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O-Alkylation of Bioactive Phthalimide Derivatives Under Microwave Irradiation in Dry Media

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O-ALKYLATION OF BIOACTIVE PHTHALIMIDE DERIVATIVES UNDER MICROWAVE IRRADIATION IN DRY MEDIA♦

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Abstract: In this paper we describe the synthesis of a new series of substituted 2-(4-alkoxy or 4-acyloxyphenethyl)-phthalimide derivatives (4-11), in good yields (58-87%), exploring the remarkable fast *O*-alkylation or *O*-acylation of 2-(4-hydroxyphenethyl)-phthalimide (3) in dry media under microwave irradiation.

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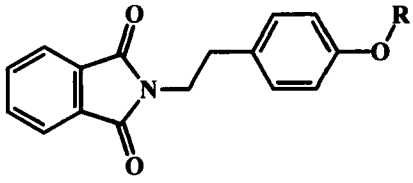
♦ This paper is contribution # 44 from LASSBio, UFRJ.

The interest in the employment of the microwave (MW) irradiation in organic synthesis has been growing in the last years.[1-3] The use of these nonconventional reaction conditions presents as common features: a short reaction time, reduction of the usual thermal degradation, and better selectivity.[4-7]

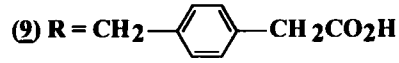
Microwave reactions involves selective absorption of MW energy by polar molecules, while non polar molecules seems to be inert to MW dieletric loss[8]. The initial experiments with MW techniques centered around the use of high dieletric solvents such as dimethylsulfoxide (DMSO) and *N,N*-dimethylformamide (DMF).[9,10] The rate enhancements in such reactions are now believed to be due to rapid superheating of the polar solvents.[8] However, the employment of these solution-phase reactions is limited by the need of the use of high pressures, specialized Teflon® vessels and sealed containers.[9] For this reason, during recent years, a new practical dimension has been added to the microwave heating protocols by accomplishing reactions on solid supports under solvent-free conditions. Reactions under dry conditions (*i.e.*, in the absence of solvent, on a solid support with or without catalysts) were originally developed in the late 1980's.[9] Synthesis without solvents under microwave irradiation offers several advantages, as the possibility to employ open vessels, avoinding the risk of explosion by the use high pressures and increasing the potential of such reactions to upscale.[8]

In an attempt to identify new bioactive compounds, we report in this paper the synthesis of a series of substituted 2-(4-alkoxy or 4-acyloxyphenethyl)-

phthalimide derivatives (4-11) (Chart 1), exploring the microwave irradiation, in dry media.



(4) R = CH_2COOEt
(5) R = $CH(CH_3)COOMe$
(6) R = $(CH_2)_3CN$
(7) R = $(CH_2)_4COOEt$
(8) R = $CO(CH_2)_3CO_2H$



(10) R = $CH_2CH{=}CH_2$

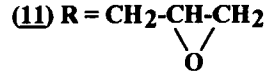


CHART 1

Results and Discussion

The new targets 2-(4-alkoxy or 4-acyloxyphenethyl)-phthalimide derivatives (4-11) were synthesized by using the route illustrated in Scheme 1. Our synthetic approach to these new compounds identify the 2-(4-hydroxyphenethyl)-phthalimide (3) as the key intermediate. This compound was obtained in 84% of yield, exploring the chemoselective condensation of phthalic anhydride (1) with tyramine (2) under reflux in acetic acid.

