Synthesis of substituted octahydrochromeno[3,2-*i*]quinazoline-2(1*H*)-thiones

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Condensation of 8-arylidenehexahydroquinazoline-2-thiones with di- and trihydroxybenzenes affords the new heterocyclic system, *viz.*, octahydrochromeno[3,2-*i*]quinazoline-2(1*H*)-thiones, in which the substituents in both the chromane and quinazoline rings can be varied over a wide range.

Key words: resorcinol, pyrogallol, acid catalysis, hexahydroquinazoline-2-thiones, dihydrobenzopyran (chromane), two-dimensional NMR spectroscopy.

Substituted 3,4-dihydro-2*H*-1-benzopyrans[1,2] (chromanes) and quinazoline derivatives[3,4] belong to important classes of biologically active compounds. Data on the simultaneous presence of these structural fragments in one molecule are lacking in the literature.

Earlier,[5] it has been demonstrated that the reactions of di- and trihydroxybenzenes of type **1** with styrenedihydropyrimidine-2-thiones under mild acidic conditions afford substituted hydroxyspiro([1]benzopyran-2,4′(1′*H*)-pyrimidine)-2′(3*H*′)-thiones(ones). It was of interest to examine the chemical possibilities of this type of addition for heterocycles containing the conjugated diene system, in particular, for substituted benzylidenehexahydroquinazoline-2-thiones **2**.

It was found that the reactions of substituted benzylidenehexahydroquinazoline-2-thiones **2a—d** with resorcinol, 2-methylresorcinol, 5-methylresorcinol, 4-chlororesorcinol, and pyrogallol in chloroform catalyzed by *p*-toluenesulfonic acid monohydrate afforded octahydrochromenoquinazoline-2-thiones **3a—h** (Scheme 1). Compounds **3** were produced in yields of at most 50% (except for **3c**, which was prepared in 75% yield).

The duration of the reactions of benzylidenehexahydroquinazoline-2-thiones **2a—d** with resorcinol and its derivatives increases in the presence of a substituent in the quinazoline ring (R = Me or Bu^t). The reactivity of polyatomic phenols decreases in the following series: pyrogallol > resorcinol > 2-methylresorcinol > 5-methylresorcinol > 4-chlororesorcinol. An increase in both the duration of the reaction and the catalyst concentration does not lead to a noticeable increase in the yield of the target product.

In spite of the presence of several chiral centers in molecule **3**, compounds **3** are produced generally as two diastereomers with one of them predominating. Products **3** differ substantially in the physical properties depending on the nature of the substituent in the resorcinol ring. For example, compound **3a** has good solubility, whereas compound **3b** is poorly soluble in most solvents. Generally, the minor diastereomer is present in an amount of at most 10%. However, the percentage of this diastereomer of compound **3d** generated from 4-chlororesorcinol increases to 40%, and this diastereomer is formed as the major product in the reaction of 5-methylresorcinol giving rise to **3g**.

The structures of compounds **3** and the characteristic features of their isomerism were revealed by NMR spectroscopy. Compounds **3b** and **3g** were studied in detail. The ^{1}H NMR spectra of these compounds were interpeted using two-dimensional ^{1}H—^{1}H COSY spectroscopy. The assignment of the signals in the ^{1}H NMR spectra allowed us to assign the signals in the ^{13}C NMR spectra using heteronuclear ^{1}H—^{13}C HSQC (protonated C atoms) and HMBC (quaternary C atom) techniques.

These studies demonstrated that, in spite of large differences in the ^{1}H NMR spectra, both compounds, **3b** and **3g**, correspond to structure **3** and differ in the orientation of the aryl substituent at the C(8) atom. In compound **3b**, as well as in compounds **3a,c—f,h**, the aryl substituent and the pyrimidine ring are on the opposite sides of the chromane system, whereas these substituents in compound **3g** are on the same side of the chromane system, resulting in shielding of the NH proton by the phenyl group, hindered rotation of the phenyl group, and

