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A three-component domino protocol for the facile synthesis of highly functionalized tetrahydroisoquinolines by creation of their benzene ring

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ABSTRACT

A simple and efficient one-pot synthesis of novel 6-amino-8-aryl-2-methyl/benzyl-7-nitro-1,2,3,4-tetrahydroisoquinoline-5-carbonitriles from the reaction of 1-methyl/benzylpiperidin-4-one with β-nitrostyrenes and malononitrile in the presence of morpholine is described. This transformation proceeds through the creation of three C=C bonds, leading to a new benzene ring, and presumably occurs via a domino sequence involving Knoevenagel, Michael, Thorpe–Ziegler, and dehydrogenation reactions.

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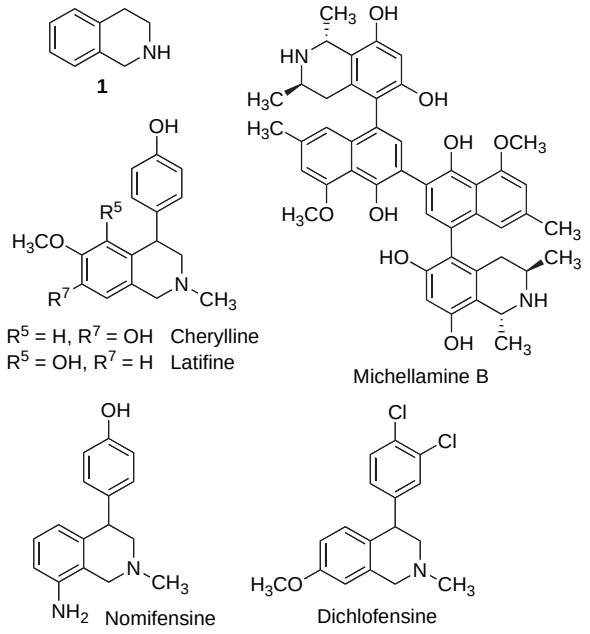
1. Introduction

The field of isoquinoline alkaloids is truly enormous and comprises 22 subgroups,[1] one of which is simple isoquinoline alkaloids, i.e., derivatives of the parent bicyclic system without additional fused rings. Among them, compounds derived from the tetrahydroisoquinoline skeleton **1** are particularly interesting. They include cactus alkaloids,[2] several mammalian alkaloids,[3] and the spirobenzylisoquinoline alkaloids.[4] Many tetrahydroisoquinoline alkaloids show interesting biological activities. Thus, the closely related cherylline[5] and latifine[6] are the active components of *Crinum powellii* and *Crinum latifolium*, respectively, which find use in Vietnamese and Chinese traditional medicines.[7] Michellamine B, isolated from the tropical liana *Ancistrocladus korupensis* and having a naphthyltetrahydroisoquinoline skeleton with axial chirality between the naphthalene and tetrahydroisoquinoline rings,[8] has been found to be fully protective against both HIV-1 and HIV-2 infected cells and identified as a candidate for further development,[9] although its cytotoxicity precluded its clinical use. The tetrahydroisoquinoline structural motif is also present in a large number of synthetic bioactive molecules,[10] including the antidepressant drugs nomifensine and dichlofensine,[11] which inhibit serotonin and dopamine uptake mechanisms.

The biological importance of tetrahydroisoquinolines has stimulated the development of a large number of synthetic approaches to this ring system. Traditionally, they have been accessed by ring closure of iminium intermediates via Pictet–Spengler reactions.[12] Other synthetic entries include intramolecular Horner[13] or Friedel–Crafts reactions,[14] followed by reduction, reductive amination-transfer hydrogenation,[15] electrophilic aromatic substitution,[16] Pd(II)- or Ag(I)-catalyzed N-alkylation,[17] and palladium-catalyzed alkylation/alkenylation-aza-Michael addition reactions.[18] However, these methods require multistep sequences and are not focused on achieving synthetic efficiency by application of the contemporary methods involving the generation of several bonds in a single



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operation.[19] Among these methods, multi-component reactions (MCRs),[20,21] which allow the simple and flexible assembly of three or more building blocks in user-friendly one-pot operations, provide convergent, atom-economic, expedient, and eco-friendly synthetic protocols for the discovery of new chemical entities (NCEs) useful in pharmaceutical and agrochemical industries, often on the basis of combinatorial library generation.[22] However, a large part of the work carried out so far on multi-component reactions pertains to the preparation of peptide-like structures employing isocyanides as building blocks. The construction of heterocycles through MCR-based strategies is not so well developed, despite the fact that about 60% of the drugs currently in the market or in the pipeline are heterocycles.[23] For the specific case of tetrahydroisoquinolines, only a few examples of multi-component syntheses are known.[24,25]

As a part of our recent research program aimed at the development of new one-pot tandem/domino multi-component protocols for the assembly of novel heterocycles[26] and/or the discovery of new lead molecules with antimycobacterial activities,[27] we report here a one-pot, three-component protocol for the synthesis of substituted tetrahydroisoquinolines based on a domino reaction between 1-alkylpiperidin-4-ones, malononitrile and β-nitrostyrene (Fig. 1). Interestingly, this strategy involves the construction of the benzene ring from a heterocyclic precursor, a disconnection almost unknown in tetrahydroisoquinoline synthesis and that has never been translated into a multi-component protocol.[28]

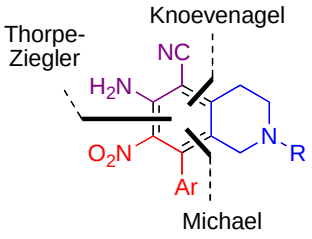


Fig. 1. Disconnections used in this work for the construction of the tetrahydroisoquinoline system.

