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A novel *tert*-amino effect based approach to 1,2,3,4-tetrahydroquinoline-2-spirocycloalkanes

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Abstract—An interaction of 2-[cyclohexyl(methyl)amino]benzaldehydes with substituted acetonitriles X-CH_2CN (X=CN, Tos, hetaryl) was found to yield 1-methyl-1,2,3,4-tetrahydrospiro(quinoline-2,1′-cyclohexane)-3-carbonitriles. The corresponding spiroquinoline-2,1′-cyclopentane analogues were obtained similarly starting from 2-[cyclopentyl(methyl)amino]benzaldehydes. The reaction was assumed to proceed via initial Knoevenagel condensation and further ring closure of the formed adduct according to the *tert*-amino effect mechanism. The structure of the prepared compounds was confirmed unambiguously by X-ray crystallographic study.

1. Introduction

1,2,3,4-Tetrahydroquinolines have wide pharmaceutical applications.[1,2] A number of 2,2-disubstituted tetrahydroquinoline derivatives occurs in the nature. Thus, the most known are the *Streptomyces* alkaloid virantmycin[3–10] and its related compounds, the benzastatins.[11–13] Moreover a large family of 2-substituted tetrahydroquinoline alkaloids has been isolated recently from the South African plant sources.[14–19] Quinoline-2-spirocycloalkanes form separate group of 2-substituted tetrahydroquinolines. In particular, the quinoline-2-spirocyclohexanes are especially attractive since 1-azaspiro[5,5]undecane moiety is the core of the histrionicotoxines,[20,21] the potent potassium channel blockators from the frog *Dendrobates histrionicus* (Fig. 1). So, the 2-spirotetrahydroquinoline system consists of the substructures of different natural products and, therefore, elaboration of new synthetic approaches to it is the prospective task.

The most suitable method for tetrahydroquinoline-2-spirocyclohexanes preparation was developed by Kouznetsov and co-workers.[22–28] It includes electrophilic cyclization of 1-allyl-1-anilinocyclohexanes readily available from the cyclohexanone derived Schiff bases and allylmagnesium bromide. It seems to be the best approach reported to date and has been successfully applied in the preparation of various natural products analogues.[29–31] However, the method has some limitations. It only allows products unsubstituted at position 3 of the quinoline moiety to be obtained and spiroquinolines bearing electron-withdrawing groups in the benzene ring are hardly available through this approach.[23,25] A few other syntheses of spirocyclic tetrahydroquinolines were also published.[32–35] Furthermore, several approaches to 1,2-dihydroquinoline-2-spirocycloalkanes were reported[36–41] and some of these compounds were reduced into corresponding tetrahydro derivatives.[37,38]

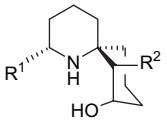

Figure 1. The histrionicotoxines. R^1 and R^2 are C_3–C_4 alkenyl.

The so-called *tert*-amino effect[†] is known as an efficient method of tetrahydroquinoline system formation (Scheme 1).[42–47] Thus, heating of compounds of type **1** in high-boiling polar solvents affords tetrahydroquinoline derivatives **2** in good yields.[42–47] The reaction is assumed to proceed via sigmatropic hydrogen 1,5-shift occurring from the canonic structure **3** and further ring closure of the bipolar intermediate

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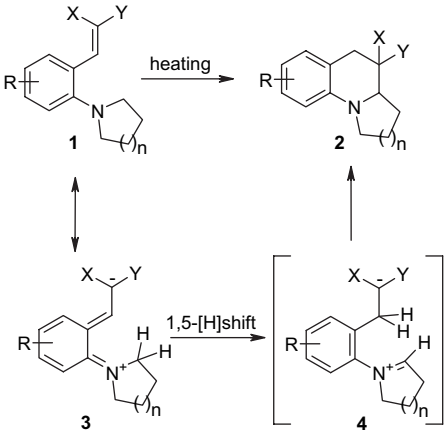
† The term was coined[48,49] to describe this type and related cyclizations.

4.[44–46] The starting materials **1** are obtained easily from the appropriate aldehydes and active methylenes X-CH_2-Y. Recently the *tert*-amino effect has been employed to prepare spirocyclic compounds using cyclic methylene components (Scheme 1, X and Y form a ring), namely the 1,3-cyclohexanedione, the Meldrum's acid, and the barbituric acid derivatives.[50–52] However, the potential of the *tert*-amino effect in the synthesis of spiro compounds is believed not to be exhausted by the use of cyclic methylenes. It seems possible to bring in a spiro-center in position 2 of tetrahydroquinoline following the scheme 1 at the expense of replacement of the pyrrolidine or piperidine moiety by other suitable amine.



Scheme 1. The *tert*-amino effect cyclization. n=1, 2. X and Y are the electron-withdrawing groups.

