THE SYNTHESIS OF SPIROCYCLIC [1,2,4]TRIAZOLO[4,3-*a*]QUINOLINES AS POTENTIAL LIGANDS FOR THE BENZODIAZEPINE RECEPTOR

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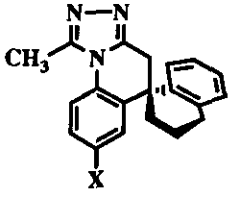
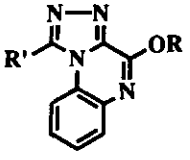
Abstract – Two spirocyclic [1,2,4]triazolo[4,3-*a*]quinolines (**1a** and **b**) have been prepared as potential ligands for the benzodiazepine receptor. Both compounds were prepared using the strategy of doubly deprotonating an acetanilide derivative followed by reaction with α-tetralone. The resulting alcohols were converted to the corresponding spirocyclic 3,4-dihydroquinolin-2-one or -2-thione by treatment with neat HF. Triazole formation was effected by standard procedures. An alternate strategy starting with an intact triazole was unsuccessful but this route led to the first example of a lateral metallation of a 4-substituted 1,2,4-triazole.

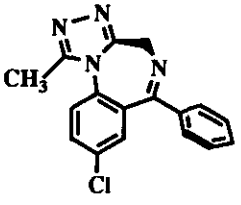
During the course of studies on rigid ligands for various CNS receptors we became interested in preparing chiral, configurationally stable ligands for the benzodiazepine receptor. The study of such compounds, when enantiomerically pure, would provide further structural insight into the benzodiazepine receptor[1] and could also yield information regarding the multiplicity of this receptor.[2] To this end, we chose to synthesize the spirocyclic triazoles (**1a**) and (**b**) (eq. 1). The observation that various 4-alkoxy-[1,2,4]triazolo[4,3-*a*]quinoxalines have micromolar binding affinities for the benzodiazepine receptor[3] and the potent receptor binding displayed by structurally related triazolobenzodiazepines such as alprazolam[4] suggested that the target spirocyclic triazoles would have the potency required to allow the relevant biological studies to be conducted. The chloro derivative (**1b**) was sought in addition to **1a** since substitution with an electron withdrawing group at the corresponding position in benzodiazepines significantly increases biological activity.[5]



1a: X = H
1b: X = Cl



4-alkoxy-[1,2,4]triazolo-[4,3-*a*]quinoxaline

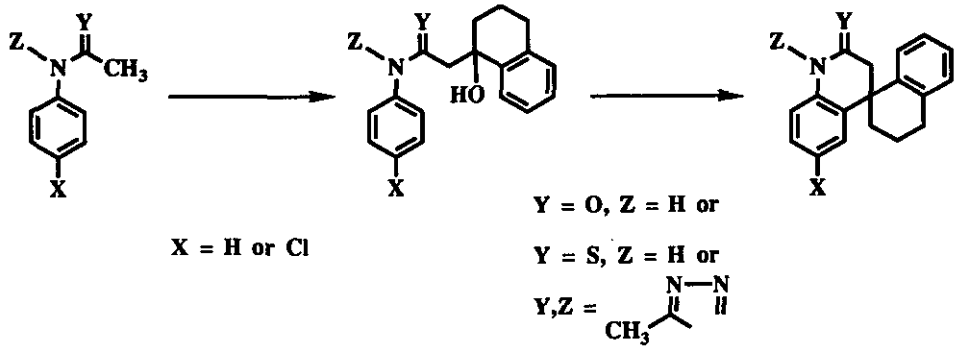


alprazolam

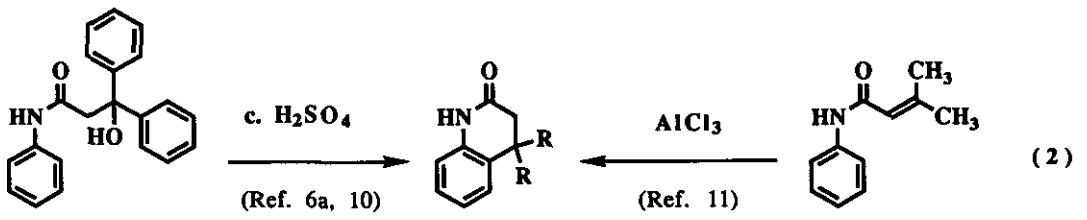
(1)

The planned synthetic route to the target spirocycles involved first forming the dianion of either acetanilide or thioacetanilide or the monoanion of 3,5-dimethyl-4-phenyl-1,2,4-triazole (or the corresponding 4-chloro derivatives), followed by reaction with α-tetralone (Scheme 1). The generation of the dianion of secondary amides by treatment with n-butyllithium and reaction of such a dianion with electrophiles has been described[6] as has the generation of the dianion of a thioamide.[7] The lateral metallation of a 3- or 5-methyl-4-substituted 1,2,4-triazole has not been described; however, the lateral metallation of 5-methyl-1-phenyl-1,2,4-triazole[8] and of various 2-methylimidazoles[9] suggested that the proposed triazole chemistry was feasible.

