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One-Step Synthesis of Dicarboxamides through Pd-Catalysed Aminocarbonylation with Diamines as N-Nucleophiles

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An efficient one-step synthetic strategy was used to prepare a set of dicarboxamides through palladium-catalysed aminocarbonylation of iodoalkenyl and iodoaryl compounds, with use of various alkyl- and aryldiamines as N-nucleophiles. The isolated yields of the dicarboxamides depended significantly on the iodo substrate and diamine structures, as well as on the reaction conditions, the best one (ca. 70%) being achieved with 1-iodocyclohexene as substrate and 1,4-diaminobutane as nucleophile, at 100 °C and 30 bar of CO. When iodobenzene was used as model aryl halide, the highest yield of the target dibenzamides (ca. 65%) was obtained with 1,4-diaminobenzene as coupling amine, at 100 °C and 10 bar of CO. Preliminary studies on their in vitro cytotoxicity against human lung carcinoma A549 cells showed *N*,*N*′-(butane-1,4-diyl)dibenzamide and androst-16-ene-based dicarboxamides to be the most efficient cytotoxic agents, with IC_{50} values of approximately 40 μM.

Introduction

Recently, dicarboxamides have been receiving significant attention, due to their numerous applications in several fields such as synthetic,[1–4] coordination[5,6] and medicinal chemistry.[7–20] The dicarboxamide functionality is a common structural motif found in a variety of bioactive compounds exhibiting beneficial properties, including anti-inflammatory,[8–10] antifungal[11] and antitumour activities.[12–14] For instance, diamide-linked γ-cyclodextrin dimers,[15] anthranilic diamide derivatives containing aryl-substituted isoxazoline moieties,[16] 2-(2-aminothiazol-4-yl)-pyrrolidine-based tartrate diamides[17] and furazan-3,4-diamide analogues[18] (Figure 1) have lately been developed and applied as selective and potent anticancer agents. Biological tests on imidazole-dicarboxamides have demonstrated their antiproliferative activity against HL-60 cells.[19] Furthermore, steroidal dicarboxamides were also found to be of great importance as molecular umbrellas in drug delivery, as antifungal and as cell antiproliferative agents.[20] Thus, the promising bioactive diversity of this class of compounds serves as a stimulus for the scientific community to develop efficient and sustainable strategies to synthesize new dicarboxamide molecules and to perform their biological evaluation.

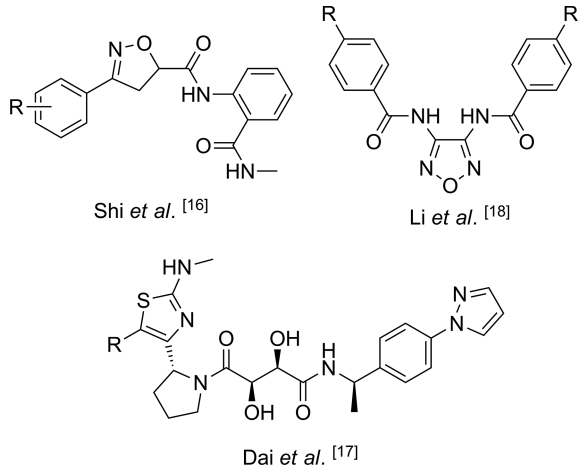

Figure 1. Structures of dicarboxamide-containing molecules with anticancer activity.

The classical methods for the synthesis of amides/diamides include the activation of the corresponding acid derivative and its coupling with amines.[21,22] However, this methodology has several disadvantages, such as limitations on the availability of the carboxylic acids, as well as con-

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tamination and toxicity issues associated with the use of highly pollutant chemicals and chemical processes involving more than one step. Alternatively, palladium-catalysed aminocarbonylation of aryl and alkenyl halides in the presence of carbon monoxide (CO), first reported by Heck in 1974,[23] is nowadays an attractive synthetic strategy for the preparation of monocarboxamides.[24–26] The Pd-catalysed carbonylation of amines for the synthesis of urea-type compounds has also been reported.[27] However, in spite of its high efficiency, Pd-catalysed aminocarbonylation has been scarcely used for the synthesis of diamides. Only a few studies relating to this subject have been reported to date; they include the synthesis of dicarboxamides through aminocarbonylation of diiodo substrates,[28] or through the application of diamines as N-nucleophiles. Among the latter, the synthesis of selenophene derivatives[29] and our recent work on the preparation of 5α-androst-16-ene dimers[30] are the only examples reported so far.

As part of our continuing research in this field, here we explore the potential of Pd-catalysed aminocarbonylation of iodoalkenyl and iodoaryl compounds as an alternative one-step synthetic route for the preparation of dicarboxamide molecules, using various diamines as N-nucleophiles. Furthermore, the activities of selected examples from these families of dicarboxamides as cytotoxic agents against A549 cancer cells have been preliminarily appraised.

Results and Discussion

The diamide motif could be obtained by applying transition-metal-catalysed carbonylation chemistry. The preparation of new dicarboxamides with modular structures by variation either of the iodo compound backbone or of the diamide linkage was envisioned, in order to modulate their electronic properties and, consequently, their solubility and biological properties (Figure 2).

