Heterocycle-bridged and Conformationally Constrained Retinoids: Synthesis of 4-(7,8,9,10-Tetrahydro-7,7,10,10-tetramethyl-4*H*-benzo[6,7]chromeno-[4,3-*d*]thiazole-2-yl)benzoic Acid

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Retinoids are a class of synthetic and natural compounds structurally related to retinoic acid. In a search for discovery of a new class of heterocycle-bridged and conformationally constrained retinoids, here we report the synthesis of 4-(7,8,9,10-tetrahydro-7,7,10,10-tetramethyl-4*H*-benzo[6,7]chromeno[4,3-*d*]thiazole-2-yl)benzoic acid (**10**) starting from 5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-ol (**13**). Several approaches was attempted to obtain target compound **10**. Structure elucidation of synthesized compounds has been made on the basis of elemental analysis and spectral data (^{1}H NMR, IR and MS).

Keywords retinoids, conformationally constrained analog, thiazole

Introduction

Retinoids belong to the steroid-thyroid-retinoid superfamily of hormones that regulate gene transcription by binding to and activating nuclear receptors.[1] Retinoic acid (**1**) plays a crucial role in many aspects of cell proliferation and differentiation, and has proved useful for the treatment of dermatologic diseases, photoaging and several cancers.[1] As a consequence, synthetic and natural retinoid analogs have a broad and different range of activities including regulation of cell differentiation and proliferation, embryonic development, bone formation, carbohydrates and lipids metabolism, carcinogenesis and immune system function.[2-4]

Retinoids bind to the six known retinoid receptors, the retinoic acid receptors—RARα, RARβ and RARγ- and retinoid X receptors—RXRα, RXRβ and RXRγ. It is believed that RARs and RXRs act mainly as RAR-RXR heterodimers, the functional units that also affect other cell signaling pathways, albeit RXR can also function autonomously.[5] *trans*-Retinoic acid (**1**) is the natural ligand for RARs, and its isomer 9-*cis*-retinoic acid (**2**) has almost the same binding affinity toward both RXRs and RARs.[6,7]

Extensive efforts have been made to synthesize receptor-selective retinoids, not only to characterize the functions of specific receptors but also to develop new therapeutic agents.[8,9]

Several potent retinoids, such as AM580 (**3**), TTNPB (**4**), and LGD1069 (**5**) have an aromatic carboxylic acid moiety instead of the polyenecarboxylic acid of retinoic acid (Figure 1). The presence of aryl rings as substitutes of terminal dienes imparts greater stability in some of the most active analogues, thus increasing the chances for therapeutic application. In this type of compounds, the hydrophobic part and the spacer between aromatic carboxylic acid and hydrophobic section can be varied with retention of high activity. Generally the 2,6,6-trimethyl-1-cyclohexenyl ring (hydrophobic part) is replaced by the lipophilic bioisostere 5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene.[10,11]

The development of new active retinoids and the identification of two distinct retinoid receptors have led to an increased understanding of the cellular effects of activation of these receptors and of mechanisms involved in the retinoid-induced apoptosis. The stereochemistry of the C-9 alkenyl portion of natural 9-*cis*-retinoic acid seemed of particular importance for the apoptotic activity, thus novel retinoid analogs bearing a sterically restricted flexibility in this region were pre-

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pared previously. The alkenyl basic motif of (*E*)-4-[2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)-propen-1-yl]benzoic acid (TTNPB) (**4**) was replaced by an isoxazoline moiety (compounds **6** and **7**) or an isoxazole (compounds **8** and **9**, Figure 2), which may enable the system to better fit the receptor and also reduced toxicity.[12]

