Bioorganic & Medicinal Chemistry 18 (2010) 2537–2548

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Synthesis and anticancer activity evaluation of 2(4-alkoxyphenyl)cyclopropyl hydrazides and triazolo phthalazines

Prithwiraj De [a,b], Michel Baltas [a,b,*], Delphine Lamoral-Theys [c], Céline Bruyère [d], Robert Kiss [d], Florence Bedos-Belval [a,b], Nathalie Saffon [e]

[a] Université de Toulouse, UPS, LSPCMIB (Laboratoire de Synthèse et Physico-Chimie de Molécules d'Intérêt Biologique), 118, Route de Narbonne, F-31062 Toulouse Cedex 9, France
[b] CNRS, LSPCMIB (Laboratoire de Synthèse et Physico-Chimie de Molécules d'Intérêt Biologique), 118, Route de Narbonne, F-31062 Toulouse Cedex 9, France
[c] Laboratoire de Chimie Analytique, Toxicologie et Chimie Physique Appliquée, Institut de Pharmacie, Université Libre de Bruxelles, Boulevard du Triomphe, 1050 Bruxelles, Belgique
[d] Laboratoire de Toxicologie, Institut de Pharmacie, Université Libre de Bruxelles, Boulevard du Triomphe,1050 Bruxelles, Belgique
[e] Université de Toulouse, UPS, Structure Fédérative Toulousaine en Chimie Moléculaire, FR 2599, 118, Route de Narbonne, F-31062 Toulouse Cedex 9, France

ARTICLE INFO

Article history:
Received 23 November 2009
Revised 16 February 2010
Accepted 21 February 2010
Available online 1 March 2010

Keywords:
Cinnamic acid
Cyclopropyl backbone
Anticancer
Cytostatic activity
Apoptosis-resistant

ABSTRACT

A series of new 2(4-alkoxyphenyl)cyclopropyl hydrazide- and triazolo-derivatives were synthesized starting from 4-hydroxycinnamic acid (**1**) in a clean, mild, efficient and straightforward synthetic protocol. These compounds consisting of different alkoxy substitution, phenylcyclopropyl backbone and different heterocyclic groups were evaluated for in vitro anticancer activity against 4 cell lines displaying certain levels of resistance to pro-apoptotic stimuli and 2 cell lines sensitive to pro-apoptotic compounds. Compounds **7f** and **8e** were most active and displaying moderate in vitro cytostatic effect through different mechanisms. Significantly, chemically modified derivatives could be obtained in order to develop novel types of compounds aiming to combat apoptosis-resistant cancers, for example, those cancers associated with dismal prognoses.

1. Introduction

Phenolic compounds are bioactive substances with a widespread occurrence in food plants.[1a–c] Among them, the hydroxyl cinnamic acid family are natural products arising from the deamination of the phenyl alanine; they are important constituents in the biochemical pathway in plants leading to the lignin[2a,b] polymer, the second most abundant biopolymer after cellulose,[3a,b] resulting from the oxidative polymerization[4] of the three hydroxycinnamoyl alcohols, that is, *p*-coumaryl, coniferyl, sinapyl alcohols.

In recent years the phenolic compounds have attracted much attention due to their antioxidative, anti-inflammatory, antimutagenic and anticarcinogenic properties.[1c,5a–d] The antimutagenic and antitumor properties[5a] of these compounds are related to their ability to prevent oxidative damage in vivo by scavenging reactive oxygen species (ROS). It is considered that they thus prevent cellular proliferation, apoptosis and damage to DNA repair enzymes or damage to DNA polymerase. The cinnamoyl functionality is also present in a variety of secondary metabolites of phenylpropanoid biosynthetic origin. Those containing a sesquiterpenyl, monoterpenyl and isopentenyl chains attached to a 4-hydroxy group represent quite a rare group of natural products.[6a] Among these the ethyl ester of 3(4′-geranyloxy-3′-methoxyphenyl)-2-*trans* propenoic acid belonging to the family of Rutaceae[6b] showed a cancer chemopreventive effect and other effects closely related to cancer growth.

In the light of these promising results on the antitumoral activities of families of natural cinnamoyl derivatives and in the context of an urgent need for the discovery and development of new anticancer agents, many research groups have focused their efforts on the synthesis of non-natural cinnamic derivatives. Among them we can mention: (i) (*E*)-4-[3′-(1-adamentyl)-4′-hydroxyphenyl]-3-chlorocinnamic acid[7] that may induce apoptosis of leukaemia cells and may thus have a potential as a therapeutic agent for treating acute myeloid leukaemia; (ii) the cinnamoyl benzotriazolyl amides and related compounds such as 4-nitrocinnamoyl benzotriazolyl amide and (*E*)-3-(4-nitrophenyl)-1-(pyridine-3-yl)prop-2-en-1-one are potential transglutaminase inhibitors;[8] (iii) pyrazine cinnamoyl derivatives possessing various homopiperazine groups attached to the pyrazine moiety exhibiting strong inhibitory activities against *Pim Kinases* that participate in cell survival pathways;[9] (iv) cinnamoyl substituted benzophenones such as *N*-[3-benzoyl-4-[(4-methylphenyl)acetylamino]phenyl]-4-propoxy cinnamic acid amide and *N*-[3-benzoyl-4-[(4-methylphenyl)acetylamino]phenyl]-4-butoxy cinnamic acid amide potential farnesyl transferase inhibitors.[6a,10] Furthermore, recent results were obtained in the field of prodrugs of anticancer agents underlying

* Corresponding author. Tel.: +33 (0) 561556289; fax: +33 (0) 561556011.
E-mail address: baltas@chimie.ups-tlse.fr (M. Baltas).

0968-0896/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmc.2010.02.041

the stabilizing effect towards hydrolysis of the acrylic double bond conjugated with the aromatic ring in various cinnamoyl esters.[11]

In continuation of our ongoing research program, directed towards design and synthesis of cinnamoyl derivatives in relation with two potential diseases (cardiovascular and tuberculosis) in the light of increase interest of this class of compounds as anticancer agents, we would like to describe in this report the synthesis of a new class of cinnamoyl derivatives possessing a cyclopropyl frame next to the aromatic ring and their activities against a series of tumor cell lines.

The cyclopropyl frame has been chosen as it can be considered isosteric to the ethylenic functionality in terms of electronic sp^2 character of the carbon atoms. In addition, the phenyl cyclopropyl frame has been reported in a series of cyclopropyl indolequinones,[12] supposed to act through ring opening of the cyclopropane ring, thus inducing potent bioreductive cytotoxicity under hypoxic conditions.

2. Chemistry

The carboxylic function of 4-hydroxycinnamic acid (**1**) was protected first in order to introduce different alkyl chains on the phenolic functionality and used as common precursor of most of the hydrazides and phthalazides obtained. Methyl-ester of (*E*)-4-hydroxy cinnamic acid[13] was prepared by refluxing in the methanol in presence of catalytic amount of concentrated H_2SO_4 and 4 Å molecular sieves for 24 h in excellent yield (95%). (*E*)-Methyl-4-hydroxycinnamate (**2**) was then subjected to alkylation by refluxing suitable alkyl halide (isopentenyl bromide, geranyl bromide, ethyl iodide or methyl iodide) in dry acetone in presence of anhydrous K_2CO_3 and KI (used only in case of alkyl bromides) to give corresponding phenoxy ethers **3a**,[14]**c–e** in excellent yields. Owing to the presence of trifluoromethyl functionality, similar reaction with 2,2′,2″-trifluoroethyl iodide resulted in a poor yield (38%) of (*E*)-methyl 4-trifluoroethoxycinnamate (**3d**). Therefore, we modified the reaction procedure and **3d** was prepared from **2** using 2,2′,2″-trifluoroethyl iodide as the alkylating agent and NaH as the base in dimethylsulfoxide at 80 °C for 24 h in 52% yield. (*E*)-Methyl 4-trifluoromethoxycinnamate (**3b**) was obtained (89%) by Wadworth–Emmons coupling reaction between commercially available 4-trifluoromethoxybenzaldehyde and methyl diethylphosphonoacetate under basic conditions[15] (Scheme 1).

In an attempt to cyclopropanate the cinnamyl double bond, we sonicated[16] a mixture of 4-methoxy cinnamic acid (1 equiv), samarium (6 equiv) and iodoform (5 equiv) in dry tetrahydrofuran under argon but no reaction was observed. In a further attempt of cyclopropanation with $Mg/TiCl_4$ (catalytic)[17] in dichloromethane-tetrahydrofuran as solvent was of no avail. Gratefully, all these esters **3a–f** were converted into corresponding cyclopropyl derivatives **4a–f** in good yields (58–65%) when treated with timethylsulfoxonium iodide[18] and sodium hydride in DMSO at 55 °C. Use of dry tetrahydrofuran or dry dichloromethane as solvent instead of dry dimethylsulfoxide did not improve the yields of cyclopropanated derivatives. The methyl-2(4-alkoxyphenyl)cyclopropyl esters **4a–f** were then saponified to the corresponding carboxylic acids **5a–f** using K_2CO_3 in aqueous methanol as reported in Scheme 2 (yields 97–99%).

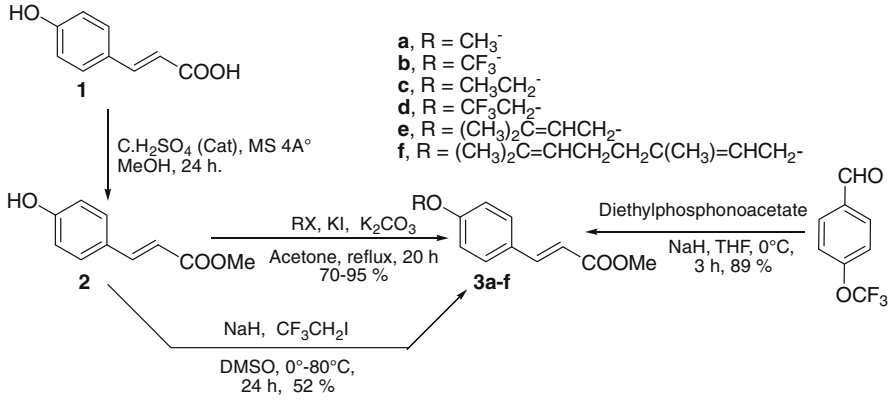
These acids **5a–f** were used as starting materials for the preparation of all compounds mentioned in Scheme 3. Coupling of acids **5a–f** with isoniazid was carried out using EDC·HCl in the presence of HOBt and diisopropylethylamine, in acetonitrile under reflux for 24 h to afford the respective *N*′-isonicotinoyl-*N*-(2-(4-alkoxyphenyl)cyclopropane carboxylhydrazides (**6a–f**) in excellent yields. With same coupling agents, reaction of acids with 1-hydrazinophthalazine hydrochloride in dichloromethane for 6 h at room temperature (25 °C) produced 2-(4-alkoxyphenyl)-*N*′-(phthalazin-1-yl)cyclopropanecarbohydrazide (**7a–f**) in good yields as reported in Scheme 3. Coupling of acids **5a–f** with 1-hydrazinophthalazine hydrochloride in acetonitrile under reflux for 48 h in presence of EDC·HCl, HOBt and diisopropylethylamine and concomitant cyclization furnished corresponding 3-(2-(4-alkoxyphenyl)cyclopropyl)-[1,2,4]triazolo[3,4-α]phthalazine (**8a–f**) in good yields (65–90%). The X-ray structure of the compound **8e**, shown in Figure 1, confirmed the formation of triazolophthalazine derivatives as well as the phenylcyclopropyl backbone of the entire series of compounds. The present reaction conditions established for the synthesis of triazolo-phthalazine derivatives add to other different methodologies available in the literature.[19a–d]

3. Biological evaluation and discussion

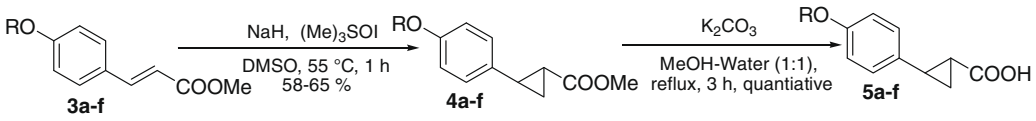
3.1. Determination of the IC_{50} in vitro growth inhibitory concentrations

The origin of the cell lines used in the current study and the culture media are fully detailed in references.[20a–c] We made use of six human cancer cell lines, four of which displaying certain levels of resistance to pro-apoptotic stimuli, that is, the U373 glioblastoma (GBM),[20b,21a] the A549 non-small-cell-lung cancer (NSCLC),[21b] the SKMEL-28 melanoma cell line[21c] and the OE21 esophageal cancer cell line.[21d] The two apoptosis-sensitive cancer cell lines include the PC-3 prostate[21e] and the MCF-7 breast[21e] cancer cell lines.

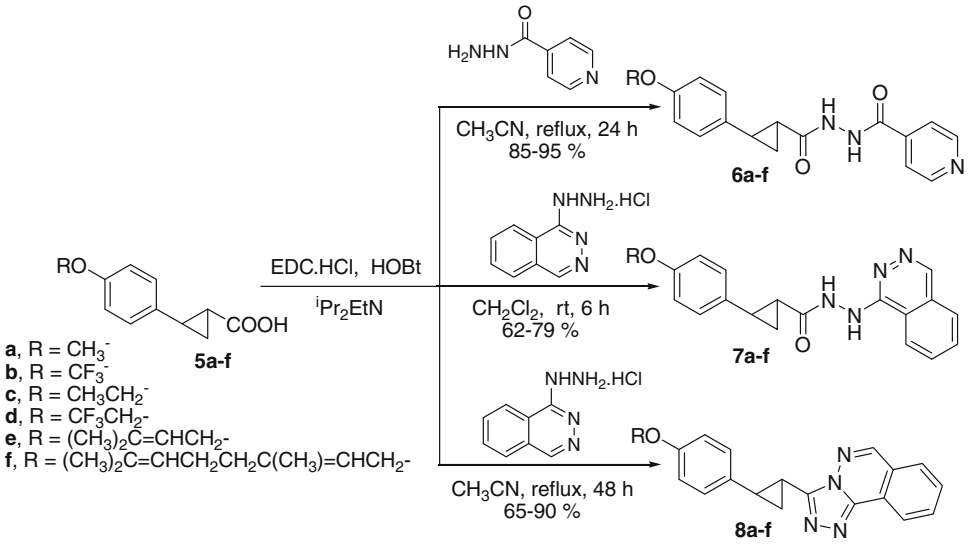
As detailed in Table 1 below, we first analyzed the in vitro antiproliferative activity of each compound under study in 3 cancer cell lines, that is, A549, PC3 and U373. If the compound revealed itself being not active (IC_{50} >100 μM) in vitro in one of these 3 cell lines, no further analysis was performed for this compound. In contrast, if the compound revealed itself to be ac-



Scheme 1. Synthesis of alkoxycinnamates.



