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# Identification of 4,6-diaryl-1,4-dihydropyridines as a new class of neuroprotective agents†

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A library of 4,6-diaryl-1,4-dihydropyridines was synthesized using a CAN-catalyzed, Hantzsch-related three component reaction starting from ammonium acetate, β-dicarbonyl compounds and a variety of α,β-unsaturated ketones including chalcones, their vinylogs and heteroanalogues. These compounds lack the structural features needed for vascular activity and were found to prevent calcium overload and behave as neuroprotective agents. One of the compounds, bearing a 2-thienyl substituent at C-4, showed the highest neuroprotective activity and was also a moderate antioxidant, being a good lead compound for further studies in this area.

## 1 Introduction

Neurodegenerative disorders constitute an increasingly serious health, social and economic problem all over the world. This alarming situation has stimulated considerable research efforts aimed at achieving a better understanding of these diseases. The most common and extensively studied neurodegenerative disorders include Alzheimer's, Parkinson's and Huntington's diseases (AD, PD, HD, respectively), together with Multiple and Amyotrophic Lateral Sclerosis (MS and ALS). In the last two decades, extensive studies on this kind of diseases led to the conclusion that these disorders show a multifactorial pathogenic character caused by different factors, including genetic, endogenous and environmental factors related to lifestyle. Although each disease is determined by its etiology and characterized by its own molecular mechanism and different clinical manifestations, there are some general traits that can be considered to be common in these disorders, including protein misfolding and aggregation, an increase of the free radical formation and of oxidative stress and a dysregulation of ionic homeostasis (especially of $Ca^{2+}$), associated with a mitochondrial dysfunction.[1]

Our interest focused on the oxidative stress that besides increasing with the age is clearly involved in the pathogenesis and evolution of a number of neurological disorders.[2] This high vulnerability of the brain to oxidative damage is related to its high level of oxygen intake, the high content of redox-active transition metal ions and a comparative lack of antioxidant protective mechanisms.[3] During the last decade, neuroprotection has been increasingly considered as a useful instrument to combat the progression of neurodegenerative disorders. Owing to the involvement of a variety of factors in the development of oxidative damage, varied strategies are being pursued in order to find molecules that could be employed as neuroprotective agents.

In recent years, an increasing body of evidence indicates that calcium dysregulation in the neuron plays a key role in the molecular mechanism of neurodegenerative disorders by inducing abnormal $Ca^{2+}$ homeostasis,[4] which strongly suggests that compounds that are able to regulate the intracellular flow of calcium maintaining it within normal levels may be effective as neuroprotective agents.[5]

Although 1,4-dihydropyridines (DHPs) can be considered a privileged structure[6] due to their pharmacological versatility,[7] their action in ion channels is certainly the best known and exploited property, and these compounds are broadly used to regulate the influx of $Ca^{2+}$ into the cells thanks to their antagonist activity on the voltage-dependent calcium channels (VDCCs).[8] Some well-known traditional dihydropyridines in clinical use have neuroprotective properties; for instance, amlodipine prevents cytotoxicity in cortical neurons isolated from stroke-prone spontaneously hypertensive rats.[9] Furthermore, the L-type voltage-sensitive calcium channel blocker S-312-d is also a neuroprotector[10] and some of the 6-amino-1,4-dihydropyridines have been shown to prevent calcium overload

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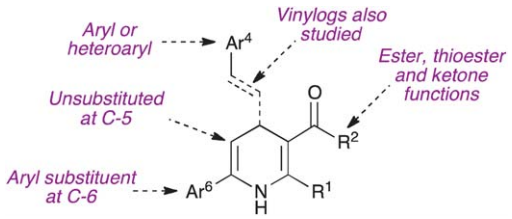
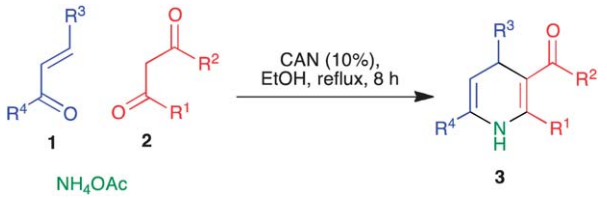
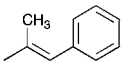