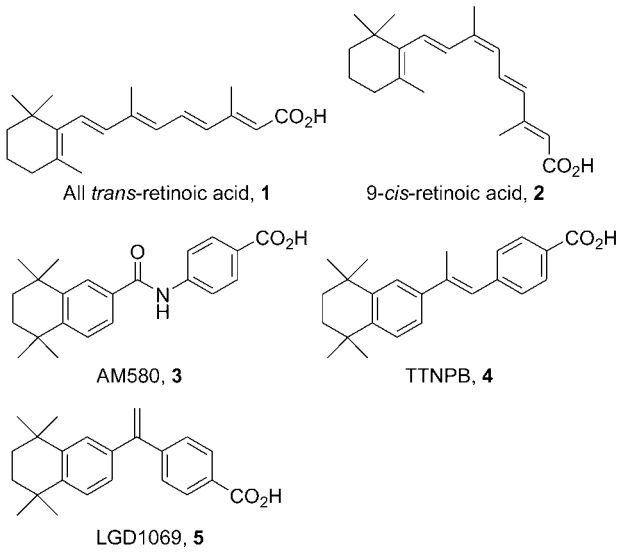

Figure 1 Structures of some natural and synthetic retinoids.

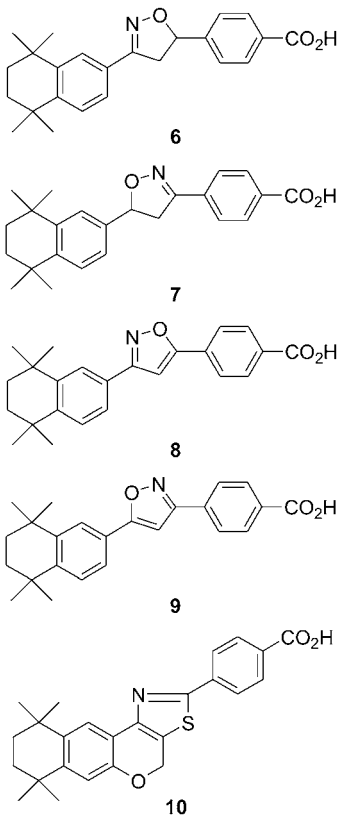

Figure 2 Structures of some heterocycle-bridged retinoids **6**—**9**, and heterocycle-bridged and conformationally constrained retinoid **10**.

In the search for the new heterocyclic retinoids, we considered that the conformational features of retinoid could be changed by the incorporation of thiazole ring and an additional oxymetylene spacer as a linker of tetrahydrotetramethylnaphthalenyl ring and aromatic carboxylic acid motifs. Thus we report here, synthesis of compound **10** as a new class of heterocycle-bridged and conformationally constrained retinoid (Figure 2).

Results and discussion

In the course of the investigation of the synthetic pathway to target compound **10**, we found that thiazole ring closure of appropriate thiobenzamide with 3-bromochromanone was key reaction.[13,14] As precursor 2,3,6,7,8,9-hexahydro-6,6,9,9-tetramethylbenzo[g]-chromen-4-one (**17**) were a synthesized as outlined in Scheme 1. At the first, the related diol (**11**) was converted to di-chloro-analog (**12**) by using concentrated hydrochloric acid saturated with hydrogen chloride gas in room temperature. Friedel-crafts dialkylation of phenol with compound **12** in the presence of $AlCl_3$ was used for preparing compound **13** in good yield. For chromanone ring construction from phenolic compound (**13**), three different routes were attempted: (i) nucleophilic substitution of 3-bromopropionic acid in the presence of NaH and DMF followed by cyclization with PPA; (ii) addition to acrylonitrile using NaOMe as a base and subsequent cyclization with H_2SO_4 under heating; (iii) acylation reaction with 3-chloropropionic acid in the presence of trifluoromethane sulfonic acid (TFMSA), followed by interamolecular nucleophilic substitution using aqueous NaOH as a base. Best result was achieved using the latter method with 41% overall yield. However, in this method, overheating (more than 80 ℃) of *β*-chloropropiophenone (**16**) resulted in HCl elimination and formation of *α*,*β*-unsaturated ketone (**18**) as a by-product. As illustrated in Scheme 2, chromanone (**17**) was brominated with copper(II) bromide in refluxing $CHCl_3$-EtOAc to give corresponding 3-bromochromanone (**19**) (in contamination with dibromo-compound) which was purified by column chromatography.[15]

