Domino reactions of tetrahydroisoquinoline difunctional compounds with 4-isothiocyanato-4-methyl-2-pentanone

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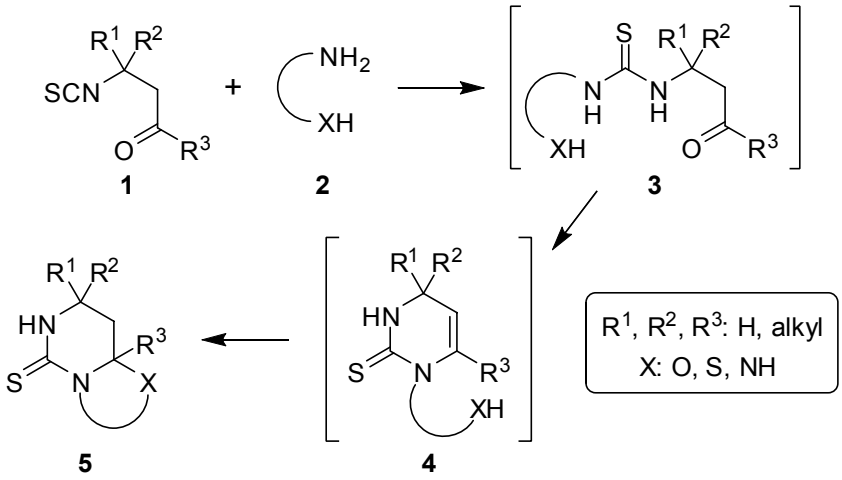
Abstract

Trans-9,10-Dimethoxy-3,3,4a-trimethyl-4,4a,6,7,11b,12-hexahydro-3*H*-pyrimido[6',1':2,3]-imidazo[5,1-*a*]isoquinoline-1(2*H*)-thione, *cis*- and *trans*-9,10-dimethoxy-3,3,4a-trimethyl-4,4a,6,7,12,13-hexahydro-3*H*,11b*H*-pyrimido[6',1':2,3]pyrimido[6,1-*a*]isoquinoline-1(2*H*)-thione, *trans*-10,11-dimethoxy-2,2,14a-trimethyl-1,7,8,12b,13,14a-hexahydro-2*H*-pyrimido-[6',1':2,3][1,3,4]oxadiazino[5,4-*a*]isoquinoline-4(3*H*)-thione and *trans*-9,10-dimethoxy-3,3,4a-trimethyl-4,4a,6a,7-tetrahydro-3*H*,6*H*,12*H*-pyrimido[6',1':2,3][1,3,4]oxadiazino-[4,5-*b*]-isoquino-line-1(2*H*)-thione, previously unknown ring-annelated isoquinoline derivatives, were prepared by diastereoselective domino ring closures of tetrahydroisoquinoline diamines or hydrazinoalcohols with 4-isothiocyanato-4-methyl-2-pentanone. The relative configurations and predominant conformations of the prepared tetracycles were determined by means of NMR spectroscopy and molecular modeling calculations.

Keywords: Diamines, hydrazinoalcohols, tetrahydroisoquinolines, β-isothiocyanatoketones, domino reactions, tetrahydropyrimidine-2(1*H*)-thiones

Introduction

β-Isothiocyanato-substituted aldehydes and ketones **1** are reagents that are widely applied for the synthesis of various heterocyclic compounds.[1-3] Their reactions with 1,2- or 1,3-aminoalcohols, aminothiols or diamines **2** result in pyrimidine-2-thione derivatives condensed with the corresponding 1,3-*X*,*N*-heterocycles (*X* = *O*, *S*, *N*) (**5**) (Scheme 1). Some compounds of type **5** proved to possess good anti-inflammatory and analgesic activities.[3] Previous mechanistic studies on these double ring closures revealed that compounds **5** were formed by domino processes,[4] via thiourea **3** and cyclic enamine intermediates **4**, involving intramolecular additions of the XH groups to the C=C bond in **4**.[5]