**Fig. 1** A summary of the structural features of the compounds studied in the present work.




**Scheme 1** CAN-catalyzed, three-component synthesis of compounds **3**.

**Table 1** Scope and yields of the dihydropyridine synthesis

| Entry | Compound | $R^1$ | $R^2$ | $R^3$ | $R^4$ | Yield (%) |
|---|---|---|---|---|---|---|
| 1 | **3a** (ref. 19) | $CH_3$ | OEt | $C_6H_5$ | $C_6H_5$ | 95 |
| 2 | **3b** | $C_2H_5$ | OEt | $C_6H_5$ | $C_6H_5$ | 92 |
| 3 | **3c** (ref. 19) | $CH_3$ | OEt | $C_6H_5$ | 4-$ClC_6H_4$ | 71 |
| 4 | **3d** (ref. 21) | $CH_3$ | $CH_3$ | $C_6H_5$ | $C_6H_5$ | 56 |
| 5 | **3e** | $CH_3$ | S$^t$Bu | $C_6H_5$ | $C_6H_5$ | 99 |
| 6 | **3f** | $CH_3$ | S$^t$Bu | 4-$MeOC_6H_4$ | $C_6H_5$ | 69 |
| 7 | **3g** | $CH_3$ | S$^t$Bu | 4-$BrC_6H_4$ | 4-$MeC_6H_4$ | 67 |
| 8 | **3h** | $CH_3$ | S$^t$Bu | 4-$MeC_6H_4$ | $C_6H_5$ | 99 |
| 9 | **3i** | $CH_3$ | S$^t$Bu | 4-$MeC_6H_4$ | 4-$MeC_6H_4$ | 97 |
| 10 | **3j** | $CH_3$ | OEt | 2-Thienyl | 4-$MeC_6H_4$ | 67 |
| 11 | **3k** | $CH_3$ | S$^t$Bu |  | $C_6H_5$ | 52[a] |

[a] The corresponding pyridine derivative was also isolated in 35% yield.

and neuronal cell death.[11] One major problem that needs to be addressed in this area is the prevalence of vascular side effects.

Against this background, we describe here the synthesis and pharmacological evaluation of a library of new dihydropyridine derivatives that were designed *not* to satisfy the well-known structure–activity relationships for vascular activity but which, at the same time, have the capacity to prevent neuronal calcium overload. Since vascular activity of dihydropyridines is known to require an ester function at C-5 and a small alkyl or aminoalkyl substituent at C-6,[12] we decided to prepare compounds with the structure shown in Fig. 1, which lack these features since they are unsubstituted at C-5 and bear an aryl group at C-6. In contrast to other families of dihydropyridines, which have been extensively studied, 6-aryl-1,4-dihydropyridines have received little attention in the medicinal chemistry literature beyond their identification as antagonists of the adenosine $A_3$ receptor[13] and as enhancers of the vanilloid receptor.[14] Most importantly for our purposes, they have been shown to lack vascular activity.[13a]

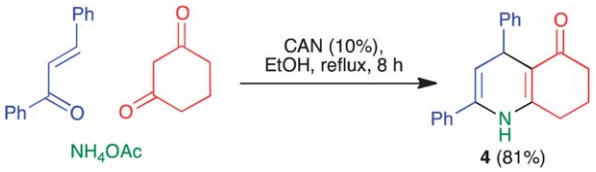
## 2 Results and discussion

### 2.1 Chemistry

Organic and medicinal chemists are increasingly conscious of the need to develop synthetic methods that go beyond the traditional requirements of chemo-, regio- and stereoselectivity, pursuing economical and environmental concerns. In this perspective, the need to increase the synthetic efficiency of the existing methods has led to the development of the concept of multibond forming reactions,[15] which minimize procedure times and waste generation because of the elimination of intermediate purification steps. In this context, the synthesis of the target compounds was achieved *via* an efficient three-component process[16] starting from 1,3-diaryl-2-propen-1-ones (chalcones) **1**, β-dicarbonyl compounds **2** and ammonium acetate as an ammonia source. All the β-dicarbonyl compounds employed, as well as some of the chalcones, were of commercial origin, whereas non-commercially available chalcones were synthesized under literature conditions.[17] After an optimization study, we carried out the synthesis of a library of eleven 6-aryl-1,4-dihydropyridine derivatives **3** in refluxing ethanol and using cerium(IV) ammonium nitrate (CAN)[18] as a Lewis acid catalyst (Scheme 1).[19] As shown in Table 1, the reaction proceeds in good to excellent yields, and was successful when using β-ketoesters (**3a–c**, **3j**), β-ketothioesters (**3e–i**, **3k**) and β-diketones (**3d**) as the dicarbonyl reagent.[20] Regarding the chalcone components, most of them had two phenyl substituents, bearing either electron-withdrawing or electron-releasing substituents (**3a–i**, entries 1–9). To increase the structural diversity in the dihydropyridine derivatives, we carried out the synthesis of compounds bearing substituents other than phenyl at the dihydropyridine C-4 position by using appropriately modified chalcones (entries 10 and 11), which led to the preparation of compounds **3j**, having an heterocyclic moiety, and **3k**, with a styryl chain. In the latter case, the target dihydropyridine was obtained together with the pyridine derivative arising from its dehydrogenation, an undesired reaction that was presumably prompted by the high degree of conjugation of the aromatized product.