Several approaches were attempted to obtain target compound **10** from 3-bromochromanone (**19**). The Hantzsch reaction of 3-bromochromanone (**19**) with 4-bromobenzothioamide in refluxing EtOH afforded the corresponding 4-bromophenylthiazole (**20**). As the next step, we had planned to exchange the bromo-group of compound **20** to a carboxylic acid substituent. However the effort to introduce the carboxylic acid substituent by butyl lithium hydride and CO_2 failed due to the decomposition. A further approach to final compound **10** was intended to proceed via 4-methylphenylthiazole intermediate (**21**) and subsequent oxidation of methyl group to the carboxylic acid substituent. Thus, 3-bromochromanone (**19**) was refluxed in EtOH with 4-methylben-

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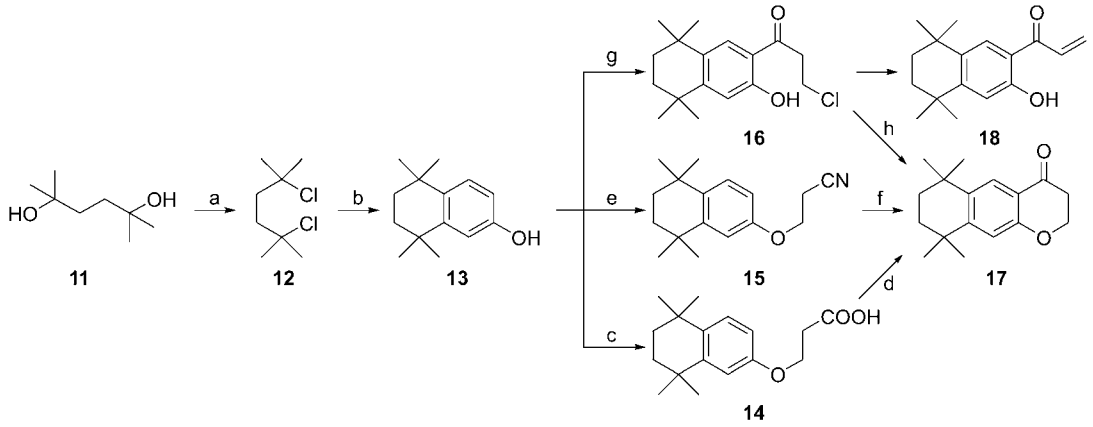
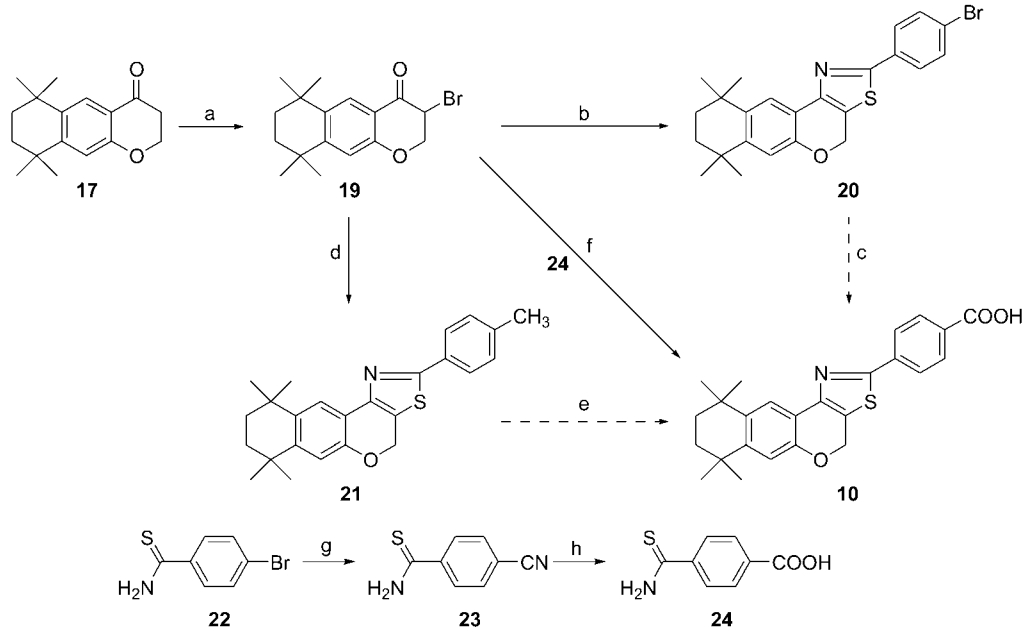
Scheme 1 Synthesis of key intermediate **17**