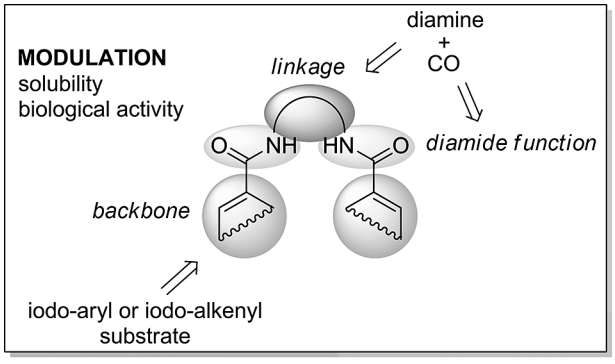
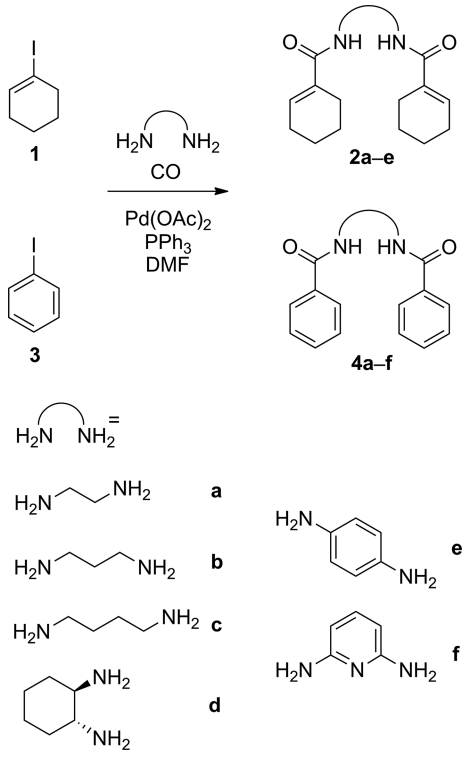


Figure 2. Design of new dicarboxamides based on aminocarbonylation.

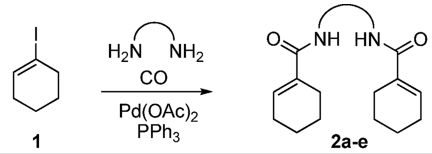
The synthesis of dicarboxamides was accomplished through reactions between either 1-iodocyclohexene (**1**) or iodobenzene (**3**), CO (1–40 bar) and the desired diamines, in the presence of a palladium catalyst formed in situ by addition of palladium(II) acetate to triphenylphosphine (in 1:2 molar ratio), together with Et_3N as base and DMF as solvent. In order to evaluate the effect of the diamide linkage, the different linear aliphatic diamines 1,2-diaminoethane (**a**), 1,3-diaminopropane (**b**) and 1,4-diaminobutane (**c**), the chiral cycloaliphatic diamine (1*S*,2*S*)-(+)-1,2-diaminocyclohexane (**d**), and the aromatic diamines 1,4-diaminobenzene (**e**) and 2,6-diaminopyridine (**f**) were used as N-nucleophiles (Scheme 1). The isolated yields for the target diamide products, obtained after workup and purification, are presented in Table 1 and Table 2.



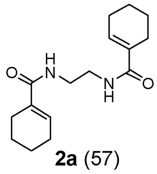
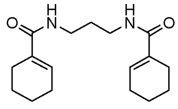
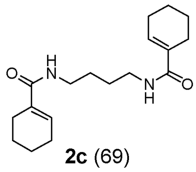
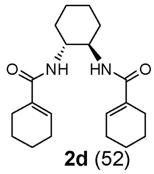
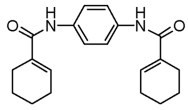
Scheme 1. Pd/PPh_3-catalysed aminocarbonylation of 1-iodocyclohexene (**1**) and iodobenzene (**3**), with use of diamines as N-nucleophiles.

To optimize the aminocarbonylation conditions for the synthesis of alkyl dicarboxamides, 1-iodocyclohexene (**1**) was chosen as the model electrophile and 1,2-diaminoethane (**a**) was selected as its coupling partner. Initially, the reaction was performed under 1 bar of CO and 50 °C, but no products were observable after 18 h (Table 1, Entry 1). This result was surprising because iodoalkenes generally undergo aminocarbonylation with monoamines under these conditions.[31] Although an increase in carbon monoxide pressure to 40 bar resulted in 27% conversion after 18 h (Table 1, Entry 2), synthetically viable yields of the target dicarboxamide **2a** could only be obtained at 100 °C (Table 1, Entries 3 and 4). Because similar results have been obtained either under 40 bar or 30 bar of carbon monoxide, the screening of other diamines in aminocarbonylation of **1** was performed at 100 °C and 30 bar of CO (Table 1, Entries 5–9). Under these conditions, the catalytic aminocarb-

Table 1. Synthesis of cyclohexenyl dicarboxamides **2** by aminocarbonylation of 1-iodocyclohexene (**1**).[a] Reaction conditions (unless otherwise stated): 1 mmol substrate **1**, 0.5 mmol diamine, 0.025 mmol $Pd(OAc)_2$, 0.05 mmol PPh_3, 0.5 mL triethylamine, 10 mL DMF, time: 3 h, levels of conversion were above 96%.



1 **2a-e**

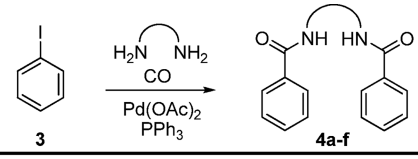
Entry	Diamine	*P* (CO) (bar)	*T* (°C)	Product isolated yield (%)[a]
1	**a**	1	50	n.d.[b]
2	**a**	40	50	n.d.[c]
3	**a**	40	100	 **2a** (57)
4	**a**	30	100	**2a** (58)
5	**b**	30	100	 **2b** (53)
6	**c**	30	100	 **2c** (69)
7	**d**	30	100	 **2d** (52)
8	**e**	30	100	 **2e** (55)

[a] Isolated yields based on the amount of substrate **1**; n.d.: not determined. [b] 1% conversion in 18 h. [c] 27% conversion in 18 h.