Scheme 1



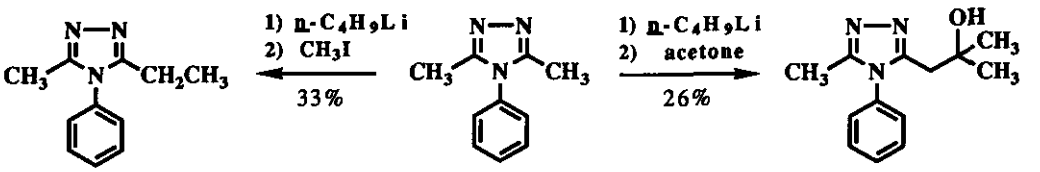
The second step of the planned sequence involved spirocyclization by treating the intermediate alcohol with an appropriate acid catalyst. This would lead to a tertiary, benzylic carbonium ion which could react with the adjacent phenyl group. The formation of 4,4-disubstituted 3,4-dihydroquinolin-2-ones using such carbonium ion chemistry, beginning with an alcohol[6a,10] or an olefin,[11] respectively, (eq. 2) provided precedent for this step. If spirocyclization was induced in a 4-phenyltriazole derivative then the reaction sequence would be complete. If spirocyclization was induced at either the amide or thioamide stage, then the final steps of the reaction sequence would be formation of the triazole ring by standard methods.



(2)

R = CH_3 or Ph

We began our study by examining the chemistry of **4** (which was prepared by reacting **3a** with acetic hydrazide)[12] (Scheme 2). As expected, treatment of **4** with 1 equivalent of n-butyllithium gave the monoanion which reacted with methyl iodide and acetone (eq. 3), as well as with α-tetralone (Scheme 2). The product of the latter reaction, **5**, is potentially a direct precursor to **1a**; however, attempts to convert this alcohol into the desired spirocycle were fruitless. Treatment with most acid catalysts (neat TFA, $AlCl_3$ in chloroform, formic acid, p-toluenesulfonic acid in toluene) led to dehydration and a mixture of the two expected olefins. Concentrated sulfuric acid at 70°C led to decomposition, while PPA at 120°C and neat HF both led to dehydration and disproportionation (i.e. the tetrahydronaphthyl and naphthyl compounds were obtained). Clearly the desired cation was forming under many of these reaction conditions but it failed to capture the adjacent phenyl ring. We presumed that protonation of, or coordination to the basic triazole ring by the acid catalyst decreased the nucleophilicity of the pendent phenyl group to such an extent that reaction with the nearby carbonium ion did not occur. This situation would not arise with the corresponding amide or thioamide.

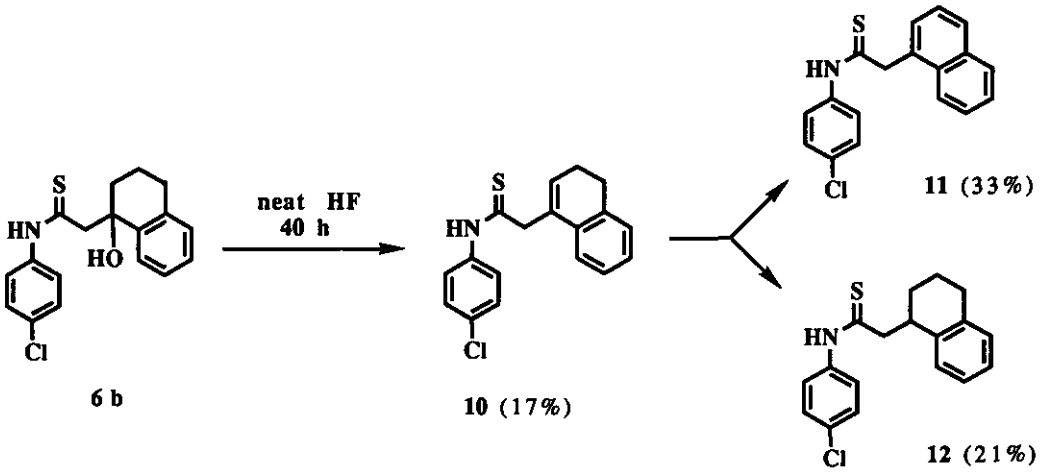


(3)

4

The dianion of thioamide (**3a**) (formed with 2 equivalents of n-butyllithium) reacted with α-tetralone to give the desired product (**6a**). This compound dehydrated upon treatment with most acid catalysts (neat TFA, conc. H_2SO_4 in TFA, conc. H_2SO_4 or PPA). Neat HF, however, induced the desired spirocyclization giving the 3,4-dihydroquinoline-2-thione (**7a**) in 51% yield. That spirocyclization had occurred was particularly evident in the ^{13}C-nmr spectrum of (**7a**) in which the loss of symmetry in the anilide phenyl ring leads to two additional resonances as compared to **6a**. Treatment of the thiolactam (**7a**) with acetic hydrazide in refluxing n-butanol gave **1a**.