Reagents and conditions: (a) Concentrated HCl, HCl gas, r.t., 98%; (b) $AlCl_3$, CH_2Cl_2, reflux, 88%; (c) bromopropionic acid, NaH, DMF, 70—80 ℃, r.t., 16 h, 37%; (d) PPA, 80 ℃, 4 h, 46%; (e) acrylonitrile, NaOMe, 70—80 ℃, 7 h, 35%; (f) aq. H_2SO_4, 95—100 ℃, 3 h, 29%; (g) trifluoromethane sulfonic acid (TFMSA), 3-chloropropionic acid, reflux, 40 min, 65—70 ℃, 68%; (h) aq. NaOH, r.t., 4 h, 63%

Scheme 2 Synthetic approaches to target compound **10**



Reagents and conditions: (a) $CuBr_2$, EtOAc-$CHCl_3$ (V : V, 50 : 50), reflux, 3 h, 57%; (b) 4-bromobenzothioamide, EtOH, reflux, 3 h, 62%; (c) buthyl lithium hydride, CO_2, −10 ℃, 2 h; (d) 4-methyl benzothioamide, EtOH, reflux, 2 h, 58%; (e) aq. H_2SO_4, reflux, 2 h; (f) EtOH, reflux, 2 h, 42%; (g) $K_4[Fe(CN)_6]\cdot 3H_2O$, $Pd(OAc)_2$, sodium carbonate, dimethylacetamide (DMAC), 120 ℃, 43%; (h) aq. H_2SO_4, reflux, 1 h, 51%

zothioamide to afford corresponding 4-methylphenylthiazole analog (**21**). Attempts to oxidation of the methyl group of 4-methylphenylthiazole intermediate (**21**) using different oxidant, such as potassium dichromate was unsuccessful because of decomposition. Finally, the alternative approach was direct incorporation of carboxylic acid in the course of thiazole formation. Therefore, 4-bromobenzothioamide (**22**) was converted to cyanobenzothioamide (**23**) using $K_4[Fe(CN)_6]\cdot 3H_2O$ in the presence of $Pd(OAc)_2$. Hydrolysis of cyanobenzothioamide (**23**) with aqueous solution of H_2SO_4 gave thiocarbamoylbenzoic acid (**24**). Compound **24** was reacted with 3-bromochromanone (**19**) to afford thiazole compound (**10**) in 37% yield.

Experimental

Chemicals and all solvents used in this study were purchased from Merck AG and Aldrich Chemical (Darmstadt and Steinheinresp, Germany). Melting points were determined on a Kofler hot stage apparatus (C. Reihert, Vienna, Austria) and uncorrected. The IR spectra were obtained on a Shimadzu 470 spectrophotometer (potassium bromide disk; Shimadzu, Tokyo,

Japan). ^{1}H NMR spectra were measured using a Bruker 80 or 500 spectrometers (Bruker, Rheinstetten, Germany), and chemical shifts are expressed as δ with tetramethylsilane (TMS) as internal standard. Merck silica gel 60 F_{254} plates were used for analytical TLC. Yields are based on the purified products and were not optimized. Column chromatography was performed on Merck silica gel (70—230 mesh).

2,5-Dichloro-2,5-dimethylhexane (12)

A solution of 2,5-dimethylhexane-2,5-diol (**11**) (30 g, 0.20 mol) in concentrated HCl was stirred for 30 min. The mixture was saturated with HCl by HCl gas for 3 h. After 2 h of stirring, the solutions change into a biphasic mixture. The mixture was cooled and the light pink solid was filtered and washed with water and crystallized in hot methanol to give compound **12** as a white solid (35.89 g). Yield 98%; m.p. 59—60 ℃; ^{1}H NMR ($CDCl_3$) δ: 1.95 (s, 4H, CH_2CH_2), 1.60 (s, 12H, $4CH_3$); IR (KBr) v: 2950 and 1387 (C—H) cm^{-1}; MS m/z (%): 184 (M^+, 63), 182 (100), 186 (11). Anal. calcd for $C_8H_{16}Cl_2$: C 52.47, H 8.81; found C 52.21, H 8.95.