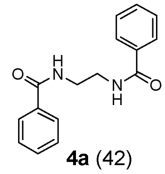
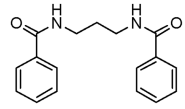
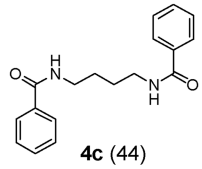
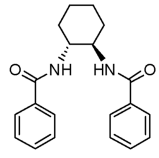
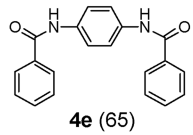
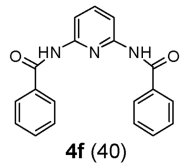
onylation of **1** with diamines **a**–**e** proceeded with practically complete conversions in 3 h, leading to the corresponding dicarboxamides **2a**–**2e** in isolated yields that varied from 52% (**2d**) up to 69% (**2c**), after workup of the crude mixture and purification.

GC–MS and NMR analysis of crude mixtures and isolated products prior to purification revealed the reactions to be chemospecific with regard to the transformation of

Table 2. Synthesis of dibenzamides **4** by aminocarbonylation of iodobenzene (**2**). Reaction conditions (unless otherwise stated): 1 mmol substrate **3**, 0.5 mmol diamine, 0.025 mmol $Pd(OAc)_2$, 0.05 mmol PPh_3, 0.5 mL triethylamine, 10 mL DMF, *T* = 100 °C, time = 3 h, levels of conversion were above 96%.



3 **4a-f**

Entry	Diamine	*P* (CO) (bar)	Product isolated yield (%)[a]
1	**a**	30	n.d.[b]
2	**a**	30	n.d.[c]
3	**a**	10	 **4a** (42)
4	**b**	10	 **4b** (35)
5	**c**	10	 **4c** (44)
6	**c**	1	**4c** (45)
7	**d**	10	 **4d** (39)
8	**e**	10	 **4e** (65)
9	**e**	1	**4e** (62)
10	**f**	10	 **4f** (40)

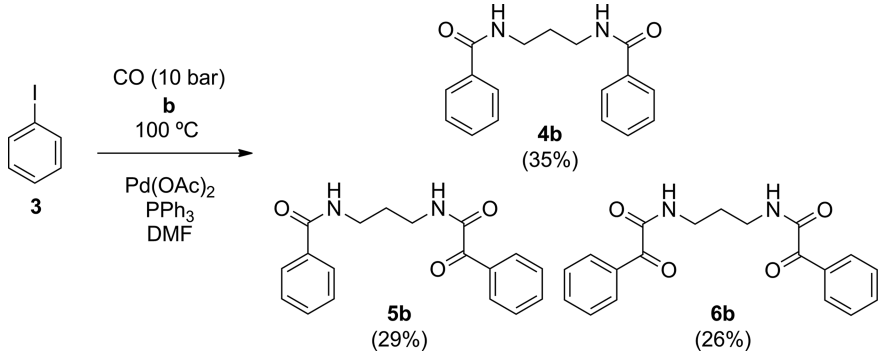
[a] Isolated yields based on the amount of substrate **3**; n.d.: not determined. [b] *T* = 50 °C, 4% conversion in 12 h. [c] *T* = 100 °C, mixture of carboxamide/ketocarboxamide products (detected by NMR and GC–MS).

the iodoalkenyl substrate into bis(carboxamides). This means that no double carbonyl insertion, which would have resulted either in carboxamide-ketocarboxamide or bis-(ketocarboxamide) derivatives, occurred. This observation is in agreement with previous findings that showed that iodoalkene substrates only undergo double carbon monoxide insertion under special conditions, such as higher carbon monoxide pressure (above 100 bar), lower temperatures (below 50 °C) and/or in the presence of bulky π-acidic phosphite ligands.[32] However, the presence of aminomonocarboxamide products was detected by GC–MS and confirmed by NMR analysis of the reaction mixtures. The use of 2,6-diaminopyridine (**f**) as N-nucleophile resulted in a complex mixture of products, and the target dicarboxamide could not be isolated.