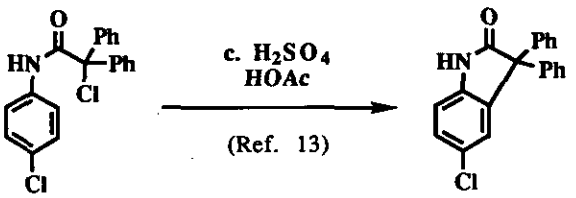
We anticipated that the chloro derivative (**1b**) could be prepared by a parallel sequence of reactions starting with 4-



(4)

6 b

chlorothioacetanilide (**3b**). Deprotonation of **3b** with 2 equivalents of n-butyllithium and reaction with α-tetralone gave the expected alcohol (**6b**). Reaction of this with neat HF, however, failed to give any of the desired spirocycle. After 40 h in neat HF, **6b** dehydrated to the endocyclic olefin (**10**) and, as was observed in the treatment of **5** with neat HF, disproportionation of the initially formed olefin occurred yielding the naphthyl and tetrahydronaphthyl derivatives (**11** and **12**) (eq. 4). Apparently, the small reduction in the nucleophilicity of the anilide phenyl ring of **6b** induced by the chloro substituent is sufficient to completely suppress reaction with the nearby carbocation. This contrasts with literature results in which a 4-chloroanilide was shown to be sufficiently nucleophilic to undergo reaction with an adjacent carbonium ion leading to formation of a 3,3-diphenyloxindole (eq. 5).[13]



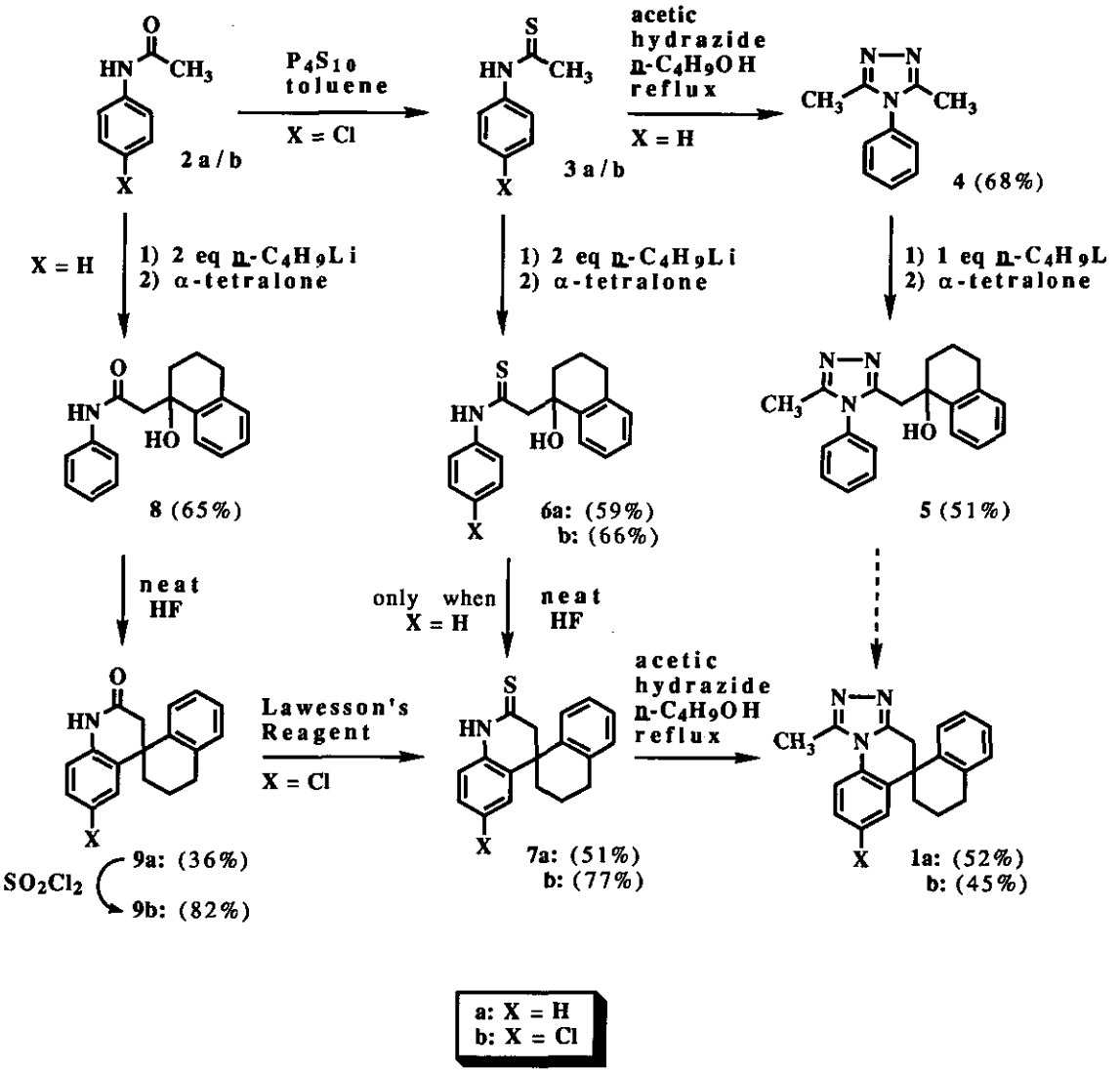
(5)

The failure of **6b** to cyclize led us to conclude that the chloro substituent would have to be introduced after spirocyclization (and before the introduction of the thioamide - owing to the likely incompatibility of the thioamide to chlorination conditions). Thus, in the same manner as we had synthesized the tetralone adducts (**6a** and **b**) from the corresponding thioacetanilides, acetanilide (**2a**) was deprotonated with 2 equivalents of n-butyllithium and reacted with α-tetralone. The resulting alcohol (**8**) was treated with neat HF as before to give the spirocyclic 3,4-dihydroquinolin-2-one (**9a**) in 36% yield. Chlorination of **9a** with sulfuryl chloride[14] produced exclusively the para chloro derivative (**9b**). This lactam was subsequently converted to the thiolactam (**7b**) with Lawesson's reagent[15] and **7b** converted to the triazole (**1b**) with acetic hydrazide in refluxing n-butanol.[12]

Biological evaluation of **1a** and **1b** revealed that both spirocyclic triazoloquinolines were only weak ligands for the benzodiazepine receptor (IC_{50}'s 3.8 μM and 27 μM, respectively, as compared to 8.1 nM for alprazolam),[16] and that neither compound possessed in vivo activity (pentylenetetrazole challenge in mice).[17] Due to this weak in vitro activity and the lack of in vivo activity, we concluded that resolution of these spirocycles into their pure enantiomers was not warranted.

