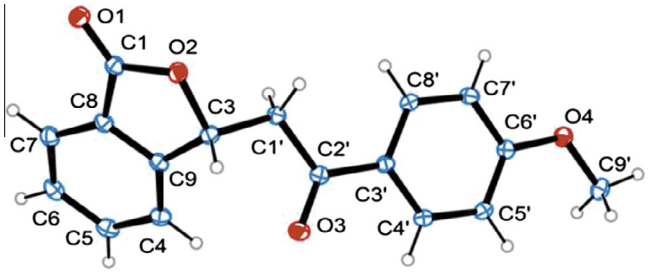


Figure 4. An ORTEP drawing of **16** with atom-numbering scheme. Displacement ellipsoids are drawn at the 30% probability level.

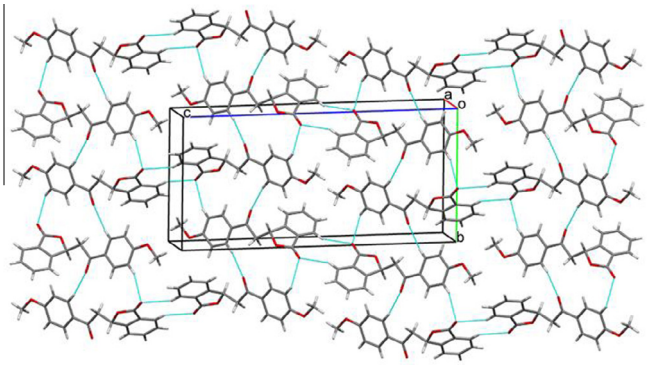


Figure 5. Packing diagram of **16**, viewed down the *c* axis. Dashed lines indicate C—H···O intermolecular interactions.

interactions link the ribbons into a three-dimensional supramolecular network (Fig. 5).

The geometric parameters for intermolecular interactions in compound **16** are listed in Table 3.

The geometric parameters (Table 2) are within the expected values for this class of compounds.[31] In the isobenzofuran-1(3*H*)-one ring system the C1—O1 bond distance is equal to 1.204(2) Å and correspond to formal double bond. The C1—O2 bond length [1.366(2) Å] indicates significant double bond character and C3—O2 [1.463(2) Å] is consistent with the expected value for a C—O single bond. The C3—C9 bond is larger than C1—C8. Similar behavior is observed for phthalide,[32] hydroxylated and methoxylated isobenzofuran-1(3*H*)-ones[33–35] and 3-(4-hexyloxyphenyl) isobenzofuran-1(3*H*)-one.[36] In the 2-aryl-2-oxoethyl moiety, all bond lengths and angles are normal and comparable with those observed in related compounds.[37–39] The double bond length of C2′—O3 corresponds to 1.207(6) Å.

The isobenzofuran-1(3*H*)-one ring in compound **16** is planar with r.m.s. deviation of 0.0189 Å from the least-squares plane defined by the ten constituent atoms. The 2-aryl-2-oxoethyl system is almost planar with r.m.s. deviation of 0.0149 Å. In compound **16** the dihedral angles between these planes is 54.12 (3)°.

Crystallography information concerning compounds **1** and **4** can be found in Supplementary material.

Isobenzofuran-1(3*H*)-ones **1**–**19** were biologically screened against HL-60 (acute myelogenous leukemia), K562 (chronic myelogenous leukemia) and NALM6 (B cell lymphoblastic leukemia) cell lines in comparison to DMSO (0.4% v/v) using the MTT cytotoxicity assay.[40,41] Results are summarized in Table 4. Twelve out of nineteen compounds were able to significantly reduce cell viability with IC_{50} equal to or below 20 μmol L^{-1} after 48 h against at least one of the evaluated leukemic cells, whereas compounds **4**, **7** and **19** were substantially ineffective. As a general trend, the active compounds were more effective against HL-60. The occurrence of a remarkable variability among the compounds suggest that the presence of various substituents in the aryl group in aliphatic moiety, and their position as well, may strongly interfere with cell viability. In particular, phthalide **18** containing the 3-methyl phenyl