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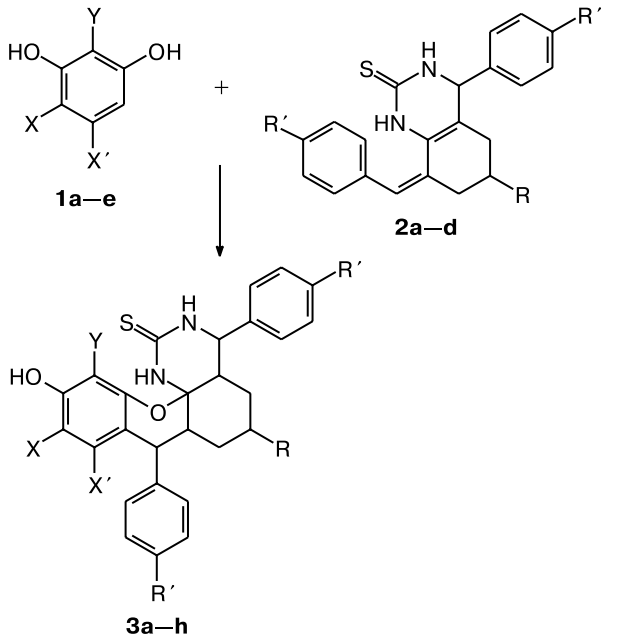
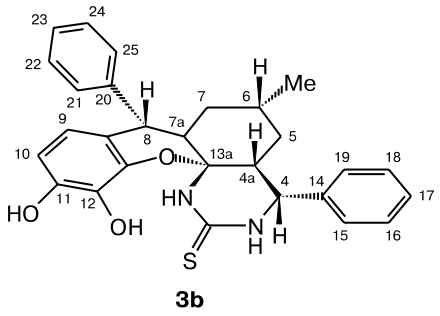
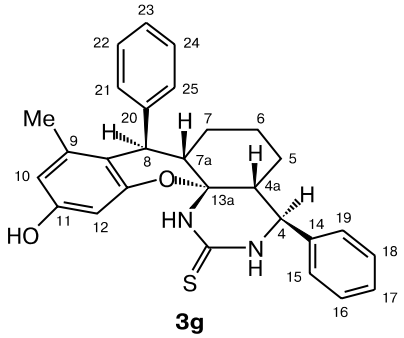
Scheme 1







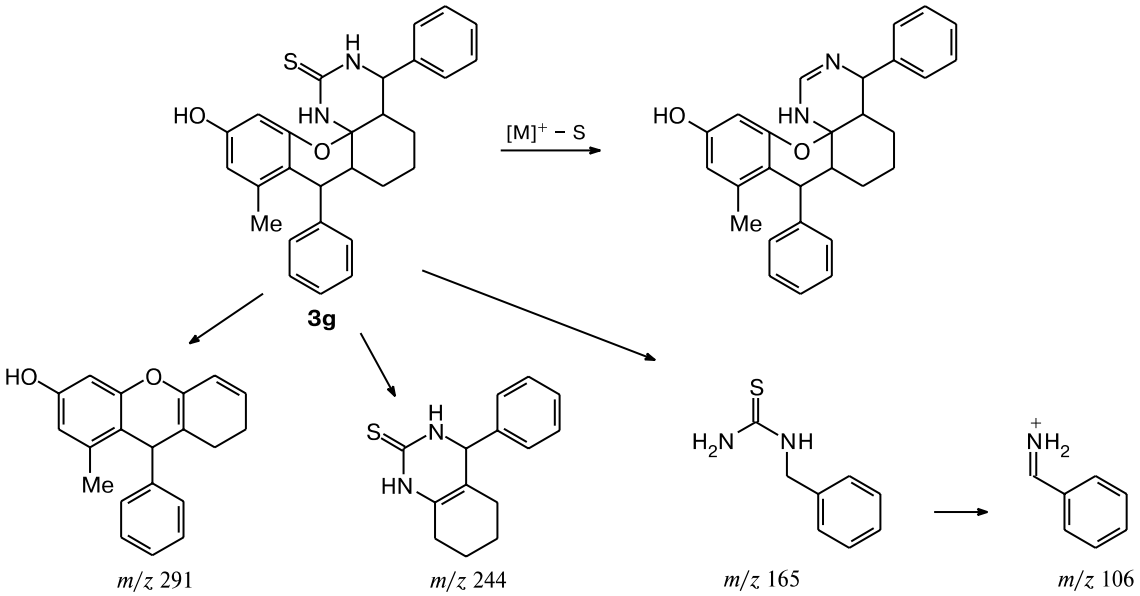
1: X = X′ = Y = H (**a**); X = X′ = H, Y = OH (**b**); X = Cl, X′ = Y = H (**c**); X = X′ = H, Y = Me (**d**); X = Y = H, X′ = Me (**e**)

2: R = R′ = H (**a**); R = Me, R′ = H (**b**); R = Bu^t, R′ = H (**c**); R = H, R′ = OMe (**d**)

	X	X′	Y	R	R′
3a	H	H	H	H	H
3b	H	H	OH	Me	H
3c	H	H	OH	H	H
3d	Cl	H	H	H	H
3e	H	H	OH	Bu^t	H
3f	H	H	Me	H	H
3g	H	Me	H	H	H
3h	H	H	OH	H	*p*-OMe

substantial changes in the chemical shifts of the H(4a) and H(8) protons. These data were obtained from analysis of the two-dimensional nuclear Overhauser effect spectra (NOESY and ROESY for compounds **3b** and **3g**, respectively). Data on the correlation peaks are given in the Experimental section. The different modes of fusion of the cyclohexane and pyrimidinethione rings were determined based on the NH(1)/H(7a) and NH(1)/H(8) correlation peaks in the NOESY spectrum of compound **3b** and the NH(1)/H(7′) correlation peak in the ROESY spectrum of compound **3g** as the key evidence.