2. Results and discussion

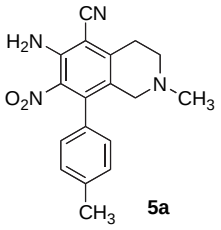
We started our optimization studies by carrying out the reaction between 1-methylpiperidin-4-one, malononitrile, and (*E*)-1-methyl-4-[2-nitro-1-ethenyl]benzene, in equimolecular amounts, using morpholine as the base and refluxing acetonitrile as the solvent. After 10 h, the domino reaction provided a promising 25% isolated yield of 6-amino-8-(4-methylphenyl)-2-methyl-7-nitro-1,2,3,4-tetrahydroisoquinoline-5-carbonitrile **5a** (Table 1, entry 1).

Table 1
Solvent- and base-screen for the synthesis of **5a**

Entry	Solvent	Base (equiv)	Time, h	Yield of **5a**[a] (%)
1	CH_3CN	Morpholine (2)	10	25
2	THF	Morpholine (2)	10	34
3	1,4-Dioxane	Morpholine (2)	12	45
4	MeOH	Morpholine (2)	7	54
5	DMSO	Morpholine (2)	10	0[b]
6	DMF	Morpholine (2)	10	0[b]
7	CH_2Cl_2	Morpholine (2)	10	0[b]
8	EtOH	Morpholine (1)	10	45
9	EtOH	Morpholine (1.5)	7	60
10	EtOH	Morpholine (2)	5	78
11	EtOH	Triethanolamine (2)	5	72
12	EtOH	Diethylamine (2)	5	70
13	EtOH	Triethylamine (2)	5	55
14	EtOH	NaOEt (2)	5	50
15	EtOH	K_2CO_3 (2)	5	35

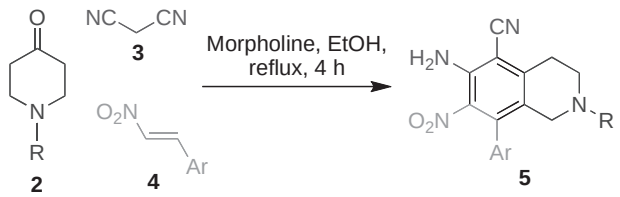
[a] Isolated yield after purification by column chromatography.
[b] No reaction took place.

This model reaction was then performed in THF, 1,4-dioxane, and methanol, which led to an enhancement of the isolated yield of the product to 34%, 45%, and 54% of **5a**, respectively (Table 1, entries 2–4). In ethanol, the reaction was completed in 5 h furnishing an isolated yield of 78% of **5a** (Table 1, entry 10), whilst the reaction completely failed to occur in DMSO, DMF, and dichloromethane (Table 1, entries 5–7), wherein the starting materials remained unchanged. This result suggests that polar protic solvents are favorable for the reaction, perhaps by stabilizing a key intermediate through hydrogen bonding, although the reason for the marked difference in yield between methanol and ethanol is not clear.



The product yield was influenced by the nature and the amount of base (Table 1, entries 8–15). Thus, an attempt to reduce the amount of morpholine led to diminished yields (entries 8–10). Furthermore, the efficacy of the bases assayed changed in the order: K_2CO_3<NaOEt<triethylamine<diethylamine≈triethanolamine<morpholine (entries 11–15). From these results, morpholine and ethanol emerged as the ideal choice of base–solvent combination for these domino reactions. The higher efficacy of organic bases, viz. morpholine, triethanolamine, and triethylamine in this reaction suggests that their conjugate acids presumably enhance the electrophilicity of (i) piperidone **2** toward Knoevenagel condensation with malononitrile and (ii) β-nitrostyrene toward Michael addition. The lower yield of **5a** obtained in the presence of triethanolamine and triethylamine suggests steric hindrance for the abstraction of proton from **7**, which could slow down the Michael addition relative to the reaction in the presence of morpholine. The fact that the reaction proceeds more efficiently in the presence of 2 equiv of morpholine is ascribable to the reversible Michael addition of the latter to the Knoevenagel condensation product, competing with its desired addition to β-nitrostyrene, which could diminish the effective concentration of the free base in the reaction mixture (see Scheme 2).

The optimal conditions thus established were then applied to the preparation of a library of 6-amino-8-aryl-2-methyl(benzyl)-7-nitro-1,2,3,4-tetrahydroisoquinoline-5-carbonitriles **5** from piperidones **2**, malononitrile **3**, and β-nitrostyrenes **4**. The reactions proceeded in 60–79% isolated yields (71% average), which are remarkable considering the large number of individual steps involved (Scheme 1 and Table 2).



Scheme 1.