Scheme 2. Synthesis of cyclopropane derivatives from alkoxycinnamates.



Scheme 3. Coupling of carboxylic acids with different hydrazine derivatives.

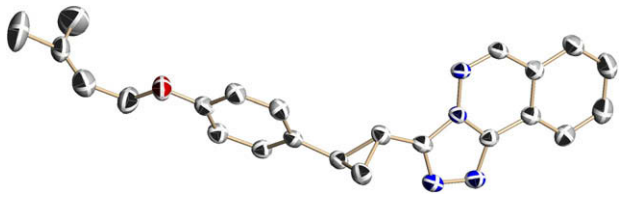


Figure 1. X-ray structure of **8e**.

tive on 3/3 cell lines, 3 additional cancer cell lines (MCF-7, OE21, SKMEL-28) were added to the in vitro screening process of anticancer activity determination.

The data in Table 1 show that when active on all six cell lines here analyzed (IC_{50} <100 μM), a given compound displayed similar in vitro anticancer activity between those cancer cell lines displaying certain levels of resistance to pro-apoptotic stimuli (A549, U373, OE21, SKMEL-28) and those cell lines sensitive to pro-apoptotic stimuli (MCF-7 and PC-3).

The data in Table 1 also reveal that of the 18 compounds under study, there are compounds **7f** and **8e** that displayed the highest in vitro anticancer activity.

3.2. Structure–activity relationship (SAR) analyses

Structure–activity relationship analyses performed with respect to the data detailed in Table 1 suggest that 2-(4-alkoxyphenyl)-*N*′-(phthalazin-1-yl)cyclopropanecarbohydrazide (**7a–f**) and 3-(2-(4-alkoxyphenyl)cyclopropyl)-[1,2,4]triazolo[3,4-α]phthalazine (**8a–f**) derivatives are more active compared to their isoniazid-analogues (**6a–f**). The observed antitumor activities can be attributed to the known ability of 1-phthalazine derivatives to behave as DNA-intercalants[22a–c] and thus possible inhibition of DNA synthesis of cancer cell lines. However, the fact that quantitative videomicroscopy demonstrated cytostatic rather than cytotoxic effects (Fig. 2) strongly suggest that the most active compounds within the current series exert their anticancer activity, at least in vitro, through mechanisms distinct of pure DNA intercalation, which is a process known to induce cytotoxic rather than cytostatic effects. In addition, within a series, that is, **7a–f**, **8a–f**, molecules with isopentenyl- and geranyl- side-chains have shown better in vitro activities compared to their saturated analogues. The role of cyclopropyl-part has also to be considered as the corresponding 4-alkoxystyryl derivatives were found to be much less active (unpublished data; not shown) compared to their cyclopropyl analogues (**6a–f**, **7a–f**, **8a–f**). Importantly, **7f** and **8e** are the two compounds with comparable and the best in vitro anticancer activities and particularly they are found to be active against U373 glioblastoma and OE21 cell lines which are known to be resistant to pro-apoptotic stimuli.

3.3. Deciphering the mechanisms of action of compounds 7f and 8e by means of quantitative videomicroscopy

Cytotoxic[23] versus cytostatic[24a,b] activity of the two most active compounds, **7f** and **8e**, was also evaluated. This has been monitored in vitro by means of computer-assisted phase-contrast microscopy (quantitative videomicroscopy). Figure 2 shows that both compounds **7f** and **8e** exerted their anticancer activity through cytostatic rather than cytotoxic effects. These experiments have been carried out on the human U373 GBM cell line and the morphological illustrations in Figure 2 clearly indicate that compounds **7f** and **8e** impaired U373 tumor cell population growth by decreasing U373 cell proliferation, thus through cytostatic effects, rather by direct killing of U373 tumor cells (which would then correspond to cytotoxic effects). The morphological illustrations in Figure 2 also reveal that the sustained cytostatic effects occurring with **7f**- and **8e**-related IC_{50} concentrations during the first two days of culture of U373 GBM cells in the presence of the compounds then led to U373 cell death during the third day of culture as revealed by the apparition of numerous round-shaped cells.

Table 1
In vitro activity of 2(4-alkoxyphenyl)cyclopropyl hydrazides

Compound	Cell lines (growth inhibitory IC_{50} values; μM)						Mean ± SEM	*C* log *P*
	First screening			Second screening				
	A549	PC3	U373	MCF7	OE21	SKMEL		
6a	>100	>100	>100	–	–	–	–	1.62
6b	56	>100	37	–	–	–	–	2.73
6c	43	>100	63	–	–	–	–	2.15
6d	10	44	19	34	31	81	37 ± 20	2.41
6e	>100	>100	>100	–	–	–	–	3.32
6f	78	>100	84	–	–	–	–	5.35
7a	96	64	83	72	48	68	72 ± 8	2.24
7b	87	92	85	54	42	29	65 ± 17	3.35
7c	>100	94	91	–	–	–	–	2.77
7d	48	67	25	8	17	29	32 ± 5	3.03
7e	82	81	81	69	38	67	70 ± 4	3.94
7f	36	24	9	23	9	25	21 ± 3	5.97
8a	40	29	28	29	26	40	32 ± 0	2.63
8b	37	49	37	37	30	57	41 ± 6	3.74
8c	66	>100	44	–	–	–	–	3.16
8d	64	38	58	37	9	29	39 ± 10	3.42
8e	56	22	4	19	8	26	23 ± 9	4.33
8f	45	8	63	9	5	72	34 ± 8	6.36

–: not determined in the second screening because at least one of three cell lines displayed an IC_{50} >100 μM during the run of the first screening.

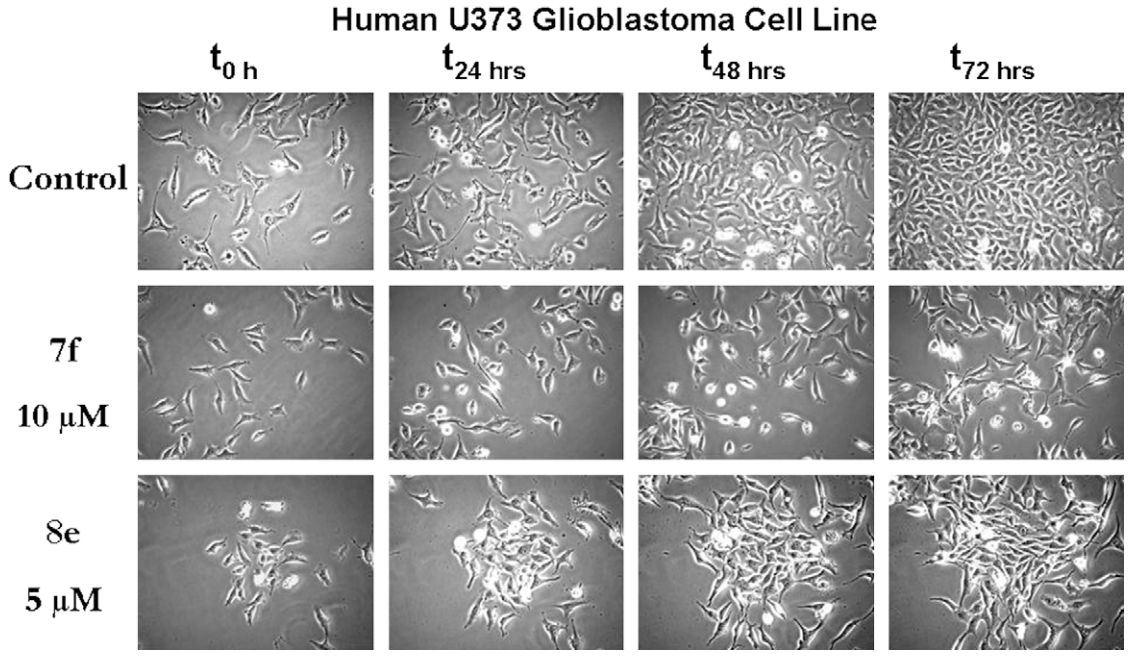


Figure 2. Quantitative videomicroscopy recording of human U373 glioblastoma cell population development for three days in the absence (control) or the presence of 10 μM **7f** or 5 μM **8e**.

We then made use of specific softwares that we developed in order to be able to determine the levels of mitoses in cell cultures and also the durations of mitoses.[25] While Figure 2 strongly suggests that both **7f** and **8e** exert cytostatic anticancer activity when assayed at their IC_{50} in vitro growth inhibitory concentrations, Figure 3 reveals that the cytostatic effects associated with **7f** and **8e** differ. Indeed, while 10 μM **7f** seemed to lead to increase in mitosis durations in human U373 glioblastoma cells, 5 μM **8e** seemed to lead to the opposite features (Fig. 3A). The **7f**-induced increase in mitosis duration resulted in a decrease in mitosis numbers (Fig. 3B), thus to the cytostatic effects reported in Figure 2. The **8e**-induced decrease in mitosis duration (Fig. 3A) did not result in modifications in the mitosis numbers (Fig. 3B). Thus, while both compounds **7f** and **8e** could exert their in vitro anticancer activity through cytostatic effects, these cytostatic effects seem to differ between **7f** and **8e**: **7f** could exert mitosis-dependent cytostatic effects, while **8e** could exert mitosis-independent cytostatic ones. In other words, the data illustrated in Figures 2 and 3 suggests that **7f** and **8e** could exert their cytostatic effects through distinct signalling pathways.

4. Conclusion

A series of new 2(4-alkoxyphenyl) cyclopropyl hydrazide derivatives were synthesized. Clean reaction, excellent yields and mild reaction condition are the key features of these protocols of coupling compared to other available methods. The compounds were found to exert cytostatic activity on the 6-human cancer cell-lines. Two compounds, with isopentenyl-(**8e**) and geranyl-(**7f**) side-chain attached

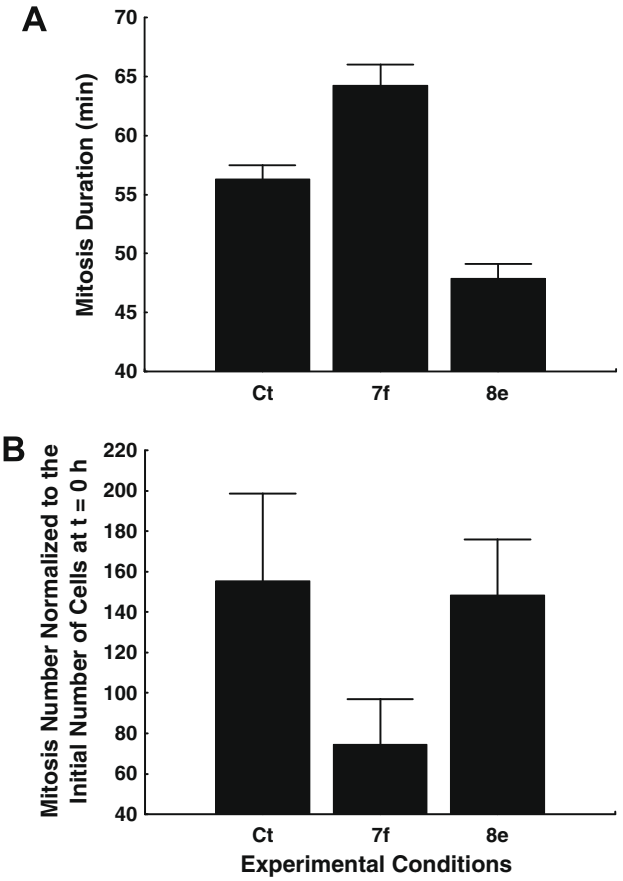


Figure 3. Quantitative videomicroscopy recording of mitosis duration (Fig. 3A) and mitosis levels (Fig. 3B) in human U373 glioblastoma cell populations left untreated (control; Ct) or treated for three days with 10 μM **7f** or 5 μM **8e**.

to the 4-hydroxyphenyl frame, were particularly more active than the remaining compounds against cancer cell-lines resistant to pro-apoptotic stimuli. The two compounds exert their cytostatic effects through distinct signalling pathways. Therefore, **7f** and **8e** are considered to be hits to combat apoptosis-resistant cancers, for example, those cancers associated with dismal prognoses. Efforts are on to establish the mechanism of action, modify the structures considering the lipophilicity (*C* log *P*) point of view, that is, modification of the side-chains as well as heterocyclic part.

5. Experimental section

5.1. Determination of the IC_{50} in vitro growth inhibitory concentrations

We evaluated the IC_{50} in vitro growth inhibitory values of the compounds under study by means of the MTT colorimetric assay as detailed elsewhere.[19a–c] Briefly, the cell lines were incubated for 24 h in 96-microwell plates (at a concentration of 10,000 to 40,000 cells/mL culture medium depending on the cell type) to ensure adequate plating prior to cell growth determination. The assessment of cell population growth by means of the MTT colorimetric assay is based on the capability of living cells to reduce the yellow product MTT (3-(4,5)-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) to a blue product, formazan, by a reduction reaction occurring in the mitochondria. The number of living cells after 72 h of culture in the presence (or absence: control) of the various compounds is directly proportional to the intensity of the blue, which is quantitatively measured by spectrophotometry—in our case using a Biorad Model 680XR (Biorad, Nazareth, Belgium) at a 570 nM wavelength (with a reference of 630 nM). Each experiment was carried out in sextuplicate.

5.2. Chemical synthesis and characterization data

5.2.1. General procedure

Organic solvents were purified when necessary by methods described by D. D. Perrin, W. L. F. Armarengo, and D. R. Perrin (*Purification of Laboratory Chemicals*; Pergamon: Oxford, 1986) or were purchased from Aldrich Chemie.

