1-Oxo-2-hydroxy-1,2-dihydroacronycine: A Useful Synthon in the Acronycine Series for the Introduction of Amino Substituents at 6-Position and for the Conversion into Isopropylfuroacridones

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Thermic aromatic nucleophilic displacement of the methoxy group at C-6 of (±)-1-oxo-2-hydroxy-1,2-dihydroacronycine (2) by an amine is a reaction that gives a facile entry to acronycine derivatives bearing an amino substituent at this position. The introduction of the amino substituents was confirmed with a long-range $^{1}H–^{15}N$ correlation NMR spectrum at natural abundance. Under basic conditions, compound 2 can also be rearranged to the corresponding isopropylfuroacridone 12, in 80% yield.

Key words acronycine; furanoacridone; alkaloid; cytotoxicity; ^{15}N-NMR

The pyranoacridone alkaloid acronycine (**1**), first isolated from *Acronychia baueri* SCHOTT (Rutaceae) in 1948 was later found to be a potent anticancer agent.[1—5] Its main interest lies in its broad spectrum of activity, which includes numerous solid tumors.[2—8] Nevertheless, clinical trials have been so far severely hampered by its very low water solubility and have therefore given only poor results.[7] In this context, the development of new acronycine derivatives bearing amino groups and able to give water-soluble salts appears highly desirable.[10—13]

Among the various oxidation products of acronycine at the dimethylpyran ring, (±)-1-oxo-2-hydroxy-1,2-dihydroacronycine (**2**) (2-hydroxy-6-methoxy-3,3,12-trimethyl-1,2,3,12-tetrahydro-7*H*-pyrano[2,3-*c*]acridin-1,7-dione) is particularly easy to obtain by simple permanganate oxidation of the parent alkaloid.[14] This compound presents two electron withdrawing carbonyl groups at C-1 and C-7, respectively in positions *para* and *ortho* to the methoxy group at C-6. Consequently, a thermic aromatic nucleophilic displacement of the methoxy group by an amine can be envisaged at this latter position.[15,16] Such a reaction should give a facile entry to acronycine derivatives bearing an amino substituent at C-6, which could not be efficiently obtained so far, either by conversion of acronycine itself, or by total synthesis.[5]

Indeed, treatment of **2** by methylamine or hydrazine led in 60—90% yield to the nucleophilic substitution product **3** and **4**, respectively (Chart 1). The introduction of the amino substituent at position 6 was directly confirmed by a gradient inverse-detected long-range $^{1}H–^{15}N$ correlation experiment at natural abundance. In each case a clear ^{3}J correlation was observed between H-5 and N-1 of the amino substituent. For example, in the case of compound **4** proton H-5 (δ 6.33) was correlated with N-1 (δ 114.5) (Fig. 1).

It should be noted that hydrazine does not react on the carbonyl group at C-1 of **2** under these conditions, probably due to steric hindrance. In contrast, hydrazine reacts with the less hindered 2-oxo-1,2-dihydroacronycine (**5**) to give the expected hydrazone **6**, and with acronycine itself to afford the well known 1,2-dihydroacronycine (**7**),[2] emphasizing the lack of reactivity of the methoxy group at C-6 of acronycine towards nucleophilic substitution and the crucial role of the carbonyl group at C-1 of **2**.

When ammonia is used as the nucleophile agent, the expected 6-amino derivative **8** is only obtained in small yield (10%) when the reaction is carried out under pressure in a sealed tube. Under those conditions the major product **9** results from a degradation of the pyrano ring of the starting material. A similar byproduct **10** was also observed in the case of methylamine, but only in 5% yield.

When **2** is treated by the more bulky ethylamine, ethylamino substitution product **11** is only obtained in 10% yield and 2-hydroxy-2-isopropyl-5-methoxy-11-methyl-1,2-dihydrofurano[2,3-*c*]acridin-1,6(11*H*)dione (**12**) is the major product of the reaction, isolated in 50% yield. This rearrangement compound most probably arises through an alkaline-catalyzed mechanism (Fig. 2), previously described for the isomerization of ketohydroxypyranocoumarins into their furocoumarin isomers under basic conditions.[17] In good agreement with this statement, **12** is the only product, isolated in 80% yield when **2** is treated by propylamine, butylamine, dimethylamine or sodium methoxide in methanol. It must be noted that compound **12** is a useful synthon for the preparation of acronycine analogues with a D-furano ring.