Scheme 2



We hypothesize that the reaction starts with the addition of resorcinol and its derivatives as CH-acids at the double bond of the Ar—CH= fragment. In this case, the presence of a bulky substituent at position 4 or 5 of resorcinol hinders free rotation of the aryl substituent about the CH—quinazoline bond, which is responsible for the *cis* arrangement of the aryl substituent with respect to the tetrahydropyrimidine-2-thione ring. The reactions of 4- and 5-unsubstituted compounds give products with a *trans* arrangement of the substituents.

Compounds **3** were also studied by mass spectrometry. These compounds are characterized by low volatility. The major directions of fragmentation of the molecules involve elimination of sulfur ($[M^+ - S]$) and the formation of two ions characterized by the most intense peaks. These peaks correspond to the quinazoline fragment containing one phenyl substituent (*m/z* 244) and the benzylideneimmonium fragment (*m/z* 106). Compound **3g** is characterized by the formation of 9-phenyl-7,9-dihydro-8*H*-xanthen-3-ol (*m/z* 291) as the minor product (Scheme 2).

Experimental

The NMR spectra were measured on a Bruker DRX-500 instrument in DMSO-d_6 at 30 °C. The signals of the residual protons of the solvent in the ^{1}H NMR spectra (δ_H 2.50) or the signal of DMSO-d_6 in the ^{13}C NMR spectra (δ_C 39.5) were used as the standard. Two-dimensional spectra were recorded using the Bruker software. The mixing time in the NOESY and ROESY spectra was 0.3 s. The HMBC experiments were optimized for the spin-spin coupling constant $J_{H,C}$ = 8 Hz. The mass spectra were obtained on an MX-1321 spectrometer with direct inlet of a sample at 100—150 °C and at an accelerating voltage of 70 eV.

The starting compounds **2** were synthesized according to known procedures.[4]

Synthesis of substituted 3,4,4a,5,6,7,7a,8-octahydrochromeno[3,2-*i*]quinazoline-2(1*H*)-thiones (3) (general procedure). A suspension of styrenepyrimidinethione **2** (0.01 mol), di- or trihydroxybenzene **1** (0.015 mol), and *p*-toluenesulfonic acid monohydrate (0.52 g, 0.003 mol) in $CHCl_3$ (20—30 mL) was refluxed for 1.5—20 h until a precipitate formed. The precipitate was filtered off and washed with isopropyl alcohol and water. If the precipitate was not formed, $CHCl_3$ was evaporated and the oil was crystallized from Pr^{i}OH.

The reaction times, yields, melting points, and elemental analysis data for compounds **3a—h** are given in Table 1.

11-Hydroxy-4,8-diphenyl-3,4,4a,5,6,7,7a,8-octahydrochromeno[3,2-*i*]quinazoline-2(1*H*)-thione (3a). MS, *m/z* (I_{rel} (%)): 442 $[M]^+$ (10), 410 (15), 366 (9), 275 (11), 244 (40), 199 (18), 106 (100), 91 (15), 78 (15). ^{1}H NMR, δ: 0.90—1.40 (m, 5 H); 1.78 (br.d, 1 H, H_{eq}(5), J = 12.6 Hz); 1.93 (ddd, 1 H, H(4a), $J_{4a,5}$ = 11.5 Hz, $J_{4a,4}$ = 10.7 Hz, $J_{4a,5'}$ = 3.0 Hz); 2.45 (ddd, 1 H, H(7a), $J_{7',7a}$ = 11.8 Hz, $J_{7,7a}$ = 3.0 Hz, $J_{7a,8}$ = 5.7 Hz); 4.41 (d, 1 H, H(4), $J_{4,4a}$ = 10.7 Hz); 5.12 (d, 1 H, H(8), $J_{8,7a}$ = 5.7 Hz); 6.30 (m, 2 H, H(10), H(12)); 6.62 (d, 1 H, H(9), J = 8.5 Hz); 7.10—7.40 (m, 10 H, 2 Ph); 8.41 and 8.73 (both s, 1 H each, NH); 9.10 (s, 1 H, OH).