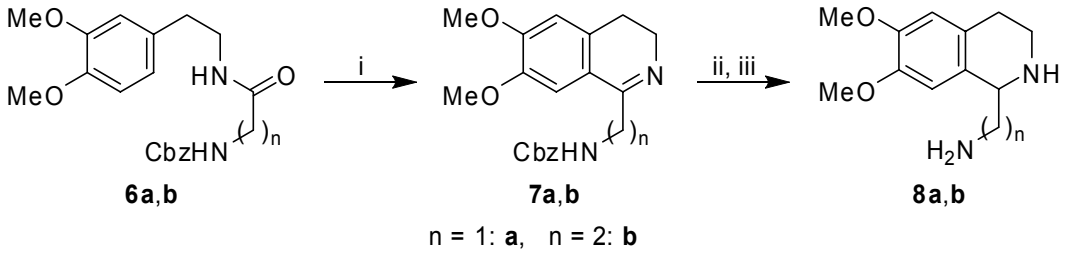
Scheme 1

Despite the numerous examples of the synthetic applicabilities of β-isothiocyanatoketones, their reactions with tetrahydroisoquinoline difunctional compounds have not yet been reported. Accordingly, as a continuation of our previous work on the preparation and structural analysis of tetrahydroisoquinoline-condensed saturated heterocycles,[6-8] our present aim was to study the reactions of 4-isothiocyanato-4-methyl-2-pentanone with tetrahydroisoquinoline diamines and hydrazinoalcohols.

Results and Discussion

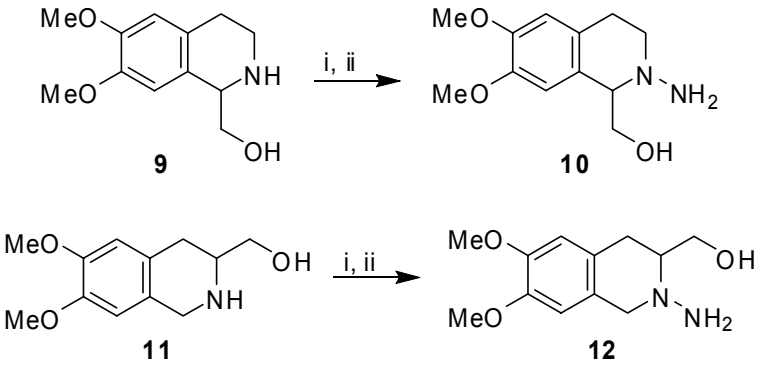
Syntheses

The homologous tetrahydroisoquinoline diamines **8a** and **8b** were prepared by a three-step procedure starting from the corresponding *N*-[2-(3,4-dimethoxyphenyl)ethyl]-substituted, *N*-protected amino carboxamides **6a**,**b** (Scheme 2).[6a,b]



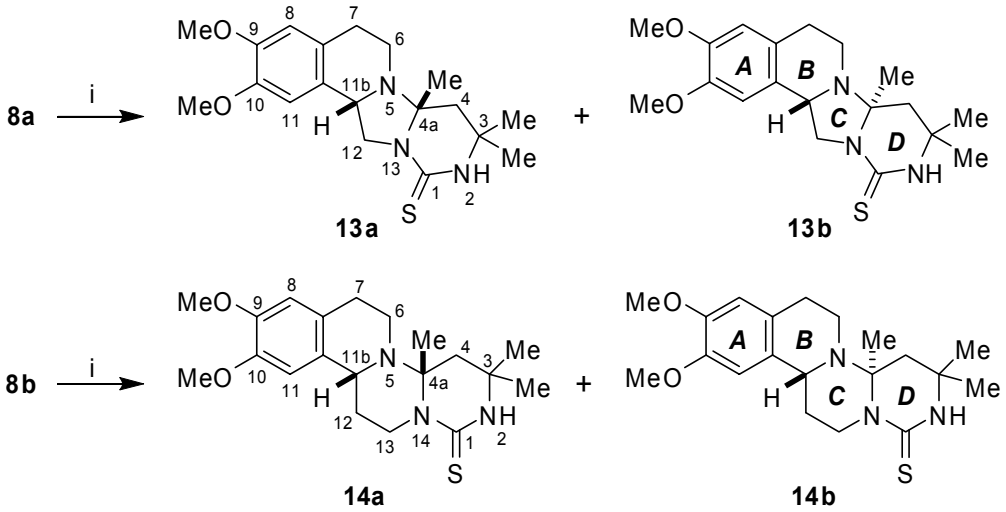
Scheme 2. Reagents and conditions:[6a,b] i: $POCl_3$, $CHCl_3$, reflux, 3 h, 71-88%; ii: $NaBH_4$, MeOH, 0 ºC, 3 h, then r.t., 3 h, 82-83 %; iii: 33% HBr in AcOH, r.t., 30 min, then NaOH, 74-78%.