Melting points (mp) were obtained on a Buchi apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Perkin–Elmer 1725 infrared spectrophotometer and the data are reported in cm^{-1}. Proton nuclear magnetic resonance (^1H NMR) spectra were obtained with a Bruker AC-300 spectrometer. Chemical shifts were reported in parts per million (ppm) relative to tetramethylsilane (TMS), and signals are given as follows: s, singlet; d, doublet; t, triplet; m, multiplet. Mass spectra were recorded on an R 10–10 C Nermag (70 eV) quadripolar spectrometer using desorption chemical ionization (DCI), electrospray (ES) or fast atomic bombardment (FAB) techniques. For better NMR data analysis, compounds were numerated as (Fig. 4)

5.2.2. Preparation of (*E*)-methyl-3-(4-alkoxyphenyl)prop-2-enoate (3a–f)

To compound **2** (0.5 g, 2.8 mmol, 1 equiv) in dry acetone (15 mL), was added KI (added only in case of alkyl bromide; 0.6 g, 4.2 mmol, 1.5 equiv), K_2CO_3 (0.58 g, 4.2 mmol, 1.5 equiv) and alkyl halide (4.2 mmol, 1.5 equiv). The reaction mixture was refluxed for 20 h then cooled to room temperature and filtrated. The filtrate was evaporated to dryness and water (20 mL) was added into the residue and extracted with EtOAc (20 mL × 3). The combined organic layer was dried with Na_2SO_4, and evaporated in vacuo. The residue was purified by chromatography over silica gel (1:4 EtOAc/petroleum ether) to afford compound **3a–f** as white solids.

5.2.2.1. (*E*)-Methyl-3-(4-methoxyphenyl)prop-2-enoate (3a). Compound **3a** was prepared according to reported[14] mentioned procedure using methyl iodide in 95% yield. Spectral data matches as reported.

5.2.2.2. (*E*)-Methyl-3-(4-ethoxyphenyl)prop-2-enoate (3c). Compound **3c** was prepared from ester **2** according to procedure mentioned above by using ethyl iodide. White solid (0.40 g, 70%, mp 57–58 °C).

IR (KBr, ν_{max}) cm^{-1}: 2977, 1708, 1604, 1513, 1254.

^1H NMR ($CDCl_3$, 300 MHz) δ ppm: 1.42 (t, 3H, J = 7.0 Hz, $H_{2'}$), 3.79 (s, 3H, H_{10}), 4.06 (q, 2H, J = 7,0 Hz, $H_{1'}$), 6.30 (d, 1H, J = 16.0 Hz, C_8), 6.90 (d, 2H, J = 8.8 Hz, H_3, H_5), 7.46 (d, 2H, J = 8.8 Hz, H_2,H_6), 7.64 (d, 1H, J = 16.0 Hz, H_7).

^{13}C NMR ($CDCl_3$, 75 MHz) δ ppm: 14.73 (CH_3), 51.57 (C_{10}), 63.62 (CH_2), 114,79 (C_2, C_6), 115.11 (C_8), 126.93 (C_4), 129.11 (C_3, C_5), 144.59 (C_7), 160.79 (C_1), 167.79 (C_9).

MS (DCI, CH_4, pos.) m/z: 207.1 (MH^+).

5.2.2.3. (*E*)-Methyl-3-[4-(3-methylbut-2-enyloxy)phenyl]prop-2-enoate (3e). Compound **3e** was prepared from ester **2** according to procedure mentioned above by using 3,3′-dimethylallyl bromide. White solid (0.59 g, 86%, mp 55–57 °C).

IR (KBr, ν_{max}) cm^{-1}: 2945, 1716, 1635, 1513, 1251, 1167, 986, 837.

^1H NMR ($CDCl_3$, 300 MHz) δ ppm: 1.69 (s, 3H, $H_{4'}$), 1.74 (s, 3H, $H_{5'}$), 3.73 (s, 3H, CH_3), 4.49 (d, 2H, J = 6.6 Hz, $H_{1'}$), 5.42 (th, 1H, ^3J = 6.6 Hz, ^4J = 1.5 Hz, $H_{2'}$), 6.24 (d, 1H, J = 15.9 Hz, H_8), 6.84 (d,

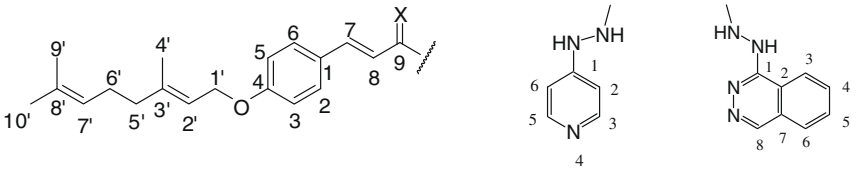


Figure 4.

2H, J = 8.5 Hz, H_3, H_5), 7.41 (d, 2H, J = 8.5 Hz, H_2, H_6), 7.60 (d, 1H, J = 15.9 Hz, H_7).

^{13}C NMR ($CDCl_3$, 75 MHz) δ ppm: 14.20 ($C_{4'}$), 18.22 (s, 1C, $C_{5'}$), 51.55 (CH_3), 64 .91 ($C_{1'}$), 114.89 (C_3, C_5), 115.14 (C_8), 119.22 ($C_{2'}$), 126.99 (s, 1C, C_1), 129.70 (C_2, C_6), 138.66 ($C_{3'}$), 144.60 (C_7), 160.74 (C_4), 167.80 (C_9).

MS (DCI, NH_3, pos.) m/z: 247.2 (MH^+), 264.2 (MNH_4^+).

5.2.2.4. (*E*)-Methyl-3-{4-[(*E*)-3,7-dimethylocta-2,6-dienyloxy]-phenyl}prop-2-enoate (3f). Compound **3f** was prepared from ester **2** according to procedure mentioned above by using geranyl bromide. White solid (0.83 g, 95%, mp 72–75 °C).

IR (KBr, ν_{max}) cm^{-1}: 3168, 2942, 2854, 1720, 1637, 1603, 1572, 1511.

^{1}H NMR ($CDCl_3$, 300 MHz) δ ppm: 1.60 (s, 3H, $CH_{9'}$), 1.67 (s, 3H, $H_{4'}$), 1.74 (s, 3H, $H_{10'}$), 2.10 (m, 4H, $H_{5'}$ and $H_{6'}$), 3.79 (s, 3H, CH_3), 4.57 (d, 2H, J = 6.6 Hz, $H_{1'}$), 5.07 (m, 1H, $H_{7'}$), 5.48 (t, 1H, = 6.5 Hz, $H_{2'}$), 6.31 (d, 1H, J = 15.9 Hz, H_8), 6.91 (d, 2H, J = 8.9 Hz, H_3, H_5), 7.47 (d, 2H, J = 8.9 Hz, H_2, H_6), 7.64 (d, 1H, J = 15.9 Hz, H_7).

^{13}C NMR ($CDCl_3$, 75 MHz) δ ppm: 16.68 ($C_{9'}$), 25.67 ($C_{4'}$), 26.26 ($C_{6'}$), 39.17 ($C_{10'}$), 39.51 ($C_{5'}$), 51.53 (CH_3), 64 .88 ($C_{1'}$), 110.03 (C_8), 115.11 (C_3, C_5), 118.84 ($C_{2'}$), 123.73 ($C_{7'}$), 126.97 (C_1), 129.69 (C_2, C_6), 131.83 ($C_{8'}$), 141.66 ($C_{3'}$), 144.61 (C_7), 160.16 (C_4), 167.78 (C_9).

MS (APCI, MeOH, pos.) m/z: 315.25 (MH^+).

5.2.2.5. (*E*)-Methyl-3-[4-trifluoromethoxyphenyl]prop-2-enoate (3b). A clean dry round bottom flask (100 mL) with a stir bar was charged with NaH (60% dispersion in mineral oil; 950 mg, 23.7 mmol, 1.5 equiv) under argon. It was then washed with petroleum ether (5 mL × 2). Dry THF (40 mL) was added to the reaction flask and stirred at 0 °C (ice bath) for 15 min. Methyldiethylphos phonoacetate (3.5 mL, 19 mmol, 1.2 equiv) was slowly added to the suspension over 10 min. It was then allowed to stir at 0 °C for 30 min when a colorless solution resulted. A solution of 4-trifluoromethoxybenzaldehyde (2.3 mL, 15.8 mmol, 1 equiv) in dry THF (12 mL) was slowly added to the reaction flask over 10 min. The reaction was then allowed to stir at room temperature (25 °C) for 20 h. TLC was monitored using 10% ethylacetate in petroleum ether (R_f aldehyde: 0.7, product: 0.6) as eluant. A saturated NH_4Cl (2 mL) solution was then added to quench the reaction. THF was removed under reduced pressure and water (30 mL) was added to the reaction mixture. It was then extracted with ethylacetate (60 mL × 3). The organic layer was dried over $MgSO_4$. Removal of solvent gave a crude mass (3.8 g) which was filtered through short silica gel plug (20 g) using 3% ethylacetate in petroleum ether as eluant to get pure white solid (*E*)-methyl-3-[4-trifluoromethoxyphenyl]prop-2-enoate (**3b**, 3.3 g, 89%, mp 43–45 °C).

IR (KBr, ν_{max}) cm^{-1}: 2951, 1708, 1604, 1515, 1245, 1170, 974, 830.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 3.74 (s, 3H, $-COOCH_3$), 6.35 (d, 1H, J = 15.9 Hz, H_7), 7.17 (d, 2H, J = 9 Hz, H_3, H_5), 7.48 (d, 2H, J = 9 Hz, H_2, H_6), 7.60 (d, 1H, J = 15.9 Hz, H_8).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 51.7 ($-COOCH_3$), 115.2 (C_3, C_5), 118.6 (C_8), 122.0, (q, J = 277 Hz, CF_3), 129.4 (C_2, C_6), 132.9 (C_1), 143.0 (C_7), 157.1 (C_4), 167.0 (C_9).

LRMS (APCI, M+H) Calcd for $C_{13}H_{14}O_3$, 275.17; found, 275.14.

5.2.2.6. (*E*)-Methyl-3-[4-(2,2′,2″-trifluoroethoxy)phenyl]prop-2-enoate (3d). A clean dry round bottom flask (50 mL) with a stir bar was charged with NaH (60% dispersion in mineral oil; 240 mg, 6 mmol, 1.2 equiv) under argon. Dry dimethylsulfoxide (4 mL) was added to the reaction flask and stirred at 0 °C for 15 min. A solution of phenol (**1**) (890 mg, 5 mmol, 1 equiv) in dimethylsulfoxide (2 mL) was slowly added to the suspension over 10 min (1 mL DMSO was used for rinsing). It was then allowed to stir at 0 °C for 30 min when a dark yellow solution resulted. Trifluoroethyl iodide (1.5 mL, 15 mmol, 3 equiv) was added to the reaction flask. The reaction was then stirred at 80 °C for 24 h and monitored by TLC (1:9 EtOAc/petroleum ether). A saturated NH_4Cl solution (2 mL) was added to quench the reaction. Water (20 mL) was added and then extracted with diethyl ether (30 mL × 3). The organic layer was dried over $MgSO_4$. The solvent was removed in vacuo and the residue was purified by silica gel chromatography (3% EtOAc in petroleum ether) to afford compound **3d** White solid, (0.68 g, 52%, mp 96–98 °C).

IR (KBr, ν_{max}) cm^{-1}: 2951, 1708, 1604, 1515, 1245, 1170, 974, 830.

^{1}H NMR ($CDCl_3$, 300 MHz) δ ppm: 3.80 (s, 3H, CH_3), 4.38 (q, 2H, J = 8.0 Hz, $-OCH_2$), 6.34 (d, 1H, J = 16.0 Hz, H_8), 6.95 (d, 2H, J = 8.8 Hz, H_2, H_6), 7.50 (d, 2H, J = 8.5 Hz, H_3, H_5), 7.65 (d, 1H, J = 16.0 Hz, H_7).

^{13}C NMR ($CDCl_3$, 75 MHz) δ ppm: 51.69 (CH_3), 65.66 (q, 1C, ^2J = 35.9 Hz, CH_2), 115.18 (C_{2-6}), 116.51 (C_8), 123.15 (q, 1C, J = 277.9 Hz, $C_{2'}$), 128.90 (C_4), 129.61 (C_{3-5}), 143.87 (C_7), 158.80 (C_1), 167.52 (C_9).

MS (DCI, CH_4, pos.) m/z: Calcd. For $C_{12}H_{12}F_3O_3$, 261.06; found, 261.07.

5.2.3. Preparation of methyl-2-(4-alkoxyphenyl)cyclopropanecarboxylate (4a–f): general procedure

A clean dry round bottom flask (10 mL) with a magnetic stir bar was charged with NaH (60% suspension; 0.05 g, 1.2 mmol, 1.2 equiv) and trimethylsulfoxonium iodide (0.24 g, 1.1 mmol, 1.1 equiv) under argon. Dry dimethylsulphoxide (2 mL) was added to the flask and stirred at room temperature (25 °C) for 40 min when the effervescence ceased and a milky-white suspension resulted. A solution of cinnamate derivative (1 mmol, 1 equiv) in dry dimethylsulphoxide (1 mL) was then added to the reaction mixture and stirred at 50 °C for 1 h. TLC was monitored in 5% ethylacetate in petroleum ether. It was then cooled to room temperature and brine (20 mL) was added to the reaction mixture. The quenched reaction mixture was then extracted with diethyl ether (30 mL × 3). The combined organic layer was dried over anhydrous $MgSO_4$. Removal of solvent gave crude mixture. The sticky mass was then purified over silica gel (70–200 mesh) using 3% ethylacetate-petroleum ether as eluant.

5.2.3.1. Methyl-2-(4-methoxyphenyl)cyclopropanecarboxylate (4a). Compound **4a** was prepared using **3a** as starting material. White solid (0.13 g, 65%, mp 51–53 °C).

IR (KBr, ν_{max}) cm^{-1}: 3007, 2953, 2912, 2837, 1728, 1613, 1516, 1443, 1339, 1340, 1293, 1254, 1202, 1177, 1029.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.21 (m, 1H, >CH_2), 1.49 (m, 1H, >CH_2), 1.77 (m, 1H, H_7), 2.43 (m, 1H, H_8), 3.65 (s, 3H, –$COOCH_3$), 3.72 (s, 3H, –OCH_3), 6.76 (d, 2H, J = 9 Hz, H_3, H_5), 6.97 (d, 2H, J = 9 Hz, H_2, H_6).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 16.7 (>CH_2), 23.6 (C_8), 25.7 (C_7), 51.8 (–$COOCH_3$), 55.3 (–OCH_3), 113.9 (C_3, C_5), 127.4 (C_2, C_6), 131.9 (C_1), 158.3 (C_4), 174.0 (C_9).

LRMS (APCI, M+Na) Calcd for $C_{12}H_{14}O_3Na$, 229.09; found, 229.05.