Table 3
Geometric parameters for intermolecular interactions in compound **16**

Donor—H···acceptor	d(D—H)	d(H···A)	d(D···A)	<(DHA)
C4—H4···O3	0.93	2.44	3.083(2)	126.6
C7—H7···O1^{i}	0.93	2.59	3.457(2)	154.5
C5′—H5′···O1^{ii}	0.93	2.56	3.352(2)	143.1
C8′—H8′···O3^{iii}	0.93	2.39	3.300(2)	165.6
C1′—H1′2···Cg1^{iv}	0.97	2.78	4.365(2)	136
C9′—H9′2···Cg1^{v}	0.96	2.73	3.746(2)	136

Symmetry codes: (i) 4 − *x*, 1 − *y*, 2 − *z*; (ii) 5/2 − *x*, −1/2 + *y*, 3/2 − *z*; (iii) 5/2 − *x*, 1/2 + *y*, 3/2 − *z*; (iv) 1 + *x*, *y*, *z*; (v) −1 + *x*, *y*, *z*. Cg1 is phenyl ring.

Table 2
Selected bond lengths (Å), angles (°) and torsion angles (°) for compound **16**

Bond length	
C(1)—O(1)	1.204(2)
C(1)—O(2)	1.366(2)
C(3)—O(2)	1.463(2)
C(1)—C(8)	1.469(2)
C(3)—C(9)	1.511(2)
C(2′)—O(3)	1.207(6)
C(1)—O(1)	1.204(2)
Bond angles	
O(1)—C(1)—C(8)	130.9(1)
O(2)—C(3)—C(9)	103.5(1)
C(9)—C(3)—C(1′)	117.9(1)
C(7)—C(8)—C(1)	128.8(1)
C(4)—C(9)—C(3)	131.3(1)
C(2′)—C(1′)—C(3)	112.0(1)
O(4)—C(6′)—C(7′)	115.3(1)
O(4)—C(6′)—C(5′)	124.4(1)
Torsion angles	
C(1)—O(2)—C(3)—C(1′)	128.1(1)
O(2)—C(3)—C(1′)—C(2′)	164.5(1)
C(4)—C(9)—C(3)—C(1′)	60.5(2)
C(9)—C(3)—C(1′)—C(2′)	−79.1(2)
C(8)—C(9)—C(3)—C(1′)	−121.8(1)
C(3)—C(1′)—C(2′)—C(3′)	−175.6(1)

Table 4
IC_{50} values (μmol L^{-1})[a] obtained when K562, HL-60, NALM6 and PBMC were treated with compounds **1**–**19**

Compound	IC_{50} (μmol L^{-1})			
	K562	HL60	NALM6	PBMC
1	93.0	15.7	27.9	>200
2	31.8	45.7	>200	>200
3	55.3	28.2	19.2	>200
4	>200	>200	113.6	>200
5	100.7	105.9	166.3	>200
6	48.0	49.7	20.3	>200
7	>200	>200	163.00	>200
8	57.4	12.0	26.3	>200
9	24.3	21.3	14.5	>200
10	12.3	62.7	7.78	>200
11	23.4	16.0	13.3	>200
12	32.9	15.1	14.3	>200
13	30.9	12.1	24.1	>200
14	46.3	20.1	30.0	>200
15	48.2	5.01	13.2	>200
16	87.9	58.0	61.1	>200
17	38.2	40.2	51.2	>200
18	8.83	13.5	5.24	>200
19	>200	>200	>200	>200

[a] IC_{50}: compound concentration required to inhibit 50% of viable cells, determined after 48 h of continuous treatment.

group corresponded to the most active derivative. Also, the presence of a methoxy phenyl group (compound **15**) gave a derivative which presented IC_{50} below 10 μmol L^{-1} against HL-60. It should be mentioned that no plain correlation could be found between IC_{50} values and the substitution pattern of the phenyl ring.

The compounds **1**–**19** were also screened against peripheral blood mononuclear cells (PBMC), but no significant effect was observed within the evaluated concentration range (Table 4). This observation provides evidences for the fact that these phthalides are selective for the analyzed cell lines analyzed.