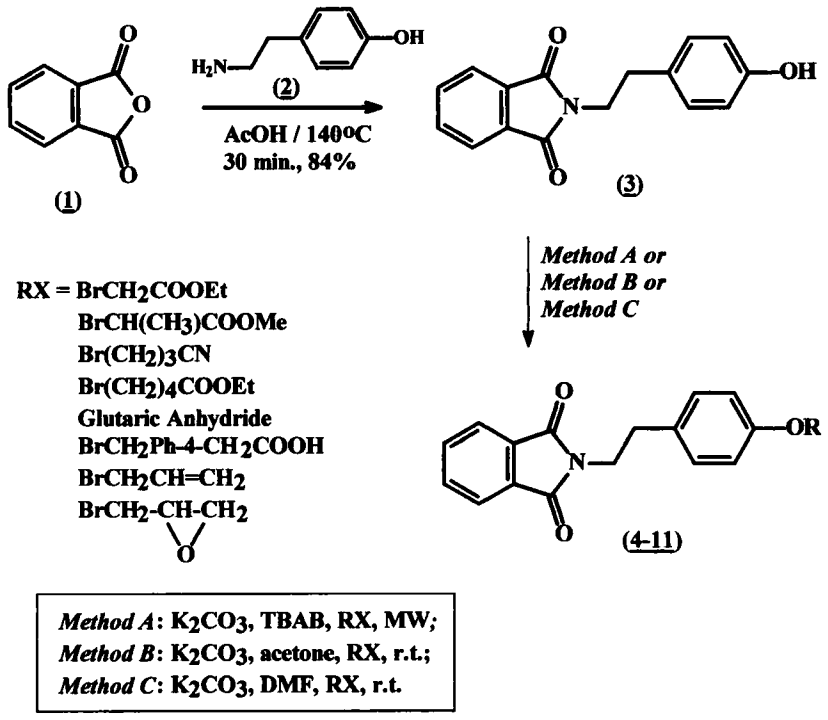
With (3) in hand, the next step was carried out by simply mixing of the phenol intermediate (3) with an excess of 25% of the alkyl halide and catalytic amount of tetrabutylammonium bromide (TBAB), in an open Erlenmeyer flask. These mixtures were adsorbed on potassium carbonate (12 equiv.) and irradiated

in a domestic microwave oven (900 MHz) for a time ranging between 3-20 min, when tlc indicated the end of the reactions (Method A). These results are summarized in Table 1.

Simultaneously, the intermediate (3) was submitted to the classical method of phenol alkylation (Method B),[11] with potassium carbonate in acetone at room temperature, using appropriate alkyl halides. The results, compared with those found using microwave irradiation, are described in Table 1.

Considering that solvent effects could play an important role in the mechanisms of organic reactions,[12,13] we investigate the change of acetone (Method B) as solvent to the dipolar aprotic *N,N*-dimethylformamide (Method C). In fact, the results obtained by this method (see Table 1), demonstrated a considerable reduction in the reaction time, in agreement with the predictions based on the solvation rule.[13] However, the comparison of methods A and B/C clearly indicated that the reaction carried out under MW irradition in dry media is at least 50 fold faster than those carried out under classical conditions, indicating the great advantage of this process in the synthesis of bioactive compounds.

In conclusion, we have disclosed in this paper a very simple, clean, economical, and remarkable fast method for the *O*-alkylation or *O*-acylation of 2-(4-hydroxyphenethyl)-phthalimide (3), using a household microwave oven as the irradiation source. Moreover, this new procedure represents an attractive synthetic alternative to classical conditions of *O*-alkylation.

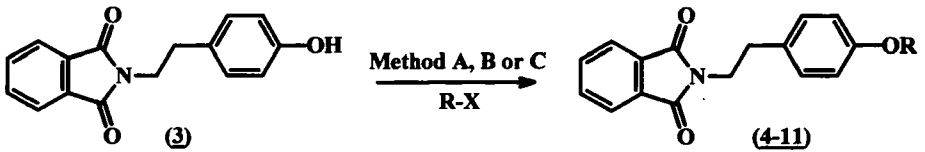


SCHEME 1

Experimental

Melting points were determined with a Quimis 340 apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were determined in deuterated solvents containing *ca.* 1% tetramethylsilane as an internal standard with Brucker AC 200 spectrometer. Splitting patterns were as follows: s, singlet; d, doublet; dd, double doublet; t, triplet; q, quartet; qt, quintet; m, multiplet; br, broad. Microanalysis data was obtained with Perkin Elmer 240 analyzer, using Perkin Elmer AD-4 balance.