5.2.3.2. Methyl-2-(4-trifluoromethoxyphenyl)cyclopropanecarboxylate (4b). Compound **4b** was prepared using **3b** as starting material. Colorless oil (0.16 g, 61%).

IR (neat, ν_{max}) cm^{-1}: 3050, 2956, 1713, 1641, 1589, 1510, 1438, 1266, 1214, 1162, 1011, 990.

^{1}H NMR (300 MHz, acetone-d_6) δ ppm: 1.34 (m, 1H, >CH_2), 1.45 (m, 1H, >CH_2), 1.89 (m, 1H, H_7), 2.45 (m, 1H, H_8), 3.61 (s, 3H, –$COOCH_3$), 7.17 (d, 2H, J = 9 Hz, H_3, H_5), 7.25 (d, 2H, J = 9 Hz, H_2, H_6).

^{13}C NMR (75 MHz, acetone-d_6) δ ppm: 16.9 (>CH_2), 23.9 (C_8), 25.4 (C_7), 51.9(–$COOCH_3$), 121.0 (C_3, C_5), 122.1 (q, J = 284 Hz, –CF_3), 127.5 (C_2, C_6), 138.7 (C_1), 147.8 (C_4), 173.5 (C_9).

LRMS (ESCl, M+Na) Calcd for $C_{12}H_{11}F_3O_3Na$, 283.07; found, 283.05.

5.2.3.3. Methyl-2-(4-ethoxyphenyl)cyclopropanecarboxylate (4c). Compound **4c** as prepared using **3c** as starting material. White solid (0.13 g, 60%, mp 57–58 °C).

IR (KBr, ν_{max}) cm^{-1}: 3007, 2979, 2957, 2926, 1732, 1612, 1515, 1454, 1434, 1398, 1340, 1288, 1250, 1199, 1174, 1049.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.30 (m, 1H, >CH_2), 1.43 (t, 3H, J = 6.9 Hz, –OCH_2CH_3), 1.58 (m, 1H, >CH_2), 1.85 (m, 1H, H_7), 2.51 (m, 1H, H_8), 3.74 (s, 3H, –$COOCH_3$), 4.03 (q 2H, J = 6.9 Hz, –OCH_2CH_3), 6.84 (d, 2H, J = 9 Hz, H_3, H_5), 7.05 (d, 2H, J = 9 Hz, H_2, H_6).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 13.7 (>CH_2), 15.0 (–CH_2CH_3), 22.0 (C_8), 24.1 (C_7), 51.8 (–$COOCH_3$), 61.8 (–OCH_2CH_3), 112.8 (C_3, C_5), 125.7 (C_2, C_6), 130.1 (C_1), 156.0 (C_4), 172.4 (C_9).

LRMS (APCI, M+Na) Calcd for $C_{13}H_{16}O_3Na$, 243.11; found, 243.19.

5.2.3.4. Methyl-2-[4-(2,2′,2″-trifluoroethoxy)phenyl]cyclopropanecarboxylate (4d). Compound **4d** was prepared using **3d** as starting material. Colorless oil (0.17 g, 63%).

IR (neat, ν_{max}) cm^{-1}: 3047, 2979, 2956, 2924, 1714, 1639, 1589, 1510, 1438, 1266, 1214, 1162, 1011, 987.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.22 (m, 1H, >CH_2), 1.52 (m, 1H, >CH_2), 1.78 (m, 1H, H_7), 2.43 (m, 1H, H_8), 3.65 (s, 3H, –$COOCH_3$), 4.25 (q, 2H, J = 4.8 Hz, –OCH_2CF_3), 6.79 (d, 2H, J = 9 Hz, H_3, H_5), 6.99 (d, 2H, J = 9 Hz, H_2, H_6) .

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 16.8 (>CH_2), 23.7 (C_8), 25.5 (C_7), 51.9 (–$COOCH_3$), 66.1, (q, J = 35.9 Hz, –OCH_2CF_3), 115.0 (C_3, C_5), 124.4, (q, J = 277 Hz, –CF_3), 127.6 (C_2, C_6), 134.0 (C_1), 156.1 (C_4), 173.8 (C_9).

LRMS (APCI, M+H) Calcd for $C_{13}H_{14}O_3$, 275.17; found, 275.14.

5.2.3.5. Methyl-2-(4-(3-methylbut-2-enyloxy)phenyl)cyclopropanecarboxylate (4e). Compound **4e** was prepared using **3e** as starting material. White solid (0.15 g, 58%, mp 50–52 °C).

IR (KBr, ν_{max}) cm^{-1}: 3004, 2958, 2926, 2854, 1732, 1612, 1578, 1514, 1451, 1433, 1399, 1384, 1339, 1288, 1248, 1199, 1173, 1123, 1050, 1004, 984.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.22 (m, 1H, >CH_2), 1.51 (m, 1H, >CH_2), 1.67 (s, 3H, $H_{4'}$), 1.71 (s, 3H, $H_{5'}$), 1.72 (m, 1H, H_7), 2.42 (m, 1H, H_8), 3.64 (s, 3H, –$COOCH_3$), 4.41 (d, 2H, J = 6.6 Hz, $H_{1'}$), 5.06 (m, 1H, $H_{2'}$), 6.77 (d, 2H, J = 9 Hz, H_3, H_5), 6.96 (d, 2H, J = 9 Hz, H_2, H_6).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 14.2 ($C_{4'}$), 15.6 ($C_{5'}$), 17.1 (>CH_2), 22.6 (C_8), 24.7 (C_7), 50.8 (–$COOCH_3$), 63.8 (–OCH_2–), 113.6 (C_3, C_5), 118.6 ($C_{2'}$), 126.3 (C_2, C_6), 130.8 ($C_{3'}$), 137.1 (C_1), 156.6 (C_4), 175.3 (C_9).

LRMS (APCI, M+Na) Calcd for $C_{16}H_{20}O_3Na$, 283.14; found, 283.1

5.2.3.6. Methyl-2-(4-((*E*)-3,7-dimethylocta-2,6-dienyloxy) phenyl)cyclopropanecarboxylate (4f). Compound **4f** was prepared using **3f** as starting material. White solid (0.19 g, 59%, mp 49–51 °C).

IR (KBr, ν_{max}) cm^{-1}: 3007, 2963, 2918, 2852, 1730, 1613, 1515, 1451, 1398, 1335, 1288, 1248, 1197, 1171, 1123, 1004, 820.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.20 (m, 1H, >CH_2), 1.50 (m, 1H, >CH_2), 1.54 (s, 3H, $H_{9'}$), 1.66 (s, 3H, $H_{10'}$), 1.66 (s, 3H, $H_{4'}$), 1.76 (m, 1H, H_7), 2.03 (m, 4H, $H_{5'}$, $H_{6'}$), 2.43 (m, 1H, H_8), 3.65 (s, 3H, –$COOCH_3$), 4.46 (d, 2H, J = 6.6 Hz, –OCH_2–), 5.06 (m, 1H, $H_{7'}$), 5.43 (m, 1H, $H_{2'}$), 6.77 (d, 2H, J = 9 Hz, H_3, H_5), 6.96 (d, 2H, J = 9 Hz, H_2, H_6).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 15.63 (>CH_2), 15.68 ($C_{9'}$), 16.6 ($C_{4'}$), 22.6 (C_8), 24.7($C_{6'}$), 24.7 (C_7), 25.2 ($C_{5'}$), 38.5 ($C_{10'}$), 50.8 (–$COOCH_3$), 63.9 (–CH_2O–), 113.7 (C_3, C_5), 118.4 ($C_{2'}$), 122.7 ($C_{7'}$), 126.3 (C_2, C_6), 130.7 ($C_{8'}$),140.1 ($C_{3'}$), 146.4 (C_1), 156.6 (C_4), 173.1 (C_9).

LRMS (APCI, M+Na): Calcd for $C_{21}H_{28}O_3Na$, 351.20; found, 351.1.

5.2.4. Preparation of 2-(4-alkoxyphenyl)cyclopropanecarboxylic acid (5a–f): general procedure

A round bottom flask (25 mL) with a magnetic stir bar was charged with methyl-2-(4-alkoxyphenyl)cyclopropanecarboxylate (**4a–f**, 1 mmol, 1 equiv). Methanol (10 mL) was added to it and stirred till it made a homogeneous solution. An aqueous solution (5 mL) of K_2CO_3 (0.42 g, 3 mmol, 3 equiv) was added to it and stirred at 70 °C for 3 h when all starting material had disappeared. TLC was monitored in 5% ethylacetate in petroleum ether. Methanol was removed under reduced pressure and it was cooled to 0 °C in ice bath. HCl (3 N) was then added to the reaction mixture till pH 3 (pH paper) and a white precipitation was observed. It was then extracted with ethylacetate (30 mL × 3). The organic layer was dried over $MgSO_4$. Removal of solvent gave the corresponding carboxylic acid as white solid. The acid obtained was used for the next reaction without further purification.

5.2.4.1. 2-(4-Methoxyphenyl)cyclopropanecarboxylic acid (5a). Compound **5a** was prepared using **4a** as starting material. White solid (0.19 g, quantitative, mp 87–89 °C).

IR (KBr, ν_{max}) cm^{-1}: 3425, 3010, 2953, 2836, 2541, 1876, 1676, 1913, 1517, 1457, 1433, 1334, 1292, 1255, 1221, 1175, 1109, 1024, 939.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.30 (m, 1H, >CH_2), 1.56 (m, 1H, >CH_2), 1.77 (m, 1H, H_7), 2.52 (m, 1H, H_8), 3.73 (s, 3H, –OCH_3), 6.76 (d, 2H, J = 9 Hz, H_3, H_5), 6.98 (d, 2H, J = 9 Hz, H_2, H_6).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 17.2 (>CH_2), 23.6 (C_8), 26.6 (C_7), 55.3 (–OCH_3), 113.9 (C_3, C_5), 127.5 (C_2, C_6), 131.4 (C_1), 158.4 (C_4), 179.4 (C_9).

LRMS (ES−, M−H) Calcd for $C_{11}H_{11}O_3$, 191.02; found, 191.02.

5.2.4.2. 2-(4-Trifluoromethoxyphenyl)cyclopropanecarboxylic acid (5b). Compound **5b** was prepared using **4b** as starting material. White solid (0.24 g, quantitative, mp 78–80 °C).

IR (KBr, ν_{max}) cm^{-1}: 3410, 2926, 2650, 1697, 1514, 1459, 1436, 1336, 1256, 1198, 1164, 11.3, 1017, 937.

^{1}H NMR (300 MHz, acetone-d_6) δ ppm: 1.33 (m, 1H, >CH_2), 1.62 (m, 1H, >CH_2), 1.89 (m, 1H, H_7), 2.55 (m, 1H, H_8), 7.20 (d, 2H, J = 9 Hz, H_3, H_5), 7.27 (d, 2H, J = 9 Hz, H_2, H_6).

^{13}C NMR (75 MHz, acetone-d_6) δ ppm: 17.4 (>CH_2), 23.9 (C_8), 26.3 (C_7), 121.1 (C_3, C_5), 122.1 (q, J = 284 Hz, –CF_3), 127.6 (C_2, C_6), 138.2 (C_1), 147.9 (C_4), 179.5 (C_9).

LRMS (APCI, M+NH_4) Calcd for $C_{11}H_{13}NF_3O_3$, 264.08; found, 264.10.

5.2.4.3. 2-(4-Ethoxyphenyl)cyclopropanecarboxylic acid (5c). Compound **5c** was prepared using **4c** as starting material. White solid (0.20 g, quantitative, mp 70–72 °C).

IR (KBr, ν_{max}) cm^{-1}: 3410, 2979, 2927, 2881, 2650, 1702, 1611, 1515, 1459, 1395, 1335, 1288, 1249, 1229, 1179, 1116, 1049, 936.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.36 (m, 1H, >CH_2), 1.42 (t, 3H, J = 6.9 Hz, –OCH_2CH_3), 1.64 (m, 1H, >CH_2), 1.85 (m, 1H, H_7), 2.59 (m, 1H, H_8), 4.03 (q, 2H, J = 6.9 Hz, –OCH_2CH_3), 6.84 (d, 2H, J = 9 Hz, H_3, H_5), 7.06 (d, 2H, J = 9 Hz, H_2, H_6).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 13.7 (–CH_2CH_3), 16.1 (>CH_2), 22.7 (C_8), 25.6 (C_7), 62.4 (–O**C**H_2CH_3), 113.5 (C_3, C_5), 126.4 (C_2, C_6), 130.1 (C_1), 156.7 (C_4), 179.0 (C_9).

LRMS (ES+, M+Na) Calcd for $C_{12}H_{14}O_3Na$, 229.08; found, 229.11.

5.2.4.4. 2-[4-(2,2′,2″-Trifluoroethoxy)phenyl]cyclopropanecarboxylic acid (5d). Compound **5d** was prepared using **4d** as starting material. White solid (0.26 g, quantitative, mp 93–95 °C).

IR (KBr, ν_{max}) cm^{-1}: 3405, 2920, 2563, 1687, 1615, 1517, 1460, 1437, 1327, 1299, 1238, 1178, 1151, 1084, 1029, 977.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.29 (m, 1H, >CH_2), 1.58 (m, 1H, >CH_2), 1.78 (m, 1H, H_7), 2.51 (m, 1H, H_8), 4.26 (q, 2H, J = 4.8 Hz, –OCH_2CF_3), 6.80 (d, 2H, J = 9 Hz, H_3, H_5), 7.00 (d, 2H, J = 9 Hz, H_2, H_6) .

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 17.2 (>CH_2), 23.7 (C_8), 26.4 (C_7), 65.9 (q, J = 35.9 Hz, –OCH_2CF_3), 115.1 (C_3, C_5), 123.8, (q, J = 277 Hz, –CF_3), 127.6 (C_2, C_6), 133.5 (C_1), 156.3 (C_4), 179.8 (C_9).

LRMS (ES−, M−H) Calcd for $C_{12}H_{10}F_3O_3$, 259.06; found, 259.15.

5.2.4.5. 2-[4-(3-Methylbut-2-enyloxy)phenyl]cyclopropanecarboxylic acid (5e). Compound **5e** was prepared using **4e** as starting material. White solid (0.24 g, 98%, mp 86–88 °C).