In following assays, we evaluated if the most active compound on the three investigated lineages could affect cellular apoptosis program by approaching double staining by propidium iodide and Annexin V/FITC (Fig. 6). After 12 h of treatment with compound **18**, an increase of Annexin V/FITC positive NALM6 was observed in comparison to treatment with the vehicle DMSO (0.4% v/v). The percentage of cells in early or late events of apoptosis practically doubled, changing from 6.86% to 11.90% and 0.31% to 0.68% respectively. The absence of necrotic cells in these assays is of particular interest and represents an interesting finding in terms of application as anticancer agent. Despite these observations, further in deep biological studies are certainly needed to determine the exact mechanism of action of derivative **18** in cancer cells.

The synthesized compounds were subjected to a computational study to predict their physicochemical properties since these are related with absorption, distribution, metabolism, excretion and toxicity (ADMET) properties.[42] A screening was carried out for compliance to the Lipinski rule of five[43] and other related criteria added by Veber[44] and Ertl.[45] The molecular attributes analyzed included the calculated octan-1-ol/water partition coefficient (*c*Log*P*), number of hydrogen bond acceptors (HBA), number of hydrogen-bond donors (HBD), molecular weight (MW) and number of rotatable bonds (*n*Rotb). Another recognized parameter for the membrane permeation and prerequisite for the bioavailability, the topological polar surface area (TPSA),[45] was also considered (Table 5). Physicochemical parameters (Tables 5 and 6) were calculated using Osiris Property Explorer[46] and Molinspiration (http://www.molinspiration.com/cgi-bin/properties), integral part of some pharmaceutical companies' in-house substance registration[46] and used by several research groups.[22,47–51]

The calculated Log*P* values for compounds **1**–**19** (2.455–3.743) predict an appropriate lipophilicity that would facilitate their penetration across biological membranes, since drugs interacting with enzyme inside the human body have Log*P* values between 2 and 5.[52]

Aqueous solubility of a compound significantly affects its absorption and distribution characteristics. A parameter used to evaluate aqueous solubility is Log*S*. All compounds present solubility values within the desired range (−6.5 to 0.5).[53]

Taking into consideration the parameters described above, it is expected that compounds **1**–**19** exhibit high bioavailability. This fact is corroborated by the determined TPSA values (43.376–89.2 $Å^2$) and calculated percentages of absorption (%ABS). In general, the determined TPSA values for compounds **1**–**19** can be considered appropriated ones since compounds with TPSA $\geqslant$140 $Å^2$ are thought to have poor oral bioavailability and TPSA $\leqslant$61 $Å^2$ are regarded to have good bioavailability.[45] Moreover, compounds presenting TPSA values smaller than 60 $Å^2$ are good ones to penetrate the blood–brain barrier.[47] As can be seen in Table 5, the TPSA values predicted for phthalides **1** and **8**–**19** are less than the 60 $Å^2$. The percentages of absorption (%ABS) values are greater than 78% for all compounds, and ten phthalides out of nineteen exhibit the expected rate of absorption of 94%. In addition, the compounds **1**–**19** possess moderate number of rotatable bonds (3–4) and therefore, exhibit moderate conformational flexibility (Table 5).

Osiris Property Explorer software was used to predict the risk of toxicity of the synthesized compounds on the following criteria: mutagenic, tumorigenic, irritant and reproductive effective. Toxicity risk alerts are an indication that the compound may be harmful concerning the risk category specified. Isobenzofuranones **1**–**19** present low risk of mutagenic, reproductive effective and tumorigenic, but high risk of being irritant. This is an important information but not decisive for a drug. In fact, among the 3343 commercially available drugs used to develop Osiris Property Explorer software, 4% had high risk of being irritant and 4% medium risk according to this software package (http://www.organic-chemistry.org/prog/peo/tox.html).

