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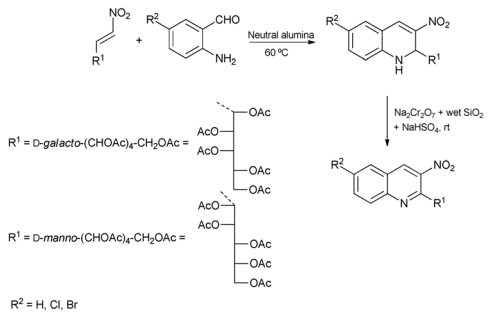

Antiproliferative activity of new 2-glyco-3-nitro-1,2-dihydroquinolines and quinolines synthesized under solventless conditions promoted by neutral alumina

V. Luque-Agudo, José M. Padrón, E. Román, J. A. Serrano and M. V. Gil*

This paper describes the syntheses of new 2-glyco-3-nitro-1,2-dihydroquinolines and 2-glyco-3-nitroquinolines by one-pot aza-Michael–Henry-dehydration reactions using green procedures, such as a minimal amount of solvent combined with an heterogeneous catalyst (neutral alumina). The reactivity of a nitro group-double bond system has also been investigated; thus, addition of indole or pyrrole to *N*-formylated 1,2-dihydroquinolines has been studied. Finally, the antiproliferative activity of these new compounds has been evaluated against a panel of six human solid tumor cell lines, and compared to pharmacological reference compounds, finding that their activity is in the low micromolar range and that the carbohydrate moiety configuration modulates GI_{50} values.

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PAPER

Antiproliferative activity of new 2-glyco-3-nitro-1,2-dihydroquinolines and quinolines synthesized under solventless conditions promoted by neutral alumina†

V. Luque-Agudo,[a] José M. Padrón,[b] E. Román,[a] J. A. Serrano[a] and M. V. Gil *[a]

Cite this: DOI: 10.1039/c8nj03372b

Received 6th July 2018,
Accepted 2nd October 2018

DOI: 10.1039/c8nj03372b

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This paper describes the syntheses of new 2-glyco-3-nitro-1,2-dihydroquinolines and 2-glyco-3-nitroquinolines by one-pot aza-Michael–Henry–dehydration reactions using a minimal amount of solvent and neutral alumina as the heterogeneous catalyst. The reactivity of the nitro group–double bond system has also been investigated; thus, the addition of indole or pyrrole to *N*-formylated 1,2-dihydroquinolines has been studied. Finally, the cytotoxicity and antiproliferative activity of these new compounds have been evaluated against a panel of six human solid tumor cell lines and compared to pharmacological reference compounds, finding that their activity is in the low micromolar range and that the carbohydrate moiety configuration modulates the GI_{50} values.

Introduction

Quinoline **1** was first isolated from coal tar in 1834 by F. F. Runge, and it is still the main source of commercial quinoline.[1] Cinchona bark extract (genus *Rubiaceae*) has been extensively used to combat malaria. Detailed analysis allowed the identification of more than 20 alkaloids, where quinine **2**, cinchonidine **3**, quinidine **4** and cinchonine **5** (Fig. 1) were those with the highest biological activity. In general terms, quinoline **1** derivatives exhibit different biological activities,[2–5] and their syntheses have been reviewed.[6]

In spite of their numerous applications, there are only a few reported examples of quinoline **1** derivatives containing acyclic or cyclic carbohydrate moieties, and none at C-2.[7–11]

Regarding the synthesis of nitroquinolines, three general methods have usually been used for their preparation, such as nitration of quinolines,[12] reaction of 3-nitroquinolines *N*-oxides with a limited number of reagents,[13] and a modified Friedländer synthesis.[14,15]

Dihydroquinolines also present a broad spectrum of biological activities and are very important in medicinal and pharmaceutical chemistry.[16] Synthetic methods of chiral 1,2-dihydroquinolines are very limited;[17,18] thus, due to the potential application of these substances, the synthetic challenge of preparing them using carbohydrates, which are considered as attractive products for drug design, as chiral auxiliaries has been considered.