While these novel spirocyclic triazoloquinolines did not serve the purpose for which they were prepared, their synthesis led to the demonstration that 3- or 5-methyl-4-substituted 1,2,4-triazoles can be laterally metallated and that the metallated derivatives react efficiently with electrophiles. In addition, the sequence of reactions: dimetallation of an acetanilide derivative, followed by reaction with an aldehyde or ketone and Friedel-Crafts cyclization, which constitutes a general strategy towards the synthesis of 4-substituted 3,4-dihydroquinolin-2-ones, has been additionally exemplified through the preparation of the chiral spirocycles (**7a**) and (**9a**). The range of substituents that may be present on the acetanilide unit in order for this synthetic strategy to be successful has been further defined by the successful cyclization of **6a** and **8** and by the failure of **6b** to cyclize.

Scheme 2


2 a / b
P4S10 toluene
X = Cl
3 a / b
acetic hydrazide n-C4H9OH reflux
X = H
4 (68%)
X = H
1) 2 eq n-C4H9Li 2) α-tetralone
1) 2 eq n-C4H9Li 2) α-tetralone
1) 1 eq n-C4H9L 2) α-tetralone
8 (65%)
6a: (59%) b: (66%)
5 (51%)
neat HF
only when X = H
neat HF
Lawesson's Reagent
X = Cl
acetic hydrazide n-C4H9OH reflux
SO2Cl2
9a: (36%)
9b: (82%)
7a: (51%) b: (77%)
1a: (52%) b: (45%)
a: X = H
b: X = Cl

EXPERIMENTAL

General Procedures: Nmr spectra were obtained on a Bruker AM-300 spectrometer. Low resolution mass spectra were obtained on a Finnigan EI-CI mass spectrometer and exact masses were determined on a A.E.I. MS30 spectrometer. Melting points are uncorrected and were determined in open capillaries. Elemental analyses were performed by the Analytical Department in the Central Research Division of Pfizer Inc. Solvents and reagents were used as obtained from commercial sources unless otherwise noted.

3,5-Dimethyl-4-phenyl-1,2,4-triazole (4): Thioacetanilide (**3a**) (15.12 g, 0.10 mol) and acetic hydrazide (14.82 g, 0.20 mol) were refluxed together in n-butanol (100 ml) for 16 h. The cooled mixture was concentrated in vacuo and the residual solid recrystallized from ethyl acetate (300 ml) to give 9.90 g (57%) of fine colorless needles. A second crop was obtained by concentrating the filtrate, dissolving the residue in water and extracting with chloroform (3X). The combined chloroform extracts were washed with water and saturated sodium chloride solution, dried over $MgSO_4$, filtered and concentrated to a white solid. Recrystallization of this from ethyl acetate gave 1.99 g (11%) of fine colorless needles: mp: 236-238°C (lit.,[18] 237°C); ^{1}H-nmr ($CDCl_3$) δ: 2.30 (s, 6H), 7.2-7.4 (m, 2H), 7.5-7.6 (m, 3H); ^{13}C-nmr ($CDCl_3$) δ: 11.2, 126.8, 129.7, 130.1, 134.3, 151.4; mass spectrum m/z (relative intensity): M^+ 173 (100), 132 (56), 131 (72), 118 (60), 105 (33), 91 (87), 77 (75). Anal. Calcd for $C_{10}H_{11}N_3$: C, 69.34; H, 6.40; N, 24.26. Found: C, 69.27; H, 6.38; N, 24.28.

(R,S)-3-((1-Hydroxy-1,2,3,4-tetrahydro-1-naphthyl)methyl)-5-methyl-4-phenyl-1,2,4-triazole (5): Triazole (4) (866 mg, 5.00 mmol) in dry THF (50 ml) at 5°C was treated with n-butyllithium (2.6 ml, 2.3 M in hexane, 6.0 mmol) keeping the temperature <10°C. The orange slurry was stirred at 5°C for 20 min. α-Tetralone (745 mg, 5.1 mmol) in THF (10 ml) was then added dropwise keeping the temperature <10°C. After 20 min the orange solution was quenched with saturated NH_4Cl solution, EtOAc was added and the organic layer was separated. After drying over $MgSO_4$, filtration and concentration of the organic layer an oil was obtained that was flash chromatographed (5:95 - MeOH:EtOAc). Fractions containing the product were concentrated and the residual solid was crystallized from hexane/EtOAc to give 822 mg (51%) of off-white crystals: mp 122-124°C; ^{1}H-nmr ($CDCl_3$) δ: 1.35-1.5 (m, 1H), 1.75-1.9 (m, 1H), 1.9-2.0 (m, 2H), 2.25 (s, 3H), 2.55-2.65 (m, 1H), 2.7-2.8 (m, 1H), 2.87 (d, J=15.4 Hz, 1H), 3.04 (d, J=15.4 Hz, 1H), 5.10 (s, 1H), 6.8-6.95 (m, 2H), 6.95-7.05 (m, 1H), 7.1-7.15 (m, 2H), 7.35-7.4 (m, 1H), 7.4-7.5 (m, 3H); ^{13}C-nmr ($CDCl_3$) δ: 11.1, 20.1, 29.1, 36.0, 37.1, 71.9, 126.1, 126.3, 127.0, 127.1, 128.5, 129.8, 129.9, 133.4, 136.3, 141.1, 151.1, 152.5; mass spectrum m/z (relative intensity): M^+ + 1 320 (4), M^+ 319 (3), 276 (21), 173 (100). Anal. Calcd for $C_{20}H_{21}N_3O$: C, 75.20; H, 6.63; N, 13.16. Found: C, 74.81; H, 6.56; N, 13.08.