The study of the cytotoxic properties of the new acronycine derivatives **3**, **4**, **6** and **12** was carried out *in vitro* on L-1210 leukemia cells.[18] The results (IC_{50}) are summarized in Table 1. The new compounds exhibited moderate cytotoxic activity, which is in agreement with our previous hypothesis that cytotoxicity in this series is correlated with the presence of a good leaving group at the benzylic position, able to ensure sufficient reactivity toward nucleophilic agents.[7] However, the comparison with the cytotoxicity of **2** shows that either the amino substitution at position 6 or the rearrangement of the D-ring from pyrano to furano are two promising modifications which must be further explored in the acronycine series. Additionally, the potential formation of water-soluble salts of the synthesized amino derivatives is of great importance because they are some of the very few examples of amino substituted acronycine analogues.

Experimental

General Experimental Procedures Melting points were measured with a Büchi apparatus and are uncorrected. Spectra were recorded on the follow-

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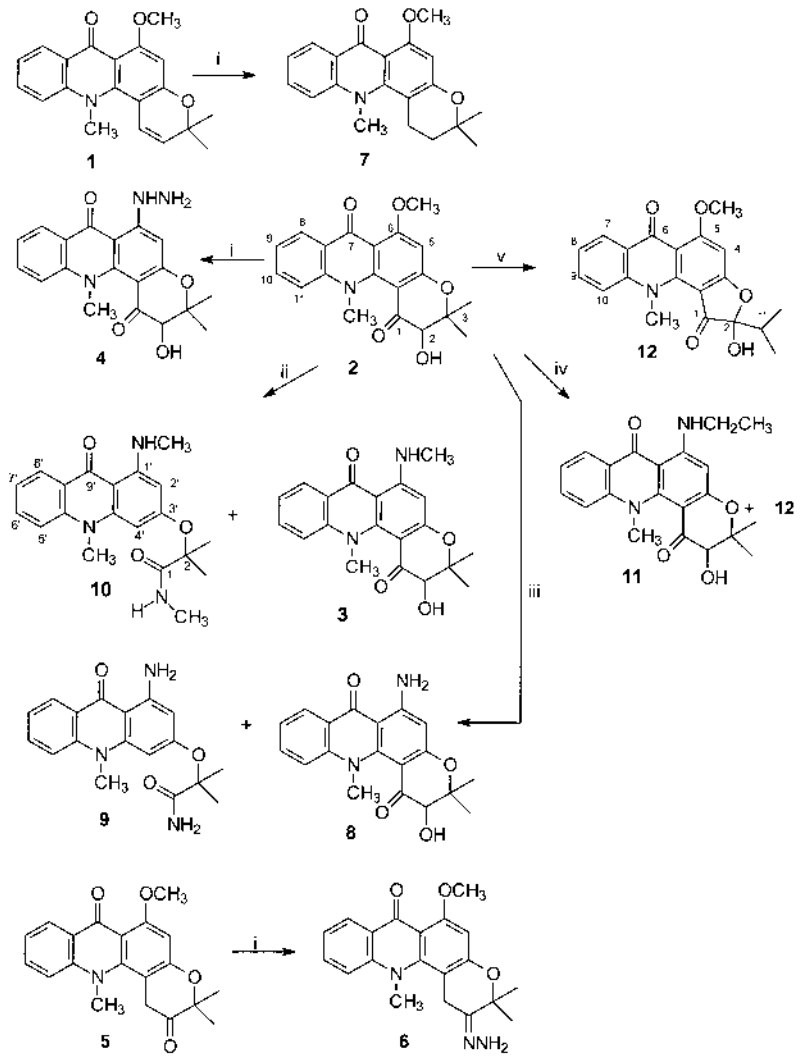

[a]Key: i) NH_2NH_2, EtOH, 80°C ii) CH_3NH_2, EtOH, 80°C iii) NH_3, EtOH, 80°C iv) $CH_3CH_2NH_2$, EtOH, 80°C v) NaOH, MeOH, 70°C

