An Efficient Synthesis of a Class of Novel *N*-Alkyl-*N*-aryl-4-hydroxy-1-methyl-2-oxo-1,2-dihydro-3-quinolinecarbothioamides

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The novel title compounds have been prepared in high yield by an optimized amide coupling followed by a Dieckmann cyclization. Additionally, this new route is amenable to preparative scale synthesis.

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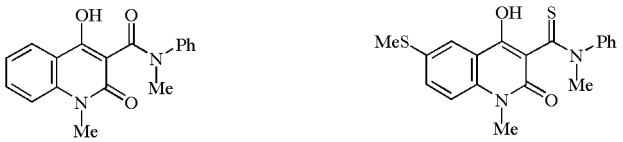
Introduction.

Recently we have been investigating a series of compounds based on the structure of the known immunomodulator, linomide [1] (Figure 1), in order to find a new compound with an improved pharmacological profile (*i.e.*, more potent, less toxic). We identified such a compound, FR142107 (**1a**, Figure 1), in which linomide has been substituted in the 6 position by a methylthio moiety and the exo amide changed to a thioamide [2]. Compound **1a** belongs to a class of newly synthesized compounds, which is the subject of this paper.



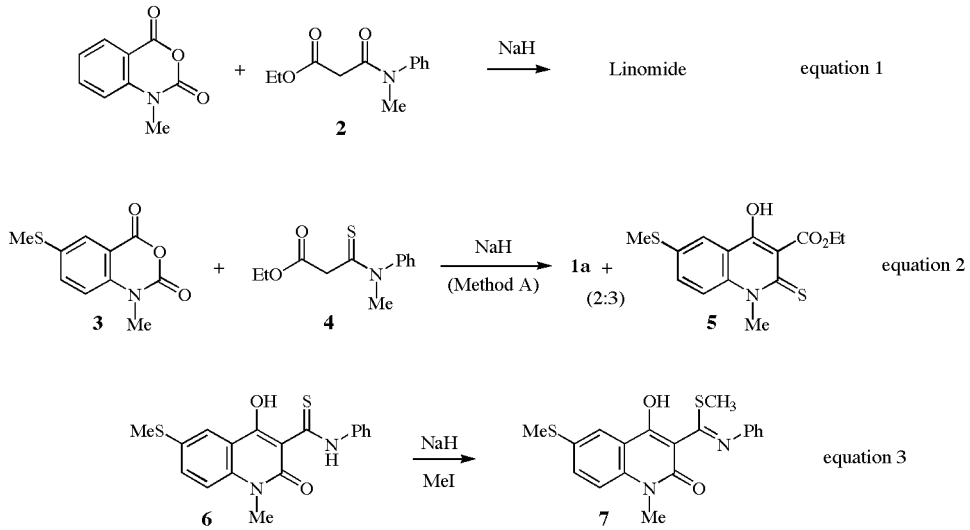
Linomide FR142107 (**1a**)

Figure 1

Initially **1a** was synthesized using the same procedure as for linomide except using the thioamide **4** instead of malonamide **2** (Method A, Equations 1 and 2) [3]. However, because of the high reactivity in the cyclization step of the thioamide compared to the ester of **4**, a mixture of products was obtained with the desired **1a** as the minor compound. The product **1a** could be easily separated from the by-product **5** by taking advantage of the relatively high acidity of **5** compared to **1a** (see experimental) and several analogues of **1a** were conveniently and quickly synthesized by Method A as a first approach.

However, when **1a** was chosen for further biological evaluation, we needed access to larger amounts of **1a** than could be synthesized by this convenient albeit low yield route. We thought it unlikely that the 2:3 ratio of the products could be changed significantly by simply changing the reaction parameters. A number of different approaches were considered. Thiolation of the easily obtainable amides did not appear promising due to competing other reactive functional groups. Acylation with *N*-methyl-*N*-phenylthiocarbamoyl chloride looked problematic. Alkylation of the easily obtained 4-hydroxy-1-methyl-6-(methylthio)-2-oxo-*N*-phenyl-1,2-dihydro-3-quinolinecarbothioamide (**6**, Equation 3) with methyl iodide did not provide the desired **1a** but the S-methylated **7**.

Finally we decided to use a stepwise procedure starting with the anthranilic ester **8a** (Method B, Scheme 1).