IR (KBr, ν_{max}) cm^{-1}: 3417, 2966, 2919, 2865, 2645, 2549, 1697, 1614, 1516, 1460, 1434, 1384, 1337, 1289, 1253, 1230, 1178, 1109, 1049, 1003, 938.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.37 (m, 1H, >CH_2), 1.65 (m, 1H, >CH_2), 1.76 (s, 3H, $H_{4'}$), 1.82 (s, 3H, $H_{5'}$), 1.85 (m, 1H, H_7), 2.59 (m, 1H, H_8), 4.51 (d, 2H, J = 6.6 Hz, $H_{1'}$), 5.50 (m, 1H, $H_{2'}$), 6.87 (d, 2H, J = 9 Hz, H_3, H_5), 7.06 (d, 2H, J = 9 Hz, H_2, H_6).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 16.1(>CH_2), 17.2 ($C_{4'}$), 22.7 (C_8), 24.7 ($C_{5'}$), 25.6 (C_7), 63.7 (–OCH_2–), 113.8 (C_3, C_5), 118.1 ($C_{2'}$), 126.4 (C_2, C_6), 130.3 ($C_{3'}$), 136.8 (C_1), 156.7 (C_4), 179.0 (C_9).

LRMS (ES+, M+Na) Calcd for $C_{15}H_{18}O_3Na$, 269.14; found, 269.20.

5.2.4.6. 2-{4-[(*E*)-3,7-Dimethylocta-2,6-dienyloxy]phenyl}cyclopropanecarboxylic acid (5f). Compound **5f** was prepared using **4f** as starting material. White solid (0.31 g, quantitative, mp 83–85 °C).

IR (KBr, ν_{max}) cm^{-1}: 3415, 2966, 2928, 2875, 2641, 1885, 1700, 1611, 1579, 1515, 1458, 1433, 1380, 1335, 1287, 1248, 1229, 1179, 1110, 1049, 996,937.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.29 (m, 1H, >CH_2), 1.55 (m, 1H, >CH_2), 1.55 (s, 3H, $H_{9'}$), 1.63 (s, 3H, $H_{10'}$), 1.67 (s, 3H, $H_{4'}$), 1.76 (m, 1H, H_7), 2.04 (m, 4H, $H_{5'}$, $H_{6'}$), 2.51 (m, 1H, H_8), 4.46 (d, 2H, J = 6.6 Hz, –OCH_2–), 5.04 (m, 1H, $H_{7'}$), 5.42 (m, 1H, $H_{2'}$), 6.78 (d, 2H, J = 9 Hz, H_3, H_5), 6.98 (d, 2H, J = 9 Hz, H_2, H_6).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 16.6 ($C_{9'}$), 17.2 (>CH_2), 17.7 ($C_{4'}$), 23.7 (C_8), 25.7($C_{6'}$), 26.3 (C_7), 26.6 ($C_{5'}$), 39.5 ($C_{10'}$), 64.9 (–CH_2O–), 114.8 (C_3, C_5), 119.5 ($C_{2'}$), 123.8 ($C_{7'}$), 127.4 (C_2, C_6), 131.3 ($C_{8'}$),131.8 ($C_{3'}$), 141.2 (C_1), 157.7 (C_4), 179.9 (C_9).

LRMS (ES−, M−H) Calcd for $C_{20}H_{25}O_3$, 313.20; found, 337.24.

5.2.5. Preparation of *N′*-Isonicotinoyl-*N*-2-(4-alkoxyphenyl) cyclopropanecarboxylhydrazide (6a–f): general procedure

A clean dry round bottom flask (10 mL) with a magnetic stir bar was charged with carboxylic acid (**5a–f**, 1 mmol, 1 equiv), isoniazide (0.20 g, 1.5 mmol, 1.5 equiv), HOBt (0.15 g, 1.1 mmol, 1.1 equiv) and EDC·HCl (0.21 g, 1.1 mmol, 1.1 equiv) under argon. Dry CH_3CN (5 mL) was added to it and stirred. Diisopropylethylamine (0.5 mL, 3 mmol, 3 equiv) was added to the reaction mixture and refluxed for 24 h. TLC was monitored in ethylacetate. Acetonitrile was removed under reduced pressure. Ethylacetate (60 mL) was added to the crude yellow mass and the solution was thoroughly washed with water (30 mL × 3). The organic layer was then dried over $MgSO_4$. Removal of the solvent gave a crude yellowish mass. It was the purified over silica gel (70–200 mesh) using 80% ethylacetate in Petroleum ether to afford **6a–f**.

5.2.5.1. *N′*-Isonicotinoyl-*N*-2-(4-methoxyphenyl)cyclopropane carboxylhydrazide (6a). Compound **6a** was prepared using **5a** as starting material. White crystalline solid (0.26 g, 85%, mp.193–195 °C).

IR (KBr, ν_{max}) cm^{-1}: 3160, 3015, 2962, 2925, 2855, 1730, 1579, 1592, 1550, 1517, 1470, 1409, 1298, 1250, 1229, 1186, 1160, 1083, 1027, 993.

^{1}H NMR (300 MHz, C_6D_6: DMSO-d_6(5:1)) δ ppm: 1.07 (m, 1H, >CH_2), 1.59 (m, 1H, >CH_2), 2.25 (m, 1H, H_7), 2.55 (m, 1H, H_8), 3.39 (s, 3H, –OCH_3), 6.70 (d, 2H, J = 9 Hz, H_3, H_5), 6.92 (d, 2H, J = 9 Hz, H_2, H_6), 7.88 (m, 2H, H_3, H_5 py), 8.59 (m, 2H, H_2, H_6 py), 10.66 (br s, 1H, >NH), 11.03 (br s, 1H, >NH),

^{13}C NMR (75 MHz, C_6D_6: DMSO-d_6(5:1)) δ ppm: 15.8 (>CH_2), 24.1 (C_8), 24.6 (C_7), 55.0 (–OCH_3), 114.2 (C_3, C_5), 127.6 (C_2, C_6), 127.61 (C_3, C_5 py), 133.1 (C_1), 140.3 (–NH=C(O)–C<), 150.6 (C_2, C_6 py), 158.5 (C_4), 164.4 (–NH=C(O)–C<), 171.5 (C_9).

HRMS (TOF MS CI+, M+H) Calcd for $C_{17}H_{18}N_3O_3$, 312.1348; found, 312.1339.

5.2.5.2. *N′*-Isonicotinoyl-*N*-2-(4-trifluoromethoxyphenyl)cyclopropanecarboxylhydrazide (6b). Compound **6b** was prepared using **5b** as starting material. White crystalline solid (0.33 g, 91%, mp.176–177 °C).

IR (KBr, ν_{max}) cm^{-1}: 3164, 3015, 2352, 1990, 1631, 1579, 1591, 1550, 1514, 1503, 1475, 1410, 1305, 1217, 1162, 1108, 1084, 1042, 994, 936.

^{1}H NMR (300 MHz, C_6D_6: DMSO-d_6(5:1)) δ ppm: 1.00 (m, 1H, >CH_2), 1.49 (m, 1H, >CH_2), 2.14 (m, 1H, H_7), 2.40 (m, 1H, H_8), 6.87 (m, 4H, H_2, H_6, H_3, H_5), 7.77 (m, 2H, H_3, H_5 py), 8.52 (m, 2H, H_2, H_6 py), 10.53 (br s, 1H, >NH), 10.9 (br s, 1H, >NH).

^{13}C NMR (75 MHz, C_6D_6: DMSO-d_6(5:1)) δ ppm: 16.3 (>CH_2), 24.1 (C_8), 24.3 (C_7), 114.2 (C_3, C_5), 127.6 (C_2, C_6), 127.61 (C_3, C_5 py), 133.1 (C_1), 140.4 (–NH=C(O)–C<), 150.4 (C_2, C_6 py), 158.2 (C_4), 164.2 (–NH=C(O)–C<), 170.8 (C_9).

^{19}F NMR (282 MHz, DMSO-d_6) δ ppm: −56.86 (s, 3F)

HRMS (TOF MS CI+, M+H) Calcd for $C_{17}H_{15}F_3N_3O_3$, 366.1066; found, 366.1067.

5.2.5.3. *N′*-Isonicotinoyl-*N*-2-(4-ethoxyphenyl)cyclopropane carboxylhydrazide (6c). Compound **6c** was prepared using **5c** as starting material. White crystalline solid (0.29 g, 90%, mp.195–197 °C).

IR (KBr, ν_{max}) cm^{-1}: 3166, 3015, 2979, 1876, 1657, 1579, 1591, 1551, 1516, 1502, 1475, 1410, 1398, 1294, 1249, 1231, 1186, 1168, 1114, 1065, 1047, 994, 942.

^{1}H NMR (300 MHz, C_6D_6: DMSO-d_6(5:1)) δ ppm: 1.03 (m, 1H, $>CH_2$), 1.03 (t, 3H, J = 6.9 Hz, $-OCH_2CH_3$), 1.55 (m, 1H, $>CH_2$), 2.20 (m, 1H, H_7), 2.49 (m, 1H, H_8), 3.60 (q, 2H, J = 6.9 Hz, $-OCH_2CH_3$), 6.65 (d, 2H, J = 9 Hz, H_3, H_5), 6.87 (d, 2H, J = 9 Hz, H_2, H_6), 7.82 (m, 2H, H_3, H_5 py), 8.52 (m, 2H, H_2, H_6 py), 10.60 (br s, 1H, >NH), 10.98 (br s, 1H, >NH).

^{13}C NMR (75 MHz, C_6D_6: DMSO-d_6(5:1)) δ ppm: 14.6 ($-CH_2CH_3$), 15.6 ($>CH_2$), 23.8 (C_8), 24.4 (C_7), 63.0 ($-OCH_2CH_3$), 114.5 (C_3, C_5), 121.8 (C_3, C_5 py), 127.3 (C_2, C_6), 132.8 (C_1), 140.1 (–NH=C(O)–C<), 150.4 (C_2, C_6 py), 157.6 (C_4), 164.2 (–NH=C(O)–C<), 171.3 (C_9).

HRMS (TOF MS CI+, M+H) Calcd for $C_{18}H_{20}N_3O_3$, 326.1505; found, 326.1503.

5.2.5.4. *N′*-Isonicotinoyl-*N*-2-[4-(2,2′,2″-trifluoroethoxy)phenyl] cyclopropanecarboxylhydrazide (6d). Compound **6d** was prepared using **5d** as starting material. White crystalline solid (0.35 g, 93%, mp.198–200 °C).

IR (KBr, ν_{max}) cm^{-1}: 3163, 3008, 2365, 1654, 1590, 1551, 1518, 1502, 1477, 1411, 1281, 1249, 1251, 1183, 1163, 1113, 1084, 1003, 974.

^{1}H NMR (300 MHz, C_6D_6: DMSO-d_6(5:1)) δ ppm: 0.99 (m, 1H, $>CH_2$), 1.69 (m, 1H, $>CH_2$), 2.31 (m, 1H, H_7), 2.60 (m, 1H, H_8), 3.76 (q, 2H, J = 4.8 Hz, $-OCH_2CF_3$), 6.53 (d, 2H, J = 9 Hz, H_3, H_5), 6.77 (d, 2H, J = 9 Hz, H_2, H_6), 7.81 (m, 2H, H_3, H_5 py), 8.52 (m, 2H, H_2, H_6 py), 10.73 (br s, 1H, >NH), 10.99 (br s, 1H, >NH).

^{13}C NMR (75 MHz, C_6D_6: DMSO-d_6(5:1)) δ ppm: 15.9 ($>CH_2$), 24.1 (C_8), 24.5 (C_7), 65.8 (q, J = 35.9 Hz, –O H_2CF_3), 115.1 (C_3, C_5), 122.0 (C_3, C_5 py), 127.6 (C_2, C_6), 135.2 (C_1), 140.2 (–NH=C(O)–C<), 150.6 (C_2, C_6 py), 156.1 (C_4), 164.3 (–NH=C(O)–C<), 171.3 (C_9).

^{19}F NMR (282 MHz, DMSO-d_6) δ ppm: −72.51 (t, J = 8.4 Hz, 3F).

HRMS (TOF MS CI+, M+H) Calcd for $C_{18}H_{17}F_3N_3O_3$, 380.1222; found, 380.1226.

5.2.5.5. *N′*-Isonicotinoyl-*N*-2-[4-(3-methylbut-2-enyloxy)phenyl]cyclopropanecarboxylhydrazide (6e). Compound **6e** was prepared using **5e** as starting material. White crystalline solid (0.32 g, 90%, mp.188–190 °C).

IR (KBr, ν_{max}) cm^{-1}: 3159, 3008, 2967, 2929, 2861, 1591, 1550, 1515, 1502, 1473, 1410, 1385, 1294, 1246, 1186, 1160, 1111, 1083, 1044, 1013, 941.

^{1}H NMR (300 MHz, C_6D_6: DMSO-d_6(5:1)) δ ppm: 1.00 (m, 1H, $>CH_2$), 1.38 (s, 3H, $H_{4'}$), 1.45 (s, 3H, $H_{5'}$), 1.54 (m, 1H, $>CH_2$), 2.20 (m, 1H, H_7), 2.49 (m, 1H, H_8), 4.25 (d, 2H, J = 6.6 Hz, $H_{1'}$), 5.32 (m, 1H, $H_{2'}$), 6.70 (d, 2H, J = 9 Hz, H_3, H_5), 6.87 (d, 2H, J = 9 Hz, H_2, H_6), 7.83 (m, 2H, H_3, H_5 py), 8.52 (m, 2H, H_2, H_6 py), 10.60 (br s, 1H, >NH), 10.98 (br s, 1H, >NH).

^{13}C NMR (75 MHz, C_6D_6: DMSO-d_6(5:1)) δ ppm: 15.6($>CH_2$), 17.8 ($C_{4'}$), 23.9 (C_8), 24.4 (C_7), 25.3 ($C_{5'}$), 64.6 ($-OCH_2-$), 114.7 (C_3, C_5), 120.4 (C_3, C_5 py), 121.8 ($C_{2'}$), 127.3 (C_2, C_6), 132.8 ($C_{3'}$), 136.6 (C_1), 140.1 (–NH=C(O)–C<), 150.4 (C_2, C_6 py), 157.6 (C_4), 164.2 (–NH=C(O)–C<),171.3 (C_9).

HRMS (TOF MS CI+, M+H) Calcd for $C_{21}H_{24}N_3O_3$, 366.1818; found, 366.1812.

5.2.5.6. *N′*-Isonicotinoyl-*N*-2-{4-[(*E*)-3,7-dimethylocta-2,6-dienyloxy]phenyl} cyclopropanecarboxylhydrazide (6f). Compound **6f** was prepared using **5f** as starting material. White crystalline solid (0.41 g, 95%, mp.186–188 °C).