5,6,7,8-Tetrahydro-5,5,8,8-tetramethylnaphthalen-2-ol (13)

To a stirring solution of compound **12** (36.6 g, 0.20 mol) and phenol (18.8 g, 0.20 mol) in dried dichloromethane (100 mL), aluminum chloride (10.5 g, 0.08 mol) was added over 15 min. After stirring for an additional 30 min at room temperature, the reaction mixure was refluxed for 45 min. After cooling, 25 mL of hydrochloric acid (25%) was added at room temperature. The precipitated solid was filtered and the aqueous layer was extracted with $CHCl_3$ (50 mL) and dried over Na_2SO_4. After concentration, the residue was crystallized from petroleum ether-chloroform to afford **13** as a white solid (35.96 g). Yield 88%; m.p. 164—166 ℃; ^{1}H NMR ($CDCl_3$) δ: 7.23 (d, J=2.3 Hz, 1H, aromatic), 7.11 (s, 1H, OH), 6.55—6.77 (m, 2H, aromatic), 1.65 (s, 4H, CH_2CH_2), 1.24 (s, 12H, $4CH_3$); IR (KBr) v: 3200 (OH) cm^{-1}; MS m/z (%): 204 (M^+, 18), 190 (100), 147 (45), 118 (15), 91 (20), 57 (17). Anal. calcd for $C_{14}H_{20}O$: C 82.30, H 9.87; found C 82.44, H 9.69.

3-(1,2,3,4-Tetrahydro-1,1,4,4-tetramethylnaphthalen-6-yloxy)propanoic acid (14)

To a mixture of sodium hydride (8.15 g, 50%, 0.16 mol) in DMF (45 mL) was added 5,5,8,8-tetrahydronaphtalen-2-ol (**13**, 8.15 g, 0.04 mol) in DMF (15 mL) at 10—15 ℃ and the mixture was stirred at room temperature for 0.5 h. Then a solution of 3-bromopropionic acid (72 g, 0.07 mol) in DMF (15 mL) was added and the mixture was stirred at room temperature for 14 h. The reaction mixture was diluted with HCl, and extracted with ethyl acetate (100 mL×2). The combined ethyl acetate layer was washed with water (50 mL), brine (30 mL), and dried over sodium sulfate. The residue obtained after evaporation of the solvent was chromatographed over silica gel column using petroleum ether-ethyl acetate (V∶V, 75∶25) as eluent to give the title product as a yellow powder (4.09 g). Yield 37%; m.p. 77—79 ℃; ^{1}H NMR ($CDCl_3$) δ: 10.25 (s, 1H, COOH), 7.60 (d, J=4.5 Hz, 1H, aromatic), 6.60—6.81 (m, 2H, aromatic), 4.21—4.25 (m, 2H, OCH_2), 3.91—3.95 (m, 2H, CH_2COOH), 1.70 (s, 4H, CH_2CH_2), 1.31 (s, 12H, $4CH_3$); IR (KBr) v: 3220 (OH), 1715 (C=O) cm^{-1}; MS m/z (%): 276 (M^+, 22), 259 (55), 190 (100), 137 (40), 118 (25), 90 (25), 50 (15).

3-(1,2,3,4-Tetrahydro-1,1,4,4-tetramethylnaphthalen-6-yloxy) propanenitrile (15)

A mixture of 5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-ol (**13**, 10.2 g, 0.05 mol), acrylonitrile (5.3 g, 0.1 mol) and sodium methoxide (1.0 g) was refluxed for 5 h. After this period, the excess acrylontrile was distilled off under vacuum and the residue was treated with ethyl acetate and stirred for 5 min. The precipitated solids were filtered and the filtrate was washed with water, brine solution and dried (Na_2SO_4). After evaporation of the solvent, the residue was chromatographed over silica gel using CH_2Cl_2-EtOAc (V∶V, 90∶10) as eluent to give the desired product **15** as a white powder (4.50 g). Yield 35%; m.p. 77—78 ℃; ^{1}H NMR ($CDCl_3$) δ: 7.58 (s, 1H, aromatic), 6.24—6.31 (m, 2H, aromatic), 3.40—3.44 (m, 2H, OCH_2), 3.13—3.17 (m, 2H, CH_2CN), 1.75 (s, 4H, CH_2CH_2), 1.38 (s, 12H, $4CH_3$); IR (KBr) v: 2304 (CN) cm^{-1}; MS m/z (%): 257 (M^+, 40), 188 (100), 112 (35), 98 (15), (20), 60 (25).