Amide coupling with the appropriate acid **9a** followed by Dieckmann cyclization would provide the desired material without any regiochemical problems. This method looked appealing because of the many known methods for amide coupling [4], and the many examples of similar Dieckmann cyclizations [5].

Results and Discussion.

The known isatoic anhydride **3** [6] was converted to the amine **8a** (Scheme 1) in nearly quantitative yield with catalytic sodium ethoxide in refluxing ethanol for 30 minutes [7]. The preparation of acid **9a** has been previously described by us [8] and proceeds in 93% yield by hydrolysis of **4** with aqueous sodium hydroxide in methanol. The coupling reaction proved more difficult than anticipated. The weakly basic and hindered secondary amine **8a**, strongly hydrogen bonded to the adjacent ester group, and the unstable acid **9a** provided challenging criteria that many coupling conditions could not meet. For instance, although carbodiimide reagents gave some desired coupling product **10a**, the main product was **11**, probably obtained by the path shown in Scheme 2. A large amount of decarboxylation product **12** was also obtained, which demonstrated the short half-life of the acid **9a** in solution. The Mukaiyama reagent [9] and *N,N'*-disuccinimidyl carbonate (DSC) [10] were also unsatisfactory (63% and 10% maximum yield respectively).

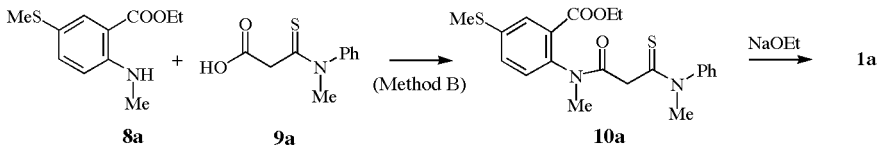
Table 1

Reaction Conditions and Yields of Compound **10a** by the Mixed Anhydride Method (Method B)

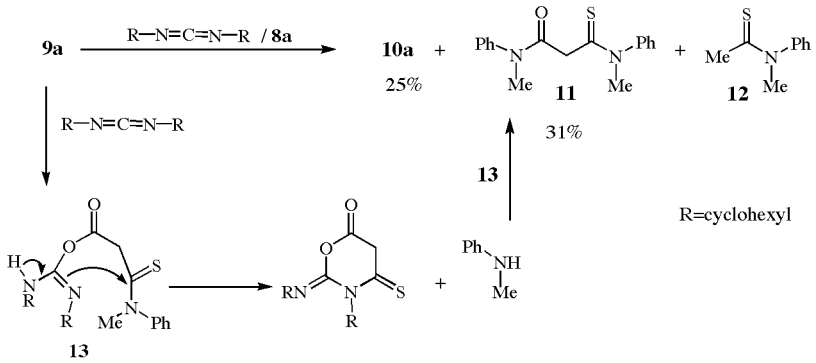
Entry	equiv. of **9a**	reagent (equiv.)	Base (equiv.)	yield (%)[a]
1	1.2	[b] (1.2)	*N*-methylmorpholine	0
2	1.2	[b] (1.2)	pyridine (1.2)	10
3	1.2	[c] (1.2)	pyridine (1.2)/triethylamine (1.2)	55
4	2.2	[c] (2.2)	pyridine (2.2)/triethylamine (2.2)	76
5	1.2	[c] (1.2)	pyridine (2.4)	90
6	1.2	[c] (1.2)	2,6-lutidine (2.4)	50
7	1.2	[c] (1.2)	pyridine (2.4)[d]	50
8	1.5	[c] (1.5)	pyridine (3.0)[e]	98[f]

[a]: hplc yield; [b]: isobutyl chloroformate; [c]: pivaloyl chloride; [d]: inverse addition (mixed anhydride was added to **8a**); [e]: molecular sieves used; [f]: isolated yield: 82%.

Scheme 1



Scheme 2



Finally a modified mixed anhydride method was found to be acceptable. Using the standard procedure as for peptide synthesis [11] in which isobutyl chloroformate was used as the activating reagent, did not perform well (Table 1; entries 1,2). However, using the more reactive pivaloyl chloride provided a 55% yield on the first attempt (entry 3). Increasing the equivalents of the acid **9a** and reagent relative to the amine **8a** increased the yield, but not in a linear fashion (entry 4). Use of only pyridine instead of pyridine plus triethylamine gave another increase in the yield (entry 5), but the use of lutidine instead of pyridine (entry 6) or inverse addition (activated acid added to **8a**, entry 7) was not beneficial. The final improvements came by increasing the equivalents of **9a** and pivaloyl chloride to 1.5, and the use of powdered molecular sieves (4A) (entry 8). The use of molecular sieves was especially useful for maintaining

consistency between experiments, notably during the hot and humid summer months in Japan.