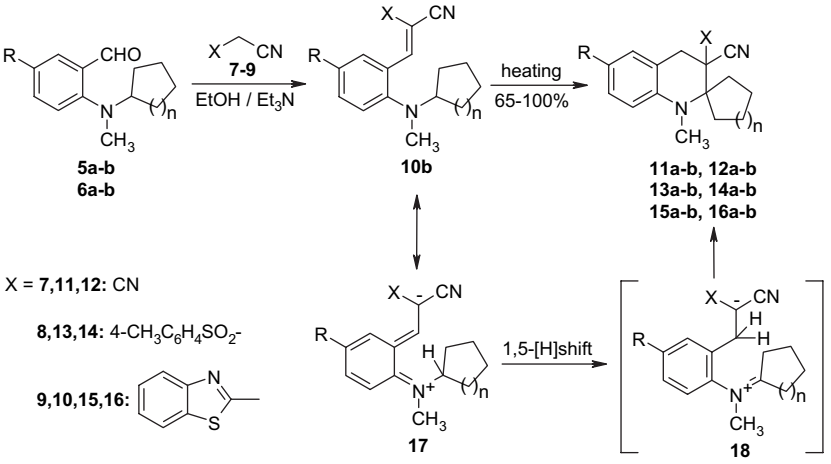
This idea was examined in the course of our research on the *tert*-amino effect[53] and spiro-heterocycles synthesis,[54,55] and the results obtained are reported herein.

2. Results and discussion

The desired aminoaldehydes **5**, **6** (Scheme 2) were prepared from 2-fluoro- and 2-chloro-5-nitrobenzaldehydes and appropriate *N*-methylcycloalkylamines. Treatment of aldehydes **5**, **6** with the nitriles **7–9** in ethanol in the presence of triethylamine was found to give the target spirocyclic quinolines **11–16** in 65–100% yields. In a single case only the reaction product appeared to be Knoevenagel adduct **10b**. Nevertheless, it was also converted into the corresponding quinoline **16b** in quantitative yield by refluxing in DMF. Apparently the derivatives **11–16** are formed according to the *tert*-amino effect mechanism (Scheme 2).[44–46] Thus, the sigmatropic hydrogen 1,5-shift occurring from the canonic structure **17** affords the bipolar intermediate **18**, which undergoes further ring closure into quinolines **11–16**. Moreover, under the conditions of Knoevenagel condensation, the cyclization of the adducts **10** turned out to be fast enough to disable their isolation, except the case of **10b**. At the same time during the previous studies[42–47,53] on the *tert*-amino effect with the same methylene compounds **7–9** and 2-pyrrolidino- or piperidinobenzaldehydes only dinitriles **2** (X=Y=CN) were obtained directly without isolation of the corresponding precursors **1**. For nitriles **8**, **9** the appropriate derivatives **1** were prepared separately and their cyclization required more drastic conditions.[53] Hence, the cycloalkyl(methyl)amino moiety is more reactive toward the *tert*-amino effect cyclization than the pyrrolidine fragment stated hitherto as the most active one.[44–46]

Within the series of compounds **11–16** the five-member derivatives (n=1) were more reactive than the six-member ones (n=2) requiring shorter reaction times and giving higher yields of the products. Furthermore, the nitro substituted compounds (R=NO_2) exhibited lower reactivity toward the cyclization than their unsubstituted analogues (R=H), whereas the nitriles **7–9** could be placed in the following reactivity order: **8**>**7**≫**9**. The latter observations are in complete agreement with the reported data.[44–46,53] Accordingly, compound **10b** is the least reactive sample and, therefore, a higher boiling solvent, DMF is needed for cyclization.

The structure of the prepared compounds **11–16** was initially deduced from ^{1}H and ^{13}C NMR spectroscopic data and then confirmed unambiguously by X-ray crystallographic study carried out for the derivative **14a** (Fig. 2). According to the



Scheme 2. Compounds **5**, **11**, **13**, **15**: n=1; compounds **6**, **10**, **12**, **14**, **16**: n=2. R=**a**: H, **b**: NO_2.

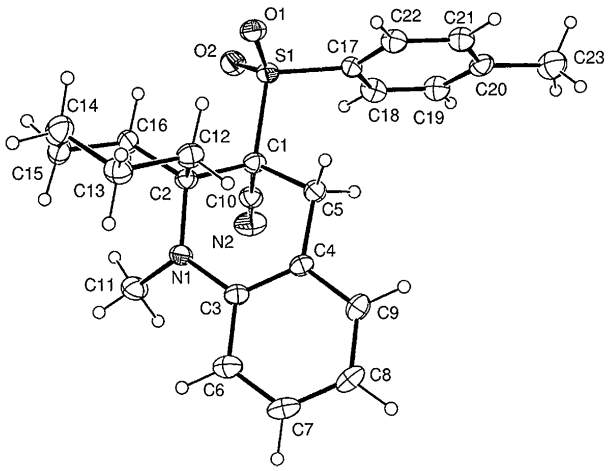


Figure 2. X-ray molecular structure of compound **14a** with the atom numbering used in the crystallographic analysis.

crystal data[‡] the cyclohexane ring adopts chair conformation. The tetrahydropyridine moiety is slightly twisted. Thus, the atoms N1, C3, C4, and C5 are almost coplanar (with precision of 0.05 Å). The atoms C2 and C1 are deviated from this plane at +0.54 Å and −0.28 Å, respectively.

To resume, the present investigation has resulted in a novel approach to 1,2,3,4-tetrahydroquinoline-2-spirocyclopentanes and -cyclohexanes. The cycloalkylamino moiety has been shown to be applicable in the *tert*-amino effect and its reactivity has been compared with that of pyrrolidine.[44–46] A spiro-center has been first generated at the expense of amine fragment during the *tert*-amino effect process. The present synthesis complements well the Kouznetsov's procedure[22–28] since it allows preparation of spiroquinolines substituted at the position 3 unavailable through the known approach.[22–28] Further research on the scope of this method for the preparation of quinolines spiro-fused with other carbo- and heterocycles of different sizes is being carried out and the results will be reported.