The structure of 6-amino-8-aryl-2-methyl-7-nitro-1,2,3,4-tetrahydroisoquinoline-5-carbonitriles **5** is in agreement with one and two-dimensional NMR spectroscopic data as described below for the case of **5a** as a representative example. In the ^{1}H NMR spectrum

Table 2
Yields of 6-amino-8-aryl-2-methyl/benzyl-7-nitro-1,2,3,4-tetrahydroisoquinoline-5-carbonitriles **5**

Entry	R	Cmpd	Ar	Yield of **5**[a] (%)
1	CH_3	**5a**	4-MeC_6H_4	78
2	CH_3	**5b**	4-$^iPrC_6H_4$	71
3	CH_3	**5c**	4-$MeOC_6H_4$	68
4	CH_3	**5d**	4-BrC_6H_4	60
5	CH_3	**5e**	4-FC_6H_4	69
6	CH_3	**5f**	2,4-$Cl_2C_6H_3$	62
7	CH_3	**5g**	2-$MeOC_6H_4$	68
8	CH_3	**5h**	3-BrC_6H_4	72
9	$CH_2C_6H_5$	**5i**	4-MeC_6H_4	74
10	$CH_2C_6H_5$	**5j**	4-$^iPrC_6H_4$	72
11	$CH_2C_6H_5$	**5k**	4-ClC_6H_4	76
12	$CH_2C_6H_5$	**5l**	4-BrC_6H_4	79
13	$CH_2C_6H_5$	**5m**	4-FC_6H_4	68
14	$CH_2C_6H_5$	**5n**	2,4-$Cl_2C_6H_3$	70

[a] Isolated yield after purification by column chromatography.

of **5a**, the 3-CH_2 hydrogens appearing as a triplet at 2.67 ppm (J=5.7 Hz) showed HMBC correlations with C-1, C-4, and C-4a, appearing, respectively, at 55.8, 29.4, and 143.0 ppm. The triplet from 4-CH_2 hydrogens at 3.08 ppm (J=5.7 Hz) showed (i) H–H-COSY correlation with 3-CH_2 hydrogens (ii) C–H-COSY correlation with C-4 at 29.4 ppm, and (iii) HMBCs with C-4a at 143.0 ppm, C-5 at 98.6 ppm, C-8a at 124.6 ppm. The singlet of 1-CH_2 hydrogens at 3.04 ppm showed (i) a C–H-COSY correlation with carbon signal at 55.8 ppm due to C-1 and (ii) HMBCs with C-4a at 143.0 ppm and C-8a at 124.6 ppm. The 2H singlet at 5.37 ppm that vanished after D_2O wash, assignable to NH_2 hydrogens, showed HMBCs with C-5 at 98.6 ppm and C-7 at 138.4 ppm (Fig. 2). The structure of the tetrahydroisoquinolines **5** was further confirmed by a single crystal X-ray crystallographic study of **5g**[29] (Fig. 3).

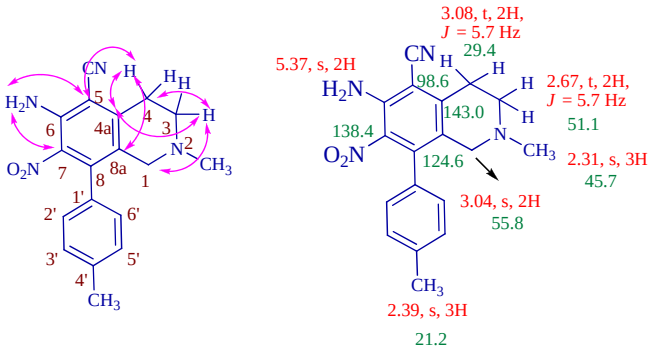


Fig. 2. Selected HMBCs and chemical shifts of **5a**.

As shown in Scheme 2, the three-component reactions presumably proceed through a domino mechanism initiated by the condensation of the starting 1-alkylpiperidin-4-one **2** with malononitrile **3** yielding an α,β-unsaturated nitrile **6**, which then undergoes a Michael addition to the β-nitrostyrene **3** to furnish anion **7**. This intermediate affords **8** via an intramolecular Thorpe–Ziegler cyclization–tautomerization. Finally, **8** is aromatized by dehydrogenation to afford compounds **5**. In support of this proposal, we will mention that base-promoted treatment of alkylidenemalononitriles with nitroolefins in the presence of base has been recently found to lead to carbocyclic systems with a substitution pattern similar to the tetrahydroisoquinolines of the present study.[30,29] In order to verify the applicability of these observations to our three-component reaction, we studied its generalization to the synthesis of carbocycles by reaction of cyclic ketones, viz. cyclopentanone **10** and cyclohexanone **11**, with malononitrile and β-nitrostyrene in the presence of morpholine. As expected, these reactions afforded good yields of highly functionalized carbocycles