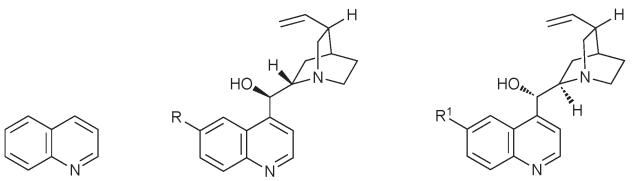

Fig. 1 Structures of compounds **1–5**.

Alternative reaction media are being considered in order to comply with the current legislation on environmental, safety and health policies, such as performing the reactions in the absence of solvent,[19] and the combination of this technique with the use of heterogeneous catalysts, which constitutes one of the most powerful green synthetic tools.

In this work, the synthesis of 3-nitro-1,2-dihydroquinolines and 3-nitroquinolines bearing carbohydrate moieties at C-2 has been carried out under solventless conditions promoted by neutral alumina, considering, additionally, their possible antiproliferative activity. To the best of our knowledge, there are no reported examples of this type of compound. Due to this lack of available literature, we have based our synthesis on that reported by Yao *et al.*[15] and adapted it to the asymmetric version using nitroolefins derived from carbohydrates as chiral

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† Electronic supplementary information (ESI) available. See DOI: 10.1039/c8nj03372b

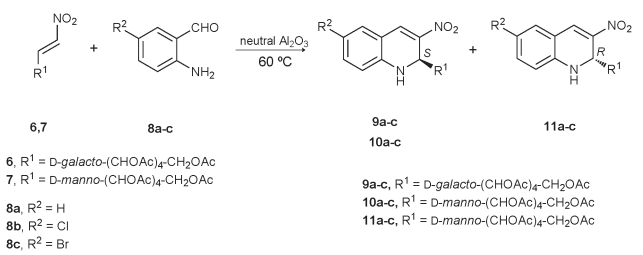
inducers. Ballini *et al.*[20] improved the reaction conditions by avoiding the use of DABCO and benzene. Moreover, since the influence of the structure of the carbohydrate moiety on the cytotoxic and antiviral activity of certain 3-nitrochromenes has been described,[21] the influence of the stereochemistry of the carbohydrate moiety inserted at C-2 of the novel synthesized quinoline-derivatives on their antiproliferative activity has been studied.

Results and discussion

2-Glyco-3-nitro-1,2-dihydroquinolines **9a–11c** were prepared by one-pot aza-Michael–Henry-dehydration reactions between carbohydrate derived nitroalkenes **6** and **7** and 2-aminobenzaldehydes **8a–c**, using neutral alumina as the catalyst,[20] heating at 60 °C and adding dichloromethane (3.12 mol%) to homogenize the mixture (Scheme 1). The results are summarized in Table 1. Both nitroalkenes were used to compare the asymmetry induced by the chiral center at C-3 of compounds **6** and **7** and to study whether that skeleton affects the potential antiproliferative activity of the new compounds (Table 2).

The assignment of C-2 configuration for **9a–c** and **10a–c** + **11a–c** was tentatively made, considering that nitroalkenes **6** and **7** adopt a preferred conformation[22] in which their C-2 *Si* and *Re* faces, respectively, are less hindered for the nucleophilic attack of the amine group present in **8a–c**, and, therefore, more favourable (Fig. 2). Processes involving nitroalkene **6** were completely diastereoselective, since only one of the two possible diastereoisomers was detected. The observed diastereoselectivity could be explained taking into account the steric hindrance caused by the acetate group at C-3 of compound **6**, not found in **7**.

Our group proposes a correlation between the value of $J_{1',2}$ and the absolute configuration assigned to C-2 in 3-nitro-1,2-dihydroquinolines with peracetylated carbohydrate moieties:



Scheme 1 Reaction between nitroalkenes **6** and **7** and aminobenzaldehydes **8a–c**.