3-Ethyl-5-methyl-4-phenyl-1,2,4-triazole: By the same procedure used to prepare **5**, triazole (4) (173 mg, 1.0 mmol), n-butyllithium (0.52 ml, 2.3 M in hexane, 1.2 mmol), and MeI (284 mg, 2.0 mmol) yielded after recrystallization from EtOAc/hexane 62 mg (33%) of white crystals: mp 145-147°C; ^{1}H-nmr ($CDCl_3$) δ: 1.23 (t, J=7.7 Hz, 3H), 2.28 (s, 3H), 2.60 (q, J=7.7 Hz, 2H), 7.1-7.4 (m, 2H), 7.4-7.7 (m, 3H); mass spectrum m/z (relative intensity): 188 (35), M^+ 187 (69), 186 (100), 131 (51), 118 (47), 110 (56), 91 (63), 77 (57). Anal. Calcd for $C_{11}H_{13}N_3$: C, 70.56; H, 7.00; N, 22.44. Found: C, 70.50; H, 7.04; N, 22.27.

3-(2-Hydroxy-2-methyl-1-propyl)-5-methyl-4-phenyl-1,2,4-triazole: By the same procedure used to prepare **5**, triazole (**4**) (173 mg, 1.0 mmol), n-butyllithium (0.52 ml, 2.3 M in hexane 1.2 mmol) and acetone (116 mg, 2.0 mmol) yielded after recrystallization from hexane/ EtOAc 60 mg (26%) of thick colorless needles: mp 125-126°C; ^{1}H-nmr ($CDCl_3$) δ: 1.27 (s, 6H), 2.28 (s, 3H), 2.67 (s, 2H), 7.05-7.3 (m, 2H), 7.4-7.7 (m, 3H); mass spectrum m/z (relative intensity): M^+ +1 232 (1), 216 (13), 173 (93), 172 (100), 77 (44). Anal. Calcd for $C_{13}H_{17}N_3O$: C, 67.50; H, 7.41; N, 18.17. Found: C, 67.29; H, 7.22; N, 18.05.

(R,S,)-2-(1-Hydroxy-1,2,3,4-tetrahydro-1-naphthyl)-*N*-phenylthioacetamide (6a): Thioacetanilide (**3a**) (7.56 g, 50.0 mmol) in dry THF (200 ml) at -40°C was treated with n-butyllithium (47.8 ml, 2.3 M in hexane, 110 mmol) keeping the temperature around -40°C. After complete addition the mixture was allowed to stir at 0°C for 1 h. The mixture was recooled to -40°C and α -tetralone (7.31 g, 50.0 mmol) added keeping the temperature around -40°C. The reaction mixture was stirred at 0°C for 2 h and was then poured into saturated NH_4Cl solution and diluted with Et_2O. The organic layer was separated, washed with saturated NH_4Cl solution and dried over $MgSO_4$. Filtration and concentration gave a brown oil which was taken up in a hot mixture of hexane (100 ml) and EtOAc (30 ml). The crystals that formed upon cooling were collected and air-dried yielding 8.76 g (59%) of fine yellow needles: mp 126-128°C; ^{1}H-nmr ($CDCl_3$) δ: 1.85-2.1 (m, 3H), 2.3-2.4 (m, 1H), 2.8-2.9 (m, 3H), 3.31 (d, J=14.9 Hz, 1H), 3.42 (d, J=14.9 Hz, 1H), 7.1-7.15 (m, 1H), 7.2-7.3 (m, 3H), 7.35-7.45 (m, 2H), 7.55-7.6 (m, 1H), 7.75-7.8 (m, 2H), 10.28 (br s, 1H); ^{13}C-nmr ($CDCl_3$) δ: 20.3, 29.3, 35.4, 59.2, 73.8, 123.3, 125.9, 126.58, 126.60, 127.9, 128.9, 129.2, 136.4, 139.0, 141.4, 200.0; mass spectrum m/z (relative intensity): M^+ 297 (20), 279 (36), 264 (31), 246 (16), 151 (98), 150 (93), 147 (85), 146 (95), 118 (100), 110 (77), 93 (86), 91 (95), 90 (74), 77 (81). Anal. Calcd for $C_{18}H_{19}NOS$: C, 72.69; H, 6.44; N, 4.71. Found: C, 73.09; H, 6.44; N, 4.78.