IR (KBr, ν_{max}) cm^{-1}: 3166, 3019, 2968, 2920, 1591, 1551, 1515, 1474, 1410, 1389, 1293, 1246, 1186, 1160, 1110, 1083, 997.

^{1}H NMR (300 MHz, C_6D_6: DMSO-d_6(5:1)) δ ppm: 1.00 (m, 1H, $>CH_2$), 1.36 (s, 3H, $H_{9'}$), 1.42 (s, 3H, $H_{10'}$), 1.47 (s, 3H, $H_{4'}$), 1.48 (m, 1H, $>CH_2$), 1.92 (m, 4H, $H_{5'}$, $H_{6'}$), 2.18 (m, 1H, H_7), 2.48 (m, 1H, H_8), 4.28 (d, 2H, J = 6.6 Hz, $-OCH_2-$), 4.96 (m, 1H, $H_{7'}$), 5.36 (m, 1H, $H_{2'}$), 6.69 (d, 2H, J = 9 Hz, H_3, H_5), 6.87 (d, 2H, J = 9 Hz, H_2, H_6), 7.81 (m, 2H, H_3, H_5 py), 8.52 (m, 2H, H_2, H_6 py), 10.56 (br s, 1H, >NH), 10.95 (br s, 1H, >NH).

^{13}C NMR (75 MHz, C_6D_6: DMSO-d_6(5:1)) δ ppm: 15.8 ($>CH_2$), 16.5($C_{9'}$), 17.3 ($C_{4'}$), 24.1 (C_8), 24.6 (C_7), 25.7($C_{6'}$), 26.5 ($C_{5'}$), 39.5 ($C_{10'}$), 64.9 ($-OCH_2-$), 115.0 (C_3, C_5), 121.8 ($C_{2'}$), 122.0 (C-3, C-5 py),124.2 ($C_{7'}$), 127.51(C_2, C_6), 127.59 ($C_{8'}$),128.8 ($C_{3'}$), 133.0 (C_1), 140.1 (–NH=C(O)–C<), 150.6 (C-2, C-6 py), 157.9 (C_4), 164.4 (–NH=C(O)–C<), 171.5 (C_9).

HRMS (TOF MS CI+, M+H) Calcd for $C_{26}H_{32}N_3O_3$, 434.2444; found, 434.2449.

5.2.5.7. Preparation of 2-(4-alkoxyphenyl)-*N′*-(phthalazin-1-yl)cyclopropanecarbohydrazide (7a–f): general procedure. A clean dry round bottom flask (10 mL) with a magnetic stir bar was charged with carboxylic acid (**5a–f**, 1 mmol), 1-hydrazinophthalazine hydrochloride (0.294 g, 1.5 mmol, 1.5 equiv), HOBt (0.15 g, 1.1 mmol, 1.1 equiv) and EDC·HCl (0.21 g, 1.1 mmol, 1.1 equiv) under argon. Dry dichloromethane (5 mL) was added to it and stirred. Diisopropylethylamine (0.7 mL, 4 mmol, 4 equiv) was added to the reaction mixture and stirred at room temperature for 6 h. TLC was monitored in ethylacetate. Dichloromethane was removed under reduced pressure. Ethylacetate (60 mL) was added to the crude yellow mass and the solution was thoroughly washed with water (30 mL × 3). The organic layer was then dried over $MgSO_4$. Removal of the solvent gave a crude yellowish mass. It was the purified over silica gel (70–200 mesh) using 80% ethylacetate in Petroleum ether to afford **7a–f**.

5.2.5.8. 2-(4-Methoxyphenyl)-*N′*-(phthalazin-1-yl)cyclopropanecarbohydrazide (7a). Compound **7a** was prepared using **5a** as starting material. Yellow solid (0.22 g, 65%, mp.188–190 °C decomposes).

IR (KBr, ν_{max}) cm^{-1}: 3363, 3317, 3272, 3179, 3006, 2924, 2837, 2360, 1674, 1640, 1611, 1580, 1514, 1455, 1431, 1339, 1301, 1245, 1181, 1139, 1109, 1032, 946.

^{1}H NMR (300 MHz, C_6D_6: DMSO-d_6(5:1) + few drops of CF_3COOD) δ ppm: 1.31 (m, 1H, $>CH_2$), 1.38 (m, 1H, $>CH_2$), 1.94 (m, 1H, C_7), 2.68 (m, 1H, C_8), 3.64 (s, 3H, $-OCH_3$), 6.81 (d, 2H, J = 9 Hz, H_3, H_5), 7.06 (d, 2H, J = 9 Hz, H_2, H_6), 8.17 (m, 3H, H_3, H_4, H_5 phthalazine), 8.55 (m, 1H, H_6 phthalazine), 9.07 (s, 1H, H_8 phthalazine).

^{13}C NMR (75 MHz, C_6D_6: DMSO-d_6(5:1) + few drops of CF_3COOD) δ ppm: 16.3 ($-CH_2-$), 25.1 (C_8), 26.5 (C_7), 55.2 ($-OCH_3$), 114.2, 114.3 (C_3, C_5), 118.5 (C-phthalazine), 124.4 (CH-phthalazine), 127.5, 127.6 (C_2, C_6), 128.1 (C_1), 130.2 (CH-phthalazine), 132.5 (C-phthalazine), 135.5 (CH-phthalazine), 136.7 (CH-phthalazine), 145.9 (–N=CH–), 151.8 (C_4), 157.4 (–NH–C=N–), 172.5 (C_9).

HRMS (TOF MS CI+, M+H) Calcd for $C_{19}H_{17}N_4O$, 351.1508; found, 351.1508.

5.2.5.9. 2-(4-Trifluoromethoxyphenyl)-*N′*-(phthalazin-1-yl)cyclopropanecarbohydrazide (7b). Compound **7b** was prepared using **5b** as starting material. Yellow solid (0.26 g, 67%, mp.184–186 °C decomposes).

IR (KBr, ν_{max}) cm^{-1}: 3210, 3061, 2926, 1728, 1630, 1605, 1580, 1548, 1511, 1481, 1452, 1410, 1371, 1344, 1259, 1225, 1164, 1085, 1038, 1018.

^{1}H NMR (300 MHz, C_6D_6: DMSO-d_6(5:1) + few drops of CF_3COOD) δ ppm: 1.34 (m, 1H, $>CH_2$), 1.46 (m, 1H, $>CH_2$), 2.19 (m, 1H, H_7), 2.64 (m, 1H, H_8), 7.17 (m, 4H, H_2, H_3, H_5, H_6), 8.12 (m, 3H, H_3, H_4, H_5 phthalazine), 8.59 (m, 1H, H_6 phthalazine), 9.02 (s, 1H, H_8 phthalazine).

^{13}C NMR (75 MHz, C_6D_6: DMSO-d_6(5:1) + few drops of CF_3COOD) δ ppm: 16.6 ($-CH_2-$), 24.9 (C_8), 26.2 (C_7), 118.4 (C-phthalazine), 120.9 (C_3, C_5), 124.4 (CH-phthalazine), 128.2 (C_2,

C_6), 129.2 (CH-phthalazine), 135.0 (CH-phthalazine), 136.2 (C-phthalazine), 136.8 (CH-phthalazine), 140.3 (C_1), 146.0 (–N=CH–), 148.1 (C_4), 152.5 (–NH–C=N–), 172.1 (C_9).

^{19}F NMR (282 MHz, C_6D_6: DMSO-d_6(5:1) + few drops of CF_3COOD) δ ppm: −53.15 (s, 3F)

HRMS (TOF MS CI+, M+H) Calcd for $C_{19}H_{16}F_3N_4O_2$, 389.1225; found, 389.1245.

5.2.5.10. 2-(4-Ethoxyphenyl)-*N*′-(phthalazin-1-yl)cyclopropanecarbohydrazide (7c). Compound **7c** was prepared using **5c** as starting material. Yellow solid (0.21 g, 62%, mp.191–193 °C decomposes).

IR (KBr, ν_{max}) cm^{-1}: 3338, 3220, 2978, 1636, 1609, 1551, 1514, 1478, 1447, 1406, 1339, 1290, 1235, 1177, 1142, 1115, 1083, 1047.

^{1}H NMR (300 MHz, DMSO-d_6 + few drops of CF_3COOD) δ ppm: 1.22 (t, 3H, J = 6.9 Hz, –CH_3), 1.27 (m, 1H, >CH_2), 1.38 (m, 1H, >CH_2), 1.95 (m, 1H, H_7), 2.28 (m, 1H, H_8), 3.90 (q, 2H, J = 6.9 Hz, $H_{1'}$), 6.77 (d, 2H, J = 9 Hz, H_3, H_5), 7.03 (d, 2H, J = 9 Hz, H_2, H_6), 8.16 (m, 3H, H_3, H_4, H_5 phthalazine), 8.56 (d, 1H, J = 8.4 Hz, H_6 phthalazine), 9.05 (s, 1H, H_8 phthalazine).

^{13}C NMR (75 MHz, DMSO-d_6 + few drops of CF_3COOD) δ ppm: 14.2 (–OCH_2CH_3), 15.7 (–CH_2–), 23.8 (C_8), 24.6 (C_7), 62.8 ($C_{1'}$), 114.2 (C_3, C_5), 118.0 (C-phthalazine), 123.9 (CH-phthalazine), 127.0 (C_2, C_6), 127.6 (C-phthalazine), 128.6 (CH-phthalazine), 131.8 (C_1), 134.4 (CH-phthalazine), 136.2 (CH-phthalazine), 145.4 (–N=CH–), 152.0 (C_4), 157.1 (–NH–C=N–), 172.0 (C_9).

HRMS (TOF MS CI+, M+H) Calcd for $C_{20}H_{21}N_4O_2$, 349.1665; found, 349.1651.

5.2.5.11. 2-[4-(2,2′,2″-Trifluoroethoxy)phenyl]-*N*′-(phthalazin-1-yl)cyclopropanecarbohydrazide (7d). was prepared using **5d** as starting material. Yellow solid (0.29 g, 73%, mp.188–190 °C decomposes).

IR (KBr, ν_{max}) cm^{-1}: 3348, 3262, 2322, 1669, 1636, 1556, 1516, 1477, 1455, 1432, 1338, 1287, 1239, 1156, 1139, 1110, 1083, 976.

^{1}H NMR (300 MHz, C_6D_6: DMSO-d_6(5:1) + few drops of CF_3COOD) δ ppm: 1.40 (m, 1H, >CH_2), 1.65 (m, 1H, >CH_2), 2.28 (m, 1H, H_7), 2.62 (m, 1H, H_8), 4.60 (q, 2H, J = 8.1 Hz, –OCH_2CF_3), 6.93 (d, 2H, J = 9 Hz, H_3, H_5), 7.11 (d, 2H, J = 9 Hz, H_2, H_6), 8.17 (m, 3H, H_3, H_4, H_5 phthalazine), 8.55 (m, 1H, H_6 phthalazine), 9.07 (s, 1H, H_8 phthalazine).

^{13}C NMR (75 MHz, C_6D_6: DMSO-d_6(5:1) + few drops of CF_3COOD) δ ppm: 15.8 (–CH_2–), 23.9 (C_8), 24.5 (C_7), 64.5 (q, J = 37.5 Hz, –CH_2CF_3), 114.8 (C_3, C_5), 118.0 (C-phthalazine), 123.9 (CH-phthalazine), 127.2 (C_2, C_6), 127.6 (C-phthalazine), 128.7(CH-phthalazine), 133.9 (C_1),134.5 (CH phthalazine), 136.3 (CH phthalazine), 146.2 (–N=CH–), 155.64 (C_4), 158.9 (–NH–C=N–),171.9 (C_9).

^{19}F NMR (282 MHz, C_6D_6: DMSO-d_6(5:1) + few drops of CF_3COOD) δ ppm: −68.37 (t, J = 9.3 Hz, 3F)

HRMS (TOF MS CI+, M+H) Calcd for $C_{20}H_{18}F_3N_4O_2$, 403.1382; found, 403.1397.

5.2.5.12. 2-[4-(3-Methylbut-2-enyloxy)phenyl]-*N*′-(phthalazin-1-yl)cyclopropanecarbohydrazide (7e). Compound **7e** was prepared using **5e** as starting material. Yellow solid (0.26 g, 68%, mp.185–187 °C decomposes).

IR (KBr, ν_{max}) cm^{-1}: 3202, 3031, 2970, 2915, 1640, 1608, 1572, 1552, 1513, 1447, 1407, 1372, 1338, 1290, 1229, 1176, 1144, 1107, 1083, 1039, 1001, 908.

^{1}H NMR (300 MHz, C_6D_6: DMSO-d_6(5:1) + few drops of CF_3COOD) δ ppm: 1.28 (m, 1H, >CH_2), 1.39 (m, 1H, >CH_2), 1.56 (s, 3H, $H_{4'}$), 1.58 (s, 3H, $H_{5'}$), 2.30 (m, 1H, H_7), 2.68 (m, 1H, H_8), 4.38 (d, 2H, J = 6.6 Hz, $H_{1'}$), 5.29 (m, 1H, $H_{2'}$), 6.75 (d, 2H, J = 9 Hz, H_3, H_5), 7.01 (d, 2H, J = 9 Hz, H_2, H_6), 8.08 (m, 3H, H_3, H_4, H_5 phthalazine), 8.56 (m, 1H, H_6 phthalazine), 8.98 (s, 1H, H_8 phthalazine),

^{13}C NMR (75 MHz, DMSO-d_6 + few drops of CF_3COOD) δ ppm: 16.3 (>CH_2), 18.0 ($C_{4'}$), 24.4 (C_8), 25.1 (C_7), 25.5 ($C_{5'}$), 64.6 ($C_{1'}$), 115.1 (C_3, C_5), 118.6 (C-phthalazine), 120.5 ($C_{2'}$), 124.6 (HC-phthalazine), 127.5, 127.6 (C_2, C_6), 128.3 ($C_{3'}$), 130.1 (HC-phthalazine), 132.6 (C_1), 134.9 (HC-phthalazine), 135.5 (HC-phthalazine), 137.2 (C-phthalazine), 146.1 (C_8 phthalazine), 152.5 (C_4), 157.5 (HN=C–N), 172.6 (C_9).

HRMS (TOF MS CI+, M+H) Calcd for $C_{23}H_{25}N_4O_2$, 389.1978; found, 389.1986.