TABLE 1: Synthesis of new phthalimides derivatives (4-11) employing different methods of *O*-alkylation or *O*-acylation of the phenol intermediate (3).



Alkyl halides (RX)	Method A[a]		Method B[b]		Method C[c]		Product	R	mp (°C)
	t (min)	Yield (%)	t (h)	Yield (%)	t (h)	Yield (%)			
Ethyl 2-bromoacetate	7	87	24	81	2.5	90	4	CH_2CO_2Et	105-107
Methyl 2-bromo-propionate	3	85	48	61	5	68	5	$CH(CH_3)CO_2Me$	86-88
4-Bromobutyronitrile	3	70	16	75	5	83	6	$(CH_2)_3CN$	122-124
Ethyl 5-bromovalerate	10	78	72	64	4	55	7	$(CH_2)_4CO_2Et$	80-82
Glutaric anhydride	15	61	72	67	20	63	8	$CO(CH_2)_3CO_2H$	140-142
4-Bromomethyl-phenylacetic acid	20	58	---[d]	---[d]	48	86	9	CH_2Ph-4-CH_2CO_2H	200-202
Allyl bromide	7	70	18	92	4	66	10	$CH_2CH{=}CH_2$	130-132
Epibromohydrin	7	74	---[d]	---[d]	5	85	11	$CH_2CH(O)CH_2$	125-127

[a] K_2CO_3, TBAB, MW irradiation (900MHz); [b] K_2CO_3, acetone, rt; [c] K_2CO_3, DMF, rt; [d] Only starting material was identified after 72h.

The progress of all reactions was monitored by tlc which was performed on 2.0 cm X 5.0 cm aluminum sheets precoated with silica gel 60 (HF-254, Merck) to a thickness of 0.25 mm. The developed chromatograms were visualized under ultraviolet light (254-265 nm). For column chromatography Merck silica gel (70-230 mesh) was used. Solvents used in reactions were dried, redistillated prior to use and stored over 3-4 A molecular sieves.

2-(4-Hydroxyphenethyl)-1,3-isoindolinedione (3)[16]

A solution of 0.5 g (3.61 mmol) of tyramine (2) and 0.5 g (3.38 mmol) of phthalic anhydride (2) in 5 mL of glacial acetic acid was maintained under reflux for 30 minutes. Cooling of this mixture leads to separation of a nearly white powder, which was filtered out and washed twice with 10 mL of water, to furnish 0.76 g (84%) of desired 2-(4-hydroxyphenethyl)-phthalimide derivative (3), mp 220-222 °C. **^{1}H NMR** (200 MHz, DMSO-d_6): δ 2.77 (t, 2H, J = 7.35 Hz, $R(CO)_2NCH_2\underline{C}H_2R$), 3.69 (t, 2H, J = 7.35 Hz, $R(CO)_2N\underline{C}H_2CH_2R$), 6.62 (d, 2H, J= 8.25 Hz, H-2' and H-6'), 6.95 (d, 2H, J = 8.27 Hz, H-3'and H-5'), 7.80 (s, 4H, H-4, H-5, H-6 and H-7) ppm; **^{13}C NMR** (50 MHz, DMSO d_6): δ 33.50 ($R(CO)_2NCH_2\underline{C}H_2$), 39.78 ($R(CO)_2N\underline{C}H_2CH_2$), 115.87 (C-2' and C-6'), 123.65 (C-4 and C-7), 130.12 (C-3' and C-5'), 130.17 (C-4'), 132.14 (C-3a and C-7a), 135.04 (C-5 and C-6), 156.47 (C-1'), 168.32 (C-1 and C-3) ppm.