Mechanistically, the three-component reaction proceeds by a Hantzsch-related mechanism that involves the initial generation of an enamine from ammonia and the starting β-dicarbonyl compound **2**, followed by Michael addition to the enone system in chalcone **1** and a final 6-*exo*-trig cyclization–dehydration sequence. This was proved by the fact that isolated ethyl 3-aminocrotonate, a commercially available enaminone that is one of the putative intermediates of our reaction, gave compound **3a** in 90% yield upon treatment with chalcone under our standard reaction conditions.

To further validate our synthetic method, and also to extend the range of structures available for the SAR study, we examined briefly the preparation of fused dihydropyridine systems by employing 1,3-cyclohexanedione as a cyclic β-diketone substrate. This reaction afforded the previously known[22] hexahydroquinoline derivative **4** in 81% yield (Scheme 2).




**Scheme 2** Three-component reaction leading to the hexahydroquinoline derivative **4**.

### 2.2 Pharmacology

To assess the neuroprotective effect of these new compounds against $[Ca^{2+}]$ overload, we first studied whether they had any effect on the $Ca^{2+}$ entry elicited by $K^+$ promoted depolarization in SH-SY5Y human neuroblastoma cells. The well-known 1,4-dihydropyridine drug nifedipine (10 μM) was used as the reference compound. A preliminary study involved assaying all synthesized dihydropyridines as inhibitors of the $Ca^{2+}$ entry at a 10 μM concentration. As shown in Table 2, most compounds **3** (with the exception of **3i**), and also hexahydroquinoline **4**, showed statistically significant activity with values of the blockade of the $Ca^{2+}$ entry ranging from 32% to 54%. Two of the compounds, namely **3b** and **3f**, have a potency similar to that of nifedipine and were studied in more detail. As shown in Fig. 2, both of them exhibited a dose-dependent response with $IC_{50}$ values of 12.8 and 26.8 μM, respectively. $Ca^{2+}$ entry blockade potencies were 9- and 20-fold less active, respectively, than nifedipine ($IC_{50}$ = 1.35 μM) used as control under the same conditions.

After assessing their activity as inhibitors of calcium overload, the neuroprotective activity of compounds **3** and **4** was examined. As shown in Table 3, most of the dihydropyridines induced a good neuroprotective effect at the assayed concentration (5 μM). It is remarkable that most compounds **3** had rather similar potencies, with values ranging between 30% and 36%, with the hexahydroquinoline derivative **4** being slightly less active. The most interesting compound in this regard was **3j**, bearing a 2-thienyl substituent at C-4, which afforded a neuroprotection above 50%.

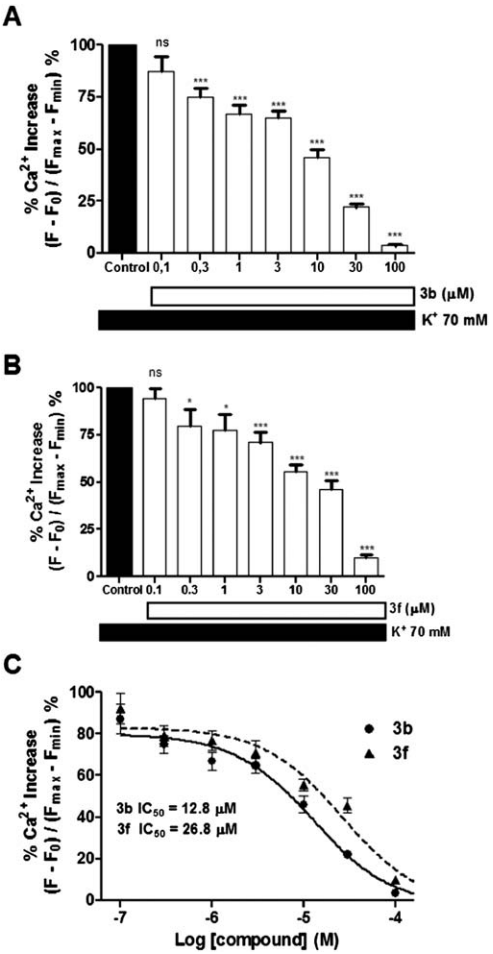



**Fig. 2** Blockade by **3b** (A) and **3f** (B) of the $[Ca^{2+}]_c$ increase induced by high $K^+$ in SH-SY5Y cells. Panel C shows non-linear regressions of % of response to 70 mM $K^+$ in the presence of increasing concentrations of compound **3b** (circles, continuous line) or compound **3f** (triangle, dotted line) and calculated $IC_{50}$. Data are expressed as means ± SEM of at least three independent experiments in triplicate. *** $p < 0.001$; ** $p < 0.01$ and * $p < 0.05$.