5.2.5.13. 2-{4-[(*E*)-3,7-Dimethylocta-2,6-dienyloxy]phenyl}-*N*′-(phthalazin-1-yl) cyclopropanecarbohydrazide (7f). Compound **7f** was prepared using **5f** as starting material. Yellow solid (0.36 g, 79%, mp.184–186 °C decomposes).

IR (KBr, ν_{max}) cm^{-1}: 3424, 3214, 3029, 2920, 1640, 1608, 1573, 1551, 1513, 1448, 1407, 1373, 1340, 1290, 1234, 1178, 1145, 1083, 1003, 908.

^{1}H NMR (300 MHz, C_6D_6: DMSO-d_6(5:1) + few drops of CF_3COOD) δ ppm: 1.28 (m, 1H, >CH_2), 1.40 (m, 1H, >CH_2), 1.45 (s, 3H, $H_{9'}$), 1.51 (s, 3H, $H_{10'}$), 1.58 (s, 3H, $H_{4'}$), 2.30 (m, 1H, H_7), 2.69 (m, 1H, H_8), 4.41 (d, 2H, J = 6.6 Hz, $H_{1'}$), 4.96 (m, 1H, $H_{7'}$), 5.30 (m, 1H, $H_{3'}$), 6.77 (d, 2H, J = 9 Hz, H_3, H_5), 7.03 (d, 2H, J = 9 Hz, H_2, H_6), 8.14 (m, 3H, H_3, H_4, H_5 phthalazine), 8.56 (m, 1H, H_6 phthalazine), 9.03 (s, 1H, H_8 phthalazine).

^{13}C NMR (125 MHz, C_6D_6: DMSO-d_6(5:1) + few drops of CF_3COOD) δ ppm: 15.6 ($C_{9'}$), 16.2 (–CH2–), 17.4 ($C_{4'}$), 25.1 (C_8), 25.4 (C_7), 26.14 (>CH_2), 26.17 (>CH_2), 39.6 ($C_{10'}$), 64.7 ($C_{1'}$), 115.09, 115.00 (C_3, C_5), 118.6 (C-phthalazine), 120.1 ($C_{2'}$), 124.0 ($C_{8'}$), 124.4 (CH-phthalazine), 124.6 ($C_{3'}$), 127.6, 127.4 (C-2, C-6), 128.1 (C-phthalazine), 130.0 (CH-phthalazine), 131.3 ($C_{7'}$) 132.4 (C_1), 134.8 (CH-phthalazine), 136.7 (CH-phthalazine), 145.8 (–N=CH–), 157.6 (C_4), 157.9 (–NH–C=N–),172.5 (C_9).

HRMS (TOF MS CI+, M+H) Calcd for $C_{28}H_{33}N_4O_2$, 457.2604; found, 457.2580.

5.2.6. Preparation of 3-(2-(4-alkoxyphenyl)cyclopropyl)-[1, 2, 4]triazolo[3, 4-α]phthalazine (8a–f): General Procedure

A clean dry round bottom flask (10 mL) with a magnetic stir bar was charged with carboxylic acid (**5a–f**, 1 mmol, 1 equiv), 1-hydrazinophthalazine hydrochloride (0.294 g, 1.5 mmol, 1.5 equiv), HOBt (0.15 g, 1.1 mmol, 1.1 equiv) and EDC·HCl (0.21 g, 1.1 mmol, 1.1 equiv) under argon. Dry acetonitrile (5 mL) was added to it and stirred. Diisopropylethylamine (0.7 mL, 4 mmol, 4 equiv) was added to the reaction mixture and refluxed for 48 h. TLC was monitored in ethylacetate. Acetonitrile was removed under reduced pressure. Ethylacetate (60 mL) was added to the crude yellow mass and the solution was thoroughly washed with water (30 mL × 3). The organic layer was then dried over $MgSO_4$. Removal of the solvent gave a crude yellowish mass. It was then purified over silica gel (70–200 mesh) using 80% ethylacetate in Petroleum ether to afford **8a–f**.

5.2.6.1. 3-[2-(4-Methoxyphenyl)cyclopropyl]-[1, 2, 4]triazolo[3, 4-α]phthalazine (8a). Compound **8a** was prepared using **5a** as starting material. White crystalline solid (0.23 g, 74%, mp.187–189 °C).

IR (KBr, ν_{max}) cm^{-1}: 3435, 3056, 3016, 3002, 2949, 2832, 1898, 1610, 1579, 1513, 1456, 1440, 1354, 1302, 1281, 1249, 1180, 1141, 1118, 1034, 993, 977.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.57 (m, 1H, >CH_2), 1.98 (m, 1H, >CH_2), 2.65 (m, 1H, H_7), 2.77 (m, 1H, H_8), 3.74 (s, 3H, –OCH_3), 6.82 (d, 2H, J = 9 Hz, H_3, H_5), 7.13 (d, 2H, J = 9 Hz, H_2, H_6), 7.73 (m, 1H, H_3 phthalazine), 7.85 (m, 2H, H_4, H_5 phthalazine), 8.53 (s, 1H, H_6 phthalazine), 8.59 (m, 1H, H_8 phthalazine).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 15.9 (C_8), 16.6 (>CH_2), 26.0 (C_7), 55.3 (–OCH_3), 113.9 (C_3, C_5), 123.2 (C-phthalazine), 123.7

(HC-phthalazine), 127.4 (C_2, C_6), 128.0 (HC-phthalazine), 131.0 (HC-phthalazine), 132.5 (C_1), 134.1 (HC-phthalazine), 142.2 (C-phthalazine), 147.6 (C_8 phthalazine), 152.2 (N=C–N), 158.3 (C_4), 164.5 (N=C–N).

HRMS (TOF MS Cl+, M+H) Calcd for $C_{19}H_{17}N_4O$, 317.1402; found, 317.1404.

5.2.6.2. 3-[2-(4-Trifluoromethoxyphenyl)cyclopropyl]-[1, 2, 4] triazolo[3, 4-α]phthalazine (8b). Compound **8b** was prepared using **5b** as starting material. White crystalline solid (0.30 g, 81%, mp.191–193 °C).

IR (KBr, ν_{max}) cm^{-1}: 3431, 3059, 1904, 1630, 1591, 1561, 1531, 1511, 1458, 1420, 1353, 1289, 1204, 1166, 1115, 1079, 1054, 1018, 993, 976.

^1H NMR (300 MHz, $CDCl_3$) δ ppm: 1.59 (m, 1H, $>CH_2$), 2.04 (m, 1H, $>CH_2$), 2.73 (m, 1H, H_7), 2.84 (m, 1H, H_8), 7.11 (d, 2H, J = 9 Hz, H_3, H_5), 7.21 (d, 2H, J = 9 Hz, H_2, H_6), 7.74 (m, 1H, H_3 phthalazine), 7.87 (m, 2H, H_4, H_5 phthalazine), 8.55 (s, 1H, H_6 phthalazine), 8.62 (m, 1H, H_8 phthalazine),

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 16.3 (C_8), 17.0 ($>CH_2$), 25.8 (C_7), 121.1 (C_3, C_5), 123.1(C-phthalazine), 123.4 (HC-phthalazine), 127.6 (C_2, C_6), 128.1 (HC-phthalazine), 130.9 (HC-phthalazine), 130.9 (C_1), 134.1 (HC-phthalazine), 139.4 (C-phthalazine), 147.4 (C_4), 147.6 (C_8 phthalazine), 152.2 (N=C–N), 164.5 (N=C–N).

^{19}F NMR (282 MHz, $CDCl_3$) δ ppm: −57.90 (s, 3F)

HRMS (TOF MS Cl+, M+H) Calcd for $C_{19}H_{14}F_3N_4O$, 371.1110; found, 371.1110

5.2.6.3. 3-[2-(4-Ethoxyphenyl)cyclopropyl]-[1, 2, 4]triazolo[3, 4-α]phthalazine (8c). Compound **8c** was prepared using **5c** as starting material. White crystalline solid (0.29 g, 90%, mp.187–189 °C).

IR (KBr, ν_{max}) cm^{-1}: 3441, 3059, 3017, 2976, 2926, 1897, 1628, 1610, 1580, 1514, 1478, 1456, 1416, 1395, 1353, 1300, 1281, 1247, 1181, 1141, 1114, 1047, 992, 977.

^1H NMR (300 MHz, $CDCl_3$) δ ppm: 1.34 (t, 3H, J = 6.9 Hz, –CH_3), 1.54 (m, 1H, $>CH_2$), 1.97 (m, 1H, $>CH_2$), 2.65 (m, 1H, H_7), 2.68 (m, 1H, H_8), 3.96 (q, 2H, J = 6.9 Hz, –OCH_2–), 6.79 (d, 2H, J = 9 Hz, H_3, H_5), 7.12 (d, 2H, J = 9 Hz, H_2, H_6), 7.73 (m, 1H, H_3 phthalazine), 7.86 (m, 2H, H_4, H_5 phthalazine), 8.52 (s, 1H, H_6 phthalazine), 8.60 (m, 1H, H_8 phthalazine).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 14.9 (–CH_3), 16.4 (C_8), 16.6 ($>CH_2$), 25.9 (C_7), 63.4 ($C_{1'}$), 114.5 (C_3, C_5), 123.3 (C-phthalazine), 123.7 (HC-phthalazine), 127.6 (C_2, C_6), 128.0 (HC-phthalazine), 130.6 (HC-phthalazine), 132.6 (C_1), 133.9 (HC-phthalazine),142.8 (C-phthalazine), 147.4 (C_8 phthalazine), 152.1 (N=C–N), 157.8 (C_4), 164.1 (N=C–N).

HRMS (TOF MS Cl+, M+H) Calcd for $C_{20}H_{19}N_4O$, 331.1559; found, 331.1554.

5.2.6.4. 3-{2-[4-(2,2′,2′′-Trifluoroethoxy)phenyl]cyclopropyl}-[1, 2, 4]triazolo[3, 4-α]phthalazine (8d). Compound **8d** was prepared using **5d** as starting material. White crystalline solid (0.32 g, 83%, mp.177–179 °C).

IR (KBr, ν_{max}) cm^{-1}: 3427, 3059, 3016, 2953, 1906, 1628, 1610, 1532, 1514, 1475, 1459, 1421, 1353, 1299, 1245, 1178, 1157, 1119, 1079, 1056, 994, 977.

^1H NMR (300 MHz, $CDCl_3$) δ ppm: 1.55 (m, 1H, $>CH_2$), 1.99 (m, 1H, $>CH_2$), 2.67 (m, 1H, H_7), 2.80 (m, 1H, H_8), 4.28 (q, 2H, J = 8.1 Hz, $H_{1'}$), 6.84 (d, 2H, J = 9 Hz, H_3, H_5), 7.15 (d, 2H, J = 9 Hz, H_2, H_6), 7.72 (m, 1H, H_3 phthalazine),7.86 (m, 2H, H_4, H_5 phthalazine), 8.53 (s, 1H, H_6 phthalazine), 8.58 (m, 1H, H_8 phthalazine).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 16.1 (C_8), 16.6 ($>CH_2$), 25.6 (C_7), 65.8 (q, J = 37.5 Hz, –OCH_2–), 115.1 (C_3, C_5), 123.1 (C-phthalazine), 123.2 (HC-phthalazine), 123.6 (q, J = 278.0 Hz, –CF3), 127.7 (C_2, C_6), 128.0 (HC-phthalazine), 130.6 (HC-phthalazine), 133.9 (HC-phthalazine), 134.9 (C_1), 147.4 (C_8 phthalazine),151.8 (C-phthalazine),156.1 (N=C–N), 158.4 (C_4),169.5 (N=C–N).

^{19}F NMR (282 MHz, $CDCl_3$) δ ppm: −73.94 (t, J = 7.9 Hz, 3F).

HRMS (TOF MS Cl+, M+H) Calcd for $C_{20}H_{16}F_3N_4O$, 385.1276; found, 385.1258.

5.2.6.5. 3-{2-[4-(3-Methylbut-2-enyloxy)phenyl]cyclopropyl}-[1, 2, 4]triazolo[3, 4-α]phthalazine (8e). Compound **8e** was prepared using **5e** as starting material. White crystalline solid (0.24 g, 65%, mp.187–189 °C).

IR (KBr, ν_{max}) cm^{-1}: 3427, 3057, 3018, 2965, 2923, 2870, 1979, 1899, 1728, 1677, 1630, 1611, 1578, 1512, 1471, 1456, 1415, 1382, 1354, 1300, 1279, 1241, 1178, 1141, 1118, 1080, 1052, 1003, 992, 975.

^1H NMR (300 MHz, $CDCl_3$) δ ppm: 1.57 (m, 1H, $>CH_2$), 1.68 (s, 3H, $H_{4'}$), 1.74 (s, 3H, $H_{5'}$), 2.00 (m, 1H, $>CH_2$), 2.68 (m, 1H, H_7), 2.78 (m, 1H, H_8), 4.44 (d, 2H, J = 6.6 Hz, $H_{1'}$), 5.44 (m, 1H, $H_{2'}$), 6.83 (d, 2H, J = 9 Hz, H_3, H_5), 7.12 (d, 2H, J = 9 Hz, H_2, H_6), 7.77 (m, 1H, H_3 phthalazine), 7.88 (m, 2H, H_4, H_5 phthalazine), 8.56 (s, 1H, H_6 phthalazine), 8.65 (m, 1H, H_8 phthalazine).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 15.9 ($C_{4'}$), 16.5 ($>CH_2$), 18.2 (C_8), 25.85 (C_7), 25.87 ($C_{5'}$), 64.8 ($C_{1'}$), 114.7 (C_3, C_5), 119.7 ($C_{2'}$), 123.10 (HC-phthalazine), 123.18 (C-phthalazine), 123.7 ($C_{3'}$), 127.4 (C_2, C_6),130.5 (HC-phthalazine), 132.7 (C_1), 133.8 (HC-phthalazine), 138.1 (C-phthalazine), 142.7 (N=C–N), 147.2 (C_8 phthalazine),152.1 (C_4), 157.5 (N=C–N).

HRMS (TOF MS Cl+, M+H) Calcd for $C_{23}H_{23}N_4O$, 371.1872; found, 371.1869.

5.2.6.6. 3-{2-(4-[(*E*)-3,7-Dimethylocta-2,6-dienyloxy]phenyl) cyclopropyl}-[1, 2, 4]triazolo[3, 4-α]phthalazine (8f). Compound **8f** was prepared using **5f** as starting material. White crystalline solid (0.33 g, 75%, mp.187–189 °C).