11,12-Dihydroxy-6-methyl-4,8-diphenyl-3,4,4a,5,6,7,7a,8-octahydrochromeno[3,2-*i*]quinazoline-2(1*H*)-thione (3b). MS, *m/z* (I_{rel} (%)): 472 $[M]^+$ (9.2), 346 (27.8), 259 (100). ^{1}H NMR, δ: 0.60 (d, 1 H, C(6)Me, J = 6.0 Hz); 0.74 (dq, 1 H, H(7), $J_{7,7'}$ = 12.2 Hz, $J_{7,6}$ = 12.0 Hz); 0.94 (d, 2 H, H(5′), H(7′), $J_{5',6}$ = $J_{7',6}$ = 3.0 Hz); 1.06 (dq, 1 H, H(5), $J_{5,5'}$ = 12.0 Hz, $J_{5,6}$ = 12.2 Hz); 1.19 (m, 1 H, H(6)); 1.84 (ddd, 1 H, H(4a), $J_{4a,5}$ =

Table 1. Melting points, yields, and elemental analysis data for compounds **3a—h**

Compound	M.p.[a]/°C	Yield (%)	Reaction time/h	Diastereomer ratio[b]	Found / Calculated (%)			Molecular formula
					C	H	N	
3a	237—239 (decomp.)	53	2.5	15 : 1	73.35 73.27	5.86 5.92	6.43 6.33	$C_{27}H_{26}N_2O_2S$
3b	280—282 (decomp.)	43	10	10 : 1	71.19 71.16	5.93 5.97	5.88 5.93	$C_{28}H_{28}N_2O_3S$
3c	277—280 (decomp.)	75	1.5	10 : 1	70.78 70.72	5.69 5.71	6.08 6.11	$C_{27}H_{26}N_2O_3S$
3d	247—250 (decomp.)	45	24	2 : 1	68.01 67.98	5.26 5.28	5.85 5.87	$C_{27}H_{25}ClN_2O_2S$
3e	272—275 (decomp.)	33	24	20 : 1	72.31 72.34	6.62 6.66	5.41 5.44	$C_{31}H_{34}N_2O_3S$
3f	218—220 (decomp.)	30	18	10 : 1	73.70 73.65	6.20 6.18	6.15 6.14	$C_{28}H_{28}N_2O_2S$
3g	235—240 (decomp.)	43	16	1 : 20	73.69 73.65	6.16 6.18	6.12 6.14	$C_{28}H_{28}N_2O_2S$
3h	240—242 (decomp.)	47	8	20 : 1	67.19 67.16	5.81 5.83	5.39 5.40	$C_{29}H_{30}N_2O_5S$

[a] The compounds were additionally purified from the minor diastereomer.
[b] The ratio was determined from the integral curves for the characteristic H(4a) and H(8) protons in the ^{1}H NMR spectra.