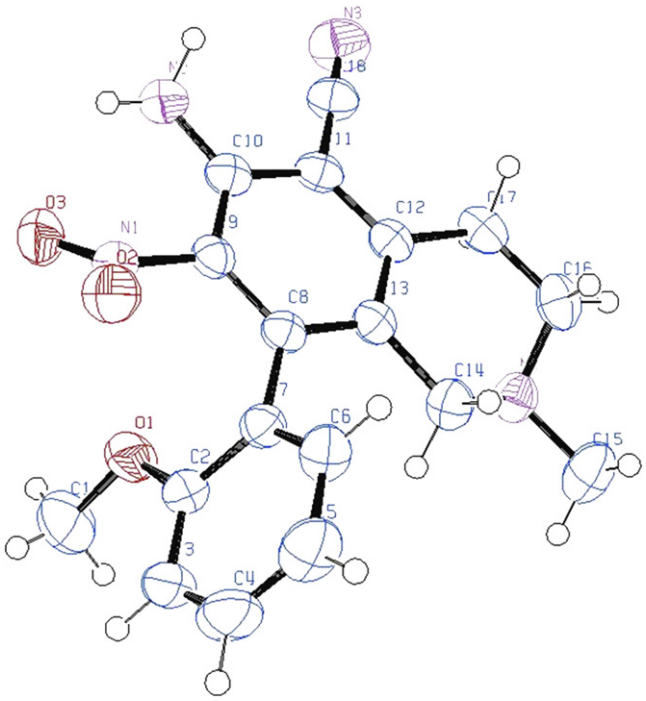
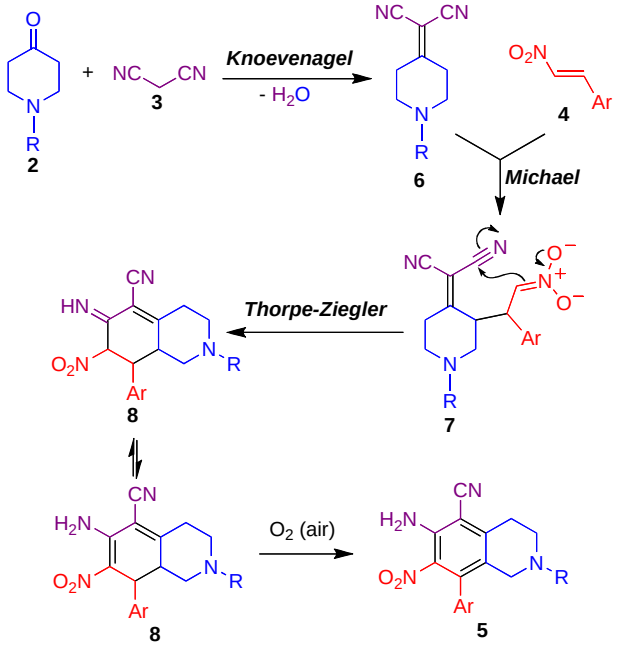
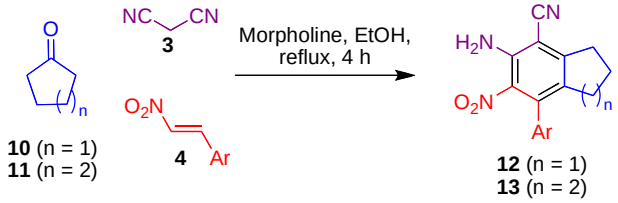


Fig. 3. ORTEP diagram of **5g**.

12 and **13**, respectively (Scheme 3 and Table 3). Besides being applicable to the preparation of bicyclic systems, these conditions were clearly more advantageous than the previously mentioned



Scheme 2.



Scheme 3.

Table 3
Yields of indane (n=1) and tetraline (n=2) derivatives

Entry	n	Cmpd	Ar	Yield[a] (%)
1	1	**12a**	4-MeC_6H_4	71
2	1	**12b**	4-ClC_6H_4	72
3	2	**13a**	4-MeC_6H_4	75
4	2	**13b**	4-ClC_6H_4	70

[a] Isolated yield after purification by column chromatography.

two-component literature methods requiring two steps and the combination of two catalysts.

3. Conclusion

In conclusion, the present work describes a facile and convergent one-pot three-component protocol for the synthesis of polysubstituted tetrahydroisoquinolines of potential pharmaceutical and biological importance, via a domino Knoevenagel condensation/Michael addition/Thorpe–Ziegler cyclization/air-promoted dehydrogenation sequence. Besides being able to generate three C=C bonds in a single synthetic operation, this methodology has the advantage of requiring simple and inexpensive starting materials and catalysts and is therefore suitable for library generation. Biological screening of the synthesized tetrahydroisoquinolines is currently in progress.

4. Experimental section

4.1. General

Melting points were measured in open capillary tubes and are uncorrected. The ^{1}H NMR, ^{13}C NMR, DEPT, H–H-COSY, C–H-COSY, and HMBC spectra were recorded on a Bruker (Avance) 300 MHz NMR instrument using TMS as internal standard and $CDCl_3$ as solvent. Standard Bruker software was used throughout. Chemical shifts are given in parts per million (δ scale) and the coupling constants are given in hertz. Silica gel-G plates (Merck) were used for TLC analysis with a mixture of petroleum ether (60–80 °C) and ethyl acetate as eluent. Elemental analyses were performed on a Perkin–Elmer 2400 Series II Elemental CHNS analyzer.