IR (KBr, ν_{max}) cm^{-1}: 3436, 3057, 3018, 3003, 2964, 2917, 2854, 2359, 1979, 1729, 1673, 1629, 1611, 1579, 1514, 1456, 1416, 1379, 1354, 1301, 1279, 1265, 1246, 1179, 1141, 1119, 1052, 1002, 992, 975.

^1H NMR (300 MHz, $CDCl_3$) δ ppm: 1.63 (s, 3H, $H_{9'}$), 1.65 (m, 1H, $>CH_2$), 1.69 (s, 3H, $H_{10'}$), 1.75 (s, 3H, $H_{4'}$), 2.05 (m, 1H, $>CH_2$), 2.12 (m, 4H, $H_{5'}$, $H_{6'}$), 2.75 (m, 1H, H_7), 2.85 (m, 1H, H_8), 4.55 (d, 2H, J = 6.6 Hz, $H_{1'}$), 5.11 (m, 1H, $H_{7'}$), 5.50 (m, 1H, $H_{2'}$), 6.90 (d, 2H, J = 9 Hz, H_3, H_5), 7.19 (d, 2H, J = 9 Hz, H_2, H_6), 7.80 (m, 1H, H_3 phthalazine), 7.95 (m, 2H, H_4, H_5 phthalazine), 8.61 (s, 1H, H_6 phthalazine), 8.68 (m, 1H, H_8 phthalazine).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 15.9 ($C_{9'}$), 16.61 ($>CH_2$), 16.67 ($C_{4'}$), 17.71($C_{6'}$), 25.7 ($C_{8'}$), 25.9 ($C_{7'}$), 26.3 ($C_{5'}$), 39.5 ($C_{10'}$), 64.9 ($C_{1'}$), 114.7 (C_3, C_5), 119.5 ($C_{7'}$), 123.1 (C-phthalazine), 123.2 ($C_{2'}$), 123.7 (HC-phthalazine), 123.8 ($C_{8'}$), 127.4 (C_2, C_6), 128.0 (HC-phthalazine), 130.6 (HC-phthalazine), 131.8 ($C_{3'}$), 132.6 (C_1), 133.9 (HC-phthalazine), 142.1 (C-phthalazine), 142.6 (N=C–N), 147.2 (C_8 phthalazine), 152.1 (C_4), 157.5 (N=C–N).

HRMS (TOF MS Cl+, M+H) Calcd for $C_{28}H_{31}N_4O$, 439.2498; found, 439.2503.

5.2.7. X-ray data

Crystal data for (**8e**): $C_{23}H_{22}N_4O$, M = 370.45, monoclinic, *Pc*, a = 19.0593(6) Å, b = 7.6970(3) Å, c = 6.6124(2) Å, β = 94.911(2)°, V = 966.47(6) Å^3, Z = 2, T = 193(2) K. 13083 reflections (3839 independent, R_{int} = 0.0389) were collected at low temperatures using an oil-coated shock-cooled crystal on a Bruker-AXS SMART APEX II diffractometer with MoKα radiation (λ = 0.71073 Å). The structure was solved by direct methods (SHELXS-97, G. M. Sheldrick, *Acta Crystallogr.* **1990**, *A46*, 467–473) and all non-hydrogen atoms were refined anisotropically using the full-matrix least-squares method on F^2 (SHELXL-97, Program for Crystal Structure Refinement, G. M. Sheldrick, University of Göttingen, 1997). Largest electron density

residue: 0.350 e Å^{-3}, R_1 (for $I > 2\sigma(I)$) = 0.0544 and wR_2 = 0.1445 (all data) with $R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$ and $wR_2 = (\Sigma w\ (F_o^2 - F_c^2)^2/\Sigma w(F_o^2)^2)^{0.5}$. CCDC 755182 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

Acknowledgements

We thank the European Community. Thanks are also due to the CNRS (France), 'Université Paul Sabatier' (Toulouse, France), ITAV (Toulouse, France) and Fonds Yvonne Boël (Brussels, Belgium) for financial support. R.K. is a director of research with the FNRS (Belgium).

References and notes

1. (a) Yokoyama, W. H. *Trends Food Sci. Technol.* **2004**, *15*, 528–531; (b) Ho, C. T. Phenolic Compounds in Food: An Overview. In *Phenolic Compounds in Food and their Effects on Health: Vol. II Antioxydants and Cancer Prevention*; Huang, M. T.; Ho, C. T.; Lee, C. Y., Eds.; ACS Symposium Series; Washington, 1992, pp 2–7.; (c) Lamoral-Theys, D.; Pottier, L.; Dufrasne, F.; Nève, J.; Dubois, J.; Kornienko, A.; Kiss, R.; Ingrassia, L. *Curr. Med. Chem.* **2010**, *17*, 812.
2. (a) Boerjan, W.; Ralph, J.; Baucher, M. *Annu. Rev. Plant Biol.* **2003**, *54*, 519; (b) Humphreys, J. M.; Chapple, C. *Curr. Opin. Plant Biol.* **2002**, *5*, 224.
3. (a) Wardrop, A. B. In *Lignins: Occurence Formation Structure and Reactions*; Sarkanen, K. V., Ludwig, C. H., Eds.; Wiley Interscience: New-York, 1971; pp 43–94; (b) Whetten, R. W.; Mackay, J. J.; Sederoff, R. R. *Ann. Rev. Plant Physiol. Plant Mol. Biol.* **1998**, *49*, 585.
4. Freudenberg, K. *Nature* **1959**, *183*, 1152.
5. (a) Yang, C. S.; Landau, J. M.; Huang, M.-T.; Newmark, H. L. *Annu. Rev. Nutr.* **2001**, *21*, 381; (b) Surh, Y.-J. *Mutat. Res./Fundam. Mol. Mech. Mutagen.* **1999**, *428*, 305; (c) Davies, K. J. A. *Int. Union Biochem. Mol. Biol.* **2000**, *50*, 279; (d) Armesto, N.; Ferrero, M.; Fernandez, S.; Gotor, V. *J. Org. Chem.* **2003**, *68*, 5784.
6. (a) Epifano, F.; Curini, M.; Genovese, S.; Blaskovich, M.; Hamilton, A.; Sebti, S. M. *Bioorg. Med. Chem.* **2007**, *17*, 2639. and references cited therein; (b) Prager, R. H.; Thregold, H. M. *Aust. J. Chem.* **1966**, *19*, 451.
7. Dawson, M. I.; Xia, Z.; Liu, G.; Fontana, J. A.; Farhana, L.; Patel, B. B.; Arumugarajah, S.; Bhuiyan, M.; Zhang, X.-K.; Han, Y.-H.; Stallcup, W. B.; Fukushi, J.-I.; Mustelin, T.; Tautz, L.; Su, Y.; Harris, D. L.; Waleh, N.; Hobbs, P. D.; Jong, L.; Chao, W.-R.; Schiff, L. J.; Sani, B. P. *J. Med. Chem.* **2007**, *50*, 2622.
8. Pardin, C.; Pelletier, J. N.; Lubelle, W. D.; Keillor, J. W. *J. Org. Chem.* **2008**, *73*, 5766.
9. Qian, K.; Wang, L.; Cywin, C. L.; Farmer, B. T.; Hickey, E.; Homon, C.; Jakes, S.; Kashem, M. A.; Lee, G.; Leonard, S.; Li, J.; Magboo, R.; Mao, W.; Pack, E.; Peng, C.; Prokopowicz, A.; Welzel, M.; Wolak, J.; Morwick, T. *J. Med. Chem.* **2009**, *52*, 1814.
10. Mitsch, A.; Wißner, P.; Böhm, M.; Silber, K.; Klebe, G.; Sattler, I.; Schlitzer, M. *Arch. Pharm. Pharm. Med. Chem.* **2004**, *337*, 493.
11. Do, Q.; Tian, W.; Yougnia, R.; Gaslonde, T.; Pfeiffer, B.; Pierré, A.; Léonce, S.; Kraus-Berthier, L.; David-Cordonnier, M.-H.; Depauw, S.; Lansiaux, A.; Mazinghien, R.; Koch, M.; Tillequin, F.; Michel, S.; Dufat, H. *Bioorg. Med. Chem.* **2009**, *17*, 1918.
12. Moody, C.; Norton, C.; Slawin, A.; Taylor, S. *Anticancer Drug Des.* **1998**, *13*, 611.
13. Percec, V.; Peterca, M.; Sienkowska, M. J.; Ilies, M. A.; Aquad, E.; Smidrkal, J.; Heiney, P. A. *J. Am. Chem. Soc.* **2006**, *128*, 3324.
14. Andrus, M. B.; Song, C.; Zang, J. *Org. Lett.* **2002**, *4*, 2079.
15. Charette, A. B.; Molinaro, C.; Brochu, C. *J. Am. Chem. Soc.* **2001**, *123*, 12168.
16. Concellón, J. M.; Rodríguez-Solla, H.; Simal, C. *Org. Lett.* **2007**, *9*, 2685.
17. Tsai, C.-C.; Hsieh, I.-H.; Cheng, T.-T.; Tsai, P.-K.; Lin, K.-W.; Yan, T.-H. *Org. Lett.* **2006**, *8*, 2261.
18. Corey, E. J.; Chaykovosky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353.
19. (a) Akbarzadeh, T.; Tabatabai, S. A.; Khoshnoud, M. J.; Shafaghi, B.; Shafiee, A. *Bioorg. Med. Chem.* **2003**, *11*, 769; (b) Borioni, A.; Mustazza, C.; Sestili, I.; Sbraccia, M.; Turchetto, L.; Giudice, M. R. D. *Arch. Pharm. Chem. Life Sci.* **2007**, *340*, 17; (c) Francis, J. E.; Cash, W. D.; Barbaz, B. S.; Bernard, P. S.; Lovell, R. A.; Mazzenga, G. C.; Friedmann, R. C.; Hyun, J. L.; Braunwalder, A. F.; Loo, P. S.; Bennette, D. A. *J. Med. Chem.* **1991**, *34*, 281; (d) Zimmer, H.; Kokosa, J. M.; Shah, K. J. *J. Org. Chem.* **1975**, *40*, 2901.
20. (a) Van Quaquebeke, E.; Simon, G.; Andre, A.; Dewelle, J.; Yazidi, M. E.; Bruyneel, F.; Tuti, J.; Nacoulma, O.; Guissou, P.; Decaestecker, C.; Braekman, J. C.; Kiss, R.; Darro, F. *J. Med. Chem.* **2005**, *48*, 849; (b) Ingrassia, L.; Lefranc, F.; Dewelle, J.; Pottier, L.; Mathieu, V.; Spiegl-Kreinecker, S.; Sauvage, S.; El Yazidi, M.; Dehoux, M.; Berger, W.; Van Quaquebeke, E.; Kiss, R. *J. Med. Chem.* **2009**, *52*, 1100; (c) Lamoral-Theys, D.; Andolfi, A.; Van Goietsenoven, G.; Cimmino, A.; Le Calvé, B.; Wauthoz, N.; Mégalizzi, V.; Gras, T.; Bruyère, C.; Dubois, J.; Mathieu, V.; Kornienko, A.; Kiss, R.; Evidente, A. *J. Med. Chem.* **2009**, *52*, 6244.
21. (a) Lefranc, F.; Mijatovic, T.; Kondo, Y.; Sauvage, S.; Roland, I.; Debeir, O.; Krstic, D.; Vasic, V.; Gailly, P.; Kondo, S.; Blanco, G.; Kiss, R. *Neurosurgery* **2008**, *62*, 211; (b) Mijatovic, T.; Mathieu, V.; Gaussin, J. F.; De Neve, N.; Ribaucour, F.; Van Quaquebeke, E.; Dumont, P.; Darro, F.; Kiss, R. *Neoplasia* **2006**, *8*, 402; (c) Mathieu, V.; Pirker, C.; Martin de Lassalle E.; Vernier, M.; Mijatovic, T.; De Nève, N.; Gaussin, J.F.; Dehoux, M.; Lefranc, F.; Berger, W.; Kiss, R., *J. Cell. Mol. Med.* **2009**, *13*, 3960; (d) Bruyère, C.; Mijatovic, T.; De Nève, N.; Gaussin, J.F.; Gras, T.; Nindfa, P.; Dehoux, M.; Saussez, S.; Kiss, R. In *Proceedings of the 100th Annual Meeting of the American Association for Cancer Research*. *Abstract nr 4135*. Denver, Philadelphia, April 18–22, 2009.; (e) Dumont, P.; Ingrassia, L.; Rouzeau, S.; Ribaucour, F.; Thomas, S.; Roland, I.; Darro, F.; Lefranc, F.; Kiss, R. *Neoplasia* **2007**, *9*, 766.
22. (a) Rodríguez-Ciria, M.; Sanz, A. M.; Yunta, M. J. R.; Gomez-Conteras, F.; Navarro, P.; Fernandez, I.; Pardo, M.; Cano, C. *Bioorg. Med. Chem.* **2003**, *11*, 2143; (b) Rhee, H.-K.; Park, H. J.; Lee, S. K.; Lee, C.-O.; Park, C. H.-K. *Abstract of Papers*, 232nd ACS National Meeting, San Francisco, CA, USA, September 10–14, 2006.; (c) Gandolfi, C. A.; Beggiolin, G.; Menta, E.; Palumbo, M.; Sissi, C.; Spinelli, S.; Johnson, F. *J. Med. Chem.* **1995**, *38*, 526.
23. Ozalp-Yaman, S.; de Hoog, P.; Amadei, G.; Pitié, M.; Gamez, P.; Dewelle, J.; Mijatovic, T.; Meunier, B.; Kiss, R.; Reedijk, J. *Chem. Eur. J.* **2008**, *14*, 3418.
24. (a) De Hauwer, C.; Camby, I.; Darro, F.; Migeotte, I.; Decaestecker, C.; Verbeek, C.; Danguy, A.; Pasteels, J. L.; Brotchi, J.; Salmon, I.; Van Ham, P.; Kiss, R. *J. Neurobiol.* **1998**, *37*, 373; (b) Debeir, O.; Van Ham, P.; Kiss, R.; Decaestecker, C. *IEEE Trans. Med. Imaging* **2005**, *24*, 697.
25. Debeir, O.; Mégalizzi, V.; Warzée, N.; Kiss, R.; Decaestecker, C. *Exp. Cell. Res.* **2008**, *314*, 2985.