(R,S,)-3,4-Dihydrospiro[naphthalene-1(2*H*),4'(1'*H*)-quinoline]-2'(3'*H*)-thione (7a): Thioamide (**6a**) (2.97 g, 10.0 mmol) in a vented polyethylene bottle was treated with neat HF (25 ml) and allowed to stand overnight at room temperature. The remaining HF was removed with a stream of N_2, the residue dissolved in EtOAc and washed with H_2O (2X) and saturated $NaHCO_3$ solution. The organic layer was dried over $MgSO_4$, filtered and concentrated to give a yellow solid. This was taken up in hot hexane (100 ml) and EtOAc was added to effect solution. Cooling yielded 995 mg (36%) of product as yellow crystals. The filtrate from the recrystallization contained predominantly olefin. Concentration of the filtrate gave a yellow solid which was treated with neat HF for 48 h. After workup as above 411 mg (15%) of product as light yellow crystals was obtained: mp 225-226°C; ^{1}H-nmr ($CDCl_3$) δ: 1.6-2.05 (m, 4H), 2.85 (br t, J=6.0 Hz, 2H), 3.35 (d, J=16.7 Hz, 1H), 3.39 (d, J=16.7 Hz, 1H), 6.66 (d, J=7.7 Hz, 1H), 6.87 (dd, J=1.1, 7.7 Hz, 1H), 6.97 (dt, J=1.1, 7.7 Hz, 1H), 7.05-7.25 (m, 5H), 9.63 (br s, 1H); ^{13}C-nmr (Me_2SO-d_6) δ: 18.0, 29.6, 34.3, 40.7, 53.1, 116.3, 123.8, 126.0, 126.3, 127.2, 127.8, 128.2, 129.0, 134.1, 135.9, 137.9, 138.9, 197.2; mass spectrum m/z (relative intensity): M^+ 279 (100), 250 (27), 246 (55), 236 (21), 218 (25), 217 (23), 91 (23). Anal. Calcd for $C_{18}H_{17}NS$: C, 77.37; H, 6.13; N, 5.01. Found: C, 76.71; H, 6.17; N, 4.96. Exact mass calcd.: 279.1081. Found: 279.1036.

(R,S,)-3,4-Dihydro-1'-methylspiro[naphthalene-1(2*H*),5'(4'*H*)-[1,2,4]triazolo[4,3-*a*]quinoline] (1a): Thioamide (**7a**) (330 mg, 1.18 mmol) and acethydrazide (175 mg, 2.36 mmol) were refluxed together in n-butanol (20 ml) for 4 days. The cooled mixture was concentrated and the residue was taken up in EtOAc. This solution was washed with H_2O (3X) and saturated NaCl solution and dried over $MgSO_4$. Filtration and concentration gave a gummy yellow solid which was recrystallized from EtOAc/hexane to give 185 mg (52%) of yellow prisms: mp 165-166°C; ^{1}H-nmr ($CDCl_3$) δ: 1.5-

1.8 (m, 4H), 2.81 (s, 3H), 2.86 (t, J=6.1 Hz, 2H), 3.41 (d, J=15.7 Hz, 1H), 3.43 (d, J=15.7 Hz, 1H), 6.75 (dd, J=1.5, 7.8 Hz, 1H), 7.1-7.3 (m, 5H), 7.34 (dt, J=1.5, 8.0 Hz, 1H), 7.51 (dd, J=1.0, 8.0 Hz, 1H); ^{13}C-nmr ($CDCl_3$) δ: 14.2, 18.7, 30.3, 35.1, 35.7, 43.4, 117.3, 126.4, 126.5, 127.0, 127.6, 128.7, 129.6, 130.5, 132.6, 138.4, 138.7, 139.3, 148.1, 150.8; mass spectrum m/z (relative intensity): M^+ 301 (57), 300 (100). Anal. Calcd for $C_{20}H_{19}N_3$: C, 79.70; H, 6.35; N, 13.94. Found: C, 78.22; H, 6.49; N, 13.68. Exact mass calcd.: 301.1579. Found: 301.1515.

(R,S,)-*N*-(4-Chlorophenyl)-2-(1-hydroxy-1,2,3,4-tetrahydro-1-naphthyl)thioacetamide (6b): By the same procedure used to prepare **6a**, **3b**[19] (10.0 g, 0.054 mol), n-butyllithium (81 ml, 1.6 M in hexane, 0.13 mol), and α-tetralone (7.9 g, 0.054 mol) yielded 11.8 g (66%) of **6b** as a light brown solid: mp 143-145°C; ^{1}H-nmr ($CDCl_3$) δ: 1.85 - 2.1 (m, 3H), 2.3-2.4 (m, 1H), 2.69 (br s, 1H), 2.8-2.9 (m, 2H), 3.32 (d, J=14.9 Hz, 1H), 3.41 (d, J=14.9 Hz, 1H), 7.1-7.5 (m, 1H), 7.2-7.3 (m, 3H), 7.36 (d, J=8.8 Hz, 2H), 7.5-7.6 (m, 1H), 7.72 (d, J=8.8 Hz, 2H), 10.35 (br s, 1H); ^{13}C-nmr ($CDCl_3$) δ: 20.3, 29.2, 35.4, 59.2, 73.9, 124.4, 125.8, 126.6, 128.0, 128.9, 129.3, 131.5, 136.4, 137.5, 141.2, 200.2; mass spectrum m/z (relative intensity): M^+ 331/333 (9/3), 313/315 (17/7), 298/300 (12/4), 280/282 (8/3), 185/187 (65/26), 146 (100), 118 (71). Anal. Calcd for $C_{18}H_{18}NOCIS$: C, 65.14; H, 5.46; N, 4.22; Cl, 10.68. Found: C, 65.18; H, 5.50; N, 4.16; Cl, 10.66.