3-Chloro-1-(1,2,3,4-tetrahydro-6-hydroxy-1,1,4,4-tetramethylnaphthalen-7-yl)propan-1-one (16)

To a stirring mixture of 3-chloropropionic acid (8.7 g, 0.08 mol) and **13** (16.3 g, 0.08 mol), was added trifluoromethanesulfonic acid (54 mL, 0.35 mol) over a 30 min period while keeping the temperature less than 5 ℃. The solution was allowed to stir at 5 ℃ for 30 min. After stirring, the mixture was refluxed for 40 min at 65 ℃ (Attention: in this stage, if the temperature is exceeded more than 80 ℃ and the reaction is continued for more than 40 min, the elimination reaction occurred to give a by-product **18**), cooled to room temperature and poured into water. The aqueous mixture was extracted with $CHCl_3$ (20 mL×3). The combined organic layers were dried over Na_2SO_4 and filtered. The solvent was removed in reduced pressure to give **16** as red oil. This product was purified by column chromatography eluting with *n*-hexane-dichloromethane (V∶V, 1∶9) to give a yellow powder (16.04 g). Yield 68%; m.p. 78—79 ℃; ^{1}H NMR ($CDCl_3$) δ: 11.20 (s, 1H, OH), 7.74 (s, 1H, aromatic), 6.87 (s, 1H, aromatic), 3.91 (t, J=5.7 Hz, 2H, CH_2Cl), 3.59 (t, J=5.3 Hz, 2H, $COCH_2$), 1.62 (s, 4H, CH_2CH_2), 1.24 (s, 12H, $4CH_3$); IR (KBr) v: 3414 (OH), 1642 (C=O) cm^{-1}; MS m/z (%): 294 (M^+, 100), 296 (32), 295 (17). Anal. calcd for $C_{17}H_{23}ClO_2$: C 69.26, H 7.86; found C 69.30, H 8.01.

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2,3,6,7,8,9-Hexahydro-6,6,9,9-tetramethylbenzo[g]-chromen-4-one (17)

Preparation from compound **14**: A mixture of 3-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphtalen-2-yl-oxy) propionic acid (**14**, 2.76 g, 0.01 mol) and polyphosphoric acid (8.0 g) was stirred at 80 ℃ for 2 h and then at room temperature for 2 h. The mixture was diluted with ice-cold water and extracted with ether (100 mL×2). The combined ethereal solution was washed with aqueous sodium carbonate (10%, 40 mL), water (100 mL), brine (60 mL), and dried (Na_2SO_4). After evaporation, the residue was chromatographed over silica gel column using petroleum ether-ethyl acetate (*V*∶*V*, 85∶15) as eluent to give acid compound **17**, as a white solid (1.19 g). Yield 46%.

Preparation from compound **15**: A mixture of 2-(1,2,3,4-tetrahydro-1,1,4,4-tetramethyl naphthalen-6-yloxy) propanenitrile (**15**, 2.57 g, 0.01 mol) and aqueous sulfuric acid (50%, 50 mL) was refluxed for 3 h. After cooling, the mixure was extracted with ethyl acetate. The combined ethyl acetate layer was concentrated and the residue was chromatographed over silica gel column using hexane-ethyl acetate (*V*∶*V*, 60∶40) as eluent to give compound **17** (0.75 g). Yield 29%.