**Table 2** Effects of 1,4-dihydropyridine derivatives on the $[Ca^{2+}]_c$ increase elicited by 70 mM $K^+$ in SH-SY5Y cells (% inhibition with respect to a control without any drug)

| | $K^+$ (70 mM) | |
|---|---|---|
| Compound | % Blockade $Ca^{2+}$ increase | Statistical significance[a] |
| Nifedipine 10 μM | 59.75 ± 1.51 | *** |
| **3a** | 32.45 ± 3.69 | *** |
| **3b** | 53.84 ± 3.88 | *** |
| **3c** | 44.90 ± 2.11 | *** |
| **3d** | 33.82 ± 3.96 | *** |
| **3e** | 35.14 ± 5.24 | *** |
| **3f** | 52.26 ± 4.59 | *** |
| **3g** | 35.37 ± 4.31 | *** |
| **3h** | 36.80 ± 4.62 | *** |
| **3i** | 12.60 ± 4.03 | *** |
| **3j** | 36.59 ± 4.58 | *** |
| **3k** | 39.97 ± 5.23 | *** |
| **4** | 41.20 ± 5.77 | *** |

[a] Data are expressed as means ± SEM of at least four different cultures in triplicate. *** $p < 0.001$; all compounds were assayed at a concentration of 10 μM.

The similar level of activity found for most compounds hampers the deduction of clear-cut structure–activity relationships for neuroprotection in our compounds. Nevertheless, our data indicate that the presence of an electron-withdrawing group at C-3 is necessary but its nature does not seem to be important, with esters, thioesters and ketones leading to similar activities. Similarly, both electron-withdrawing and electron-releasing groups are tolerated in the aromatic rings. The higher activity found for the 4-(2-thienyl) derivative **3j** could be related to the operation of additional mechanisms (see below).

Oxidative mechanisms are very important in neurodegeneration and antioxidant properties are considered as an important feature of any potential neuroprotective compound.[23] Indeed, owing to its multifactorial nature, neurodegeneration is one of the therapeutic fields best suited to the multi-target

approach to therapy.[24,25] For these reasons, we also examined the potential of our compounds in this regard by studying their effect as neuroprotectants towards oxidative stress induced by free-radical generation induced *via* oxygen and glucose deprivation (OGD). For this assay, nifedipine (0.3 μM) and melatonin (0.1 μM) were used as reference $Ca^{2+}$ entry blockade and antioxidant compounds, respectively. In this case, we only obtained

**Table 3** Neuroprotective effect of 1,4-dihydropyridine derivatives **3** and **4** (5 μM) in the presence of 70 mM [$K^+$] in neuroblastoma cells

| | $K^+$ (70 mM co-incubation) | | |
|---|---|---|---|
| Compound | % Survival | % Protection | Statistical significance[a] |
| BASAL | 100 | — | — |
| 70 mM $K^+$ | 51.69 ± 2.17 | — | — |
| Nifedipine 0.3 μM | 58.71 ± 2.19 | 15.76 ± 3.70 | * |
| **3a** | 67.64 ± 3.12 | 34.65 ± 5.37 | *** |
| **3b** | 67.34 ± 2.31 | 31.37 ± 3.99 | *** |
| **3c** | 69.35 ± 2.45 | 36.57 ± 5.31 | *** |
| **3d** | 67.37 ± 1.42 | 32.46 ± 3.56 | *** |
| **3e** | 67.98 ± 2.21 | 34.13 ± 4.52 | *** |
| **3f** | 66.68 ± 2.95 | 31.27 ± 6.14 | *** |
| **3g** | 67.21 ± 3.26 | 34.46 ± 4.96 | *** |
| **3h** | 67.36 ± 1.98 | 30.44 ± 4.09 | *** |
| **3i** | 69.85 ± 2.40 | 36.24 ± 4.64 | *** |
| **3j** | 75.62 ± 2.10 | 50.73 ± 3.04 | *** |
| **3k** | 68.99 ± 2.56 | 35.26 ± 4.37 | *** |
| **4** | 66.42 ± 1.34 | 28.23 ± 3.31 | *** |

[a] Data are expressed as means ± SEM of at least four different cultures in triplicate. *** $p < 0.001$; * $p < 0.05$; all compounds were assayed at a 5 μM concentration.