The regioisomeric tetrahydroisoquinoline hydrazinoalcohols **10** and **12** were obtained by the standard two-step transformation (*N*-nitrosation and subsequent reduction) of the corresponding amino alcohols **9** and **11** (Scheme 3).[7]



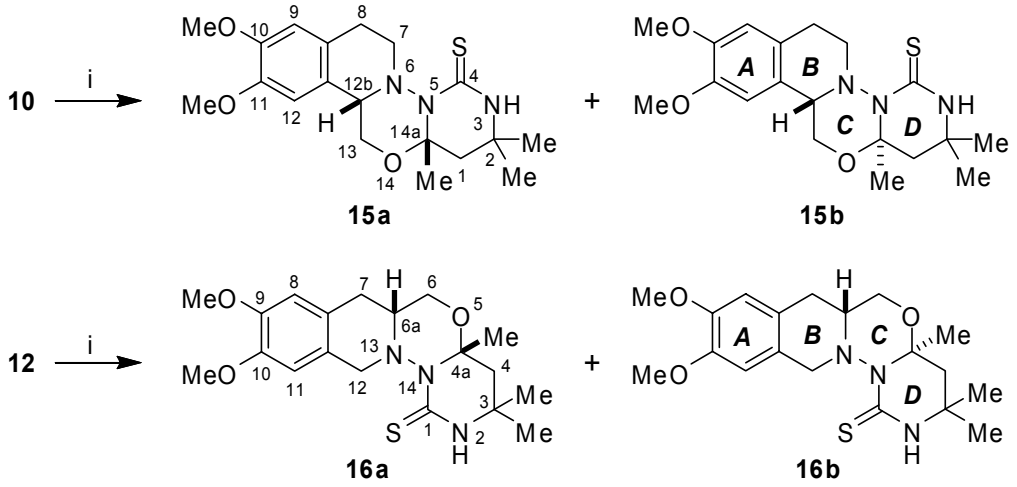
Scheme 3. Reagents and conditions:[7] i: $NaNO_2$, AcOH, H_2O, r.t., 8 h; ii: $LiAlH_4$, THF, r.t., 2 h, 52-67% (i+ii).

When diamines **8a**,**b** were refluxed with 4-isothiocyanato-4-methyl-2-pentanone[9] in toluene, diastereomers of the previously unknown ring systems pyrimido[6',1':2,3]imidazo-[5,1-*a*]isoquinoline-1(2*H*)-thione **13a**,**b** and pyrimido[6',1':2,3] pyrimido[6,1-*a*]isoquinoline-1(2*H*)-thione **14a**,**b**, differing in the position of the methyl group (Me-4a) and the hydrogen at the annelation (H-11b), were formed in moderate yields, but with considerable diastereo selectivities (Scheme 4).



Scheme 4. Reagents and conditions: (i) $MeCOCH_2C(Me)_2NCS$, toluene, reflux, 12 h; diastereomeric ratios in the crude products: **13a**:**13b** = 17:83, **14a**:**14b** = 70:30; isolated yields: 23% **13b**, 20% **14a**, 10% **14b**.

The size of the *N*,*N*-heterocyclic ring formed proved to exert a significant effect on the diastereomeric ratios, the *trans* isomer **13b** being the main product in the ring closure of **8a**, while the homologous diamine **8b** gave the *cis* tetracycle **14a** as the major diastereomer. Both the *cis* and the *trans* diastereomers of **14** could be separated by means of column chromatography, but only the major *trans* isomer **13b** could be obtained from the mixture of homologous tetracycles **13**; all of our efforts to date to isolate the minor *cis* compound **13a** in diastereomerically pure form have failed. The geometries of the diastereomers were deduced from the presence or lack of the cross-peaks between H-11b and Me-4a in the NOESY spectra.