Chart 1

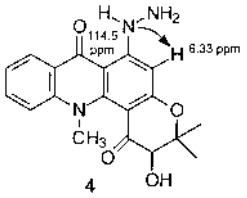

Fig. 1. Characteristic Long-range ^1H–^{15}N Correlation for **4**

ing apparatus: MS, Nermag R10-10C in desorption-chemical ionization, using NH_3 as reagent gas. NMR, Bruker AC 200, ^1H-NMR (200 MHz), ^{13}C-NMR (50 MHz) and a Bruker DRX400, ^1H-NMR (400 MHz). Chemical shifts are given in δ with tetramethylsilane (TMS) as an internal standard. Coupling constants (J) are given in Hz. The signals of ^1H and ^{13}C spectra were unambiguously assigned by using 2D NMR techniques: correlation spectroscopy (COSY), ^1H-detected heteronuclear multiple quantum coherence (HMQC) and heteronuclear multiple bond correlation (HMBC). These 2D experiments were performed using standard Bruker microprograms. For the ^1H–^{15}N GHMQC spectrum, data were acquired as 3072×400 data points with a total of 290 transients accumulated/t_1 increment. Pulse widths were 8.55 μs for ^1H and 27.7 μs for the ^{15}N at powers of 0 dB and −3 dB. The F_1 spectral window employed was set from 100—400 ppm. Pulsed field gradients, gt1—gt3, had durations of 0.8 ms. Gradient pairs were optimized as 70 : 30 : 50 for ^{15}N. Column chromatographies were conducted using flash Silica gel 60 Merck (40—63 μm), with an overpressure of 300 mbars. All new compounds gave satisfactory combustion analyses (C, H, N, within ± 0.4% of calculated values).

(±)-6-Demethoxy-6-hydrazino-2-hydroxy-1-oxo-1,2-dihydroacronycine (4) To a solution of (±)-2-hydroxy-1-oxo-1,2-dihydroacronycine (**2**) (150 mg, 0.42 mmol) in EtOH (4 ml) was added 0.4 ml hydrazine hydrate. The reaction mixture was refluxed for 4 h. Then the reagents were removed under reduced pressure and the residue was submitted to flash chromatography on silica gel with Chex : EtOAc (60 : 40 to 40 : 60) to give **4** (130 mg, 88%). mp 213 °C. ^1H-NMR (DMSO, 200 MHz) δ: 11.63 (1H, s, N<u>H</u>-NH_2), 8.22 (1H, d, J=8 Hz, H-8), 7.74 (2H, m, H-10, 11), 7.38 (1H, t, J=8 Hz, H-9), 6.33 (1H, s, H-5), 5.55 (1H, d, J=2 Hz, OH-2), 4.81 (2H, s, NH-N<u>H</u>$_2$), 3.96 (1H, d, J=2 Hz, H-2), 3.62 (3H, s, NCH_3), 1.50 (3H, s, CH_3), 1.35 (3H, s, CH_3). ^{13}C-NMR (DMSO, 50 MHz) δ: 186.51 (C-1), 176.91 (C-7), 165.19 (C-4a), 158.43 (C-6), 148.73 (C-12a), 142.77 (C-11a), 133.32 (C-10), 125.43 (C-8), 123.44 (C-7a), 122.95 (C-9), 117.93 (C-11), 103.81 (C-6a), 97.79 (C-12b), 88.51 (C-5), 81.32 (C-3), 75.32 (C-2), 44.94 (NCH_3), 25.77 (CH_3), 19.59 (CH_3). C 64.6%, H 5.4%, N 11.8%, MS-DCI m/z: 354 $(M+H)^+$.