Attempted spirocyclization of 6b by treatment with neat HF: The thioamide (**6b**) (1.5 g, 4.5 mmol) was treated with neat HF (50 ml) in the same manner as in the conversion of **8** to **9a** with the exception that the reaction mixture was allowed to stand at room temperature for 40 h before being worked up. The mixture of products obtained upon workup was separated by flash chromatography (1:1-cyclohexane: $CHCl_3$) giving 700 mg (50%) of a 1:2 mixture (by ^{1}H-nmr) of *N*-(4-chlorophenyl)-2-(3,4-dihydro-1-naphthyl)thioacetamide (**10**) (MW 313.84) and *N*-(4-chlorophenyl)-2-(1-naphthyl)thioacetamide (**11**) (MW 311.82); ^{1}H-nmr ($CDCl_3$) δ: 2.4-2.5 (m, 2H, **10**), 2.85 (t, J=8.1 Hz, 2H, **10**), 4.06 (s, 2H, **10**), 4.71 (s, 2H, **11**), 6.18 (t, J=4.5 Hz, 1H, **10**), 7.15-7.35, 7.45-7.65, 7.85-7.95 (3m, 8H, **10**, 10H, **11**), 8.05 (m, 1H, **11**), 8.29 (br s, 1H, **11**), 8.87 (br s, 1H, **10**); mass spectrum m/z (relative intensity): 315 (6), 314 (7), 313 (26), 312 (14), 311 (32); and 300 mg (21%) of *N*-(4-chlorophenyl)-2-(1,2,3,4-tetrahydro-1-naphthyl)thioacetamide (**12**) (MW 315.85): mp 126-128°C (ether-hexane); ^{1}H-nmr ($CDCl_3$) δ: 1.75-1.9 (m, 3H), 1.9-2.1 (m, 1H), 2.79 (t, J=6.1 Hz, 2H), 3.02 (dd, J=7.6, 13.2 Hz, 1H) 3.15 (dd, J=6.4, 13.2 Hz, 1H) 3.55-3.7 (m, 1H), 7.05-7.2 (m, 3H), 7.2-7.3 (m, 1H), 7.33 (d, J=8.8 Hz, 2H), 7.49 (d, J=8.8 Hz, 2H), 8.34 (br s, 1H); ^{13}C-nmr ($CDCl_3$) δ: 19.7, 27.9, 29.5, 38.3, 56.4, 125.0, 125.9, 126.5, 128.6, 129.0, 129.6, 132.1, 136.9, 137.3, 138.6, 203.7; mass spectrum m/z (relative intensity): M^+ 315/317 (14/5), 282/284 (100/42), 185/187 (75/31).

(R,S,)-2-(1-Hydroxy-1,2,3,4-tetrahydro-1-naphthyl)-*N*-phenylacetamide (8): By the same procedure used to prepare **6a**, acetanilide (**2a**) (7.3 g, 0.054 mol), n-butyllithium (81 ml, 1.6 M in hexane, 0.13 mol) and α-tetralone (7.9 g, 0.054 mol) yielded 9.8 g (65%) of a white crystalline solid: mp 101-103°C; ^{1}H-nmr ($CDCl_3$) δ: 1.8-2.05 (m, 3H), 2.15-2.25 (m, 1H), 2.65 (d, J=14.8 Hz, 1H), 2.80 (m, 2H), 3.00 (d, J=14.8 Hz, 1H), 3.48 (s, 1H), 7.1-7.15 (m, 2H), 7.15-7.35 (m, 2H), 7.35-7.4 (m, 2H), 7.5-7.55 (m, 2H), 7.55-7.6 (m, 1H), 8.17 (s, 1H); ^{13}C-nmr ($CDCl_3$) δ: 20.2, 29.4, 36.3, 49.4, 72.1, 120.0, 124.4, 126.1, 126.6, 127.7, 129.0, 129.1, 136.4, 137.9, 141.2, 169.5; mass spectrum m/z: M^+ 281 (34), 263 (85), 147 (80), 144 (96), 135 (99), 129 (71), 93 (100). Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.83; H, 6.80; N, 4.97. Found: C, 76.86; H, 6.85; N, 4.97.

(R,S,)-3,4-Dihydrospiro[naphthalene-1(2*H*),4'(1'*H*)quinoline]-2'(3'*H*)-one (9a): Amide (**8**) (1.5 g, 5.3 mmol) in a vented polyethylene bottle was treated with neat HF (50 ml) and allowed to stand at room temperature for 18 h. The remaining HF was removed in a stream of N_2, the residue was dissolved in ether and carefully washed with saturated $NaHCO_3$ solution. The separated ether layer was dried over $MgSO_4$, filtered and concentrated to a white solid. This was slurried in ethanol and the solid collected and dried yielding 500 mg (36%) of product: mp 239-241°C; ^{1}H-nmr ($CDCl_3$) δ: 1.65-1.85 (m, 2H), 1.9-2.0 (m, 2H), 2.76 (d, J=16.1, 1H), 2.86 (t, J=6.3 Hz, 2H), 3.16 (d, J=16.1 Hz, 1H), 6.59 (br d, J=7.7 Hz, 1H), 6.8-6.95 (m, 2H), 7.1-7.35 (m, 5H), 8.61 (br s, 1H); ^{13}C-nmr ($CDCl_3$) δ: 18.6, 30.3, 35.2, 42.4, 45.2, 115.6, 123.1, 126.3, 126.7, 127.5, 128.7, 128.9, 129.4, 133.1, 136.0, 138.5, 139.6, 170.2; mass spectrum m/z (relative intensity): M^+ 263 (64), 234 (100), 220 (31). Anal. Calcd for $C_{18}H_{17}NO$: C, 82.09; H, 6.50; N, 5.31. Found: C, 82.03; H, 6.51; N, 5.37.