Table 1 Reaction times, yields and product ratios for **9a** and **10a–c** + **11c** products

	6			**7**		
R^2	*t* (days)	Yield (%)	Product	*t* (days)	Yield (%)	Product (ratio)
H	1	89	**9a**	1.5	88	**10a** + **11a** (1 : 1.6)
Cl	2	63	**9b**	1.5	92	**10b** + **11b** (1 : 1.6)
Br	3	59	**9c**	2	87	**10c** + **11c** (1 : 1.1)

Table 2 Correlation between C-2 configuration and value of $J_{1',2}$

Compound	$J_{1',2}$ (Hz)	C-2 configuration
9a	9.5	*S*
9b	9.5	*S*
9c	9.5	*S*
10a	0	*S*
11a	6.0	*R*
10b	1.0	*S*
11b	5.5	*R*
10c	1.0	*S*
11c	5.0	*R*

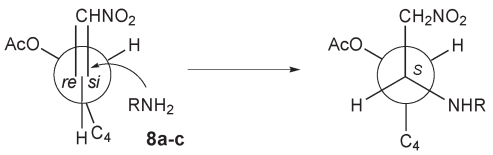


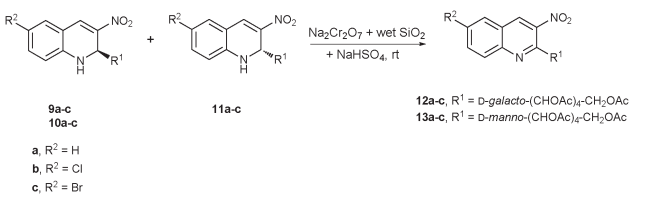
Fig. 2 Preferential attack of **8a–c** on nitroalkene **6**.

thus, if C-1′ presents the *S* configuration (D-*galacto*), for compounds with C-2(*S*) configuration, the coupling constants $J_{1',2}$ will be large (5–10 Hz), whereas for compounds having the C-2(*R*) configuration, these same constants will have a small value (0–2 Hz). When C-1′ presents the *R* configuration (D-*manno*), the values of the coupling constants are opposite with respect to those of the previous case. This correlation has also been observed, and in some cases confirmed by X-ray diffraction, in other 3-nitro-2*H*-thiochromenes and in 3-nitro-2*H*-chromenes synthesized in our lab.[23]

3-Nitroquinolines **12a–c** and **13a–c** were obtained by treatment of 1,2-DHQs **9a–c** or **10a–c** + **11a–c** with a mixture of sodium dichromate, wet silica gel (50% w/w) and sodium bisulfate[24] at room temperature (Scheme 2), with short reaction times and in good yields (Table 3).

Deacetylated quinolines **14a–15c** were synthesized (Scheme 3) to improve the solubility of the new compounds in aqueous medium, which is the closest medium to cellular tissue. The results are summarized in Table 4.

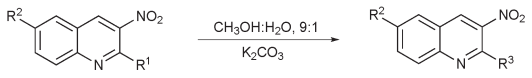
The *trans*-nitro group–double bond system is preserved in the skeleton of the 1,2-DHQs; for this reason, we studied their reactivity as acceptors in Michael additions. Thus, reactions between 1,2-DHQs, which were firstly *N*-formylated[25] to avoid oxidation to the corresponding quinolines, and indole **17** or pyrrole **18** were carried out using basic alumina as the catalyst,[26] heating at 70 °C and adding dichloromethane (3.12 mol%) (Schemes 4 and 5).



Scheme 2 Oxidation of **9a–c** and **10a–c** + **11a–c** to quinolines **12a–c** and **13a–c**.

Table 3 Reaction times and yields for the oxidation of 1,2-DHQs **9a–c** and **10a–c** + **11a–c** to quinolines **12a–13c**

Compound	R^2	Time (h)	Yield (%)
12a	H	1.5	83
12b	Cl	3.25	87
12c	Br	2.25	71
13a	H	0.5	47
13b	Cl	1.75	76
13c	Br	3	85



12a-c, R^1 = D-*galacto*-$(CHOAc)_4$-CH_2OAc
13a-c, R^1 = D-*manno*-$(CHOAc)_4$-CH_2OAc

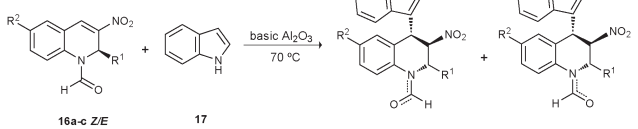
14a-c, R^3 = D-*galacto*-$(CHOH)_4$-CH_2OH
15a-c, R^3 = D-*manno*-$(CHOH)_4$-CH_2OH

a, R^2 = H
b, R^2 = Cl
c, R^2 = Br

Scheme 3 Deacetylation of carbohydrate moieties.