(±)-6-Demethoxy-2-hydroxy-6-methylamino-1-oxo-1,2-dihydroacronycine (3) and 2,*N*-Dimethyl-2-(10-methyl-1-methylamino-9-oxo-9,10-dihydroacridin-3-yloxy)propanamide (10) Treatment of **2** (100 mg, 0.28 mmol) for 24 h with 0.4 ml of a water solution of methylamine (40%) in conditions essentially similar to those described for the preparation of **4**

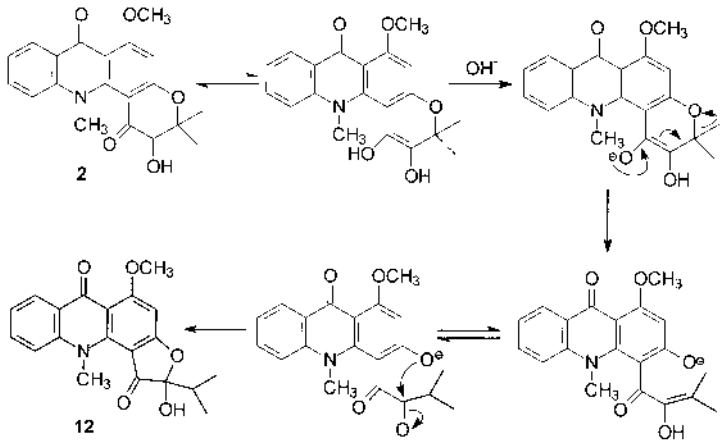

Fig. 2. Proposed Mechanism for the Rearrangement of Pyranoacridone **2** to Furanoacridone **12**

Table 1. Cytotoxic Activity[a)]

Compound	**3**	**4**	**6**	**12**	**1**	**2**
IC_{50} (μM)	52.8	33.3	38.1	23	25	75.1

a) Inhibition of L1210 cell proliferation measured by the MMT assay (mean of 2 values obtained in independent experiments).

afforded compound **3** (60 mg, 61%) and **10** (6 mg, 5%). Compound **3**: mp 205 °C. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 11.26 (1H, q, J=5 Hz, NH-CH_3), 8.38 (1H, dd, J=8, 1.5 Hz, H-8), 7.71 (1H, td, J=8, 1.5 Hz, H-10), 7.58 (1H, d, J=8 Hz, H-11), 7.37 (1H, t, J=8 Hz, H-9), 5.82 (1H, s, H-5), 4.19 (1H, d, J=2 Hz, OH-2), 4.09 (1H, d, J=2 Hz, H-2), 3.70 (3H, s, NCH_3), 2.99 (3H, d, J=5 Hz, NH-CH_3), 1.56 (6H, s, 2×CH_3). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 186.17 (C-1), 178.51 (C-7), 166.05 (C-4a), 158.86 (C-6), 149.46 (C-12a), 143.28 (C-11a), 133.05 (C-10), 126.03 (C-8), 124.39 (C-7a), 123.09 (C-9), 117.35 (C-11), 105.59 (C-6a), 96.79 (C-12b), 89.63 (C-5), 82.32 (C-3), 75.76 (C-2), 45.21 (NCH_3), 29.59 (6-NHCH_3), 27.09 (CH_3), 17.91 (CH_3). C 68.3%, H 5.7%, N 7.9%, MS-DCI *m/z*: 353 $(M+H)^+$. Compound **10**: mp 153 °C. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 10.34 (1H, q, J=5 Hz, 1-NH-CH_3), 8.40 (1H, dd, J=8, 1.5 Hz, H-8′), 7.62 (1H, td, J=8, 1.5 Hz, H-6′), 7.36 (1H, d, J=8 Hz, H-5′), 7.22 (1H, t, J=8 Hz, H-7′), 6.50 (1H, q, J=5 Hz, CONHCH_3), 5.94 (1H, d, J=1.5 Hz, H-4′), 5.75 (1H, d, J=1.5 Hz, H-2′), 3.68 (3H, s, NCH_3), 2.88 (3H, d, J=5 Hz, 1-NH-CH_3), 2.85 (3H, d, J=5 Hz, CONHCH_3), 1.64 (6H, s, 2×CH_3). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 178.95 (C-1), 175.12 (C-9′), 166.52 (C-3′), 155.02 (C-1′), 146.53 (C-4a′), 141.90 (C-10a′), 132.88 (C-6′), 126.92 (C-8′), 123.30 (C-8a′), 121.04 (C-7′), 114.11 (C-5′), 104.56 (C-9a′), 91.72 (C-4′), 90.57 (C-2′), 81.47 (C-2′), 34.43 (NCH_3), 29.52 (1′-NHCH_3), 26.28 ($CONHCH_3$), 25.54 (2×CH_3). C 67.8%, H 6.6%, N 11.8%, MS-DCI *m/z*: 354 $(M+H)^+$.