To expand the scope of the method to the synthesis of aryl dicarboxamides, the aminocarbonylation of iodobenzene (**3**) was also performed, again with diamines **a**–**f** as N-nucleophiles, and with the same in situ Pd/PPh_3 catalyst system (Scheme 1). The reaction was initially carried out at 50 °C and 30 bar of CO, with 1,2-diaminoethane (**a**) as nucleophile. Under these conditions, only 4% conversion was observed after 12 h (Table 2, Entry 1). An increase in temperature to 100 °C, with the CO pressure kept at 30 bar, led to a mixture of carboxamide/ketocarboxamide compounds (Table 2, Entry 2), a result of the possibility of double insertion of carbon monoxide. With the goal of improving the chemoselectivity towards the bis(carboxamide) product, the catalytic reaction was then performed at a lower CO pressure (10 bar), which allowed the synthesis of **4a** in 42% isolated yield (Table 2, Entry 3). Consequently, aminocarbonylation reactions between **3** and other diamines were performed at a temperature of 100 °C and a carbon monoxide pressure of 10 bar. Under these standard conditions, the catalytic aminocarbonylation of **3** with diamines **a**–**f** proceeded with complete conversion in 3 h, leading to the corresponding dicarboxamides **4a**–**4f** in moderate isolated yields, ranging from 35% (**4b**) up to 65% (**4e**), after workup and purification (Table 2, Entries 3–10). The moderate yields obtained with linear aliphatic and cycloaliphatic diamines were the result of the formation of carboxamide-ketocarboxamide and bis(ketocarboxamide) compounds as side-products, as shown by NMR examination of the crude mixtures. Remarkably, *N*,*N*′-(1,4-phenylene)dibenzamide (**4e**) was obtained in significantly higher yield than all the other dicarboxamides linked by aliphatic chains, due to a lower tendency to formation of ketocarboxamide-type products when aromatic amines are used as nucleophiles.[32] A decrease in CO pressure to 1 bar did not substantially affect the reaction chemoselectivity, with isolated yields similar to those obtained under 10 bar of CO pressure being achieved (Table 2, Entries 6 and 9 for **4c** and **4e**, respectively). In most cases, only the bis(carboxamides) **4a** and **4c**–**4f** were isolated in appreciable yields. The only exception was the case of the aminocarbonylation reaction with 1,3-diaminopropane (**b**), in which three products were isolated after purification by chromatography: the bis(carboxamide) **4b** (35%), the carboxamide-ketocarboxamide **5b** (29%) and the bis(ketocarboxamide) **6b** (26%) (Scheme 2).

Several mechanistic proposals for this reaction have been described in the literature.[33,34] With regard to the reduction of the Pd^{II} precursor to Pd^0, some authors postulate that the phosphine ligand in excess acts as reducing agent, with $O{=}P(Ph)_3$ having been identified by NMR spectroscopy.[34] Other authors propose the involvement of water in Pd-catalysed carbonylation reactions, through formation of I–Pd–CO_2H intermediates, which undergo decarboxylation and successive reductive elimination.[35] Because anhydrous conditions are used in our case, the formation of triphenylphosphine oxide, indicated by GC–MS analysis (*m*/*z* $[M]^+ = 277$), suggests that triphenylphosphine is probably involved in palladium reduction. The structures of **4a**–**f**,[36–39] **5b** and **6b** were established by NMR spectroscopy and further confirmed by high-resolution mass spectrometry. An attempt to perform the aminocarbonylation of the less reactive bromobenzene under the same conditions, with use of 1,2-diaminoethane as N-nucleophile, was unsuccessful, giving only traces of the desired diamide observed by NMR spectroscopy.

Selected dicarboxamide compounds from each family (**2a**, **2c**, **2d**, **4c** and **4f**), in addition to the previously developed steroid dimers **7c**, **7d** and **7e**[30] (Figure 3), were evaluated as cytotoxic agents against A549 human lung carcinoma cells, which have frequently been chosen by our group[40] and others[41,42] as a suitable cell culture to perform toxicity tests. Therefore, concentration–response experiments were performed to establish the cytotoxic activity of each selected compound (Figure 4).



Scheme 2. Isolated products obtained from aminocarbonylation of iodobenzene (**3**) with 1,3-diaminopropane (**b**) as N-nucleophile.

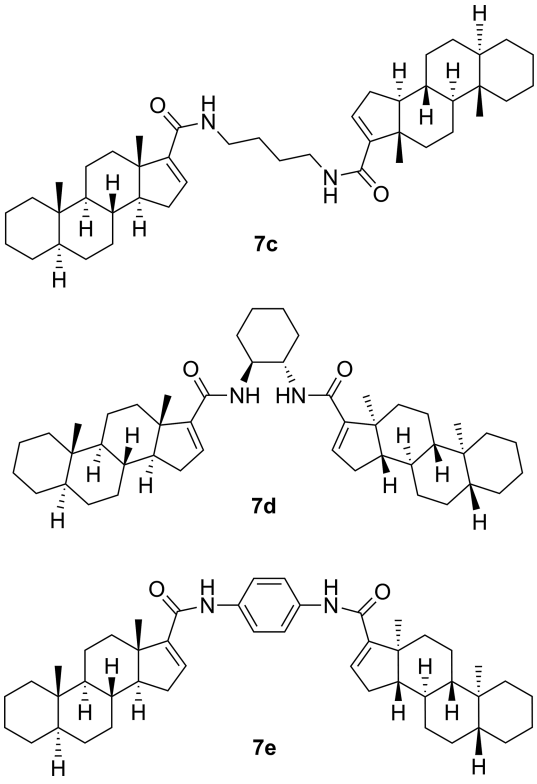


Figure 3. Dicarboxamide steroid dimers[30] also evaluated in this study as cytotoxic agents against A549 human lung carcinoma cells.

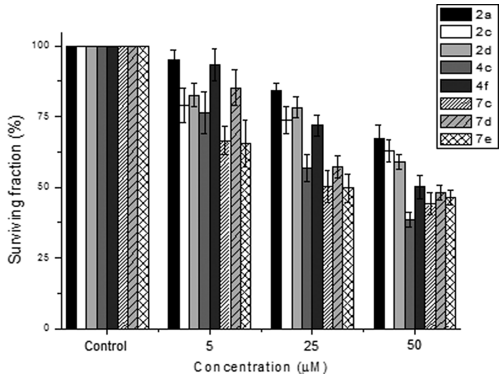


Figure 4. Cytotoxic activity of dicarboxamide compounds against A549 carcinoma cells. (The data shown are the means +/– SDs of at least three independent experiments.).