Anal. Calcd. for $C_{16}H_{13}NO_3$: C, 71.90%; H, 4.90%; N, 5.24%. Found: C, 71.84%; H, 4.95%; N, 5.27%.

General Procedures for *O*-Alkylation or *O*-Acylation of the phthalimide derivative (3).

Method A[15]:

A mixture of (3) (0.1g; 0.37 mmol), appropriate alkyl halides (0.47 mmol), catalytic amount of tetrabutylammonium bromide, and potassium carbonate (0.62g; 4.49 mmol) was heated in a domestic microwave oven in an open Erlenmeyer flask until that tlc analysis indicated the total comsuption of starting material (*vide* Table 1). Then, the reaction mixture was cooled and extracted with dichloromethane (4 X 20 mL). The organic layers were dried with anhydrous sodium sulfate, filtered, and the solvent was evaporated to dryness under reduced pressure, to give the desired phthamide derivatives (4-11) in good yield, as described in the Table 1.

Method B[11]:

To a suspension of the phthalimide derivative (3) (0.2 g; 0.74 mmol) and potassium carbonate (0.13 g; 0.97 mmol) in anhydrous acetone (30 mL) was added the appropriated alkyl halides (0.9 mmol). The reaction mixture was stirred at room temperature, under argon atmosphere, until that tlc analysis indicated the total comsuption of starting material (*vide* Table 1). Then, the solvent was evaporated at reduced pressure and the obtained residue was diluted with water (*ca.* 40 mL) and extracted with dichloromethane (4 X 20 mL). The organic layers were washed with brine, dried over anhydrous sodium sulfate,

filtered and evaporated under reduced pressure, to give the desired phthamide derivatives (4-11) in good yield, as described in the Table 1.

Method C[14]:

To a suspension of phthalimide derivative (3) (0.2 g; 0.74 mmol) and potassium carbonate (0.13 g; 0.97 mmol) in anhydrous *N,N*-dimethylformamide (30 mL) was added the appropriated alkyl halides (0.9 mmol). The reaction mixture was stirred at room temperature, under argon atmosphere, until that tlc analysis indicated the total comsuption of starting material (*vide* Table 1). Next, dilution of the reaction mixture with H_2O (*ca.* 70 mL), lead to formation of a white precipitate, which was filtered out and washed twice with 50 mL of water, to furnish the desired phthalimide derivatives (4-11) in good yield, as described in the Table 1.

Ethyl 2-{4-[2-(1,3-dioxo-2,3-dihydro-1*H*-2-isoindolyl)ethyl]phenoxy}acetate (4): ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.29 (t, 3H, J = 7.14 Hz, $RCO_2CH_2C\underline{H}_3$), 2.93 (t, 2H, J = 7.51 Hz, $R(CO)_2NCH_2C\underline{H}_2R$), 3.88 (t, 2H, J = 7.51 Hz, $R(CO)_2NC\underline{H}_2CH_2R$), 4.28 (q, 2H, J = 7.14 Hz, $RCO_2C\underline{H}_2CH_3$), 6.84 (d, 2H, J = 8.70 Hz, H-2' and H-6'), 7.18 (d, 2H, J = 8.61 Hz, H-3'and H-5'), 7.72 (m, 2H, H-5 and H-6), 7.83 (m, 2H, H-4 and H-7) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.92 ($ROCH_2CO_2CH_2\underline{C}H_3$), 33.43 ($R(CO)_2NCH_2\underline{C}H_2$), 39.07 ($R(CO)_2N\underline{C}H_2CH_2$), 61.06 ($ROCH_2CO_2\underline{C}H_2CH_3$), 65.23 ($RO\underline{C}H_2CO_2CH_2CH_3$), 114.50 (C-2' and C-6'), 122.93 (C-4 and C-7), 129.66 (C-3' and C-5'), 130.93

(C-4'), 131.78 (C-3a and C-7a), 133.65 (C-5 and C-6), 156.34 (C-1'), 167.87 ($ROCH_2\underline{C}O_2CH_2CH_3$), 168.69 (C-1 and C-3) ppm.