Table 4 Reaction times and yields for deacetylated compounds **14a–c** and **15a–c**

Compound	R^2	Time (h)	Yield (%)
14a	H	1	93
14b	Cl	1	95
14c	Br	1	66
15a	H	1.5	42
15b	Cl	1	53
15c	Br	1	67



16a-c *Z/E* **17** **19a-b** *Z* **20a-c** *E*

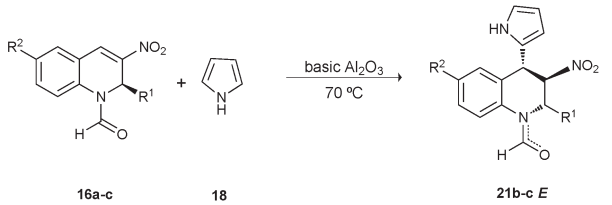
R^1 = D-*galacto*-$(CHOAc)_4$-CH_2OAc
16a, R^2 = H
16b, R^2 = Cl
16c, R^2 = Br

Scheme 4 Addition of indole **17** to compounds **16a–c**.

For processes involving indole **17**, the two *Z*/*E* rotamers of the same diastereoisomer were isolated, except in the case of **16c**, in which only **20c** was isolated. However, for those involving pyrrole **18**, only *E* rotamers were isolated in pure form, although *Z* ones were also detected by ^{1}H-NMR analysis of the crude reaction. As the NOE experiments were inconclusive, the assignment of *Z*/*E* isomerism was performed by taking into account previous studies. Nagarajan *et al.*[27] concluded that in the case of *N*-formyltetrahydroquinolines, the major isomer is *E*, according to the comparison of chemical shifts of their NMR spectra signals and those of lilolidone, an analogue product.

Antiproliferative activity

Previous theoretical quantitative structure–activity relationship studies applied to *trans*-2-(2-nitrovinyl)-furan predicted that more than 50% of the biological activity lies in the *trans*-nitro group–double bond system.[28] Antiproliferative activity results of structurally-related compounds synthesized by our group[23,29] support this hypothesis. For that reason, the previously mentioned activity of compounds **9a–16c**, including the starting nitroolefins **6** and **7**, was evaluated against a panel of six human solid tumor cell lines: A-549 (non-small cell lung), SW1573 (non-small cell lung), HBL-100 (breast), T-47D (breast), HeLa (cervix) and WiDr (colon). The GI_{50} values (concentration of compound required to inhibit 50% of tumor cell growth) are depicted in Table 5. Evaluation was accomplished by using a slightly modified version of the protocol of the National Cancer Institute (NCI) of the United States.[30,31] The standard anticancer drugs etoposide, cisplatin and 5-fluorouracil were used as references for comparative purposes.



16a-c **18** **21b-c** *E*

R^1 = D-*galacto*-$(CHOAc)_4$-CH_2OAc
16a, R^2 = H
16b, R^2 = Cl
16c, R^2 = Br

Scheme 5 Addition of pyrrole **18** to compounds **16a–c**.

As can be observed in Table 5, the GI_{50} values of the selected compounds are, in general, worse than those of the reference patterns. Antiproliferative activity oscillates between moderate and low, but, despite that, some conclusions can be inferred:

Among the acetylated 3-nitro-1,2-dihydroquinolines with the D-*galacto*-configuration moiety, **9a–c**, the activity decreases in the order R^2 = H > Cl > Br, for all tumor cell lines. For this set of compounds, **9b** was found to be more effective than 5-fluorouracil against T-47D and WiDr cell lines, and is also slightly less active than the pharmacological patterns etoposide and cisplatin.

The activity of the acetylated 3-nitroquinolines with the D-*galacto*-configuration moiety, **12a–c**, is lower than that of their precursors, the 1,2-dihydroquinolines. However, the C-6-bromo-substituted compound **12c** has moderate activity, exhibiting values comparable to those of **9a** for the HeLa cell line. Even so, compound **12b** remains the most active in the series against T-47D and WiDr over 5-fluorouracil.

It is noteworthy that upon deacetylating the carbohydrate moiety of the 3-nitroquinolines, all compounds turn out to be inactive against all cell lines, except **14c**, which exhibits moderate activity, with values very similar to those of 5-fluorouracil against T-47D and WiDr.