4.2. Synthesis of tetrahydroisoquinolines (5), indanes (12), and tetralines (13). General procedure

A mixture of 1-methylpiperidin-4-one or 1-benzylpiperidin-4-one (2.65 mmol), malononitrile (2.65 mmol), the suitable δ-nitrostyrene (2.65 mmol), and morpholine (5.30 mmol) was refluxed in ethanol (10 ml) for the time mentioned in Table 1. The reaction mixture during reflux reached a maximum temperature of 80 °C, which was measured by inserting the thermometer inside the reaction mixture. After completion of the reaction as monitored by TLC, the reaction mixture was concentrated under vacuum and the residue was subjected to column chromatography using a petroleum ether/ethyl acetate mixture (1:1) as eluent to afford the pure product **5**.

*4.2.1. 6-Amino-8-(4-methylphenyl)-2-methyl-7-nitro-1,2,3,4-tetrahydroisoquinoline-carbonitrile (**5a**).* Isolated as a pale yellow solid, yield: 78%, mp=193–194 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 2.31 (s, 3H, N–CH_3), 2.39 (s, 3H, CH_3), 2.67 (t, 2H, J=5.7 Hz, H-3), 3.04 (s, 2H, H-1), 3.08 (t, 2H, J=5.7 Hz, H-3), 5.37 (s, 2H, NH_2), 7.03 (d, 2H, J=7.8 Hz, Ar–H), 7.22 (d, 2H, J=7.8 Hz, Ar–H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 21.2, 29.4, 45.7, 51.1, 55.8, 98.6, 114.9, 124.6, 127.5, 129.4, 131.2, 135.7, 138.4, 140.0, 141.7, 143.0. Anal. Calcd for $C_{18}H_{18}N_4O_2$: C, 67.07; H, 5.63; N, 17.38%. Found C, 67.12; H, 5.60; N, 17.43%.

*4.2.2. 6-Amino-8-(4-isopropylphenyl)-2-methyl-7-nitro-1,2,3,4-tetrahydroisoquinoline-5-carbonitrile (**5b**).* Isolated as a pale yellow solid, yield: 71%, mp=185–186 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.30 (d, 6H, J=6.6 Hz, $2CH_3$), 2.34 (s, 3H, N–CH_3), 2.69 (t, 2H, J=5.9 Hz, H-3), 2.92–3.01 (m, 1H, CH), 3.07 (s, 2H, H-1), 3.11 (t, 2H, J=5.9 Hz, H-4), 5.39 (s, 2H, NH_2), 7.08 (d, 2H, J=8.1 Hz, Ar–H), 7.29 (d, 2H, J=8.1 Hz, Ar–H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 23.8, 29.4, 33.8, 45.7, 51.2, 55.8, 98.5, 114.9, 124.7, 126.8, 127.6, 128.0, 131.4, 140.0, 141.7, 143.0, 149.2. Anal. Calcd for $C_{20}H_{22}N_4O_2$: C, 68.55; H, 6.33; N, 15.99%. Found C, 68.63; H, 6.29; N, 15.92%.

*4.2.3. 6-Amino-8-(4-methoxyphenyl)-2-methyl-7-nitro-1,2,3,4-tetrahydroisoquinoline-5-carbonitrile (**5c**).* Isolated as a pale yellow solid, yield: 68%, mp=185–186 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 2.27 (s, 3H, N–CH_3), 2.63 (t, 2H, J=5.7 Hz, H-3), 2.95 (s, 2H, H-1), 3.03 (t, 2H, J=5.7 Hz, H-3), 5.32 (s, 2H, NH_2), 6.90 (d, 2H, J=8.4 Hz, Ar–H), 7.02 (d, 2H, J=7.8 Hz, Ar–H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 29.3, 45.7, 51.1, 55.2, 55.8, 98.5, 114.2, 114.9, 124.8, 126.2, 128.9, 135.9, 139.6, 141.7, 142.9, 159.7. Anal. Calcd for $C_{18}H_{18}N_4O_3$: C, 63.89; H, 5.36; N, 16.56%. Found C, 63.95; H, 5.31; N, 16.50%.

*4.2.4. 6-Amino-8-(4-bromophenyl)-2-methyl-7-nitro-1,2,3,4-tetrahydroisoquinoline-5-carbonitrile (**5d**).* Isolated as a pale yellow solid, yield: 60%, mp=214–215 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 2.27 (s, 3H, N–CH_3), 2.62 (t, 2H, J=5.7 Hz, H-3), 2.94 (s, 2H, H-1), 3.04 (t, 2H, J=5.7 Hz, H-3), 5.50 (s, 2H, NH_2), 6.99 (d, 2H, J=8.1 Hz, Ar–H), 7.53 (d, 2H, J=8.1 Hz, Ar–H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 29.4, 45.7, 51.0, 55.7, 99.2, 114.7, 122.9, 124.3, 129.3, 132.0, 133.3, 134.9, 138.7, 142.1, 143.7. Anal. Calcd for $C_{17}H_{15}BrN_4O_2$: C, 52.73; H, 3.90; N, 14.47%. Found C, 52.79; H, 3.85; N, 14.52%.