**Table 4** Neuroprotective effect of 1,4-dihydropyridine derivatives **3** and **4** (5 μM) on SH-SH5Y cells subjected to oxygen and glucose deprivation (OGD) conditions[a]

| | OGD SH-SY5Y (4 h co-incubation + 20 h post-incubation) | | |
|---|---|---|---|
| Compound | % Survival | % Protection | Statistical significance[a] |
| BASAL | 100 | | — |
| OGD | 52.04 ± 1.63 | | — |
| Nifedipine 0.3 μM | 55.03 ± 2.78 | 12.40 ± 3.81 | ns |
| Melatonin 0.1 μM | 65.75 ± 2.08 | 28.85 ± 2.87 | *** |
| **3a** | 60.76 ± 3.17 | 22.76 ± 5.97 | ns |
| **3b** | 57.62 ± 3.70 | 17.69 ± 6.50 | ns |
| **3c** | 58.90 ± 2.93 | 19.26 ± 5.07 | ns |
| **3d** | 53.89 ± 1.61 | 9.06 ± 3.30 | ns |
| **3e** | 61.48 ± 3.59 | 24.91 ± 5.99 | ns |
| **3f** | 57.56 ± 2.95 | 17.38 ± 3.97 | ns |
| **3g** | 60.33 ± 2.00 | 21.83 ± 3.93 | ns |
| **3h** | 64.68 ± 5.13 | 31.16 ± 8.27 | ns |
| **3i** | 56.05 ± 2.42 | 12.66 ± 5.64 | ns |
| **3j** | 64.70 ± 2.90 | 31.04 ± 4.61 | * |
| **3k** | 63.85 ± 4.02 | 35.82 ± 7.18 | * |
| **4** | 62.10 ± 3.82 | 26.80 ± 6.62 | ns |

[a] Data are expressed as means ± SEM of at least four different cultures in triplicate. *** $p < 0.001$; * $p < 0.05$; all compounds were assayed at a 5 μM concentration.

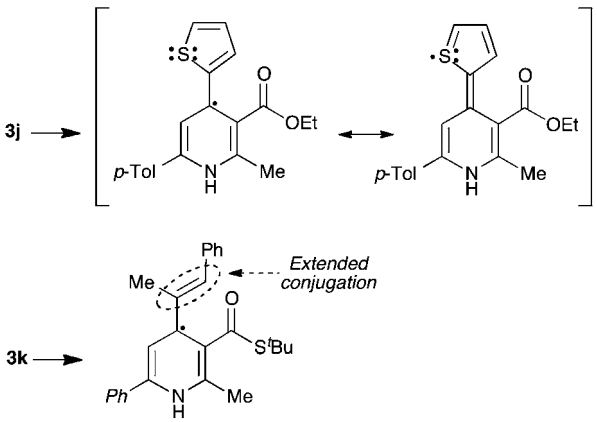



**Fig. 3** An explanation for the increased radical scavenging activity of compounds **3j** and **3k**, based on the improved delocalization of an unpaired electron at $C_4$.

statistically significant results for two compounds (**3j** and **3k**), which afforded a moderate protection (Table 4). This activity may help to explain the high potency of **3j** as a neuroprotector, which is not accompanied by the highest activity as an inhibitor of the calcium entry. Regarding the mechanism for this neuroprotection, dihydropyridines have been proved to act as radical scavengers,[26] and in the case of compounds **3j** and **3k** the antioxidant activity can be proposed to be associated with the ability of the substituents at C-4 to delocalize an unpaired electron at C-4 more efficiently than the aryl ring usually present in our compounds, owing to delocalization onto the thiophene ring sulfur atom (**3j**) or to the presence of a more extended conjugate system at C-4 (**3k**) (Fig. 3). Further studies involving dihydropyridines **3** with a higher capacity to stabilize radical species are in progress, in order to provide additional data on the role of radical scavenging as an additional mechanism contributing to neuroprotection by these compounds.

## 3 Conclusions

In conclusion, we have proved that 4,6-diaryl-1,4-dihydropyridines are a new class of neuroprotective agents, which lack the structural features needed for cardiovascular activity. They are able to prevent calcium overload, but additional mechanisms probably aid their activity as neuroprotecting agents. Thus, one of the compounds, bearing a 2-thienyl substituent at C-4, shows the highest neuroprotective activity against calcium overload and is also neuroprotective in oxidative stress. This compound can be considered as a good lead for further studies in this area, where drugs acting on more than a single target offer distinct advantages.

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