Pure compound **10a**, bearing a D-*manno*-configuration moiety, has relatively high GI_{50} values, being inactive against T-47D and WiDr cell lines. However, it is interesting that the activity of the **10c** + **11c** mixture, which shows a markedly good activity profile, is more effective than 5-fluorouracil and similar to the activity exhibited by cisplatin.

Table 5 Antiproliferative activity (GI_{50}) against human solid tumor cell lines and human fibroblasts[a]

Compound	A549 (lung)	HBL-100 (breast)	HeLa (cervix)	SW1573 (lung)	T-47D (breast)	WiDr (colon)	BJ-hTert (fibroblast)
$GI_{50} \pm s_D$ (μM)							
6	17 ± 4	14 ± 2	16 ± 2	1.7 ± 0.7	19 ± 2	18 ± 3	42 ± 11
7	20 ± 2	10 ± 3	18 ± 1	2.1 ± 0.4	22 ± 4	24 ± 5	11 ± 3
9a	29 ± 4	73 ± 29	33 ± 8	67 ± 26	71 ± 25	53 ± 16	>100
12a	70 ± 28	72 ± 26	38 ± 7	72 ± 39	>100	90 ± 18	n.t.
14a	>100	>100	>100	>100	>100	>100	n.t.
10a	57 ± 4	34 ± 8	30 ± 1	26 ± 8	>100	>100	n.t.
15a	>100	>100	>100	>100	>100	>100	n.t.
16a	56 ± 17	83 ± 23	43 ± 4	63 ± 10	54 ± 15	56 ± 16	>100
9b	25 ± 9	26 ± 6	24 ± 9	40 ± 9	23 ± 6	30 ± 3	>100
12b	37 ± 5	>100	26 ± 6	90 ± 1	32 ± 1	47 ± 13	n.t.
14b	>100	>100	>100	>100	>100	>100	n.t.
15b	>100	>100	>100	>100	>100	>100	n.t.
16b	15 ± 2	17 ± 1	16 ± 3	12 ± 3	18 ± 4	19 ± 4	>100
9c	88 ± 17	97 ± 5	52 ± 3	91 ± 12	93 ± 12	82 ± 24	>100
12c	53 ± 16	89 ± 2	44 ± 9	41 ± 13	82 ± 17	59 ± 9	>100
14c	29 ± 5	32 ± 3	32 ± 7	54 ± 1	50 ± 10	49 ± 1	>100
10c + **11c**	3.3 ± 0.4	8.2 ± 2.6	3.4 ± 0.6	2.6 ± 0.6	2.6 ± 0.2	4.3 ± 0.4	>100
15c	>100	>100	>100	>100	>100	>100	n.t.
16c	19 ± 4	31 ± 8	18 ± 4	15 ± 3	28 ± 7	26 ± 4	>100
Etoposide	0.7 ± 0.2	2.3 ± 0.9	3.0 ± 0.9	15 ± 2	22 ± 6	23 ± 3	1.3 ± 0.6
5-Fluorouracil	2.2 ± 0.3	5.5 ± 2.3	15 ± 5	4.3 ± 1.6	47 ± 18	49 ± 7	5.5 ± 0.5
Cisplatin	2.1 ± 0.6	1.9 ± 0.2	2.0 ± 0.3	3.0 ± 0.4	15 ± 3	26 ± 6	14 ± 3

[a] Values are mean of two to four experiments. n.t. = not tested.

A significant change of activity was observed upon the *N*-formylation of the 1,2-dihydroquinolines; thus, all of them present between moderate and good GI_{50} values, being of the same order or even lower in the cases of **16b** and **16c** for tumor cell lines HeLa, T-47D and WiDr, with respect to 5-fluorouracil.

For the 3-nitro-1,2-dihydroquinolines and their derivatives, **19a–b**, **20a–c** and **21b–c**, it can be concluded that the C-6 substituent of the ring influences the antiproliferative activity of these compounds, but it is not possible to infer a clear trend in this regard.