(±)-6-Amino-6-demethoxy-2-hydroxy-1-oxo-1,2-dihydroacronycine (8) and 2-(1-Amino-10-methyl-9-oxo-9,10-dihydroacridin-3-yloxy)-2-methyl-propanamide (9) Treatment of **2** (55 mg, 0.15 mmol) for 24 h with 1 ml of a water solution of ammonia (28% w/v) in a sealed tube and in conditions essentially similar to those described for the preparation of **4** afforded compound **8** (5 mg, 10%) and **9** (27 mg, 51%). Compound **8**: mp 200 °C. ^{1}H-NMR (DMSO, 200 MHz) δ: 9.95 (2H, s, NH_2), 8.25 (1H, dd, J=8, 1.5 Hz, H-8), 7.79 (2H, m, H-10,11), 7.41 (1H, td, J=8, 1.5 Hz, H-9), 5.91 (1H, s, H-5), 5.74 (1H, d, J=2 Hz, OH-2), 4.00 (1H, d, J=2 Hz, H-2), 3.62 (3H, s, NCH_3), 1.49 (3H, s, CH_3), 1.36 (3H, s, CH_3). ^{13}C-NMR (DMSO, 50 MHz) δ: 186.77 (C-1), 177.01 (C-7), 164.40 (C-4a), 158.07 (C-6), 149.16 (C-12a), 143.07 (C-11a), 133.44 (C-10), 125.46 (C-8), 123.60 (C-7a), 122.87 (C-9), 117.93 (C-11), 107.41 (C-6a), 98.59 (C-12b), 93.14 (C-5), 81.32 (C-3), 76.90 (C-2), 44.92 (NCH_3), 25.70 (CH_3), 19.58 (CH_3). C 67.6%, H 5.5%, N 8.2%, MS-DCI *m/z*: 339 $(M+H)^+$. Compound **9**: mp 120 °C. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 8.46 (1H, dd, J=8, 1.5 Hz, H-8′), 7.67 (1H, td, J=8, 1.5 Hz, H-6′), 7.42 (1H, d, J=8 Hz, H-5′), 7.22 (1H, t, J=8 Hz, H-7′), 6.12 (1H, d, J=1.5 Hz, H-4′), 5.91 (1H, d, J=1.5 Hz, H-2′), 3.68 (3H, s, NCH_3), 1.66 (6H, s, 2×CH_3). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 178.04 (C-1), 174.99 (C-9′), 165.82 (C-3′), 156.42 (C-1′), 147.23 (C-4a′), 142.98 (C-10a′), 133.45 (C-6′), 127.02 (C-8′), 122.80 (C-8a′), 121.08 (C-7′), 114.19 (C-5′), 105.06 (C-9a′), 96.22 (C-4′), 91.67 (C-2′), 81.37 (C-2′), 34.45 (NCH_3), 25.04 (2×CH_3). C 66.6%, H 5.7%, N 12.8%, MS-DCI *m/z*: 326 $(M+H)^+$.

(±)-6-Ethylamino-6-demethoxy-2-hydroxy-1-oxo-1,2-dihydroacronycine (11) Treatment of **2** (100 mg, 0.28 mmol) for 24 h with 0.3 ml of a water solution of ethylamine (70% w/v) and in conditions essentially similar to those described for the preparation of **4** afforded **11** (13 mg, 13%) and **12** (50 mg, 50%). Compound **11**: mp 208 °C. ^{1}H-NMR (DMSO, 200 MHz) δ: 11.00 (1H, s, NH-CH_2), 8.26 (1H, d, J=8 Hz, H-8), 7.80 (2H, m, H-10, 11), 7.44 (1H, t, J=8 Hz, H-9), 5.88 (1H, s, H-5), 5.84 (1H, d, J=2 Hz, OH-2), 3.99 (1H, d, J=2 Hz, H-2), 3.63 (3H, s, NCH_3), 3.30 (2H, quintet, J=7 Hz, NH-C$H_2$$CH_3$), 1.52 (3H, s, CH_3), 1.39 (3H, s, CH_3), 1.30 (3H, t, J=7 Hz, NH-CH_2CH_3). C 68.7%, H 6.0%, N 7.5%, MS-DCI *m/z*: 367 $(M+H)^+$.