3. Experimental

3.1. General

N-Methylcyclopentylamine[56] and 2-benzothiazole-acetonitrile **9**[57] were prepared as reported. Other reagents were commercially available. All melting points were determined in open capillary tubes in a Thiele apparatus and were uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Varian UNITY*plus* 400 (400 MHz for ^{1}H and 100 MHz for ^{13}C) spectrometer in DMSO-d_6 or $CDCl_3$ solutions. Chemical shifts (δ) are given in parts per million downfield from internal Me_4Si. *J* values are in hertz. The purity of all compounds prepared was checked by ^{1}H NMR and LC/MS on an Agilent 1100 instrument.

[‡] Crystallographic data (excluding structural factors) for the structure in this paper have been deposited at the Cambridge Crystallographic Data Center as supplementary publication number CCDC 604539. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

3.1.1. Aminobenzaldehydes 5a, 6a. Powdered K_2CO_3 (3.04 g, 0.022 mol) was added to a solution of 2-fluorobenzaldehyde (2.48 g, 0.02 mol) and appropriate amine (0.022 mol) in DMF (10 mL) and the resulted mixture was refluxed with stirring for 6 h. After cooling it was poured into water (25 mL) and extracted with EtOAc (2×10 mL). The extract was washed with saturated aqueous NH_4Cl solution, dried (Na_2SO_4), and evaporated in vacuo to give crude compounds **5a**, **6a** as red oils. Further purification by chromatography on silica gel with EtOAc–hexane (1:4, v/v) mixture as eluent afforded derivatives **5a**, **6a** as yellow oils.

3.1.1.1. 2-[Cyclopentyl(methyl)amino]benzaldehyde (5a). Yield 48%. Yellow oil; ν_{max} (KBr) 2931, 2855, 1685, 1595, 1477, 1452, 1386, 1293, 1272, 1191, 1148, 1081, 1003, 942, 832, 760 cm^{-1}. δ_H 1.54–1.84 (8H, m, 4CH$_2$), 2.79 (3H, s, NCH$_3$), 3.64 (1H, m, N-CH<), 7.08 (1H, t, *J*=7.6, 5-H), 7.19 (1H, d, *J*=7.6, 3-H), 7.49 (1H, t, *J*=7.6, 4-H), 7.80 (1H, d, *J*=7.6, 6-H), 10.37 (1H, s, CHO). δ_C 23.1 (2CH$_2$), 29.3 (2CH$_2$), 38.2 (CH$_3$), 62.3 (NCH<), 111.7 (3-C), 122.9 (5-C), 131.4 (6-C), 132.2 (4-C), 134.3 (1-C), 157.1 (2-C), 197.8 (CO). Found: 76.92 C, 8.40 H, 7.04 N; $C_{13}H_{17}NO$ requires 76.81 C, 8.43 H, 6.89 N.

3.1.1.2. 2-[Cyclohexyl(methyl)amino]benzaldehyde (6a). Yield 57%. Yellow oil; ν_{max} (KBr) 2919, 2882, 1680, 1588, 1467, 1447, 1342, 1293, 1251, 1155, 1138, 1081, 991, 987, 871, 797 cm^{-1}. δ_H 1.01–1.02 (3H, m, *c*-hexyl), 1.41–1.50 (2H, m, *c*-hexyl), 1.54–1.57 (1H, m, *c*-hexyl), 1.70–1.78 (4H, m, *c*-hexyl), 2.73 (3H, s, NCH$_3$), 2.94 (1H, m, N-CH<), 6.97 (1H, t, *J*=8.4, 5-H), 7.05 (1H, d, *J*=8.4, 3-H), 7.41 (1H, t, *J*=8.4, 4-H), 7.73 (1H, d, *J*=8.4, 6-H), 10.15 (1H, s, CHO). δ_C 24.1 (CH$_2$), 25.4 (2CH$_2$), 26.8 (2CH$_2$), 42.6 (CH$_3$), 59.1 (NCH<), 115.2 (3-C), 123.7 (5-C), 133.1 (6-C), 133.6 (4-C), 136.4 (1-C), 157.3 (2-C), 198.7 (CO). Found: 77.51 C, 8.66 H, 6.35 N; $C_{14}H_{19}NO$ requires 77.38 C, 8.81 H, 6.45 N.

3.1.2. 2-Amino-5-nitrobenzaldehydes 5b, 6b. Powdered K_2CO_3 (3.04 g, 0.022 mol) was added to a solution of 2-chloro-5-nitrobenzaldehyde (3.71 g, 0.02 mol) and appropriate amine (0.022 mol) in DMF (10 mL) and the resulted mixture was refluxed with stirring for 4 h. After cooling it was poured into water (25 mL) and the solid formed was filtered and recrystallized from *i*-PrOH to yield compounds **5b**, **6b**.

3.1.2.1. 2-[Cyclopentyl(methyl)amino]-5-nitrobenzaldehyde (5b). Yield 63%. Yellow powder; mp 79 °C (from *i*-PrOH); ν_{max} (KBr) 2964, 2864, 1677, 1598, 1507, 1316, 1256, 1158, 1072, 949, 823, 748 cm^{-1}. δ_H 1.55 (2H, m, CH$_2$), 1.71 (4H, m, 2CH$_2$), 1.94 (2H, m, CH$_2$), 2.91 (3H, s, NCH$_3$), 4.14 (1H, m, N-CH<), 7.22 (1H, d, *J*=9.2, 3-H), 8.16 (1H, dd, J^3=9.2, J^4=2.4, 4-H), 8.48 (1H, d, J^4=2.4, 6-H), 9.95 (1H, s, CHO). δ_C 21.3 (2CH$_2$), 24.2 (2CH$_2$), 38.0 (CH$_3$), 63.8 (NCH<), 126.9 (2-C), 128.4 (1-C), 129.5 (4-C), 134.7 (6-C), 138.6 (5-C), 155.5 (2-C), 193.7 (CO). Found: 62.80 C, 6.56 H, 11.20 N; $C_{13}H_{16}N_2O_3$ requires 62.89 C, 6.50 H, 11.28 N.