We observed that *N*,*N*′-(butane-1,4-diyl)dibenzamide (**4c**) was the most efficient cytotoxic agent when a high agent concentration (50 μM) was used, resulting in the death of 65% of the A549 cells. However, at lower agent concentrations (5–25 μM), the steroidal dimeric compounds **7c** and **7e** revealed cytotoxic activities similar to or even higher than that of **4c**. With regard to the dicarboxamides based on bis(cyclohexenyl) skeletons, we could see that the cytotoxicities of compounds **2c** and **2d** were relatively higher than that of **2a**. When the activities of compounds containing 1,4-butylenediamide bridges were compared, the phenyl and steroidal skeletons **4c** and **7c**, respectively, showed higher cytotoxic activities than the cyclohexenyl-derived dimer **2c**, over the whole range of concentrations.

The IC50 values expressed in μM, summarised in Table 3, establish the relative order of effectiveness for the dicarboxamides' cytotoxicities: **4c** ≈ **7c** ≈ **7e** > **7d** ≈ **4f** > **2d** > **2c** > **2a**. From these results we can conclude that the bioactivity of symmetric bis(carboxamides) of this type can be modulated by adjustments both on the diamide linkage and on the iodo compound backbone. However, the observed slight differences in cytotoxicity might equally well be due to differences in solubility, metabolic stability or permeability of the compounds themselves. It should be noted that the cytotoxic activities of the most efficient dicarboxamide compounds from this series against A549 cancer cells are comparable with the values for other cytotoxic agents previously described in the literature.[41,42]

Table 3. IC_{50} (μM) inhibitory concentrations with A549 human lung carcinoma cells.

Diamide	**2a**	**2c**	**2d**	**4c**	**4f**	**7c**	**7d**	**7e**
IC_{50} (μM)	65	60	55	40	50	40	50	40

Conclusions

This synthetic methodology constitutes a versatile, one-step and atom-economical route for the preparation of alkenyl and aryl dicarboxamides by catalytic aminocarbonylation. The selectivity for dicarboxamides is dependent on the substrate, reaction conditions and diamine structure, the highest yield having been obtained with 1-iodocyclohexene (**1**) as substrate and 1,4-diaminobutane (**c**) as N-nucleophile, at 100 °C and 30 bar of CO. Preliminary investigations into the cytotoxic effects of the studied dicarboxamide compounds against A549 cancer cells suggest that the cytotoxic activity depends not only on the diamide moiety but also on the iodoalkene/iodoarene skeleton, with the lowest IC_{50} values being observed with *N*,*N*′-(butane-1,4-diyl)dibenzamide (**4c**) and the 5α-androst-16-ene-based dicarboxamides **7c** and **7e**. These promising results show that the application of the catalytic diaminocarbonylation reaction as a synthetic tool may open new perspectives for the preparation of libraries of bioactive dimeric compounds through fine-tuning both of the dicarboxamide linkage and of the iodo compound structure.

Experimental Section

General Information: Manipulation of all moisture-sensitive reagents was carried out under argon with use of Schlenk and needle/syringe techniques. Glassware was dried in an oven at 200 °C and cooled under argon. NMR spectra were recorded in $CDCl_3$, [D_7]-DMF or [D_6]DMSO with Varian Inova 400 and Bruker Avance 400 spectrometers, at 400.13 MHz for ^1H NMR and at 100.62 MHz for ^{13}C NMR spectroscopy. Chemical shifts (δ) are reported in ppm

relative to $CHCl_3$ (7.26 and 77.16 ppm for ^1H and ^{13}C, respectively), relative to DMF (8.03 and 163.15 ppm for ^1H and ^{13}C) or relative to DMSO (2.50 ppm for ^1H and 39.52 ppm for ^{13}C). Samples of the catalytic reactions were analysed with a Hewlett Packard 5830A gas chromatograph fitted with a capillary column coated with OV-1 [internal standard: naphthalene; injector temp. 250 °C; oven: starting temp. 50 °C (hold-time 11 min), heating rate 15 °C min^{-1}, final temp. 320 °C; detector temp. 180 °C; carrier gas: helium (rate: 1 mL min^{-1})]. The FT-IR spectra were taken in KBr pellets with an IMPACT 400 spectrometer (Nicolet) and use of a DTGS detector in the 400–4000 cm^{-1} region; the resolution was 4 cm^{-1}. High-resolution mass spectrometry analysis was carried out with a Bruker Microtof apparatus, equipped with selective ESI detector. The diamines, palladium(II) acetate, triphenylphosphine and iodobenzene were purchased from Sigma–Aldrich. 1-Iodocyclohexene (**1**)[31] was prepared from cyclohexanone by a modified Barton procedure.[43] The steroid dicarboxamides **7c**, **7d** and **7e** were synthesised by aminocarbonylation of 17-iodo-5α-androst-16-ene as previously reported.[30]

Synthesis of Dicarboxamides through Catalytic Aminocarbonylation: In a typical reaction, $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), triphenylphosphine (13.2 mg, 0.05 mmol), the iodo substrate (1 mmol), the diamine nucleophile (0.5 mmol) and triethylamine (0.5 mL) were dissolved in dried DMF (10 mL) under argon in a 100 mL autoclave. The atmosphere was changed to carbon monoxide and the autoclave was pressurised to the desired pressure (30 bar CO for cyclohexenedicarboxamides and 1 bar CO for dibenzamides). The reaction was allowed to proceed for 3 h with stirring at 100 °C, and products were analysed by GC–MS and NMR spectroscopy. The mixture was then concentrated and the solvents were evaporated to dryness. The residue was dissolved in chloroform (20 mL) and washed with water (3 × 20 mL). The organic phase was dried with Na_2SO_4, filtered and concentrated to a crystalline material or waxy residue. All compounds were subjected to column chromatography [Silicagel 60 (Merck), 0.063–0.200 mm], or simply recrystallised from solvents (the exact ratios are specified below for each compound).