Scheme 5. Reagents and conditions: (i) $MeCOCH_2C(Me)_2NCS$, toluene, r.t., 20 h; diastereomeric ratios in the crude products: **15a**:**15b** = ~0:~100, **16a**:**16b** = ~0:~100; isolated yields: 21% **15b**, 22% **16b**.

In the reactions of regioisomeric hydrazinoalcohols **10** and **12** with 4-isothiocyanato-4-methyl-2-pentanone, the *trans* isomers of the new ring systems pyrimido-[6',1':2,3][1,3,4]oxadiazino[5,4-*a*]isoquinoline-4(3*H*)-thione **15b** and pyrimido-[6',1'-2,3][1,3,4]oxadiazino[4,5-*b*]isoquinoline-1(2*H*)-thione **16b** were formed in moderate yields. Not even traces of the corresponding *cis* counterparts **15a**, **16a** could be detected in the crude products. The *trans* arrangements of the hydrogen at the annelation of rings B/C (H-12b or H-6a) and the methyl substituent at the annelation of the rings C/D (Me-14a or Me-4a) were deduced from the lack of their cross-peaks in the NOESY spectra of the isolated tetracycles **15b** and **16b**.

Conformations

For nitrogen-bridged saturated heterocycles, the steric structure can be characterized by conformational equilibria of *cis*[1]*–trans–cis*[2] type. In the *trans* structure, rings B/C are *trans*-connected, with the *trans-diaxial* arrangement of the hydrogen at the annelation and the nitrogen

lone pair. In the two other configurations, rings B/C are *cis*-connected, where for the *cis*[1] conformation the hydrogen at the annelation is in the *equatorial* position, while for the *cis*[2] conformation it is in the *axial* position relative to tetrahydropyridine ring B.[6-8,10] For **13-16**, only the geometries of the rings B/C could be determined, since the thioxo group makes the nitrogen at the neighboring annelation (rings C/D) nearly planar (for the meanings of rings B-D see the Schemes 4 and 5).

To determine the mode of connection of rings B/C, 2D NMR spectroscopic methods were used, since the *cis* or *trans* connections of these rings produce different patterns of the cross-peaks derived from the 1,3-*diaxial* protons in the NOESY spectra. For **13b** and **14b**, the NOESY spectra exhibited H-11b−H-4_{ax}, H-11b−H-6_{ax}, and H-4_{ax}−H-6_{ax} NOE cross-peaks, and for **14a** H-11b−Me-4a, H-11b−H-6_{ax}, and Me-4a−H-6_{ax} NOE cross-peaks, which are typical of a *trans*-arranged ring B/C junction. For **15b**, the NOESY spectrum revealed Me-2−H-12b, H-7_{ax}−H-13, H-7_{ax}−Me-14a and H-13−Me-14a NOE cross-peaks, which unequivocally proved the *cis* connection of rings B/C. For **16b**, the NOESY cross-peaks for Me-4a with the Me-3, H-12_{ax}, and H-6_{ax} protons pointed to a *cis* B/C ring junction.