3.1.2.2. 2-[Cyclohexyl(methyl)amino]-5-nitrobenzaldehyde (6b). Yield 78%. Yellow powder; mp 68 °C (from *i*-PrOH); ν_{max} (KBr) 2925, 2853, 1681, 1602, 1571, 1494, 1328, 1257, 1166, 1069, 1001, 955, 745 cm^{-1}. δ_H 1.17 (1H,

m, *c*-hexyl), 1.36 (2H, m, *c*-hexyl), 1.66 (3H, m, *c*-hexyl), 1.86 (4H, m, *c*-hexyl), 2.91 (3H, s, NCH_3), 3.43 (1H, m, N-CH<), 7.08 (1H, d, *J*=9.6, 3-H), 8.15 (1H, d, *J*=9.6, 4-H), 8.48 (1H, s, 6-H), 9.90 (1H, s, CHO). δ_C 21.5 (CH_2), 24.1 ($2CH_2$), 33.5 ($2CH_2$), 37.4 (CH_3), 66.5 (NCH<), 126.1 (3-C), 128.4 (4-C), 132.2 (6-C), 133.1 (1-C), 136.5 (5-C), 155.4 (2-C), 192.6 (CO). Found: 64.22 C, 6.90 H, 10.77 N; $C_{14}H_{18}N_2O_3$ requires 64.11 C, 6.92 H, 10.68 N.

3.1.3. Spiroquinoline-3,3-dicarbonitriles 11a, 12a. Triethylamine (0.1 mL, 0.7 mmol) was added to a solution of the aldehyde **5a** or **6a** (4 mmol) and malonodinitrile **7** (0.26 g, 4 mmol) in EtOH (5 mL) and the resulted mixture was refluxed for 3 h. After cooling it was diluted with water (15 mL) and a viscous oily material precipitated. The liquid was decanted and the precipitate was chromatographed on silica gel using EtOAc–hexane (1:4, v/v) mixture as eluent. Evaporation of the appropriate fraction and drying the residue in vacuo afforded compounds **11a**, **12a** as yellowish vitreous solids.

3.1.3.1. 1-Methyl-1,2,3,4-tetrahydrospiro(quinoline-2,1′-cyclopentane)-3,3-dicarbonitrile (11a). Yield 76%. Yellowish vitreous solid becoming fluid at 30–35 °C; ν_{max} (KBr) 2955, 2878, 2246, 1601, 1580, 1496, 1456, 1342, 1312, 1178, 763, 748 cm^{-1}. δ_H 1.75–2.20 (8H, m, 2′,3′,4′,5′-CH_2), 3.05 (3H, s, NCH_3), 3.54 (2H, s, 4-CH_2), 6.82 (2H, m, 6,8-H), 7.05 (1H, d, *J*=7.2, 5-H), 7.23 (1H, t, *J*=7.2, 7-H). δ_C 25.0 (3′,4′-C), 34.3 (4-C), 35.0 (2′,5′-C), 35.8 (NCH_3), 40.0 (3-C), 70.3 (2-C), 115.0 (8-C), 115.4 (CN), 115.5 (4a-C), 118.6 (6-C), 128.7 (5-C), 128.8 (7-C), 144.0 (8a-C). Found: 76.60 C, 6.74 H, 16.66 N; $C_{16}H_{17}N_3$ requires 76.46 C, 6.82 H, 16.72 N.

3.1.3.2. 1-Methyl-1,2,3,4-tetrahydrospiro(quinoline-2,1′-cyclohexane)-3,3-dicarbonitrile (12a). Yield 67%. Yellowish vitreous solid becoming fluid at 35–40 °C; ν_{max} (KBr) 2953, 2931, 2862, 2850, 2246, 1603, 1578, 1496, 1456, 1448, 1318, 1043, 767 cm^{-1}. δ_H 1.31 (1H, m, *c*-hexane), 1.53 (2H, m, *c*-hexane), 1.74 (5H, m, *c*-hexane), 2.10 (2H, m, *c*-hexane), 3.25 (3H, s, NCH_3), 3.44 (2H, s, 4-CH_2), 6.82 (1H, t, *J*=8.4, 6-H), 6.93 (1H, d, *J*=8.4, 8-H), 7.00 (1H, d, *J*=8.4, 5-H), 7.20 (1H, t, *J*=8.4, 7-H). δ_C 22.3 (3′,5′-C), 25.0 (4′-C), 31.2 (2′,6′-C), 33.3 (4-C), 38.0 (NCH_3), 40.3 (3-C), 61.4 (2-C), 116.2 (8-C), 117.6 (CN), 118.5 (4a-C), 119.5 (6-C), 128.5 (5-C), 128.9 (7-C), 145.1 (8a-C). Found: 76.76 C, 7.30 H, 15.86 N; $C_{17}H_{19}N_3$ requires 76.95 C, 7.22 H, 15.84 N.