Drug score values can be used to judge the compound overall potential to qualify it for a drug. The values are the combination of drug likeness, toxicity risk, and some physicochemical parameters, such as *c*Log*P*, solubility, and molecular weight. The negative values of the drug-likeness calculations, between −13.4 and −0.08 (Table 6) indicate that compounds of the series **1**–**19** do not contain fragments that are frequently present in commercial

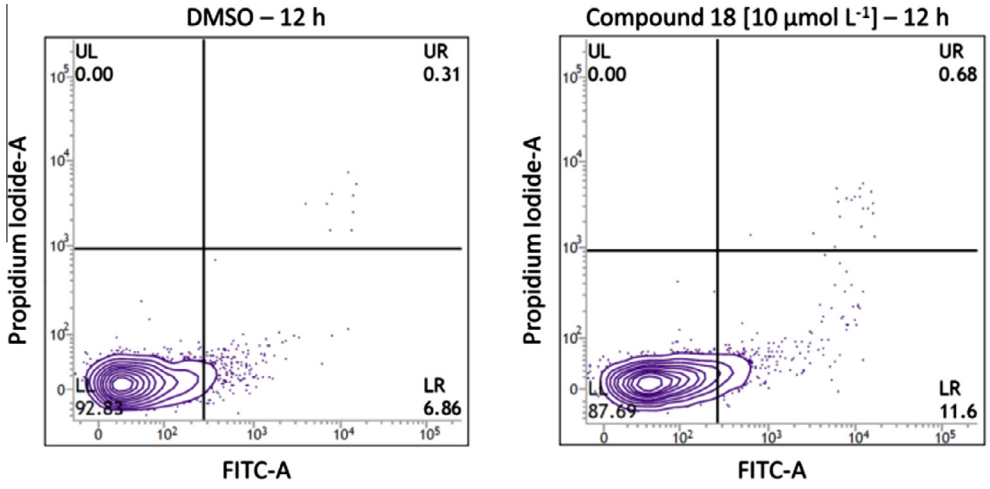


Figure 6. Compound **18** induces early apoptosis events on NALM6 cells. To assess cell death, NALM6 cells were treated with 10 μmol L^{-1} of compound **18** for 12 h. Cells treated with the vehicle DMSO (0.4% v/v) were used as controls. Subsequently, the cell death was evaluated using Annexin V/FITC and propidium iodide label. One representative experiment of three independent ones is shown.

Table 5
Predicted physicochemical parameters of 3-(2-aryl-2-oxoethyl)isobenzofuran-1(3*H*)-ones (**1**–**19**)

Compd	%ABS	MW	*c*Log*P*	Log*S*	TPSA
Rule[a]	–	⩽500	–	–	⩽140
1	94.0	252.269	2.958	−3.65	43.376
2	87.1	268.268	2.899	−3.36	63.604
3	87.1	268.268	2.455	−3.36	63.604
4	87.1	268.268	2.479	−3.36	63.604
5	78.2	297.266	2.869	−4.11	89.2
6	78.2	297.266	2.893	−4.11	89.2
7	78.2	297.266	2.917	−4.11	89.2
8	94.0	331.165	3.719	−4.49	43.376
9	94.0	331.165	3.743	−4.49	43.376
10	94.0	331.165	3.767	−4.49	43.376
11	94.0	270.259	3.074	−3.96	43.376
12	94.0	270.259	3.098	−3.96	43.376
13	94.0	270.259	3.122	−3.96	43.376
14	90.8	282.295	2.967	−3.67	52.610
15	90.8	282.295	2.991	−3.67	52.610
16	90.8	282.295	3.015	−3.67	52.610
17	94.0	266.296	3.359	−4.00	43.376
18	94.0	266.296	3.383	−4.00	43.376
19	94.0	266.296	3.407	−4.00	43.376

Compd	HBA	HBD	*n*Viol	*n*RotB	Volume
Rule[a]	⩽10	⩽5	<2	<10	
1	3	0	0	3	225.192
2	4	1	0	3	233.209
3	4	1	0	3	233.209
4	4	1	0	3	233.209
5	6	0	0	4	248.526
6	6	0	0	4	248.526
7	6	0	0	4	248.526
8	3	0	0	3	243.077
9	3	0	0	3	230.123
10	3	0	0	3	230.123
11	3	0	0	3	230.123
12	3	0	0	3	230.123
13	3	0	0	3	230.123
14	4	0	0	4	250.737
15	4	0	0	4	250.737
16	4	0	0	4	250.737
17	3	0	0	3	241.752
18	3	0	0	3	241.752
19	3	0	0	3	241.752

%ABS, percentage of absorption [%ABS = 109 − (0.345 × TPSA)]; *c*Log*P* = calculated lipophilicity; TPSA, topological polar surface area; HBA, number of H-bond acceptors; HBD, number of H-bond donors; *n*Viol, number of violations; *n*RotB, number of rotatable bonds.
[a] Represent the ideal values according to Lipinski,[43] Veber[44] and Ertl.[45]

drugs.[54,55] Drug-score values are low probably due to the little similarity to commercially available drugs and the high risk for the irritant category (Table 6).