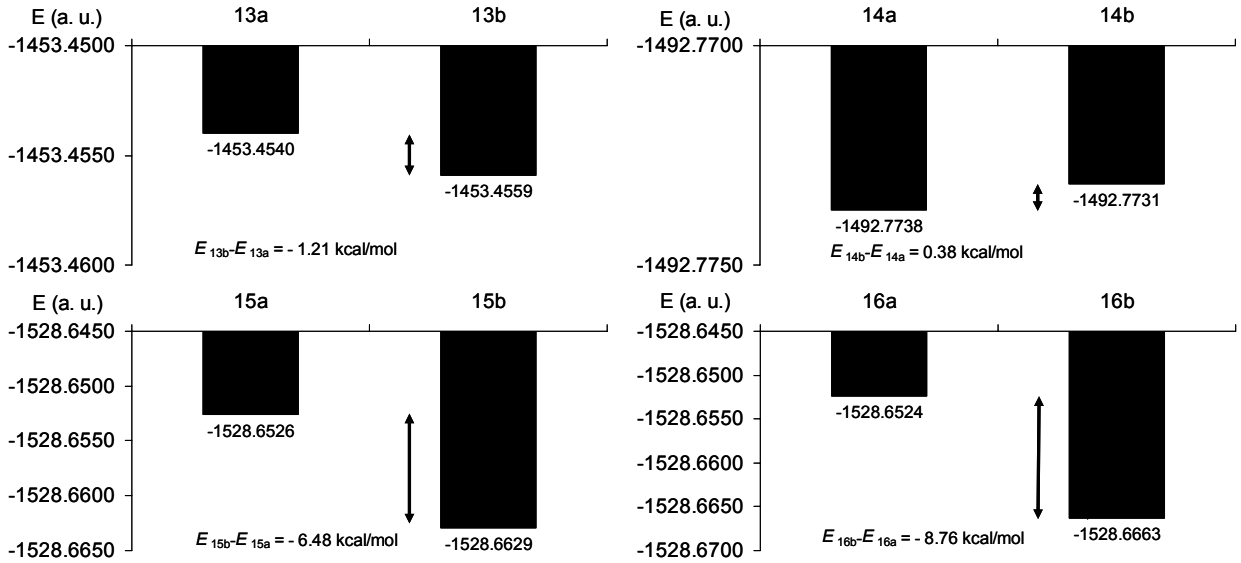


Figure 1. The energy differences between the *cis* (**a**) and *trans* (**b**) diastereomeric structures of **13-16**.

The structures of **13-16** were confirmed by molecular modeling. The conformational protocol comprised a stochastic search via the Merck Molecular Force Field (MMFF94), and a subsequent minimization of the resulting low-energy conformations by using the density functional theory (DFT) quantum mechanical method at the B3LYP/6-311G** level in vacuum for **13-16**. The DFT structures converged to the corresponding local minimum of the potential energy surface. The diastereomer energy differences between the *cis* (**a**) and *trans* (**b**) structures

proved that for **13** and **14** both isomeric structures are stable and that **15b** and the **16b** are more stable than **15a** and **16a**, as shown in Fig. 1. This is in good accordance with the observed diastereomeric ratios in the crude tetracylic products **13-16.**

The steric structures of the typical minimum-energy molecular structures for **13-16** (Fig. 2) are in good accordance with the experimental results, involving *trans*-arranged rings B/C for **13b**, **14a** and **14b** and the *cis* junction of rings B/C for **15b** and **16b**.

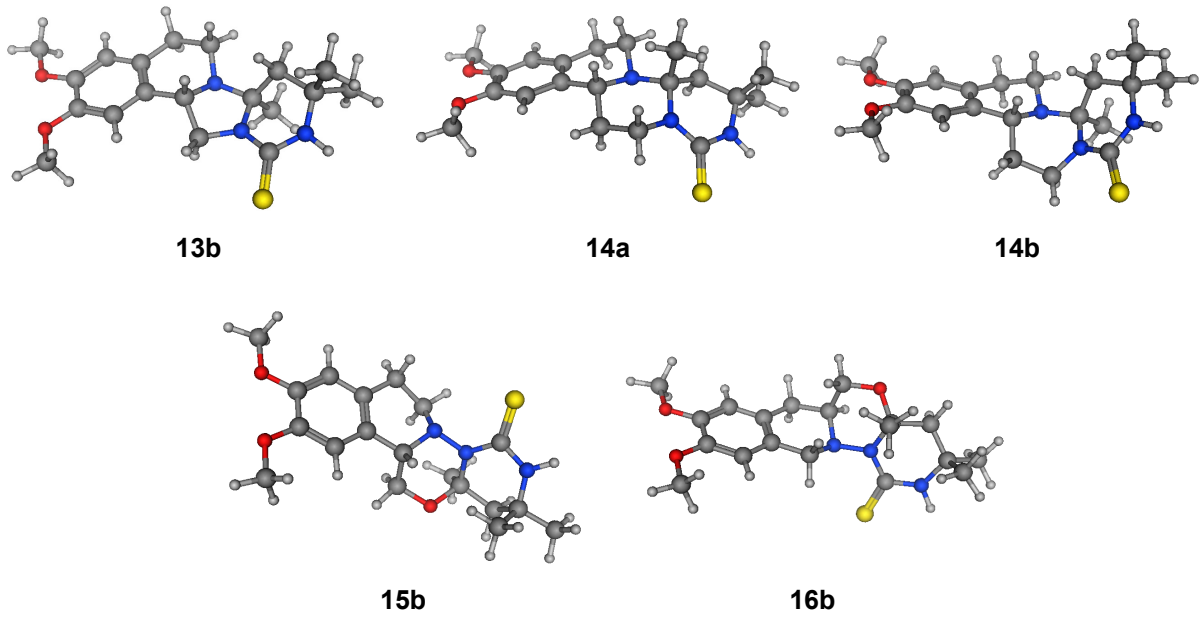


Figure 2. Final predominant minimum energy molecular structures for **13b**, **14a**, **14b**, **15b** and **16b**, obtained by using B3LYP/6-311G** calculations.