With the synthesis of intermediate **10a** completed we turned our attention to the cyclization. We were gratified to find that the cyclization proceeds smoothly with 1.1 equivalents sodium ethoxide in absolute ethanol at 5 °C for 30 minutes. Simple dilution with water followed by neutralization with 1.2 equivalents hydrochloric acid yielded beautiful, light yellow crystals of the desired **1a** in 97% yield and 98% purity.

We have now conducted this reaction reproducibly under these optimized conditions and found it to give uniformly high yields and clean reactions. We have also applied it to a number of other substrates as shown in Table 2 and Scheme 3. As can be seen, the reaction proceeds smoothly with a variety of substituents. When the acid **9** aryl moiety is unsubstituted or substituted with an electron releasing substituent, the yields are generally good (entries 1 to 4). When **9** is substituted with an electron withdrawing aryl moiety (CF_3 or Cl) and when the amine **8** is activated (entries 5, 6) yields are high but decrease when **8** is deactivated with electron withdrawing substituents (entries 7 to 9). Even in the case of the sterically hindered amine in entry 8 the reaction proceeds in good yield. The especially demanding cases using the unstable acids found in entries 10 and 11 show the versatility of this procedure.

Conclusion.

Ethyl *N*-methylanthranilates **8** were condensed with thiocarbamoylacetic acids **9** activated by the mixed anhydride method using pivaloyl chloride, followed by Dieckmann cyclization to give various *N*-alkyl-*N*-aryl-4-hydroxy-1-methyl-2-oxo-1,2-dihydro-3-quinolinecarbothioamides **1**. According to this new route (Method B), the overall yield of **1a** from the readily available isatoic anhydride **3** was improved to 80% from 25% (by Method A). This route is applicable to a variety of related compounds and is also amenable to preparative scale synthesis.

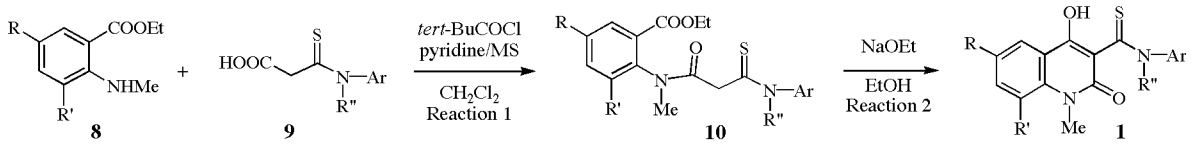
EXPERIMENTAL

Melting points were measured on a Mitamura capillary melting point apparatus and are uncorrected. IR spectra were recorded on a Shimadzu IR-408 spectrophotometer. ^{1}H-nmr spectra were taken with a Bruker AC-200 (200 MHz) instrument using tetramethylsilane as an internal standard. Electron impact ms were obtained with a Hitachi M80 mass spectrometer. Atmospheric pressure chemical ionization ms were obtained with a Hitachi M-1000 LC/QMS spectrometer. Solvents used for anhydrous reactions were dried over molecular sieves (4A). Organic extracts were dried over anhydrous magnesium sulfate. Column chromatography was performed using Kieselgel 60 (70-230 mesh, E. Merck). The purity of **1a** was determined by high performance liquid chromatography on a TSK gel ODS-80Tm (5μm) column (10 cm x 4.6 mm) eluting with phosphate buffer

Table 2
Yields of Anthranilates **10** and Quinolinecarbothioamides **1** synthesized by Method B