*4.2.5. 6-Amino-8-(4-flurophenyl)-2-methyl-7-nitro-1,2,3,4-tetrahydroisoquinoline-5-carbonitrile (**5e**).* Isolated as a pale yellow solid, yield: 69%, mp=161–162 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 2.31 (s, 3H, N–CH_3), 2.66 (t, 2H, J=5.7 Hz, H-3), 2.99 (s, 2H, H-1), 3.08 (t, 2H, J=5.7 Hz, H-3), 5.47 (s, 2H, NH_2), 7.12 (d, 4H, J=6.6 Hz, Ar–H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 29.4, 45.7, 51.1, 55.8, 99.04, 115.8, 116.1, 124.5, 129.5, 129.6, 135.3, 138.9, 142.0, 143.5, 162.3. Anal. Calcd for $C_{17}H_{15}FN_4O_2$: C, 62.57; H, 4.63; N, 17.17%. Found C, 62.63; H, 4.58; N, 17.22%.

*4.2.6. 6-Amino-8-(2,4-dichlorophenyl)-2-methyl-7-nitro-1,2,3,4-tetrahydroquinoline-carbonitrile (**5f**).* Isolated as a pale yellow solid, yield: 62%, mp=194–195 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 2.31 (s, 3H, N–CH_3), 2.66 (t, 2H, J=5.4 Hz, H-3), 2.92 (s, 2H, H-1), 3.09 (t, 2H, J=5.7 Hz, H-3), 5.85 (s, 2H, NH_2), 7.01 (d, 1H, J=8.1 Hz, Ar–H), 7.32 (d, 1H, J=8.1 Hz, Ar–H), 7.51 (d, 1H, J=2.0 Hz, Ar–H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 29.5, 45.7, 50.8, 54.8, 55.0, 100.1, 114.6, 124.4, 127.6, 129.5, 129.8, 132.6, 133.5, 135.2, 136.5, 142.9, 144.8. Anal. Calcd for $C_{17}H_{14}Cl_2N_4O_2$: C, 54.13; H, 3.74; N, 14.85%. Found C, 54.20; H, 3.68; N, 14.91%.

*4.2.7. 6-Amino-8-(2-methoxyphenyl)-2-methyl-7-nitro-1,2,3,4-tetrahydroisoquinoline-5-carbonitrile (**5g**).* Isolated as a pale yellow solid, yield: 68%, mp=177–178 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 2.26 (s, 3H, N–CH_3), 2.64 (t, 2H, J=4.5 Hz, H-3), 2.90 (s, 2H, H-1), 3.05 (t, 2H, J=4.5 Hz, H-3), 3.72 (s, 3H, OCH_3), 5.52 (s, 2H, NH_2), 6.93 (d, 2H, J=7.8 Hz, Ar–H), 7.36 (d, 2H, J=6.3 Hz, Ar–H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 29.4, 45.7, 51.1, 55.1, 55.3, 98.9, 111.1, 115.1, 120.9, 123.5, 125.1, 128.7, 130.2, 135.3, 137.5, 142.2, 143.3, 156.0. Anal. Calcd for $C_{17}H_{15}BrN_4O_2$: C, 52.73; H, 3.90; N, 14.47%. Found C, 52.79; H, 3.85; N, 14.52%.

*4.2.8. 6-Amino-8-(3-bromophenyl)-2-methyl-7-nitro-1,2,3,4-tetrahydroisoquinoline-5-carbonitrile (**5h**).* Isolated as a pale yellow solid, yield: 72%, mp=190–191 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 2.32 (s, 3H, N–CH_3), 2.66 (t, 2H, J=6.1 Hz, H-3), 2.98 (s, 2H, H-1), 3.09 (t, 2H, J=6.1 Hz, H-3), 5.57 (s, 2H, NH_2), 7.09 (dd, 1H, J=8.1,

0.9 Hz, Ar–H), 7.29 (s, 1H, Ar–H), 7.31 (t, 1H, *J*=8.1 Hz, Ar–H), 7.55 (dd, 1H, *J*=8.1, 0.9 Hz, Ar–H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 29.5, 45.8, 51.1, 55.7, 99.5, 114.7, 122.8, 124.4, 126.4, 130.3, 130.5, 131.7, 134.7, 136.5, 138.4, 142.2, 144.0. Anal. Calcd for $C_{17}H_{15}BrN_4O_2$: C, 52.73; H, 3.90; N, 14.47%. Found C, 52.79; H, 3.85; N, 14.52%.

*4.2.9. 6-Amino-2-benzyl-8-(4-methylphenyl)-7-nitro-1,2,3,4-tetrahydro-5-isoquinolinecarbonitrile (**5i**).* Isolated as a pale yellow solid, yield: 74%, mp=201–202 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 2.42 (s, 3H, CH_3), 2.68 (t, 2H, *J*=5.7 Hz, H-3), 3.05 (t, 2H, *J*=5.7 Hz, H-4), 3.22 (s, 2H, H-1), 3.55 (s, 2H, CH_2), 5.55 (s, 2H, NH_2), 7.05(d, 2H, *J*=8.1 Hz, Ar–H), 7.24 (d, 2H, *J*=8.1 Hz, Ar–H), 7.27–7.35 (m, 5H, Ar–H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 21.3, 29.3, 48.0, 54.5, 61.9, 98.6, 114.9, 124.9, 127.2, 127.5, 128.3, 128.9, 129.4, 131.3, 135.6, 137.4, 138.4, 140.1, 141.8, 143.7. Anal. Calcd for $C_{24}H_{22}N_4O_2$: C, 72.34; H, 5.57; N, 14.06%. Found C, 72.40; H, 5.51; N, 13.99%.