Conclusions

As a new extension of domino reactions of β-isothiocyanatoketones with difunctional compounds, diastereomers of partially saturated pyrimido[6',1':2,3]imidazo[5,1-*a*]isoquinoline-1(2*H*)-thione, pyrimido[6',1':2,3]pyrimido[6,1-*a*]isoquinoline-1(2*H*)-thione, pyrimido-[6',1':2,3][1,3,4]oxadiazino[5,4-*a*]isoquinoline-4(3*H*)-thione and pyrimido[6',1'-2,3][1,3,4]-oxadiazino[4,5-*b*]isoquinoline-1(2*H*)-thione were prepared by diastereoselective ring closures of tetrahydroisoquinoline diamines or hydrazinoalcohols with 4-isothiocyanato-4-methyl-2-pentanone. Neither the size of the newly formed *N*,*N*-heterocycle, nor the relative steric position of the substituents at the annelation proved to influence the *trans* connection of rings B/C in the diamine-derived tetracycles.

Experimental Section

General. NMR spectra were recorded in $CDCl_3$ at 298 K on a Bruker Avance III 600 spectrometer operating at 600.2 MHz for ^1H and 150.05 MHz for ^{13}C. Chemical shifts are reported in δ (ppm) relative to TMS as internal standard; the values of J are given in Hz. Mass spectra were recorded on a Finnigan MAT 95S instrument, using electron impact ionization. Elemental analyses were performed with a Perkin–Elmer 2400 CHNS elemental analyzer. Melting points were recorded on a Kofler hot-plate microscope apparatus and are uncorrected. For column chromatography, silica gel 60 (0.063-0.200 mm) was used. Routine thin-layer chromatography was performed on silica gel 60 F_{254} plates (Merck, Germany).

General procedure for the preparation of *trans*-9,10-dimethoxy-3,3,4a-trimethyl-4,4a,6,7,11b,12-hexahydro-3*H*-pyrimido[6',1':2,3]imidazo[5,1-*a*]isoquinoline-1(2*H*)-thione (13b) and *cis*- and *trans*-9,10-dimethoxy-3,3,4a-trimethyl-4,4a,6,7,12,13-hexahydro-3*H*,11b*H*-pyrimido[6',1':2,3]pyrimido[6,1-*a*]isoquinoline-1(2*H*)-thione (14a, 14b)

To a solution of the corresponding tetrahydroisoquinoline diamine **8a** or **8b** (2 mmol) in toluene (20 ml), 4-isothiocyanato-4-methyl-2-pentanone (315 mg, 2 mmol) was added. The mixture was stirred and refluxed for 12 h, and then evaporated under reduced pressure to afford a yellow oil containing a mixture of the diastereomers of the corresponding tetracycle. The diastereomeric ratios were determined from the ^1H NMR spectra of the crude products. Purification of the crude products by column chromatography gave **13b**, **14a** and **14b** as white solids.