Preparation from compound **16**: Compound **16** (8.8 g, 0.03 mol) was added to a solution of sodium hydroxide (1 mol/L, 50 mL) and the resulting suspension was stirred for 4 h at room temperature. Then, the reaction mixture was acidified with diluted HCl (10%). The aqueous mixture was extracted with ethyl acetate (25 mL×3), dried (Na_2SO_4) and concentrated to give compound **17** (4.88 g). Yield 63%; m.p. 101—103 ℃; ^{1}H NMR (DMSO-d_6) δ: 7.85 (s, 1H, aromatic), 6.89 (s, 1H, aromatic), 4.49 (t, J=6.6 Hz, 2H, OCH_2), 2.76 (t, J=6.6 Hz, 2H, $COCH_2$), 1.67 (s, 4H, CH_2CH_2), 1.27 (s, 12H, $4CH_3$); IR (KBr) ν: 1691 (C=O) cm^{-1}; MS *m*/*z* (%): 258 (M^+, 30), 244 (60), 242 (100), 200 (30), 127 (21), 115 (18). Anal. calcd for $C_{17}H_{22}O_2$: C 79.03, H 8.58; found C 78.88, H 8.61.

3-Bromo-2,3,6,7,8,9-hexahydro-6,6,9,9-tetramethylbenzo[g]chromen-4-one (19)

A vigorously stirring mixture of pulverized copper(II) bromide (4.6 g, 0.02 mol) and compound **17** (5.16 g, 0.02 mol) in chloroform-ethyl acetate (*V*∶*V*, 1∶1, 40 mL) was refluxed until the reaction was completed as judged by a disappearance of all black solid, and cessation of HBr evolution (3 h). After removal of the copper(I) bromide (white solid) by filtration, the solvents were evaporated from the filtrate under reduced pressure to give an oil. The residue was purified by flash column chromatography on silica gel eluting with *n*-hexane-CH_2Cl_2 (*V*∶*V*, 1∶9) to give **19** as a white solid (3.84 g). Yield 57%; m.p. 139—141 ℃; ^{1}H NMR (DMSO-d_6) δ: 7.89 (s, 1H, aromatic), 6.91 (s, 1H, aromatic), 4.67—4.50 (m, 3H, OCH_2CHBr), 1.67 (s, 4H, CH_2CH_2), 1.28 (s, 12H, $4CH_3$); IR (KBr) ν: 1690 (C=O) cm^{-1}; MS *m*/*z* (%): 339 (10), 338 (18), 336 (M^+, 20), 321 (100), 200 (16),128 (15). Anal. calcd for $C_{17}H_{21}BrO_2$: C 60.54, H 6.28; found C 60.32, H 6.11.

4-Cyanobenzothioamide (23)

A mixture of 4-bromobenzothioamide (**22**) (12.9 g, 0.06 mol), $K_4[Fe(CN)_6]\cdot 3H_2O$ (5.57 g, 0.013 mol), sodium carbonate (6.36 g, 0.06 mol) and $Pd(OAc)_2$ (5 mol%) in dimethylacetamide (100 mL) was heated to 120 ℃ under N_2 atmosphere. After completion of the reaction, the mixture was cooled to room temperature and diluted with EtOAc (20 mL). The resulting slurry was filtered and the filtrate was washed with water (25 mL×2). The organic layer was dried (Na_2SO_4) and the volatiles were removed under reduced pressure to give compound **23** as a yellow solid (4.18 g). Yield 43%; m.p. 189—190 ℃; ^{1}H NMR ($CDCl_3$) δ: 7.93—7.46 (m, 4H, ArH); IR (KBr) ν: 3498, 3380 (NH_2), 2249 (CN) cm^{-1}; MS *m*/*z* (%): 162 (M^+, 65), 136 (100), 110 (45), 87 (30), 70 (25), 63 (20), 46 (15). Anal. calcd for $C_8H_6N_2S$: C 59.23, H 3.73, N 17.27; found C 59.45, H 3.70, N 17.39.

4-Thiocarbamoylbenzoic acid (24)

A mixture of 4-cyanobenzothioamide (**23**) (4.8 g, 0.04 mol), sulfuric acid (98%, 30 mL) and water (50 mL) was stirred for 30 min at room temperature. The solution was slowly refluxed for 1 h. After cooling in an ice bath, water (50 mL) was added. The precipitated solid was filtered and washed with water. The product was purified by flash column chromatography eluting with CH_2Cl_2-ethyl acetate (*V*∶*V*, 70∶30) and crystallized from methanol to give compound **24** as a yellow solid (3.69 g). Yield 51%; m.p. 238—240 ℃; ^{1}H NMR ($CDCl_3$) δ: 10.82 (s, 1H, COOH), 7.83 (d, J=7.6 Hz, 2H, aromatic), 7.13 (d, J=7.6 Hz, 2H, aromatic); IR (KBr) ν: 3497, 3365 (NH_2), 3200 (OH), 1705 (C=O) cm^{-1}; MS *m*/*z* (%): 182 (M^+, 78), 180 (27), 136 (54), 88 (100), 77 (19). Anal. calcd for $C_8H_7NO_2S$: C 53.02, H 3.89, N 7.73; found C 52.89, H 3.89, N 7.66.