(±)-2-Hydroxy-2-isopropyl-5-methoxy-11-methyl-1,2-dihydrofurano-[2,3-*c*]acridin-1,6(11*H*) dione (12) To a solution of **2** (400 mg, 1.13 mmol) in MeOH (30 ml) was added 4 ml of NaOH 1 N. The reaction mixture was refluxed for 1.5 h and then it was neutralized with acetic acid. The solvents were removed under reduced pressure, the residue was extracted with CH_2Cl_2/H_2O and the organic layer was collected. Compound **12** (315 mg, 78%) was purified by crystallization with MeOH. mp 280 °C (dec.). ^{1}H-NMR (DMSO, 200 MHz) δ: 8.14 (1H, dd, J=8, 1.5 Hz, H-7), 7.83 (1H, s, OH-2), 7.73 (2H, m, H-9, 10), 7.36 (1H, td, J=8, 1.5 Hz, H-8), 6.64 (1H, s, H-4), 3.98 (3H, s, OCH_3), 3.86 (3H, s, NCH_3), 2.15 (1H, sept, J=7 Hz, H-1′), 1.05 (3H, d, J=7 Hz, CH_3), 0.82 (3H, d, J=7 Hz, CH_3). ^{13}C-NMR (DMSO, 50 MHz) δ: 192.58 (C-1), 175.86 (C-6), 174.40 (C-3a), 170.57 (C-5), 145.24 (C-11a), 142.46 (C-10a), 133.28 (C-9), 125.98 (C-7), 125.25 (C-6a), 123.13 (C-8), 117.28 (C-10), 108.02 (C-5a,2), 101.43 (C-11b), 89.67 (C-4), 57.15 (OCH_3), 43.22 (NCH_3), 33.42 (C-1′), 16.08 (CH_3), 15.56 (CH_3). C 67.8%, H 5.4%, N 3.8%, MS-DCI *m/z*: 354 $(M+H)^+$.

2-Hydrazo-1,2-dihydroacronycine (6) Treatment of 2-oxo-1,2-dihydroacronycine (**5**) (50 mg, 0.15 mmol) for 15 min with 0.15 ml of hydrazine hydrate in conditions essentially similar to those described for the preparation of **4** afforded after crystallization with EtOH compound **6** (28 mg, 53%). mp 185 °C. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 8.24 (1H, dd, J=8, 1.5 Hz, H-8), 7.55 (1H, td, J=8, 1.5 Hz, H-10), 7.28 (1H, d, J=8 Hz, H-11), 7.19 (1H, t, J=8 Hz, H-9), 6.28 (1H, s, H-5), 5.25 (2H, br, NH_2), 3.91 (3H, s, OCH_3), 3.77 (3H, s, NCH_3), 3.54 (2H, s, H-1), 1.53 (6H, s, 2×CH_3). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 177.84 (C-7), 160.95 (C-6), 158.93 (C-4a), 149.55 (C-12a), 149.17 (C-2), 145.81 (C-11a), 132.57 (C-10), 126.77 (C-8), 125.82 (C-7a), 121.91 (C-9), 116.43 (C-11), 111.61 (C-6a), 100.00 (C-12b), 96.04 (C-5), 78.10 (C-3), 56.19 (OCH_3), 44.74 (NCH_3), 25.17 (2×CH_3), 23.11 (C-1). C 68.3%, H 6.2%, N 11.6%, MS-DCI *m/z*: 352 $(M+H)^+$.

Cell Culture and Cytotoxicity L1210 cells were cultivated in RPMI 1640 medium (Gibco) supplemented with 10% fetal calf serum, 2 mM L-glutamine, 100 units/ml penicillin, 100 μg/ml streptomycin, and 10 mM HEPES buffer (pH=7.4). Cytotoxicity was measured by the microculture tetrazolium assay as described.[18] Cells were exposed to graded concentrations of drug (nine serial dilutions in triplicate) for 48 h. Results are expressed as IC_{50}, the concentration needed to reduce by 50% the optical density of treated cells with respect to the optical density of untreated controls.

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