*4.2.10. 6-Amino-2-benzyl-8-(4-isopropylphenyl)-7-nitro-1,2,3,4-tetrahydro-5-isoquinolinecarbonitrile (**5j**).* Isolated as a pale yellow solid, yield: 72%, mp=195–196 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.31 (d, 6H, *J*=6.9 Hz, $2CH_3$), 2.70 (t, 2H, *J*=5.7 Hz, H-3), 2.94–3.01 (m, 1H, CH), 3.06 (t, 2H, *J*=5.7 Hz, H-4), 3.18 (s, 2H, H-1), 3.55 (s, 2H, CH_2), 5.41 (s, 2H, NH_2), 7.06 (d, 2H, *J*=8.1 Hz, Ar–H), 7.25–7.28 (m, 7H, Ar–H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 23.8, 29.3, 33.8, 48.3, 54.3, 62.1, 98.6, 114.9, 125.0, 126.7, 127.2, 127.5, 128.2, 128.9, 131.5, 135.6, 137.4, 140.2, 141.7, 143.6, 149.2. Anal. Calcd for $C_{26}H_{26}N_4O_2$: C, 73.22; H, 6.14; N, 13.14%. Found C, 73.28; H, 6.08; N, 13.20%.

*4.2.11. 6-Amino-2-benzyl-8-(4-chlorophenyl)-7-nitro-1,2,3,4-tetrahydro-5-isoquinolinecarbonitrile (**5k**).* Isolated as a pale yellow solid, yield: 76%, mp=212–213 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 2.69 (t, 2H, *J*=6.0 Hz, H-3), 3.05 (t, 2H, *J*=5.7 Hz, H-3), 3.14 (s, 2H, H-1), 3.55 (s, 2H, CH_2), 5.55 (s, 2H, NH_2), 7.10 (d, 2H, *J*=8.4 Hz, Ar–H), 7.19–7.35 (m, 5H, Ar–H), 7.40 (d, 2H, *J*=8.4 Hz, Ar–H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 29.4, 48.1, 54.3, 62.0, 66.6, 99.3, 114.7, 124.6, 127.4, 128.3, 128.9, 129.0, 132.9, 134.7, 134.9, 137.2, 138.9, 142.1, 144.4. Anal. Calcd for $C_{23}H_{19}ClN_4O_2$: C, 65.95; H, 4.57; N, 13.38%. Found C, 65.88; H, 4.52; N, 13.44%.

*4.2.12. 6-Amino-2-benzyl-8-(4-bromophenyl)-7-nitro-1,2,3,4-tetrahydro-5-isoquinolinecarbonitrile (**5l**).* Isolated as a pale yellow solid, yield: 79%, mp=220–221 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 2.69 (t, 2H, *J*=5.7 Hz, H-3), 3.05 (t, 2H, *J*=5.7 Hz, H-4), 3.13 (s, 2H, H-1), 3.54 (s, 2H, CH_2), 5.55 (s, 2H, NH_2), 7.03 (d, 2H, *J*=8.4 Hz, Ar–H), 7.23–7.34 (m, 5H, Ar–H), 7.56 (d, 2H, *J*=8.4 Hz, Ar–H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 29.4, 48.1, 54.4, 62.0, 99.3, 114.7, 122.8, 124.6, 127.4, 128.3, 128.9, 129.3, 132.0, 133.4, 134.8, 137.2, 138.9, 142.1, 144.5. Anal. Calcd for $C_{23}H_{19}BrN_4O_2$: C, 59.62; H, 4.13; N, 12.09%. Found C, 59.55; H, 4.20; N, 12.15%.

*4.2.13. 6-Amino-2-benzyl-8-(4-fluorophenyl)-7-nitro-1,2,3,4-tetrahydro-5-isoquinolinecarbonitrile (**5m**).* Isolated as a pale yellow solid, yield: 68%, mp=214–215 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 2.76 (t, 2H, *J*=6.0 Hz, H-3), 3.13 (t, 2H, *J*=6.0 Hz, H-4), 3.20 (s, 2H, H-1), 3.62 (s, 2H, CH_2), 5.56 (s, 2H, NH_2), 7.19 (d, 2H, *J*=7.5 Hz, Ar–H), 7.31 (d, 2H, *J*=7.5 Hz, Ar–H), 7.34–7.41 (m, 5H, Ar–H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 29.4, 48.3, 54.3, 62.0, 99.3, 114.7, 115.9, 125.0, 127.4, 128.3, 128.9, 129.6, 130.2, 135.4, 137.3, 139.0, 141.9, 144.2, 162.7. Anal. Calcd for $C_{23}H_{19}FN_4O_2$: C, 68.65; H, 4.76; N, 13.92%. Found C, 68.59; H, 4.85; N, 13.98%.