11.6 Hz, $J_{4a,4}$ = 10.9 Hz, $J_{4a,5'}$ = 3.0 Hz); 1.96 (ddd, 1 H, H(7a), $J_{7',7a}$ = 11.6 Hz, $J_{7,7a}$ = 3.0 Hz, $J_{7a,8}$ = 4.3 Hz); 4.91 (d, 1 H, H(4), $J_{4,4a}$ = 10.9 Hz); 5.15 (d, 1 H, H(8), $J_{8,7a}$ = 4.3 Hz); 6.12 (d, 1 H, H(9), $J_{9,10}$ = 8.5 Hz); 6.36 (d, 1 H, H(10), $J_{9,10}$ = 8.5 Hz); 7.24 (d, 2 H, H(21), H(25), J = 7.7 Hz); 7.31—7.35 (m, 6 H, H(15), H(17), H(19), H(22), H(23), H(24)); 7.41 (t, 2 H, H(16), H(18), J = 7.7 Hz); 8.05 (s, 1 H, C(12)OH); 8.32 (s, 1 H, NH(1)); 8.68 (s, 1 H, C(11)OH); 8.72 (s, 1 H, NH(3)). ^{13}C NMR, δ: 21.8 (C(6)—$\underline{C}H_3$); 29.4 (C(6)); 31.8 (C(5)); 32.0 (C(7)); 38.9 (C(8)); 40.1 (C(7a)); 45.1 (C(4a)); 56.2 (C(4)); 81.6 (C(13a)); 108.5 (C(10)); 113.5 (C(8a)); 118.1 (C(9)); 126.3 (C(17)); 127.7 (C(23)); 127.8 (C(15), C(19)); 127.9 (C(22), C(24)); 128.3 (C(16), C(18)); 130.0 (C(21), C(25)); 133.4 (C(12)); 140.2 (C(14)); 140.3 (C(12a)); 141.4 (C(20)); 144.2 (C(11)); 176.4 (C(2)). NOESY spectrum, correlation peaks (intensity): NH(1)/H(4a) (w), NH(1)/H(7a) (m), NH(1)/H(8) (s), NH(3)/H(4) (m), H(4)/H(4a) (w), H(4)/H_{ax}(5′) (s), H(4)/H(15),H(19) (s), H(4a)/H(7a) (s), H(4a)/H(15),H(19) (s), H_{ax}(6)/H(4a) (s), H_{ax}(6)/H(7a) (s), H_{eq}(7)/H(21),H(25) (s), H_{ax}(7′)/H(21),H(25) (m), H(8)/H(7a) (s). HMBC NMR, correlation peaks (intensity): NH(1)/C(2) (w), NH(1)/C(4a) (m), NH(1)/C(7a) (w), NH(1)/C(13a) (s), NH(3)/C(2) (m), NH(3)/C(4) (w), NH(3)/C(4a) (s), NH(3)/C(14) (m), H(4)/C(4a) (s), H(4)/C(14) (s), H(4)/C(15),C(19) (s), H(4a)/C(4) (w), H(5)/C(13a) (s), H(5′)/C(4a) (s), H(7)/C(13a) (s), H(8)/C(7) (s), H(8)/C(7a) (s), H(8)/C(8a) (s), H(8)/C(20) (s), H(8)/C(21),C(25) (s), H(9)/C(8) (s), H(9)/C(11) (s), H(9)/C(12) (w), H(9)/C(12a) (s), H(10)/C(8a) (s), H(10)/C(11) (m), H(10)/C(12) (s), H(10)/C(12a) (w), C(11)O$\underline{H}$/C(10) (s), C(11)O$\underline{H}$/C(11) (m), C(11)O$\underline{H}$/C(12) (s), C(12)O$\underline{H}$/C(11) (s), C(12)O$\underline{H}$/C(12) (m), C(12)O$\underline{H}$/C(12a) (s), H(15),H(19)/C(4) (s), H(16),H(18)/C(14) (s), H(22),H(24)/C(20) (s).

11,12-Dihydroxy-4,8-diphenyl-3,4,4a,5,6,7,7a,8-octahydrochromeno[3,2-*i*]quinazoline-2(1*H*)-thione (3c). ^{1}H NMR, δ: 0.90—1.20 (m, 4 H); 1.42 (ddd, 1 H, H(5′), $J_{5',5}$ = 12.2 Hz, $J_{5',4a}$ = 11.7 Hz, $J_{5',6}$ = 2.9 Hz); 1.55 (br.d, 1 H, H(5), $J_{5',5}$ = 12.2 Hz); 1.73 (ddd, 1 H, H(4a), $J_{5',4a}$ = 11.7 Hz, $J_{4,4a}$ = 10.9 Hz, $J_{5,4a}$ = 2.9 Hz); 2.09 (ddd, 1 H, H(7a), $J_{7',7a}$ = 11.7 Hz, $J_{7a,8}$ = 5.9 Hz, $J_{7,7a}$ = 3.6 Hz); 4.99 (d, 1 H, H(4), $J_{4,4a}$ = 10.9 Hz); 5.18 (d, 1 H, H(8), $J_{8,7a}$ = 5.6 Hz); 6.20 (d, 1 H, H(10), J = 8.4 Hz); 6.32 (d, 1 H, H(9), J = 8.4 Hz); 7.10—7.40 (m, 10 H, 2 Ph); 7.98 and 8.18 (both s, 1 H each, NH); 8.34 and 8.36 (both s, 1 H each, OH).