(R,S,)-6'-Chloro-3,4-dihydrospiro[naphthalene-1(2*H*),4'(1'*H*)-quinoline]-2'(3'*H*)-one (9b): The spirocyclic amide (**9a**) (2.9 g, 11 mmol), and sulfuryl chloride (892 mg, 6.6 mmol) were stirred together in CH_2Cl_2 (75 ml) at room temperature for 16 h. Additional sulfuryl chloride (250 mg, 1.8 mmol) was added and stirring continued for 24 h. The precipitated product was collected, washed and dried giving 2.7 g (82%) of white solid: mp 244-246°C; ^{1}H-nmr ($CDCl_3$) δ: 1.65-1.85 (m, 2H), 1.9-2.0 (m, 2H), 2.75 (d, J=16.2 Hz, 1H), 2.87 (br t, J=5.5 Hz, 2H), 3.13 (d, J=16.2 Hz, 1H), 6.57 (d, J=2.3 Hz, 1H), 6.81 (d, J=8.4 Hz, 1H), 7.1-7.25 (m, 5H), 9.07 (br s, 1H); ^{13}C-nmr ($CDCl_3$) δ: 18.6, 30.1, 35.1, 42.5, 44.9, 116.9, 126.6, 127.0, 127.6, 128.3, 128.5, 128.6, 129.6, 134.8, 135.0, 138.4, 138.7, 170.2; mass spectrum m/z (relative intensity): M^+ 297/299 (100/33), 262 (37), 254 (31), 233 (77). Anal. Calcd for $C_{18}H_{16}NOCl$: C, 72.60; H, 5.41; N, 4.70. Found: C, 72.32; H, 5.47; N, 4.75.

(R,S,)-6'-Chloro-3,4-dihydrospiro[naphthalene-1(2*H*),4'(1'*H*)-quinoline]-2'(3'*H*)-thione (7b): Using Lawesson's procedure with toluene as the solvent,[20] the amide (**9b**) (2.7 g, 9.1 mmol) was converted to 2.9 g (77%) of the thioamide: mp 241-243°C; ^{1}H-nmr ($CDCl_3$) δ: 1.65-1.75 (m, 1H), 1.75-1.9 (m, 2H), 1.9-2.05 (m, 1H), 2.86 (br t, J=5.4 Hz, 2H), 3.30 (d, J=16.8 Hz, 1H), 3.39 (d, J=16.8 Hz, 1H), 6.64 (d, J=2.3 Hz, 1H), 6.88 (d, J=8.4 Hz, 1H), 7.04 (dd, J=1.6, 8.0 Hz, 1H), 7.1-7.25 (m, 4H), 10.14 (br s, 1H); ^{13}C-nmr ($CDCl_3$) δ: 18.3, 30.0, 34.6, 41.7, 52.5, 116.9, 126.6, 127.1, 127.7, 128.4, 128.8, 129.7, 130.1, 134.0, 136.7, 138.1, 138.6, 198.5; mass spectrum m/z (relative intensity): M^+ 313/315 (100/37), 280/282 (53/16). Anal. Calcd for $C_{18}H_{16}NClS$: C, 68.89; H, 5.14; N, 4.46. Found: C, 68.78; H, 5.37; N, 4.61.

(R,S,)-7'-Chloro-3,4-dihydro-10'-methylspiro[naphthalene-1(2*H*),5'(4'*H*)-[1,2,4]triazolo[4,3-*a*]quinoline] (1b): By the same procedure used to prepare **1a**, **7b** (1.95 g, 6.23 mmol) and acethydrazide (9.22 g, 125 mmol) in n-butanol (50 ml) yielded after recrystallization from ethanol/DMF 950 mg (45%) of pale yellow crystals: mp 287-289°C; ^{1}H-nmr ($CDCl_3$) δ: 1.5-1.65 (m, 2H), 1.65-1.8 (m, 2H), 2.79 (s, 3H), 2.86 (br t, J=5.8 Hz, 2H), 3.40 (s, 2H), 6.73 (d, J=2.4 Hz, 1H), 7.09 (dd, J=1.6, 8.0 Hz, 1H), 7.15-7.25 (m, 3H), 7.32 (dd, J=2.4, 8.6 Hz, 1H), 7.45 (d, J=8.6 Hz, 1H); ^{13}C-nmr ($CDCl_3$) δ: 14.2, 18.6, 30.2, 35.0, 35.5, 43.7, 118.5, 126.7, 127.3, 127.8, 128.6, 129.8, 130.4, 131.1, 132.2, 138.4, 138.6, 140.5, 148.0, 150.5; mass spectrum m/z (relative intensity): M^+ 335/337 (58/19), 334/336 (100/51). Anal. Calcd for $C_{20}H_{18}N_3Cl$: C, 71.53; H, 5.40; N, 12.51. Found: C, 71.32; H, 5.25; N, 12.49.

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