***N*,*N*′-(Ethane-1,2-diyl)bis(cyclohex-1-enecarboxamide) (2a):** Yield 0.080 g (58%), white solid, m.p. 218–220 °C. R_f = 0.20 (EtOAc/$CHCl_3$ 2:1). ^1H NMR (400 MHz, $CDCl_3$): δ = 6.67 (br. s, 2 H, C=CH), 6.53 (br. s, 2 H, NH), 3.47 (d, J = 2.4 Hz, 4 H, N-CH_2CH_2-N), 2.19–2.24 (m, 4 H, CH=CCH_2), 2.12–2.18 (m, 4 H, C=$CHCH_2$), 1.65–1.71 (m, 4 H, CH=CCH_2CH_2), 1.55–1.61 (m, 4 H, C=$CHCH_2CH_2$) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 169.9, 134.5, 132.7, 40.7, 25.6, 24.3, 22.3, 21.7 ppm. IR (KBr): $\tilde{\nu}$ = 3298 (v br, NH), 1659 (CO), 1611 (C=C) cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{16}H_{25}N_2O_2$ [M + H]$^+$ 277.1911; found 277.1908.

***N*,*N*′-(Propane-1,3-diyl)bis(cyclohex-1-enecarboxamide) (2b):** Yield 0.077 g (53%), beige solid, m.p. 110–112 °C. R_f = 0.50 ($CHCl_3$/CH_3OH 25:1). ^1H NMR (400 MHz, $CDCl_3$): δ = 6.71 (br. s, 2 H, NH), 6.66 (s, 2 H, C=CH), 3.31 (dd, J = 5.6, 11.2 Hz, 4 H, N-$CH_2CH_2CH_2$-N), 2.21–2.28 (m, 4 H, CH=CCH_2), 2.10–2.16 (m, 4 H, C=$CHCH_2$); 1.61–1.69 (m, 6 H, CH=CCH_2CH_2, N-$CH_2CH_2CH_2$-N), 1.54–1.60 (m, 4 H, C=$CHCH_2CH_2$) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 169.4, 133.9, 133.1, 35.8, 30.0, 25.5, 24.3, 22.3, 21.6 ppm. IR (KBr): $\tilde{\nu}$ = 3315 (v br, NH), 1659 (CO), 1617 (C=C) cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{17}H_{27}N_2O_2$ [M + H]$^+$ 291.2067; found 291.2077.

***N*,*N*′-(Butane-1,4-diyl)bis(cyclohex-1-enecarboxamide) (2c):** Yield 0.105 g (69%), white solid, m.p. 202–205 °C. R_f = 0.25 (EtOAc/$CHCl_3$ 2:1). ^1H NMR (400 MHz, $CDCl_3$): δ = 6.62 (s, 2 H, C=CH), 5.89 (br. s, 2 H, NH), 3.33 [d, J = 6.0 Hz, 4 H, N-$CH_2(CH_2)_2CH_2$-N], 2.20–2.24 (m, 4 H, CH=CCH_2), 2.13–2.17 (m, 4 H, C=$CHCH_2$), 1.56–1.71 [m, 12 H, C=$CHCH_2CH_2CH_2$, N-$CH_2(CH_2)_2CH_2$-N] ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 168.9, 133.6, 133.2, 39.2, 27.2, 25.5, 24.4, 22.3, 21.7 ppm. IR (KBr): $\tilde{\nu}$ = 3344 (v br, NH), 1662 (CO), 1616 (C=C) cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{18}H_{29}N_2O_2$ [M + H]$^+$ 305.2224; found 305.2224.

***N*,*N*′-(*trans*-Cylohexane-1,2-diyl)bis(cyclohex-1-enecarboxamide) (2d):** Yield 0.086 g (52%), beige solid, m.p. 248–250 °C. R_f = 0.55 ($CHCl_3$/CH_3OH 25:1). ^1H NMR (400 MHz, $CDCl_3$): δ = 6.58 (s, 2 H, C=CH), 6.20 (br. s, 2 H, NH), 3.74 (br. s, 2 H, N-CH-CH-N), 2.11–2.17 (m, 8 H, CH=CCH_2, C=$CHCH_2$), 1.54–1.78 [m, 12 H, C=$CHCH_2CH_2CH_2$, N-$CHCH_2(CH_2)_2CH_2$CH-N], 1.24–1.39 [m, 4 H, N-$CHCH_2(CH_2)_2CH_2$CH-N] ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 169.4, 134.1, 133.0, 54.0, 32.5, 25.6, 24.9, 24.3, 22.3, 21.7 ppm. IR (KBr): $\tilde{\nu}$ = 3320 (v br, NH), 1660 (CO), 1619 (C=C) cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{20}H_{31}N_2O_2$ [M + H]$^+$ 331.2380; found 331.2377.