*4.2.14. 6-Amino-2-benzyl-8-(2,4-dichlorophenyl)-7-nitro-1,2,3,4-tetrahydro-5-isoquinolinecarbonitrile (**5i**).* Isolated as a pale yellow solid, yield: 70%, mp=210–211 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 2.78 (t, 2H, *J*=5.7 Hz, H-3), 3.04 (s, 2H, H-1), 3.08 (t, 2H, *J*=5.7 Hz, H-4), 3.66 (s, 2H, CH_2), 5.90 (s, 2H, NH_2), 7.01 (d, 1H, *J*=8.1 Hz, Ar–H), 7.24–7.39 (m, 6H, Ar–H), 7.50 (d, 1H, *J*=1.8 Hz, Ar–H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 29.4, 48.2, 53.5, 61.9, 100.4, 114.6, 125.0, 127.4, 127.6, 128.3, 128.4, 128.9, 129.6, 129.8, 132.8, 133.6, 135.2, 136.7, 137.4, 143.0, 145.5. Anal. Calcd for $C_{23}H_{18}Cl_2N_4O_2$: C, 60.94; H, 4.00; N, 12.36%. Found C, 60.86; H, 3.94; N, 12.45%.

*4.2.15. 5-Amino-7-(4-methylphenyl)-6-nitro-4-indanecarbonitrile (**12a**).* Isolated as a pale yellow solid, yield: 71%, mp=178–179 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 2.03–2.13 (m, 2H, CH_2), 2.38 (s, 3H, CH_3), 2.66 (t, 2H, *J*=7.2 Hz, CH_2), 3.11 (t, 2H, *J*=7.2 Hz, CH_2), 5.54 (s, 2H, NH_2), 7.08 (d, 2H, *J*=7.8 Hz, Ar–H), 7.22 (d, 2H, *J*=7.8 Hz, Ar–H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 21.3, 24.6, 32.1, 33.8, 95.2, 115.2, 127.1, 129.4, 133.2, 134.0, 138.2, 138.8, 142.9, 153.5. Anal. Calcd for $C_{17}H_{15}N_3O_2$: C, 69.61; H, 5.15; N, 14.33%. Found C, 69.69; H, 5.06; N, 14.40%.

*4.2.16. 5-Amino-7-(4-chlorophenyl)-6-nitro-4-indane-carbonitrile (**12b**).* Isolated as a pale yellow solid, yield: 72%, mp=161–162 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 2.04–2.13 (m, 2H, CH_2), 2.61 (t, 2H, *J*=7.2 Hz, CH_2), 3.11 (t, 2H, *J*=7.2 Hz, CH_2), 5.70 (s, 2H, NH_2), 7.12 (d, 2H, *J*=8.1 Hz, Ar–H), 7.39 (d, 2H, *J*=8.1 Hz, Ar–H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 24.5, 32.0, 33.8, 95.8, 114.9, 128.6, 129.0, 129.4, 133.8, 134.4, 134.8, 137.6, 143.3, 154.1. Anal. Calcd for $C_{16}H_{12}ClN_3O_2$: C, 61.25; H, 3.86; N, 13.39%. Found C, 61.32; H, 3.80; N, 13.30%.

*4.2.17. 2-Amino-4-(4-methylphenyl)-3-nitro-5,6,7,8-tetrahydro-1-naphthalenecarbonitrile (**13a**).* Isolated as a pale yellow solid, yield: 75%, mp=184–185 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.64–1.65 (m, 2H, CH_2), 1.78–1.79 (m, 2H, CH_2), 2.25 (t, 2H, *J*=5.7 Hz, CH_2), 2.38 (s, 3H, CH_3), 2.95 (t, 2H, *J*=5.7 Hz, CH_2), 5.29 (s, 2H, NH_2), 7.02 (d, 2H, *J*=6.6 Hz, Ar–H), 7.22 (d, 2H, *J*=6.6 Hz, Ar–H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 21.3, 21.7, 22.5, 27.5, 29.5, 98.9, 115.3, 126.9, 127.7, 129.3, 132.4, 135.8, 138.1, 141.2, 141.5, 145.8. Anal. Calcd for $C_{18}H_{17}N_3O_2$: C, 70.34; H, 5.58; N, 13.67%. Found C, 70.44; H, 5.62; N, 13.61%.

*4.2.18. 2-Amino-4-(4-chlorophenyl)-3-nitro-5,6,7,8-tetrahydro-1-naphthalenecarbonitrile (**13b**).* Isolated as a pale yellow solid, yield: 70%, mp=191–192 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.74–1.78 (m, 2H, CH_2), 1.85–1.93 (m, 2H, CH_2), 2.29 (t, 2H, *J*=6.3 Hz, CH_2), 3.05 (t, 2H, *J*=6.3 Hz, CH_2), 5.52 (s, 2H, NH_2), 7.17 (d, 2H, *J*=8.4 Hz, Ar–H), 7.49 (d, 2H, *J*=8.4 Hz, Ar–H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 21.6, 22.4, 27.5, 29.5, 99.5, 115.1, 126.6, 128.9, 129.3, 134.0, 134.4, 135.3, 140.3, 141.5, 146.4. Anal. Calcd for $C_{17}H_{14}ClN_3O_2$: C, 62.30; H, 4.31; N, 12.82%. Found C, 62.23; H, 4.37; N, 12.75%.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2010.12.052. These data include MOL files and InChiKeys of the most important compounds described in this article.

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