10-Chloro-11-hydroxy-4,8-diphenyl-3,4,4a,5,6,7,7a,8-octahydrochromeno[3,2-*i*]quinazoline-2(1*H*)-thione (3d). MS, m/z (I_{rel} (%)): 477 $[M]^+$ (15), 244 (100), 231 (31), 148 (17), 139 (15), 106 (51), 104 (19), 91 (39), 83 (20), 79 (22), 77 (25), 44 (29). ^{1}H NMR, δ: 1.03 (dq, 1 H, H(5), $J_{5,5'}$ = 12.0 Hz, $J_{5,6}$ = 12.2 Hz); 1.09 (br.d, 2 H, H(6), $J_{6,6'}$ = 12.0 Hz); 1.16 (dq, 1 H, H(5′), $J_{5,5'}$ = 12.8 Hz); 1.29 (dd, 1 H, H(7′), $J_{7,7'}$ = 12.2 Hz, $J_{7',6}$ = 3.0 Hz); 1.56 (d, 1 H, H(7), $J_{7,7'}$ = 12.2 Hz); 1.78 (ddd, 1 H, H(4a), $J_{4a,4}$ = 11.0 Hz, $J_{4a,5'}$ = 11.6 Hz, $J_{4a,5}$ = 3.6 Hz); 1.94 (dt, 1 H, H(7a), $J_{7',7a}$ = 11.0 Hz, $J_{7a,8}$ = 5.7 Hz, $J_{7,7a}$ = 3.0 Hz); 4.48 (d, 1 H, H(4), $J_{4,4a}$ = 11.0 Hz); 5.15 (d, 1 H, H(8) $J_{7a,8}$ = 5.7 Hz); 6.50 (s, 1 H, H(12)); 6.77 (s, 1 H, H(9)); 7.23 (t, 2 H, H(17), H(23), J = 7.7 Hz); 7.30 (t, 4 H, H(16), H(18), H(22), H(24), J = 7.7 Hz); 7.37 (d, 4 H, H(15), H(19), H(21), H(25), J = 7.7 Hz); 8.24 (s, 1 H, NH(1)); 8.36 (s, 1 H, NH(3)); 9.60 (br.s, 1 H, C(11)OH). The diastereomer ratio was ~2 : 1. ^{1}H NMR, δ: 1.03 (dq, 1 H, H(5), $J_{5,5'}$ = 12.8 Hz, $J_{5,6}$ = 12.0 Hz); 1.16 (dq, 1 H, H(5′), $J_{5,5'}$ = 12.8 Hz); 1.63 (dq, 3 H, H(6), H(7′), $J_{7,7'}$ = 12.2 Hz, $J_{7,6}$ = 12.2 Hz); 1.84 (br.d, 1 H, H(7), $J_{7a,7}$ = 12.8 Hz); 1.98 (dd, 1 H, H(4a), $J_{4a,5}$ = 12.8 Hz, $J_{4a,5'}$ = 12.2 Hz); 2.46 (br.d, 1 H, H(7a), $J_{7',7a}$ = 11.6 Hz); 4.07 (d, 1 H, H(4), $J_{4,4a}$ = 11.6 Hz); 4.27 (d, 1 H, H(8), $J_{7a,8}$ = 3.7 Hz); 5.08 (s, 1 H, H(9)); 6.12 (s, 1 H, H(12)); 7.23 (t, 2 H, H(17), H(23), J = 7.7 Hz); 7.30 (t, 4 H, H(16), H(18), H(22), H(24), J = 7.7 Hz); 7.37 (d, 4 H, H(15), H(19), H(21), H(25), J = 7.7 Hz); 8.72 (br.s, 1 H, NH(1)); 8.68 (s, 1 H, NH(3)); 9.10 (br.s, 1 H, C(11)OH).

6-*tert*-Butyl-11,12-dihydroxy-4,8-diphenyl-3,4,4a,5,6,7,7a,8-octahydrochromeno[3,2-*i*]quinazoline-2(1*H*)-thione (3e). ^{1}H NMR, δ: 0.80 (s, 9 H, Me); 1.12 (br.d, 2 H, $J_{5,5'}$ = 12.2 Hz); 1.30 (br.t, 1 H, $J_{5,5'}$ = 12.2 Hz); 1.54 (br.t, 1 H, $J_{5,5'}$ = 12.2 Hz); 1.78 (dd, 2 H, $J_{5,5'}$ = 12.2 Hz, $J_{5,6}$ = 3.0 Hz); 1.98 (ddd, 1 H, H(4a), $J_{4a,4}$ = 11.6 Hz, $J_{4a,5'}$ = 12.1 Hz, $J_{4a,5}$ = 3.0 Hz); 2.98 (dd, 1 H, H(7a), $J_{8,7a}$ = 4.9 Hz, $J_{7,7a}$ = 12.1 Hz); 5.01 (d, 1 H, H(4), $J_{4,4a}$ = 11.6 Hz); 5.08 (d, 1 H, H(8), $J_{8,7a}$ = 4.9 Hz); 6.23 (d, 1 H, H(10), $J_{9,10}$ = 8.5 Hz); 6.35 (d, 1 H, H(9), $J_{9,10}$ = 8.5 Hz); 7.10—7.40 (m, 10 H, 2 Ph); 7.80 and 8.09 (both s, 1 H each, NH); 8.63 and 8.70 (both s, 1 H each, OH).