Compound 13b. Yield: 165 mg (23%), mp 194-198 °C. ^1H NMR δ: 1.35 (3H, s, Me-3), 1.38 (3H, s, Me-3), 1.48 (3H, s, Me-4a), 1.82 (1H, d, J = 13.1 Hz, H-4_{ax}), 1.97 (1H, d, J = 13.1 Hz, H-4_{eq}), 2.74 (1H, d, J = 15.3 Hz, H-7), 2.85 (1H, dt, J = 10.6, 10.5, 4.2 Hz, H-6_{ax}), 2.98-3.05 (1H, m, H-7), 3.07-3.11 (1H, m, H-6_{eq}), 3.57 (1H, t, J = 9.9 Hz, H-12), 3.84 (3H, s, OMe), 3.85 (3H, s, OMe), 3.97 (1H, dd, J = 5.7, 9.9 Hz, H-11b), 4.87 (1H, dd, J = 5.7, 10.2 Hz, H-12), 6.01 (1H, s, H-2), 6.53 (1H, s, H-11), 6.63 (1H, s, H-8); ^{13}C NMR δ: 24.0, 29.3, 30.5, 33.8, 41.2, 42.3, 52.1, 54.0, 55.9, 56.0, 56.8, 76.4, 108.1, 111.7, 126.4, 127.1, 147.5, 148.0, 176.3. MS *m/z* 361 $M^{+\bullet}$. Anal. Calcd. for $C_{19}H_{27}N_3O_2S$: C, 63.13; H, 7.53; N, 11.62; Found C, 63.29; H, 7.35; N, 11.51%.

Compound 14a. Yield: 149 mg (20%), mp 201-203 °C. ^1H NMR δ: 1.27 (3H, s, Me-3_{ax}), 1.40 (3H, s, Me-3_{eq}), 1.52 (3H, s, Me-4a), 1.80 (1H, dq, J = 4.7, 13.0 Hz, H-12), 2.00 (1H, d, J = 14.2 Hz, H-4), 2.28 (1H, qd, J = 2.8, 13.1 Hz, H-12), 2.36-2.41 (1H, m, H-6_{ax}), 2.40 (1H, d, J = 14.2 Hz, H-4), 2.58 (1H, dt, J = 3.0, 15.7 Hz, H-7), 2.96 (1H, ddd, J = 5.3, 11.3, 15.7 Hz, H-7), 3.17 (1H, ddd, J = 1.8, 5.3, 11.3 Hz, H-6_{eq}), 3.45 (1H, dt, J = 2.5, 13.4 Hz, H-13), 3.83 (6H, s, OMe), 3.97 (1H, d, J = 11.1 Hz, H-11b), 5.57 (1H, ddd, J = 2.1, 4.5, 13.6 Hz, H-13), 6.54 (1H, s, H-8), 6.55 (1H, s, H-2), 6.66 (1H, s, H-11); ^{13}C NMR δ: 18.1, 29.4, 29.6, 30.0, 31.0, 44.5, 44.8, 45.9, 49.4, 55.7, 55.9, 56.1, 73.5, 108.2, 111.2, 126.5, 130.3, 147.4, 147.6, 177.6. MS *m/z* 375 $M^{+\bullet}$. Anal. Calcd. for $C_{20}H_{29}N_3O_2S$: C, 63.97; H, 7.78; N, 11.19; Found C, 64.14; H, 7.81; N, 11.17%.

Compound 14b. Yield: 75 mg (10%), mp 160-162 °C. ^1H NMR δ: 1.32 (3H, s, Me-3), 1.36 (3H, s, Me-3), 1.60-1.64 (1H, m, H-12), 1.65 (3H, s, Me-4a), 1.81 (1H, d, J = 13.6 Hz, H-4_{eq}), 2.12

(1H, d, J = 13.6 Hz, H-4_{ax}), 2.50 (1H, dt, J = 2.5, 10.6 Hz, H-6_{ax}), 2.57-2.67 (2H, m, H-7, H-12), 2.86-2.92 (1H, m, H-7), 2.95-2.99 (1H, m, H-6_{eq}), 3.47 (1H, ddd, J = 5.5, 9.1, 13.1 Hz, H-13), 3.81 (3H, s, OMe), 3.84 (3H, s, OMe), 3.87 (1H, dd, J = 7.4, 9.3 Hz, H-11b), 5.18 (1H, dd, J = 8.8, 12.9 Hz, H-13), 6.32 (1H, s, H-2), 6.54 (1H, s, H-11), 6.56 (1H, s, H-8); ^{13}C NMR δ: 23.5, 30.3, 30.3, 33.1, 34.9, 38.0, 41.5, 41.9, 49.9, 50.1, 55.9, 55.9, 74.5, 108.9, 111.0, 125.8, 130.9, 147.2, 147.7, 180.5. MS *m/z* 375 $M^{+\bullet}$. Anal. Calcd. for $C_{20}H_{29}N_3O_2S$: C, 63.97; H, 7.78; N, 11.19; Found C, 63.80; H, 7.610; N, 11.07%.