3.1.4. Spiroquinolines 11b, 12b, 13a–b, 14a–b, 15a–b, 16a. General procedure. A solution of the aldehydes **5a–b**, **6a–b** (4 mmol), the nitriles **7–9** (4 mmol), and triethylamine (0.1 mL) in EtOH (5 mL) was heated at reflux for 3–5 h until complete disappearance of the starting aldehyde by TLC data. After cooling the precipitate formed was filtered, washed with cold *i*-PrOH, and recrystallized from an appropriate solvent to give compounds **11b**, **12b**, **13a–b**, **14a–b**, **15a–b**, **16a**.

3.1.4.1. 1-Methyl-6-nitro-1,2,3,4-tetrahydrospiro-(quinoline-2,1′-cyclopentane)-3,3-dicarbonitrile (11b). Yield 79%. Yellow powder; mp 164 °C (from EtOH); ν_{max} (KBr) 2970, 2947, 2882, 1604, 1583, 1504, 1489, 1425, 1338, 1319, 1279, 1186, 961, 937, 750 cm^{-1}. δ_H 1.88 (4H, m, *c*-pentane), 2.09 (4H, m, *c*-pentane), 3.06 (3H, s, NCH_3), 3.86 (2H, s, 4-CH_2), 6.96 (1H, d, *J*=9.2, 8-H), 8.05 (2H, m, 5,7-H). δ_C 25.6 (3′,4′-C), 33.3 (4-C), 34.0 (2′,5′-C), 36.0 (NCH_3), 40.5 (3-C), 70.9 (2-C), 113.0 (CN), 114.9 (8-C), 115.3 (4a-C), 124.7 (5-C), 124.8 (7-C), 137.3 (6-C), 148.9 (8a-C). Found: 64.70 C, 5.40 H, 18.93 N; $C_{16}H_{16}N_4O_2$ requires 64.85 C, 5.44 H, 18.91 N.

3.1.4.2. 1-Methyl-6-nitro-1,2,3,4-tetrahydrospiro-(quinoline-2,1′-cyclohexane)-3,3-dicarbonitrile (12b). Yield 75%. Yellow powder; mp 159 °C (from EtOH); ν_{max} (KBr) 2936, 2245, 1607, 1585, 1511, 1493, 1323, 1288, 1274, 1077, 958, 920, 821, 749 cm^{-1}. δ_H 1.37 (1H, m, *c*-hexane), 1.54 (2H, m, *c*-hexane), 1.81 (5H, m, *c*-hexane), 2.11 (2H, m, *c*-hexane), 3.35 (3H, s, NCH_3), 3.68 (2H, s, 4-CH_2), 7.02 (1H, d, *J*=9.2, 8-H), 8.05 (2H, m, 5,7-H). δ_C 22.3 (3′,5′-C), 24.7 (4′-C), 31.5 (2′,6′-C), 32.8 (4-C), 38.1 (NCH_3), 40.8 (3-C), 62.0 (2-C), 115.4 (8-C), 116.6 (4a-C), 117.3 (CN), 124.6 (5-C), 125.1 (7-C), 138.7 (6-C), 150.5 (8a-C). Found: 65.70 C, 5.65 H, 18.02 N; $C_{17}H_{18}N_4O_2$ requires 65.79 C, 5.85 H, 18.05 N.

3.1.4.3. 1-Methyl-3-[(4-methylphenyl)sulfonyl]-1,2,3,4-tetrahydrospiro(quinoline-2,1′-cyclopentane)-3-carbonitrile (13a). Yield 98%. White crystals; mp 92 °C (from EtOH); ν_{max} (KBr) 2956, 2928, 2865, 1594, 1492, 1456, 1327, 1300, 1150, 1084, 818, 749, 660, 577 cm^{-1}. δ_H 1.65 (1H, m, *c*-pentane), 1.82 (2H, m, *c*-pentane), 1.98 (2H, m, *c*-pentane), 2.22 (1H, m, *c*-pentane), 2.40 (3H, s, CH_3), 2.52 (2H, m, *c*-pentane), 2.96 (3H, s, NCH_3), 3.25 (1H, d, *J*=18.0, 4-H), 3.53 (1H, d, *J*=18.0, 4-H), 6.57 (1H, d, *J*=8.4, 8-H), 6.70 (1H, t, *J*=8.4, 6-H), 6.88 (1H, d, *J*=8.4, 5-H), 7.07 (1H, t, *J*=8.4, 7-H), 7.25 (2H, d, *J*=8.0, Tos), 7.73 (2H, d, *J*=8.0, Tos). δ_C 21.7 (CH_3), 23.0 (3′-C), 24.2 (4′-C), 33.7 (2′-C), 34.4 (4-C), 34.7 (5′-C), 37.4 (NCH_3), 67.1 (3-C), 70.8 (2-C), 115.1 (8-C), 117.4 (4a-C), 117.5 (CN), 118.1 (6-C), 127.7 (5-C), 128.1 (7-C), 129.3 (2,6-C_{Tos}), 130.4 (3,5-C_{Tos}), 133.5 (4-C_{Tos}), 144.5 (8a-C), 146.0 (1-C_{Tos}). Found: 69.50 C, 6.33 H, 7.50 N, 8.33 S; $C_{22}H_{24}N_2O_2S$ requires 69.44 C, 6.36 H, 7.36 N, 8.43 S.