Anal. Calcd. For $C_{20}H_{19}NO_5$: C, 67.98%, H, 5.42%, N, 3.96%. Found: C, 67.91%, H, 5.41%, N, 3.92%.

Methyl 2-{4-(1,3-dioxo-2,3-dihydro-1*H*-2-isoindolyl)ethyl]phenoxy} propanoate (5): ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.37 (d, 3H, J = 6.80 Hz, $RCH(C\underline{H}_3)CO_2CH_3$), 2.92 (t, 2H, J = 7.94 Hz, $R(CO)_2NCH_2C\underline{H}_2R$), 3.74 (s, 3H, $RCH(CH_3)CO_2C\underline{H}_3$), 3.92 (t, 2H, J = 7.93 Hz, $R(CO)_2NC\underline{H}_2CH_2R$), 4.71 (q, 1H, J = 6.81 Hz, $RC\underline{H}(CH_3)CO_2CH_3$), 6.78 (d, 2H, J = 8.64 Hz, H-2' and H-6'), 7.16 (d, 2H, J = 8.64 Hz, H-3' and H-5'), 7.68 (m, 2H, H-5 and H-6), 7.83 (m, 2H, H-4 and H-7) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ 18.73 ($ROCH(\underline{C}H_3)CO_2CH_3$), 33.76 ($R(CO)_2NCH_2\underline{C}H_2$), 39.40 ($R(CO)_2N\underline{C}H_2CH_2$), 52.47 ($ROCH(CH_3)CO_2\underline{C}H_3$), 72.65 ($RO\underline{C}H(CH_3)CO_2CH_3$), 115.30 (C-2' and C-6'), 123.35 (C-4 and C-7), 129.51 (C-3' and C-5'), 131.23 (C-4'), 131.61 (C-3a and C-7a), 134.06 (C-5 and C-6), 156.42 (C-1'), 168.32 (C-1 and C-3), 172.90 ($ROCH(CH_3)\underline{C}O_2CH_3$) ppm.

Anal. Calcd. For $C_{20}H_{19}NO_5$: C, 67.98%, H, 5.42%, N, 3.96%. Found: C, 68.04%, H, 5.35%, N, 3.90%.

4-{4-[2-(1,3-Dioxo-2,3-dihydro-1*H*-2-isoindolyl)ethyl]phenoxy}butanenitrile (6): ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.12 (qt, 2H, J = 6.15 Hz, $ROCH_2C\underline{H}_2CH_2CN$), 2.58 (t, 2H, J = 7.00 Hz, $ROCH_2CH_2C\underline{H}_2CN$), 2.94 (t, 2H,

J = 7.77 Hz, $R(CO)_2NCH_2C\underline{H}_2R$), 3.89 (t, 2H, J = 7.60 Hz, $R(CO)_2NC\underline{H}_2CH_2R$), 4.04 (t, 2H, J = 5.30 Hz, $ROC\underline{H}_2CH_2CH_2CN$), 6.62 (d, 2H, J = 8.15 Hz, H-2' and H-6'), 7.60 (d, 2H, J = 8.17 Hz, H-3' and H-5'), 7.73 (m, 2H, H-5 and H-6), 7.84 (m, 2H, H-4 and H-7) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.32 ($ROCH_2\underline{C}H_2CH_2CN$), 25.65 ($ROCH_2CH_2\underline{C}H_2CN$), 33.80 ($R(CO)_2NCH_2\underline{C}H_2$), 39.52 ($R(CO)_2N\underline{C}H_2CH_2$), 65.39 ($RO\underline{C}H_2CH_2CH_2CN$), 114.68 (C-2' and C-6'), 14.32 ($ROCH_2CH_2CH_2\underline{C}N$), 123.32 (C-4 and C-7), 130.05 (C-3' and C-5'), 130.80 (C-4'), 132.17 (C-3a and C-7a), 134.03 (C-5 and C-6), 157.23 (C-1'), 168.28 (C-1 and C-3) ppm.