11-Hydroxy-12-methyl-4,8-diphenyl-3,4,4a,5,6,7,7a,8-octahydrochromeno[3,2-*i*]quinazoline-2(1*H*)-thione (3f). ^{1}H NMR, δ: 0.90—1.40 (m, 4 H); 1.61 (m, 2 H); 1.80 (ddd, 1 H, H(7′), $J_{7',6}$ = 3.5 Hz, $J_{7',6'}$ = 11.6 Hz, $J_{7,7'}$ = 12.8 Hz); 1.93 (dd, 1 H, H(7a), $J_{7a,8}$ = 5.5 Hz, $J_{7a,7}$ = 12.8 Hz); 2.11 (s, 3 H, 12-Me); 4.53 (d, 1 H, H(4), $J_{4,4a}$ = 11.0 Hz); 5.10 (d, 1 H, H(8), $J_{7a,8}$ = 5.5 Hz); 6.38 (d, 1 H, H(10), $J_{9,10}$ = 8.5 Hz); 6.55 (d, 1 H, H(9), $J_{9,10}$ = 8.5 Hz); 7.10—7.50 (m, 10 H, 2 Ph); 8.16 and 8.24 (both s, 1 H each, NH); 8.72 (s, 1 H, OH).

11-Hydroxy-9-methyl-4,8-diphenyl-3,4,4a,5,6,7,7a,8-octahydrochromeno[3,2-*i*]quinazoline-2(1*H*)-thione (3g). MS, m/z (I_{rel} (%)): 456 $[M]^+$ (40), 365 (5), 291 (5), 244 (20), 211 (19), 174 (29), 165 (12), 115 (23), 106 (64), 91 (48), 79 (28), 77 (40), 44 (100). ^{1}H NMR, δ: 1.00 (dq, 1 H, H(7′), $J_{7',6}$ = 3.0 Hz, $J_{7',6'}$ = $J_{7',7a}$ = 13.0 Hz); 1.16 (dq, 1 H, H(5′), $J_{5',6}$ = 3.0 Hz, $J_{5',6'}$ = 13.0 Hz); 1.54 (br.q, 1 H, H(6′)); 1.60 (s, 3 H, C(9)Me); 1.78 (br.d, 1 H, H(6), $J_{6,6'}$ = 13.0 Hz); 1.90 (dd, 1 H, H(5), $J_{5,6}$ = 3.0 Hz, $J_{5,5'}$ = 13.0 Hz); 2.03 (br.d, 1 H, H(7), $J_{7,7'}$ = 13.0 Hz); 2.22 (dd, 1 H, H(7a), $J_{7a,7}$ = 3.0 Hz, $J_{7a,8}$ = 6.3 Hz); 2.35 (dd, 1 H, H(4a), $J_{4a,5}$ = 3.0 Hz, $J_{4a,5'}$ = 10.5 Hz); 4.13 (d, 1 H, H(8), $J_{7a,8}$ = 6.3 Hz); 4.35 (d, 1 H, H(4), $J_{4,4a}$ = 4.7 Hz); 5.33 (s, 1 H, H(12)); 6.14 (s, 1 H, H(10)); 6.70 (s, 1 H, NH(1)); 7.34 (br.d, 2 H, H(15), H(19), J = 7.5 Hz); 7.39 (br.t, 3 H, H(16), H(18), H(24), J = 7.7 Hz); 7.29 (m, 3 H, H(17), H(22), H(23)); 6.79 (br.d, 1 H, H(21), $J_{21,22}$ = 7.5 Hz); 7.46 (br.d, 1 H, H(25), $J_{25,24}$ = 7.5 Hz); 9.12 (br.s, 2 H, NH(3), C(11)OH). ^{13}C NMR, δ: 18.7 (C(9)—$\underline{C}H_3$); 24.2 (C(6)); 27.0 (C(7)); 29.6 (C(5)); 39.4 (C(8)); 41.1 (C(7a)); 43.6 (C(4a)); 58.4 (C(4)); 83.9 (C(13a)); 100.6 (C(12)); 110.7 (C(10)); 112.1 (C(8a)); 126.0 (C(15), C(19)); 126.2 (C(17)); 126.7 (C(21)); 127.0 (C(23)); 127.4 (C(16), C(18)); 128.3 (C(24)); 129.3 (C(22)); 131.2 (C(25)); 137.8 (C(9)); 140.2 (C(20)); 143.3 (C(14)); 152.3 (C(12a)); 156.5 (C(11)); 175.6 (C(2)). ROESY spectrum, correlation peaks (intensity): NH(1)/H_{ax}(7′) (m), NH(1)/H(21) (w), NH(1)/H(25) (w), NH(3)/H(4) (m), NH(3)/H(15),H(19) (m), H(4)/H(4a) (s), H(4)/H_{eq}(5) (s), H(4)/H_{ax}(5′) (m), H(4)/H(15),H(19) (s), H(4a)/H(4) (s), H(4a)/H_{eq}(5) (s), H(4a)/H_{ax}(5′) (m), H(4a)/H(7a) (m), H(4a)/H(15),H(19) (s), H_{ax}(6)/H(4a) (m), H_{ax}(6)/H(7a) (m),