3.1.4.4. 1-Methyl-3-[(4-methylphenyl)sulfonyl]-6-nitro-1,2,3,4-tetrahydrospiro(quinoline-2,1′-cyclopentane)-3-carbonitrile (13b). Yield 91%. Yellow crystals; mp 189–190 °C (from dioxane); ν_{max} (KBr) 2967, 1603, 1588, 1509, 1497, 1313, 1272, 1147, 810, 671, 584 cm^{-1}. δ_H 1.56 (1H, m, *c*-pentane), 1.70 (2H, m, *c*-pentane), 1.85–2.01 (3H, m, *c*-pentane), 2.30 (3H, s, CH_3), 2.37 (2H, m, *c*-pentane), 2.88 (3H, s, NCH_3), 3.70 (1H, d, *J*=18.8, 4-H), 3.80 (1H, d, *J*=18.8, 4-H), 6.55 (1H, d, J^3=9.6, 8-H), 7.27 (2H, d, *J*=8.0, Tos), 7.64 (2H, d, *J*=8.0, Tos), 7.83 (1H, dd, J^3=9.6, J^4=2.0, 7-H), 7.93 (1H, d, J^4=2.0, 5-H). δ_C 21.1 (CH_3), 22.8 (3′-C), 24.4 (4′-C), 32.9 (2′-C), 33.4 (5′-C), 34.1 (4-C), 38.1 (NCH_3), 67.9 (3-C), 70.4 (2-C), 113.3 (CN), 116.7 (4a-C), 117.2 (8-C), 123.4 (5-C), 124.3 (7-C), 129.0 (2,6-C_{Tos}), 130.2 (3,5-C_{Tos}), 132.4 (4-C_{Tos}), 137.4 (6-C), 146.5 (1-C_{Tos}), 149.2 (8a-C). Found: 62.11 C, 5.45 H, 10.03 N, 7.60 S; $C_{22}H_{23}N_3O_4S$ requires 62.10 C, 5.45 H, 9.88 N, 7.54 S.

3.1.4.5. 1-Methyl-3-[(4-methylphenyl)sulfonyl]-1,2,3,4-tetrahydrospiro(quinoline-2,1′-cyclohexane)-3-carbonitrile (14a). Yield 95%. White crystals; mp 204 °C (from

acetonitrile); ν_{max} (KBr) 2947, 2919, 2858, 1594, 1492, 1453, 1325, 1153, 1079, 756, 664, 597, 578 cm^{-1}. δ_H 1.39 (2H, m, *c*-hexane), 1.52 (1H, m, *c*-hexane), 1.64 (1H, m, *c*-hexane), 1.76 (1H, m, *c*-hexane), 1.87 (2H, m, *c*-hexane), 2.03 (1H, m, *c*-hexane), 2.40 (2H, m, *c*-hexane), 2.51 (3H, s, CH_3), 2.63 (1H, d, *J*=17.2, 4-H), 3.22 (3H, s, NCH_3), 3.37 (1H, d, *J*=17.2, 4-H), 6.70 (1H, t, *J*=7.2, 6-H), 6.85 (2H, m, 5,8-H), 7.09 (1H, t, *J*=7.2, 7-H), 7.47 (2H, d, *J*=7.6, Tos), 7.84 (2H, d, *J*=7.6, Tos). δ_C 21.7 (CH_3), 22.1 (3′-C), 22.9 (5′-C), 25.3 (4′-C), 30.5 (2′-C), 32.4 (4-C), 32.9 (6′-C), 38.2 (NCH_3), 64.7 (2-C), 67.0 (3-C), 117.8 (CN), 118.4 (8-C), 118.5 (4a-C), 119.4 (6-C), 128.2 (5-C), 128.8 (7-C), 130.5 (2,6-C_{Tos}), 130.6 (3,5-C_{Tos}), 133.4 (4-C_{Tos}), 145.5 (8a-C), 146.8 (1-C_{Tos}). Found: 70.13 C, 6.60 H, 7.22 N, 8.19 S; $C_{23}H_{26}N_2O_2S$ requires 70.02 C, 6.64 H, 7.10 N, 8.13 S.

3.1.4.6. 1-Methyl-3-[(4-methylphenyl)sulfonyl]-6-nitro-1,2,3,4-tetrahydrospiro(quinoline-2,1′-cyclohexane)-3-carbonitrile (14b). Yield 86%. Yellow crystals; mp 201 °C (from acetonitrile); ν_{max} (KBr) 2931, 1602, 1507, 1486, 1317, 1288, 1269, 1143, 1133, 919, 752, 544 cm^{-1}. δ_H 1.39 (2H, m, *c*-hexane), 1.60 (1H, m, *c*-hexane), 1.67 (1H, m, *c*-hexane), 1.80 (2H, m, *c*-hexane), 2.15 (2H, m, *c*-hexane), 2.30 (2H, m, *c*-hexane), 2.52 (3H, s, CH_3), 2.88 (1H, d, *J*=18.8, 4-H), 3.32 (3H, s, NCH_3), 3.49 (1H, d, *J*=18.8, 4-H), 6.94 (1H, d, *J*=9.2, 8-H), 7.49 (2H, d, *J*=8.0, Tos), 7.84 (2H, d, *J*=8.0, Tos), 7.90 (1H, s, 5-H), 8.00 (1H, d, *J*=9.2, 7-H). δ_C 21.7 (CH_3), 22.3 (3′-C), 22.4 (5′-C), 22.5 (2′-C), 25.0 (4′-C), 30.8 (6′-C), 32.4 (4-C), 38.4 (NCH_3), 64.4 (2-C), 67.2 (3-C), 116.4 (8-C), 117.2 (CN), 118.9 (4a-C), 124.1 (5-C), 125.0 (7-C), 130.6 (2,6-C_{Tos}), 130.7 (3,5-C_{Tos}), 133.0 (4-C_{Tos}), 138.6 (6-C), 147.1 (1-C_{Tos}), 151.2 (8a-C). Found: 62.73 C, 5.84 H, 9.50 N, 7.35 S; $C_{23}H_{25}N_3O_4S$ requires 62.85 C, 5.73 H, 9.56 N, 7.29 S.