Anal. Calcd. For $C_{20}H_{18}N_2O_3$: C, 71.84%, H, 5.43%, N, 8.38%. Found: C, 71.79%, H, 5.46%, N, 8.35%.

Ethyl 5-{4-[2-(1,3-dioxo-2,3-dihydro-1*H*-2-isoindolyl)ethyl]phenoxy} pentanoate (7): ^1H NMR (200 MHz, $CDCl_3$): δ 1.26 (t, 3H, J = 7.14 Hz, $RCO_2CH_2C\underline{H}_3$), 1.80 (m, 4H, $ROCH_2C\underline{H}_2C\underline{H}_2CH_2CO_2R$), 2.39 (t, 2H, J = 7.05 Hz, $ROCH_2CH_2CH_2C\underline{H}_2CO_2R$), 2.92 (t, 2H, J= 7.69 Hz, $R(CO)_2NCH_2C\underline{H}_2R$), 3.90 (m, 4H, $R(CO)_2NC\underline{H}_2CH_2R$ and $ROC\underline{H}_2CH_2CH_2CH_2CO_2R$), 4.15 (q, 2H, J = 7.14Hz, $RCO_2C\underline{H}_2CH_3$), 6.80 (d, 2H, J = 8.70 Hz, H-2' and H-6'), 7.15 (d, 2H, J = 8.61 Hz, H-3' and H-5'), 7.70 (m, 2H, H-5 and H-6), 7.83 (m, 2H, H-4 and H-7) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.95 ($RCO_2CH_2\underline{C}H_3$), 21.33 ($ROCH_2CH_2\underline{C}H_2CH_2CO_2R$), 28.35 ($ROCH_2\underline{C}H_2CH_2CH_2CO_2R$), 33.35 ($ROCH_2CH_2CH_2\underline{C}H_2CO_2R$), 33.60 ($R(CO)_2NCH_2\underline{C}H_2$), 39.11 ($R(CO)_2N\underline{C}H_2CH_2$), 59.93 ($ROCH_2CO_2\underline{C}H_2CH_3$), 66.96

($RO\underline{C}H_2CH_2CH_2CH_2CO_2R$), 114.18 (C-2' and C-6'), 122.81 (C-4 and C-7), 129.45 (C-3' and C-5'), 129.64 (C-4'), 131.73 (C-3a and C-7a), 133.53 (C-5 and C-6), 157.36 (C-1'), 167.77 (C-1 and C-3), 173.04 ($R\underline{C}O_2CH_2CH_3$) ppm.

Anal. Calcd. For $C_{23}H_{25}NO_5$: C, 69.86%, H, 6.37%, N, 3.54%. Found: C, 69.85%, H, 6.40%, N, 3.53%.