General procedure for the preparation of *trans*-10,11-dimethoxy-2,2,14a-trimethyl-1,7,8,12b,13,14a-hexahydro-2*H*-pyrimido[6',1':2,3][1,3,4]oxadiazino[5,4-*a*]isoquinoline-4(3*H*)-thione (15b) and *trans*-9,10-dimethoxy-3,3,4a-trimethyl-4,4a,6a,7-tetrahydro-3*H*,6*H*,12*H*-pyrimido[6',1':2,3][1,3,4]oxadiazino[4,5-*b*]isoquinoline-1(2*H*)-thione (16b)

To a solution of the corresponding tetrahydroisoquinoline hydrazinoalcohol **10** or **12** (476 mg, 2 mmol) in toluene (20 ml), 4-isothiocyanato-4-methyl-2-pentanone (315 mg, 2 mmol) was added. The mixture was stirred at room temperature for 20 h, and then evaporated *in vacuo* to afford a yellow crystalline residue. Purification of the crude product by column chromatography gave **15b** and **16b** as white crystalline substances.

Compound 15b. Yield: 158 mg (21%), mp 231-232 °C. ^{1}H NMR δ: 1.30 (3H, s, Me-2_{eq}), 1.39 (3H, s, Me-2_{ax}), 1.77 (3H, s, Me-14a), 2.13 (1H, d, J = 14.0 Hz, H-1_{ax}), 2.23 (1H, d, J = 14.0 Hz, H-1_{eq}), 2.79 (1H, td, J = 4.4, 15.2 Hz, H-8), 3.08-3.13 (1H, m, H-8), 3.42-3.47 (1H, m, H-7_{ax}), 3.82 (3H, s, OMe), 3.87 (3H, s, OMe), 3.87 (1H, overlapping, H-13_{eq}), 3.93 (1H, d, J = 11.2 Hz, H-13_{ax}), 3.95-3.99 (1H, m, H-7_{eq}), 4.70 (1H, dd, J = 3.6, 11.0 Hz, H-12b), 6.48 (1H, s, H-12), 6.52 (1H, s, H-3), 6.63 (1H, s, H-9); ^{13}C NMR δ: 24.4, 28.6, 29.6, 30.4, 47.8, 49.7, 50.2, 55.8, 55.9, 56.1, 63.1, 85.1, 109.1, 111.9, 125.2, 127.5, 147.5, 148.2, 181.0. MS *m/z* 377 $M^{+\bullet}$. Anal. Calcd. $C_{19}H_{27}N_3O_3S$: C, 60.45; H, 7.21; N, 11.13; Found C, 60.32; H, 7.07; N, 11.05%.

Compound 16b. Yield: 166 mg (22%), mp 175-177 °C. ^{1}H NMR δ: 1.28 (3H, s, Me-3_{ax}), 1.34 (3H, s, Me-3_{eq}), 1.65 (3H, s, Me-4a), 2.08 (1H, d, J = 14.0 Hz, H-4), 2.12 (1H, d, J = 14.0 Hz, H-4), 2.69 (1H, dd, J = 6.6, 15.4 Hz, H-7), 2.90 (1H, dd, J = 5.3, 15.4 Hz, H-7), 3.56-3.67 (2H, m, H-6), 3.84 (3H, s, OMe), 3.85 (3H, s, OMe), 4.04 (1H, d, J = 14.4 Hz, H-12_{ax}), 4.10-4.15 (1H, m, H-6a), 5.27 (1H, d, J = 14.4 Hz, H-12_{eq}), 6.58 (1H, s, H-11), 6.63 (1H, s, H-8), 6.65 (1H, s, H-2); ^{13}C NMR δ: 24.5, 27.1, 29.2, 31.2, 47.6, 49.6, 51.0, 51.7, 55.6, 55.6, 63.2, 87.2, 109.4, 111.6, 124.4, 127.2, 147.1, 147.1, 181.6. MS *m/z* 377 $M^{+\bullet}$. Anal. Calcd. for $C_{19}H_{27}N_3O_3S$: C, 60.45; H, 7.21; N, 11.13; Found C, 60.29; H, 7.02; N, 11.01%.

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