$H_{eq}(7)$/H(7a) (m), $H_{eq}(7)$/H(8) (m), $H_{eq}(7)$/H(25) (s), H(8)/H(7a) (s), H(8)/H(21) (w), H(8)/H(25) (m), C(9)—C$\underline{H}_3$/H(8) (m). HMBC spectrum, correlation peaks (intensity): NH(1)/C(4a) (s), NH(1)/C(13a) (m), NH(3)/C(4a) (w), H(4)/C(4a) (m), H(4)/C(5) (m), H(4)/C(13a) (m), H(4)/C(14) (s), H(4)/C(15),C(19) (m), H(4a)/C(13a) (w), H(5′)/C(4a) (w), H(6)/C(4a) (w), H(7′)/C(7a) (w), H(8)/C(7) (s), H(8)/C(13a) (s), H(8)/C(8a) (s), H(8)/C(9) (s), H(8)/C(12a) (m), H(8)/C(20) (s), H(8)/C(21) (s), H(8)/C(25) (m), C(9)—C$\underline{H}_3$/C(8a) (s), C(9)—C$\underline{H}_3$/C(9) (s), C(9)—C$\underline{H}_3$/C(10) (s), H(10)/C(8a) (s), H(10)/$\underline{C}$(9)—CH_3 (s), H(10)/C(11) (w), H(10)/C(12) (m), C(11)O$\underline{H}$/C(10) (s), C(11)O$\underline{H}$/C(11) (s), C(11)O$\underline{H}$/C(12) (s), H(12)/C(9) (s), H(12)/C(10) (s), H(12)/C(11) (m), H(12)/C(12a) (s), H(15),H(19)/C(4) (s), H(15),H(19)/C(17) (s), H(16),H(18)/C(14) (s), H(25)/C(21) (s).

11,12-Dihydroxy-4,8-bis(*p*-methoxyphenyl)-3,4,4a,5,6,7,7a,8-octahydrochromeno[3,2-*i*]quinazoline-2(1*H*)-thione (3h). MS, *m/z* (I_{rel} (%)): 518 $[M]^+$ (7), 444 (3), 321 (2), 275 (70), 243 (17), 213 (13), 178 (8), 136 (12), 121 (18), 109 (6), 77 (8), 45 (100). ^{1}H NMR, δ: 1.27 (ddd, 1 H, H(5), J = 11.8 Hz, J = 11.6 Hz, J = 2.2 Hz); 1.50 (br.s, 1 H, H(6)); 1.72 (ddd, 1 H, H(4a), $J_{4a,4}$ = 11.6 Hz, $J_{4a,5'}$ = 12.6 Hz, $J_{4a,5}$ = 2.2 Hz); 1.84 (ddd, 1 H, H(7a), $J_{7a,8}$ = 5.2 Hz, $J_{7a,7}$ = 3.2 Hz, $J_{7a,7}$ = 12.2 Hz); 3.77 and 3.80 (both s, 3 H each, OMe); 4.29 (d, 1 H, H(8), $J_{8,7a}$ = 11.7 Hz); 4.37 (d, 1 H, H(4), $J_{4a,4}$ = 4.4 Hz); 4.93 (d, 1 H, H(4), $J_{4,4a}$ = 11.6 Hz); 5.00 (d, 1 H, H(8), $J_{7a,8}$ = 5.8 Hz); 5.85 and 6.13 (both d, 1 H each, H(10), $J_{9,10}$ = 8.7 Hz); 6.27 and 6.36 (both d, 1 H each, H(9), $J_{9,10}$ = 8.7 Hz); 6.78, 6.96, 7.16, and 7.26 (all d, 2 H each, H_{Ar}, J = 8.4 Hz); 8.01 and 8.20 (both s, 1 H each, NH); 8.58 and 8.62 (both s, 1 H each, OH). ^{13}C NMR, δ: 23.56 (C(6)); 23.11 (C(5)); 38.28 (C(7)); 38.74 (C(8)); 40.43 (C(7a)); 45.32 (C(4a)); 54.96 (Me); 55.09 (Me), 55.67 (C(4)); 82.02 (C(13a)); 108.5 (C(9)); 113.30 (2 C, C(15), C(19)); 113.74 (2 C, C(22), C(24)); 113.96 (C(8a)); 118.14 (C(10), CH); 128.84 (2 C, C(21), C(25)); 130.91 (2 C, C(16), C(18)); 132.06 (C(12)OH); 133.12 (C(14)); 133.31 (C(20)); 140.192 (C(12a)); 144.15 (C(11)); 157.74 (COMe); 158.82 (COMe)); 176.17 (C=S).

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