Quantum chemical calculations were performed using Spartan' 10[56] and the Gaussian 09[57] molecular modeling softwares. The frontier orbitals and the dipole moment may be related to biological activity.[58–60] The Highest Occupied Molecular Orbital (HOMO) and the Lowest Unoccupied Molecular Orbital (LUMO) determine the way that a molecule interacts with other species. The frontier orbital gap helps characterize the chemical reactivity of the substance and the dipole moment is an important molecular descriptor that gives the measure of bond polarity throughout the molecule. These parameters were determined as previously published by our research group taking into consideration the solvent effect.[22] The calculated values are listed in Table 7.

Table 6
Drug-likeness (DL) and drug-score (DS) parameters for 3-(2-aryl-2-oxoethyl)isobenzofuran-1(3*H*)-ones series (**1**–**19**)

Compd	DL	DS	Compd	DL	DS
1	−4.30	0.26	**11**	−4.71	0.24
2	−3.09	0.27	**12**	−7.35	0.24
3	−4.31	0.26	**13**	−0.08	0.36
4	−0.99	0.33	**14**	−2.77	0.26
5	−10.5	0.24	**15**	−4.46	0.25
6	−9.71	0.24	**16**	−1.22	0.31
7	−13.4	0.24	**17**	−3.57	0.27
8	−7.08	0.21	**18**	−4.80	0.24
9	−7.92	0.21	**19**	−2.28	0.26
10	−4.14	0.22			

Table 7
Quantum-chemical descriptors for 3-(2-aryl-2-oxoethyl)isobenzofuran-1(3*H*)-ones series **1**–**19**

Compound	HOMO	LUMO	GAP[a]	Dipole moment
1	−7.26	−2.03	5.23	7.34
2	−6.55	−2.10	4.44	5.71
3	−6.54	−2.10	4.43	6.60
4	−6.55	−2.10	4.44	5.71
5	−7.27	−3.18	4.09	8.73
6	−7.27	−3.13	4.14	10.67
7	−7.27	−3.37	3.90	11.06
8	−7.05	−1.86	5.18	7.80
9	−7.03	−2.19	4.83	5.41
10	−7.07	−2.17	4.90	5.45
11	−7.21	−2.11	5.10	8.89
12	−7.15	−2.15	5.00	7.37
13	−7.22	−2.01	5.20	5.77
14	−6.52	−1.94	4.58	8.52
15	−6.45	−2.12	4.33	6.60
16	−6.54	−1.84	4.70	9.40
17	−6.97	−1.94	5.04	7.58
18	−6.94	−2.00	4.93	7.49
19	−7.01	−1.95	5.06	8.15

[a] GAP, difference between the HOMO and LUMO. Values calculated with Gaussian 09 using the B3LYP method with the 6-311++G(2d,p) basis set.

The highest and lowest energy difference between the HOMO and LUMO (gap energies) were observed for compounds **1** (5.23 eV) and **7** (3.90 eV), respectively, in case of using water as a solvent. Compound **7**, which has the highest value for the dipole moment (11.06), proved to be inactive for all cell lines used in the biological assays. Although there is a considerable variation between the frontier orbital and dipole moment values for the compounds under investigation, it was not possible to establish a clear correlation between the energy values of HOMO, LUMO, GAP and dipole moment and biological activity data.

In summary, we have demonstrated that twelve out of nineteen 3-(2-aryl-2-oxo)-isobenzofuran-1(3*H*)-one were capable of significantly inhibiting the viability of the cancer cells HL-60, K562 and NALM6. This effect seemed to be selective as no significant activity against PBMCs was observed. The most active derivative **18** was observed to induce apoptosis which paves the way toward further in deep biological studies of mechanism of action. Considering the obtained biological data as whole, the substitution pattern of the aryl ring in the aliphatic portion seems to be important in terms of biological activity.

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Supplementary data

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