***N*,*N*′-(1,4-Phenylene)bis(cyclohex-1-enecarboxamide) (2e):** Yield 0.089 g (55%), beige solid, m.p. 240–242 °C (dec.). R_f = 0.20 ($CHCl_3$/CH_3OH 10:1). ^1H NMR (400 MHz, [D$_6$]DMSO): δ = 9.51 (br. s, 2 H, NH), 7.56 (s, 4 H, Ph-H), 6.62 (br. s, 2 H, C=CH), 2.16–2.25 (m, 8 H, CH=CCH_2), 1.56–1.63 (m, 8 H, C=$CHCH_2CH_2$) ppm. ^{13}C NMR (100.6 MHz, [D$_6$]DMSO): δ = 166.7, 134.7, 134.0, 132.6, 120.2, 24.8, 24.0, 21.8, 21.3 ppm. IR (KBr): $\tilde{\nu}$ = 3320 (v br, NH), 1656 (CO), 1623 (C=C) cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{20}H_{25}N_2O_2$ [M + H]$^+$ 325.1911; found 325.1917.

***N*,*N*′-(Ethane-1,2-diyl)dibenzamide (4a):**[36] Yield 0.056 g (42%), white solid (recrystallised from EtOAc/diethyl ether 1:2), m.p. 228–230 °C. ^1H NMR (400 MHz, [D$_7$]DMF): δ = 8.69 (br. s, 2 H, NH), 7.97 (d, J = 7.2 Hz, 4 H, Ph-*ortho*), 7.46–7.58 (m, 6 H, Ph-*meta*,*para*), 3.60–3.64 (m, 4 H, N-CH_2CH_2-N) ppm. ^{13}C NMR (100.6 MHz, [D$_7$]DMF): δ = 167.9, 136.0, 132.2, 129.4, 128.3, 40.8 ppm. IR (KBr): $\tilde{\nu}$ = 3296 (v br, NH), 1633 (CO) cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{16}H_{16}N_2O_2Na$ [M + Na]$^+$ 291.1104; found 291.1096.

***N*,*N*′-(Propane-1,3-diyl)dibenzamide (4b):**[36] Yield 0.049 g (35%), beige solid, m.p. 118–120 °C. R_f = 0.15 ($CHCl_3$/EtOAc 2:1). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.87 (d, J = 7.2 Hz, 4 H, Ph-*ortho*), 7.41–7.54 (m, 6 H, Ph-*meta*,*para*), 7.28 (br. s, 2 H, NH), 3.51–3.58 (m, 4 H, N-$CH_2CH_2CH_2$-N), 1.75–1.85 (m, 2 H, N-$CH_2CH_2CH_2$-N) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 168.3, 134.4, 131.7, 128.7, 127.1, 36.4, 30.0 ppm. HRMS (ESI): *m*/*z* calcd. for $C_{17}H_{19}N_2O_2$ [M + H]$^+$ 283.1441; found 283.1434.

***N*-[3-(2-Oxo-2-phenylacetamido)propyl]benzamide (5b):** Yield 0.045 g (29%), beige solid, m.p. 63–65 °C. R_f = 0.25 ($CHCl_3$/EtOAc 2:1). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.25 (d, J = 6.0 Hz, 2 H, Ph-*ortho*), 7.89 (br. s, 1 H, NH), 7.84 (d, J = 6.0 Hz, 2 H, Ph-*ortho*), 7.41–7.48 (m, 5 H, Ph-*meta*, Ph-*para*, NH), 7.37 (t, J = 6.0 Hz, 2 H, Ph-*meta*), 3.44–3.53 (m, 4 H, N-$CH_2CH_2CH_2$-N), 1.78–1.84 (m, 2 H, *N*-$CH_2CH_2CH_2$-N) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 188.0, 168.0, 163.3, 134.5, 132.1, 132.0, 131.5, 131.0, 128.6, 128.6, 127.1, 36.4, 36.2, 29.5 ppm. HRMS (ESI): *m*/*z* calcd. for $C_{18}H_{18}N_2O_3$ [M + H]$^+$ 311.1390; found 311.1395.

***N*,*N*′-(Propane-1,3-diyl)bis(2-oxo-2-phenylacetamide) (6b):** Yield 0.044 g (26%), yellow oil. R_f = 0.5 ($CHCl_3$/EtOAc 2:1). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.33 (d, J = 7.6 Hz, 4 H, Ph-*ortho*), 7.60–7.64 (m, 2 H, Ph-*para*),7.45–7.50 (m, 4 H, Ph-*meta*), 7.40 (br. s, 2 H, NH), 3.46–3.53 (m, 4 H, N-$CH_2CH_2CH_2$-N), 1.86–1.92 (m, 2 H, N-$CH_2CH_2CH_2$-N) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ =

187.7, 162.6, 134.6, 133.4, 131.3, 128.7, 36.4, 29.5 ppm. HRMS (ESI): *m*/*z* calcd. for $C_{19}H_{18}N_2O_4$ $[M + H]^+$ 339.1339; found 339.1336.

***N*,*N*′-(Butane-1,4-diyl)dibenzamide (4c):**[32,33] Yield 0.067 g (45%), white solid (recrystallised from EtOAc/diethyl ether 1:2), m.p. 172–174 °C. ^{1}H NMR (400 MHz, [D$_7$]DMF): δ = 8.49 (br. s, 2 H, NH), 7.97 (d, J = 7.2 Hz, 4 H, Ph-*ortho*), 7.46–7.56 (m, 6 H, Ph-*meta*,-*para*), 3.42–3.45 [m, 4 H, N-$CH_2(CH_2)_2CH_2$-N], 1.69 [br. s, 4 H, N-$CH_2(CH_2)_2CH_2$-N] ppm. ^{13}C NMR (100.6 MHz, [D$_7$]DMF): δ = 167.5, 136.2, 132.1, 129.3, 128.3, 40.4, 28.1 ppm. IR (KBr): $\tilde{\nu}$ = 3318 (v br, NH), 1630 (CO) cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{18}H_{20}N_2O_2Na$ $[M + Na]^+$ 319.1417; found 319.1424.