Experimental

Materials and methods

All chemicals were purchased from commercial sources and used directly, without further purification. Preparative TLC was performed using silica gel (Merck 60 GF_{254}). TLC was performed on precoated Merck Kieselgel 60 GF_{254} aluminum backed plates; TLC spots were visualized by UV light. NMR spectra were recorded on a Bruker AC/PC instrument (500 MHz for ^1H and 125 MHz for ^{13}C) with tetramethylsilane as the internal reference and deuterated chloroform or dimethyl sulfoxide as the solvent. Coupling constants were recorded in Hz. The characterization of NMR signals was based on homonuclear double-resonance and DEPT experiments. High resolution mass spectra were recorded on an Autospec (Micromass) spectrometer, at the Centro de Investigación Tecnológica e Innovación (CITIUS) from the Universidad de Sevilla. Infrared spectra were recorded on an IR3000 Thermo Electron Corporation spectrophotometer in the range between 4000 and 600 cm^{-1}.

The evaluation of the antiproliferative activity was accomplished following the protocol of the NCI of the United States.[30,31] For each compound, the cells were exposed to serial decimal dilutions in the range of 0.001–100 μM for a period of 48 h. After exposure, the SRB method was applied to determine the optical density of each cell at 530 nm (main) and 620 nm (secondary). For each product concentration, the percentage of growth (PG) according to the NCI formulae was calculated.

Synthetic procedures

General procedure for 2-glyco-3-nitro-1,2-dihydroquinolines 9a–11c. To a heterogeneous mixture of nitroalkenes **6** and **7** 32 (1 g, 2.31 mmol) and the appropriate aminobenzaldehyde **8a–c** (2.31 mmol), neutral alumina (2.31 g) and four drops of dichloromethane (to initially homogenize the mixture) were added. The mixture was stirred at 60 °C until reaction completion (monitored by TLC, 1 : 5 hexane–diethyl ether). The crude product was extracted with methanol, filtered and washed with the same solvent until the alumina became white. If necessary, diastereoisomers were purified by PTLC (1 : 5 hexane–diethyl ether).

General procedure for 2-glyco-3-nitroquinolines 12a–13c. Quinolines were synthesized using a protocol reported in the literature.[24]

General procedure for the deacetylated products 14a–15c. To a solution of **12a–13c** (1 mmol) in 90% methanol (15 mL), potassium carbonate (0.57 g) was added. The suspension was stirred at room temperature for 1 hour (TLC, 3 : 1, benzene–methanol). The crude reaction was acidified to pH ∼ 6 with diluted HCl (if a solid appears) or Amberlite IR-120 (H^+), which was then filtered. Pure products were crystallized from methanol.

General procedure for *N*-formyl-1,2-dihydroquinolines 16a–c. A mixture of **9a–c** (1 mmol), formic acid (4.7 mmol) and acetic anhydride (4.8 mmol) was stirred at room temperature for 1–2 hours (TLC, 1 : 5 hexane–diethyl ether). After evaporation, the

residue was dissolved in dichloromethane (10 mL), washed with 5% sodium bicarbonate solution and dried with magnesium sulfate. The extract was evaporated to yield pure compounds **16a–c**.

General procedure for the addition of indole or pyrrole to *N*-formyl-1,2-dihydroquinolines. To a mixture of *N*-formyl-1,2-dihydroquinolines **16a–c** (1 mmol) and indole or pyrrole (1 mmol), activated basic alumina (1 g) and four drops of dichloromethane (to initially homogenize the mixture) were added and stirred at 60–70 °C for two days. The crude reaction was extracted with methanol and filtered. Compounds were purified by PTLC (1 : 1 hexane–ethyl acetate, 2 elutions).

Conclusions

In this paper, we report on the synthesis of new 3-nitro-1,2-dihydroquinolines and derivatives bearing a carbohydrate moiety at C-2 using green procedures, since these processes have been carried out in the absence of solvent and with a heterogeneous catalyst. Moreover, the antiproliferative activity of some of the products described herein has been studied, finding that their GI_{50} values are of the same order as those of pharmacological reference compounds in some of the cases.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was supported by the Gobierno deGobierno de Extremadura-Ayuda a Grupos de Investigación Catalogados and Fondo Europeo de Desarrollo Regional (Grant GR15022). We also thank the Universidad de Extremadura, Plan de Iniciación a la Investigación, Desarrollo Tecnológico e Innovación 2016 and Grupo Banco Santander for providing a fellowship to Verónica Luque-Agudo.

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