1-{4-[2-(1,3-Dioxo-2,3-dihydro-1*H*-2-isoindolyl)ethyl]phenyl}5-pentanedioic acid (8): ^{1}H NMR (200 MHz, DMSO d_6): δ 1.85 (qt, 2H, J = 7.32 Hz, $RCO_2CH_2C\underline{H}_2CH_2CO_2H$), 2.34 (t, 2H, J = 7.36 Hz, $RCO_2C\underline{H}_2CH_2CH_2CO_2H$), 2.60 (t, 2H, J = 7.36 Hz, $RCO_2CH_2CH_2C\underline{H}_2CO_2H$), 2.94 (t, 2H, J = 7.69 Hz, $R(CO)_2NCH_2C\underline{H}_2R$), 3.83 (t, 2H, J = 7.60 Hz, $R(CO)_2NC\underline{H}_2CH_2R$), 7.03 (d, 2H, J = 8.30 Hz, H-2' and H-6'), 7.25 (d, 2H, J = 8.35 Hz, H-3' and H-5'), 7.85 (s, 4H, H-4, H-5, H-6 and H-7), 12.15 (br, 1H, $COO\underline{H}$) ppm; ^{13}C NMR (50 MHz, DMSO d_6): δ 20.28 ($RCO_2CH_2\underline{C}H_2CH_2CO_2H$), 33.06 ($RCO_2\underline{C}H_2CH_2CH_2CO_2H$), 33.16 ($RCO_2CH_2CH_2\underline{C}H_2CO_2H$), 33.49 ($R(CO)_2NCH_2\underline{C}H_2$), 39.19 ($R(CO)_2N\underline{C}H_2CH_2$), 122.15 (C-2' and C-6'), 123.48 (C-4 and C-7), 130.06 (C-3' and C-5'), 132.18 (C-4'), 136.19 (C-3a and C-7a), 134.88 (C-5 and C-6), 149.45 (C-1'), 168.12 (C-1 and C-3), 171.83 ($R\underline{C}O_2CH_2CH_2CH_2CO_2H$), 174.41 ($RCO_2CH_2CH_2CH_2\underline{C}O_2H$) ppm.

Anal. Calcd. For $C_{21}H_{19}NO_6$: C, 66.14%, H, 5.02%, N, 3.67%. Found: C, 66.11%, H, 5.07%, N, 3.69%.

2-(4-{4-[2-(1,3-Dioxo-2,3-dihydro-1*H*-2-isoindolyl)ethyl]phenoxymethyl}phenyl) acetic acid (9): ^{1}H NMR (200 MHz, DMSO d_6): δ 2.78 (t, 2H, J = 7.80 Hz,

$R(CO)_2NCH_2C\underline{H}_2R$), 3.37 (s, 2H, $ArC\underline{H}_2CO_2H$), 3.70 (s, 2H, $ArOC\underline{H}_2Ar$), 3.73 (t, 2H, J = 7.73 Hz, $R(CO)_2NC\underline{H}_2CH_2R$), 6.65 (d, 2H, J = 8.60 Hz, H-2' and H-6'), 6.98 (d, 2H, J = 8.35 Hz, H-3' and H-5'), 7.18 (d, 2H, J = 7.39 Hz, H-2" and H-6"), 7.26 (d, 2H, J = 7.31 Hz, H-3" and H-5"), 7.81 (s, 4H, H-4, H-5, H-6 and H-7), 11.85 (br, 1H, $COO\underline{H}$) ppm; ^{13}C NMR (50 MHz, DMSO d_6): δ 32.86 ($R(CO)_2NCH_2\underline{C}H_2$), 39.09 ($R(CO)_2N\underline{C}H_2CH_2$), 42.26 ($Ar\underline{C}H_2CO_2H$), 65.28 ($RO\underline{C}H_2Ar$), 115.24 (C-2' and C-6'), 123.00 (C-4 and C-7), 127.48 (C-3" and C-5"), 129.05 (C-2" and C-6"), 129.54 (C-3' and C-5'), 129.36 (C-4'), 131.48 (C-3a and C-7a), 134.09 (C-5 and C-6), 134.70 (C-1"), 134.86 (C-4"), 155.81 (C-1'), 167.69 (C-1 and C-3), 170.83 ($ArCH_2\underline{C}O_2H$) ppm.

Anal. Calcd. For $C_{25}H_{21}NO_5$: C, 72.28%, H, 5.09%, N, 3.37%. Found: C, 72.23%, H, 5.13%, N, 3.32%.