***N*,*N*′-[(1*S*,2*S*)-Cyclohexane-1,2-diyl]dibenzamide (4d):**[36] Yield 0.063 g (39%), beige solid (recrystallised from EtOAc/diethyl ether 1:2), m.p. 230–232 °C. $[\alpha]_D^{20}$ = +70 (c = 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.70 (d, J = 7.2 Hz, 4 H, Ph-*ortho*), 7.38–7.40 (m, 2 H, Ph-*para*), 7.28–7.33 (m, 4 H, Ph-*meta*), 6.96 (br. s, 2 H, NH), 4.04 (br. s, 2 H, N-CH-CH-N), 2.16–2.24 [br. s, 2 H, N-$CHCH_aH_b(CH_2)_2CH_aH_bCH$-N], 1.85 [br. s, 2 H, *N*-$CHCH_aH_b(CH_2)_2CH_aH_bCH$-N], 1.41–1.51 [m, 4 H, N-$CHCH_2(CH_2)_2CH_2CH$-N] ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 168.4, 134.3, 131.5, 128.6, 127.1, 54.6, 32.5, 25.0 ppm. IR (KBr): $\tilde{\nu}$ = 3309 (v br, NH), 1635 (CO) cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{20}H_{23}N_2O_2$ $[M + H]^+$ 323.1754; found 323.1760.

***N*,*N*′-(1,4-Phenylene)dibenzamide (4e):**[37,38] Yield 0.103 g (65%), beige solid (recrystallised from $CHCl_3$/EtOAc 1:10), m.p. 320–322 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 10.24 (s, 2 H, NH), 7.96 (d, J = 7.2 Hz, 4 H, Ph-*ortho*), 7.75 (s, 4 H, phenylene H), 7.51–7.60 (m, 6 H, Ph-*meta*,*para*) ppm. ^{13}C NMR (100.6 MHz, [D$_6$]DMSO): δ = 165.4, 135.0 (double intensity), 131.5, 128.4, 127.6, 120.7 ppm. HRMS (ESI): *m*/*z* calcd. for $C_{20}H_{17}N_2O_2$ $[M + H]^+$ 317.1285; found 317.1280.

***N*,*N*′-(Pyridine-2,6-diyl)benzamide (4f):**[39] Yield 0.064 g (40%), white solid, m.p. 165–167 °C. R_f = 0.70 ($CHCl_3$/CH_3OH 20:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.40 (br. s, 2 H, NH), 8.08 (d, J = 8.0 Hz, 2 H, pyr-*meta*), 7.87 (d, J = 7.6 Hz, 4 H, Ph-*ortho*), 7.76 (t, J = 8.2 Hz, 1 H, pyr-*para*), 7.51–7.57 (m, 2 H, Ph-*para*), 7.43–7.49 (m, 4 H, Ph-*meta*) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 165.6, 149.8, 141.0, 134.2, 132.4, 128.9, 127.2, 110.0 ppm. IR (KBr): $\tilde{\nu}$ = 3338 (v br, NH), 1651 (CO) cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{19}H_{16}N_3O_2$ $[M + H]^+$ 318.1237; found 318.1244.

Biological Essays: The A549 cells were seeded onto a 96-well culture plate at 1×10^4 cells per 0.2 mL of culture medium. After attachment, the cells were incubated with the dicarboxamide compounds at different concentrations (10^{-4} to 10^{-6} M) for 48 h at 37 °C. After this time, the medium containing the dimers was substituted with fresh medium (0.2 mL), and incubation was carried out for 24 h. After one day, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT, 20 µL, final concentration 0.5 mg mL^{-1}) was added to each well, and incubation was continued for a further 3 h at room temperature. The precipitated formazan salt was dissolved in DMSO/methanol (1:1) solution and the MTT test was performed with the aid of an ELISA plate reader (GENios Plus, Tecan Trading AG, Switzerland). Cell survival was expressed in terms of the absorbance changes of the formazan salt, and survival rate was given as the percent ratio of viable treated cells versus the number of viable untreated cells. The number of cells was determined from linear regression of a calibration curve.

Supporting Information (see footnote on the first page of this article): Copies of the ^{1}H, ^{13}C NMR and HRMS (ESI) spectra of all compounds.

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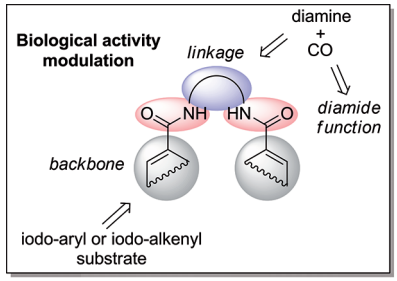
Dicarboxamides and Cytotoxicity

The one-step synthesis of a set of dicarboxamides was accomplished through palladium-catalysed aminocarbonylation of iodoalkenyl and iodoaryl compounds, with use of diamines as N-nucleophiles. The cytotoxic activities of some of the diamides against human lung carcinoma A549 cancer cells have been preliminarily appraised.



Keywords: Synthetic methods / Dicarboxamides / Carbonylation / Medicinal chemistry / Antitumor agents