3.1.4.7. 3-(Benzothiazol-2-yl)-1-methyl-1,2,3,4-tetrahydrospiro(quinoline-2,1′-cyclopentane)-3-carbonitrile (15a). Yield 81%. Yellowish powder; mp 121 °C (from dioxane); ν_{max} (KBr) 2954, 2915, 2872, 1600, 1578, 1496, 1483, 1454, 1432, 1339, 1312, 760, 729 cm^{-1}. δ_H 1.75 (5H, m, *c*-pentane), 2.07 (3H, m, *c*-pentane), 2.90 (3H, s, NCH_3), 3.50 (1H, d, *J*=17.2, 4-H), 3.79 (1H, d, *J*=17.2, 4-H), 6.73 (1H, t, *J*=7.2, 6-H), 6.86 (1H, d, *J*=7.2, 8-H), 7.03 (1H, d, *J*=7.2, 5-H), 7.15 (1H, t, *J*=7.2, 7-H), 7.42 (1H, t, *J*=8.0, H_X), 7.51 (1H, t, *J*=8.0, H_X), 8.01 (1H, d, *J*=8.0, H_X), 8.05 (1H, d, *J*=8.0, H_X). δ_C 24.9 (3′-C), 25.0 (4′-C), 32.9 (4-C), 34.4 (2′-C), 35.6 (5′-C), 37.3 (NCH_3), 50.3 (3-C), 69.6 (2-C), 113.9 (8-C), 117.8 (4a-C), 118.0 (6-C), 120.9 (CN), 122.1 (4-C_X), 122.9 (7-C_X), 125.7 (6-C_X), 126.4 (5-C_X), 128.1 (5-C), 128.8 (7-C), 135.5 (7a-C_X), 144.1 (8a-C), 150.7 (3a-C_X), 166.7 (2-C_X). Found: 73.60 C, 5.84 H, 11.86 N, 8.74 S; $C_{22}H_{21}N_3S$ requires 73.50 C, 5.89 H, 11.69 N, 8.92 S.

3.1.4.8. 3-(Benzothiazol-2-yl)-1-methyl-6-nitro-1,2,3,4-tetrahydrospiro(quinoline-2,1′-cyclopentane)-3-carbonitrile (15b). Yield 64%. Yellow powder; mp 146 °C (from dioxane); ν_{max} (KBr) 2932, 1604, 1584, 1505, 1494, 1335, 1313, 1262, 1182, 766 cm^{-1}. δ_H 1.55 (1H, m, *c*-pentane), 1.75 (3H, m, *c*-pentane), 1.99 (2H, m, *c*-pentane), 2.23 (2H, m, *c*-pentane), 3.05 (3H, s, NCH_3), 3.78 (1H, d, *J*=17.6, 4-H), 3.90 (1H, d, *J*=17.6, 4-H), 6.98 (1H, d, *J*=9.6, 8-H), 7.45 (1H, t, *J*=8.0, H_X), 7.54 (1H, t, *J*=8.0, H_X), 8.05 (4H, m, 2H_X, 5,7-H). δ_C 25.2 (3′-C), 25.3 (4′-C), 34.1 (NCH_3), 34.7 (2′-C), 36.3 (5′-C), 36.9 (4-C), 49.7 (3-C), 71.3 (2-C), 113.0 (CN), 117.6 (8-C), 120.0 (4a-C), 122.3 (4-C_X), 123.1 (7-C_X), 124.5 (6-C_X), 124.8 (5-C_X), 126.0 (5-C), 126.8 (7-C), 135.0 (7a-C_X), 137.4 (6-C), 149.7 (8a-C), 151.6 (3a-C_X), 165.5 (2-C_X). Found: 65.30 C, 4.90 H, 13.80 N, 7.86 S; $C_{22}H_{20}N_4O_2S$ requires 65.33 C, 4.98 H, 13.85 N, 7.93 S.

3.1.4.9. 3-(Benzothiazol-2-yl)-1-methyl-1,2,3,4-tetrahydrospiro(quinoline-2,1′-cyclohexane)-3-carbonitrile (16a). Yield 69%. Yellowish powder; mp 112 °C (from dioxane); ν_{max} (KBr) 2934, 2856, 1601, 1494, 1454, 1435, 1316, 970, 754, 730 cm^{-1}. δ_H 1.23 (1H, m, *c*-hexane), 1.50 (2H, m, *c*-hexane), 1.67 (4H, m, *c*-hexane), 1.88 (1H, m, *c*-hexane), 2.02 (1H, m, *c*-hexane), 2.18 (1H, m, *c*-hexane), 3.15 (3H, s, NCH_3), 3.53 (1H, d, *J*=17.2, 4-H), 3.64 (1H, d, *J*=17.2, 4-H), 6.76 (1H, t, *J*=7.6, 6-H), 6.88 (1H, d, *J*=7.6, 8-H), 7.03 (1H, d, *J*=7.6, 5-H), 7.17 (1H, t, *J*=7.6, 7-H), 7.38 (1H, t, *J*=8.0, H_X), 7.48 (1H, t, *J*=8.0, H_X), 7.87 (1H, d, *J*=8.0, H_X), 8.02 (1H, d, *J*=8.0, H_X). δ_C 22.5 (3′-C), 22.7 (5′-C), 25.2 (4′-C), 30.3 (2′-C), 32.4 (4-C), 36.2 (6′-C), 37.8 (NCH_3), 51.0 (3-C), 61.6 (2-C), 116.7 (8-C), 118.8 (4a-C), 119.5 (CN), 121.4 (6-C), 122.6 (7-C_X), 123.5 (4-C_X), 126.1 (5-C_X), 127.0 (6-C_X), 128.3 (5-C), 129.0 (7-C), 135.7 (7a-C_X), 145.6 (8a-C), 151.7 (3a-C_X), 167.2 (2-C_X). Found: 73.83 C, 6.25 H, 11.34 N, 8.48 S; $C_{23}H_{23}N_3S$ requires 73.96 C, 6.21 H, 11.25 N, 8.58 S.