2-(4-Allyloxyphenethyl)-1,3-isoindolinedione (10): ^1H NMR (200 MHz, $CDCl_3$): δ 2.87 (t, 2H, J = 7.62 Hz, $R(CO)_2NCH_2C\underline{H}_2R$), 3.87 (t, 2H, J = 7.60 Hz, $R(CO)_2NC\underline{H}_2CH_2R$), 4.43 (d, 2H, J = 4.09, $ROC\underline{H}_2CH{=}CH_2$), 5.30 (dd, 2H, J_{cis} = 11.05 and J_{trans} = 17.02 Hz, $ROCH_2CH{=}C\underline{H}_2$), 6.00 (m, 1H, $ROCH_2C\underline{H}{=}CH_2$), 6.77 (d, 2H, J = 7.99 Hz, H-2' and H-6'), 7.15 (d, 2H, J = 7.88 Hz, H-3'and H-5'), 7.70 (m, 2H, H-5 and H-6), 7.80 (m, 2H, H-4 and H-7) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ 33.84 ($R(CO)_2NCH_2\underline{C}H_2$), 39.56 ($R(CO)_2N\underline{C}H_2CH_2$), 68.90 ($RO\underline{C}H_2CH{=}CH_2$), 114.94 (C-2' and C-6'), 117.68 ($ROCH_2CH{=}\underline{C}H_2$), 123.31 (C-4 and C-7), 129.93 (C-3' and C-5'), 130.36 (C-4'), 132.22 (C-3a and C-7a), 133.50 ($ROCH_2\underline{C}H{=}CH_2$), 133.99 (C-5 and C-6), 157.48 (C-1'), 168.30 (C-1 and C-3) ppm.

Anal. Calcd. For $C_{19}H_{17}NO_5$: C, 74.25%, H, 5.58%, N, 4.56%. Found: C, 74.20%, H, 5.62%, N, 4.61%.

2-[4-(2-Oxiranylmethoxy)phenethyl]-1,3-isoindolinedione (11): ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.74 (dd, 1H, J_{gem} = 4.94 Hz and J_{trans} = 2.6 Hz, $ROCH_2CH(O)C\underline{H}_2$), 2.89 (dd, 1H, J_{gem} = 5.04 Hz and J_{cis} = 4.12 Hz, $ROCH_2CH(O)C\underline{H}_2$), 2.93 (t, 2H, J = 7.97 Hz, $R(CO)_2NCH_2C\underline{H}_2R$), 3.44 (m, 1H, $ROCH_2C\underline{H}(O)CH_2$), 3.90 (m, 3H, $R(CO)_2NC\underline{H}_2CH_2R$ and $ROC\underline{H}_2CH(O)CH_2$), 4.18 (dd, 1H, J_{gem} = 10.99 Hz and J_{trans} = 3.20 Hz, $ROC\underline{H}_2CH(O)CH_2$), 6.82 (d, 2H, J = 8.61 Hz, H-2' and H-6'), 7.16 (d, 2H, J = 8.61 Hz, H-3'and H-5'), 7.70 (m, 2H, H-5 and H-6), 7.83 (m, 2H, H-4 and H-7) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ 33.44 ($R(CO)_2NCH_2\underline{C}H_2$), 39.16 ($R(CO)_2N\underline{C}H_2CH_2$), 44.47 ($ROCH_2CH(O)\underline{C}H_2$), 49.91 ($ROCH_2\underline{C}H(O)CH_2$), 68.49 ($RO\underline{C}H_2CH(O)CH_2$), 114.45 (C-2' and C-6'), 122.95 (C-4 and C-7), 129.64 (C-3' and C-5'), 130.42 (C-4'), 131.79 (C-3a and C-7a), 133.67 (C-5 and C-6), 156.99 (C-1'), 167.92 (C-1 and C-3) ppm.

Anal. Calcd. For $C_{19}H_{17}NO_4$: C, 70.58%, H, 5.30%, N, 4.33%. Found: C, 70.62%, H, 5.28%, N, 4.35%.

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