4-(7,8,9,10-Tetrahydro-7,7,10,10-tetramethyl-4*H*-benzo[6,7]chromeno[4,3-*d*]thiazole-2-yl)benzoic acid (10)

To a solution of compound **19** (3.36 g, 0.01 mol) in EtOH (25 mL) under argon, was added **24** (3.6 g, 0.02 mol). The solution was stirred and reflux for 2 h. After cooling, solvent was evaporated under reduce pressure to give a red solid. The residue was purified by flash column chromatography on silica gel eluting with *n*-hexane-ethyl acetate (*V*∶*V*, 4∶1) to afford target compound **10** as a yellow powder (1.76 g). Yield 42%; m.p. 285—289 ℃; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 9.89 (s, 1H, COOH), 7.89 (d, J=8.25 Hz, 2H, aromatic), 7.68 (s, 1H, aromatic), 7.34 (d, J=8.25 Hz, 2H, aromatic), 6.90 (s, 1H, aromatic), 5.48 (s, 2H, OCH_2), 1.65 (s, 4H, CH_2CH_2), 1.28 (s, 6H, $2CH_3$), 1.25 (s, 6H, $2CH_3$); IR (KBr) ν: 3220 (OH), 1715 (C=O) cm^{-1}; MS *m*/*z* (%): 419 (M^+, 20), 403 (100), 376 (20), 374 (42), 334 (15), 216 (21), 114 (22). Anal. calcd for $C_{25}H_{25}NO_3S$: C 71.57, H 6.01, N 3.34; found C 71.70, H 5.95, N 3.33.

2-(4-Bromophenyl)-7,8,9,10-tetrahydro-7,7,10,10-tetramethyl-4*H*-benzo[6,7]chromeno[4,3-*d*]thiazole (20)

Compound **20** was prepared starting from compound **19** and 4-bromobenzothioamide as method described for compound **10**. Yield 62% (2.82 g, brown powder); m.p. 192—193 ℃; ^{1}H NMR (DMSO-d_6) δ: 7.90—7.38 (m, 4H, aromatic), 7.24 (s, 1H, aromatic), 6.89 (s, 1H, aromatic), 5.40 (s, 2H, OCH_2), 1.69 (s, 4H, CH_2CH_2), 1.31 (s, 12H, $4CH_3$); MS *m*/*z* (%): 455 (M^+, 38), 453 (40), 440 (36), 360 (18), 183 (16), 84 (100). Anal. calcd for $C_{24}H_{24}BrNOS$: C 63.43, H 5.32, N 3.08; found C 63.79, H 5.38, N 3.00.

2-(4-Methylphenyl)-7,8,9,10-tetrahydro-7,7,10,10-tetramethyl-4*H*-benzo[6,7]chromeno[4,3-*d*]thiazole (21)

Compound **21** was prepared starting from compound **19** and 4-methylbenzothioamide as method described for compound **10**. Yield 58% (2.26 g, white solid); m.p. 152—154 ℃; ^{1}H NMR (DMSO-d_6) δ: 7.89 (d, J=8.8 Hz, 2H, aromatic), 7.35—7.20 (m, 3H, aromatic), 6.69 (s, 1H, aromatic), 5.44 (s, 2H, OCH_2), 2.40 (s, 3H, CH_3), 1.69 (s, 4H, CH_2CH_2), 1.34—1.25 (m, 12H, $4CH_3$); MS *m*/*z* (%): 389 (M^+, 100), 373 (89), 330 (25), 148 (20), 87 (65), 84 (60), 54 (93). Anal. calcd for $C_{25}H_{27}NOS$: C 77.08, H 6.99, N 3.60; found C 76.93, H 7.12, N 3.68.

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