3.1.5. 2-(Benzothiazol-2-yl)-3-{2-[cyclohexyl(methyl)-amino]-5-nitrophenyl}-2-propenenitrile (10b). Triethylamine (0.1 mL, 0.7 mmol) was added to a solution of the aldehyde **6b** (1.67 g, 4 mmol) and the nitrile **9** (0.7 g, 4 mmol) in EtOH (5 mL) and the resulted mixture was refluxed for 3 h. After cooling the precipitated solid was filtered and recrystallized from EtOH to yield compound **10b**. Yield 94%. Yellow powder; mp 179–180 °C; ν_{max} (KBr) 2933, 2222, 1601, 1583, 1493, 1328, 1313, 1278, 1172, 1076, 1003, 758 cm^{-1}. δ_H 1.13 (3H, m, *c*-hexyl), 1.54 (1H, m, *c*-hexyl), 1.65–1.78 (4H, m, *c*-hexyl), 1.90 (2H, m, *c*-hexyl), 2.94 (3H, s, NCH_3), 3.19 (1H, m, N-CH<), 7.17 (1H, d, *J*=9.2, 3′-H), 7.45 (1H, t, *J*=7.8, H_X), 7.53 (1H, t, *J*=7.8, H_X), 8.01 (2H, m, 2H_X), 8.20 (2H, m, 4′,6′-H), 8.86 (1H, s, 3-H). δ_C 23.0 (CH_2), 26.7 (2CH_2), 28.8 (2CH_2), 41.5 (CH_3), 61.6 (NCH<), 99.2 (2-C), 116.0 (2′-C), 118.6 (CN), 119.1 (1′-C), 120.9 (7-C_X), 122.4 (6′-C), 125.3 (4-C_X), 125.5 (4′-C), 129.2 (6-C_X), 129.3 (5-C_X), 136.5 (5′-C), 140.6 (7a-C_X), 152.1 (3-C), 153.7 (3′-C), 157.5 (4a-C_X), 164.6 (2-C_X). Found: 66.20 C, 5.36 H, 13.40 N, 7.69 S; $C_{23}H_{22}N_4O_2S$ requires 66.01 C, 5.30 H, 13.39 N, 7.66 S.

3.1.6. 3-(Benzothiazol-2-yl)-1-methyl-6-nitro-1,2,3,4-tetrahydrospiro(quinoline-2,1′-cyclohexane)-3-carbonitrile (16b). A solution of the compound **10b** (0.84 g, 2 mmol) in DMF (5 mL) was heated at reflux for 3 h. After cooling it was poured into water (15 mL) and the precipitate separated was filtered. Recrystallization from dioxane afforded derivative **16b**. Yield 99%. Yellow powder; mp 215–216 °C; ν_{max} (KBr) 2947, 1604, 1584, 1506, 1492, 1320, 1289, 1260, 768, 753 cm^{-1}. δ_H 1.23 (1H, m, *c*-hexane), 1.50 (2H, m,

c-hexane), 1.74 (4H, m, *c*-hexane), 1.90 (1H, m, *c*-hexane), 2.09 (1H, m, *c*-hexane), 2.19 (1H, m, *c*-hexane), 3.28 (3H, s, NCH_3), 3.64 (1H, d, J=16.8, 4-H), 3.82 (1H, d, J=16.8, 4-H), 7.00 (1H, d, J=9.2, 8-H), 7.42 (1H, t, J=8.0, H_X), 7.51 (1H, t, J=8.0, H_X), 7.92 (1H, d, J=8.0, H_X), 8.02 (2H, m, 5-H, H_X), 8.08 (1H, d, J=9.2, 7-H). δ_C 22.4 (3′-C), 22.7 (5′-C), 24.9 (4′-C), 30.4 (2′-C), 32.9 (4-C), 35.5 (6′-C), 38.4 (NCH_3), 51.0 (3-C), 62.7 (2-C), 115.8 (8-C), 119.6 (CN), 120.7 (4a-C), 122.8 (7-C_X), 123.6 (4-C_X), 124.5 (5-C), 125.3 (7-C), 126.4 (6-C_X), 127.2 (5-C_X), 135.5 (7a-C_X), 138.4 (6-C), 151.4 (8a-C), 151.7 (3a-C_X), 166.1 (2-C_X). Found: 65.84 C, 5.39 H, 13.40 N, 7.62 S; $C_{23}H_{22}N_4O_2S$ requires 66.01 C, 5.30 H, 13.39 N, 7.66 S.

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