Entry	R	R'	R"	Ar	Isolated Yields (%) Reaction 1 (Product)		Reaction 2 (Product)	
1	MeS	H	Me	Ph	82	(**10a**)	98	(**1a**)
2	1-pyrrolyl	H	Me	Ph	63	(**10b**)	89	(**1b**)
3	Cl	H	Me	Ph	86	(**10c**)	97	(**1c**)
4	Cl	H	Me	4-MeO-Ph	76	(**10d**)	92	(**1d**)
5	MeO	H	Me	4-Cl-Ph	78	(**10e**)	84	(**1e**)
6	MeO	H	Me	3-CF_3-Ph	95	(**10f**)	78	(**1f**)
7	CF_3O	H	Me	4-Cl-Ph	52	(**10g**)	70	(**1g**)
8	Cl	Me	Me	4-Cl-Ph	59	(**10h**)	91	(**1h**)
9	Cl	H	Me	3-CF_3-Ph	53	(**10i**)	97	(**1i**)
10	Cl	H	Me	2-thienyl	26	(**10j**)	77	(**1j**)
11	Cl	H	*tert*-Bu	Ph	15	(**10k**)	63	(**1k**)

Scheme 3



(pH=3):acetonitrile (3:2) using a UV detector (254 nm) and a flow rate of 1 ml/min.

4-Hydroxy-*N*,1-dimethyl-6-(methylthio)-2-oxo-*N*-phenyl-1,2-dihydro-3-quinolinecarbothioamide (**1a**)**.**

Method A.

A solution of 2.37 g (10 mmol) of ethyl *N*-methyl-*N*-phenylthiocarbamoylacetate (**4**) and 20 ml dimethylacetamide under nitrogen was chilled to 10 °C and 0.42 g (10.5 mmol) of sodium hydride was added. After 15 minutes the cold bath was removed and the reaction was stirred at room temperature for 45 minutes. Then 2.23 g (10.0 mmol) of *N*-methyl-5-(methylthio)isatoic anhydride (**3**) was added, and the reaction vessel was placed in a 120 °C oil bath for 30 minutes. After cooling to room temperature the reaction mixture was poured into ice/water (200 ml) and concentrated hydrochloric acid (1.9 ml) was added. After 30 minutes the solid was collected by filtration and washed with 0.1 *N* hydrochloric acid (20 ml) (the obtained solid was a 2:3 mixture of **1a** and **5**). The solid was dissolved in methylene chloride (100 ml) and washed with a solution of water (50 ml) plus 1.0 *N* sodium hydroxide (5 ml). The organic phase was dried (magnesium sulfate), filtered, and evaporated to give a residue (2.2 g) as a 15:1 mixture of **1a** and **5**. This residue was purified by column chromatography (silica gel-methylene chloride:methanol) to give a homogeneous solid (1.42 g, 38.4%) which was recrystallization from diisopropyl ether:chloroform (10 ml, 1:1) to yield 0.91 g (25%) of **1a** of sufficient purity for pharmacology testing, mp 178 °C (dec.); ir (nujol): 2500-3000, 1640, 1600, 1565 cm^{-1}; ms: m/z 371 (M+1); ^1H nmr (DMSO-d_6): δ 2.48 (s, 3H), 3.40 (s, 3H), 3.73 (s, 3H), 7.10-7.40 (m, 6H), 7.46 (dd, 1H, J=8.8, 1.9 Hz), 7.68 (d, 1H, J=1.9 Hz), 10.94 (br s, 1H).

Anal. Calcd. for $C_{19}H_{18}N_2O_2S_2$: C, 61.60; H, 4.90; N, 7.56. Found: C, 61.82; H, 4.83; N, 7.51.

General Procedure for the Preparation of *N*-Alkyl-*N*-aryl-4-hydroxy-1-methyl-2-oxo-1,2-dihydro-3-quinolinecarbothioamides **1.**

Method B.

All of these reactions were carried out under a nitrogen atmosphere. A suspension of *N*-alkyl-*N*-arylthiocarbamoylacetic acid **9** (15 mmol), powdered molecular sieves (4A, 3.0 g), methylene chloride (50 ml) and pyridine (2.43 ml, 30 mmol) was stirred at room temperature for 30 minutes. Then the solution was chilled to –20 °C and pivaloyl chloride (1.84 ml, 15 mmol) was added all at once. After stirring for 10 minutes at -20 to –25 °C (a precipitate usually appears after a few minutes), the amine **8** (10 mmol) was added. After stirring for 1 minute at –20 °C, and then at 0 °C for one hour the reaction was allowed to proceed overnight at room temperature (about 20 hours). The next day the reaction solution was diluted with ethyl acetate (100 ml), washed successively with 0.1 *N* hydrochloric acid (three times, 50 ml each time), brine (50 ml), saturated aqueous sodium bicarbonate (three times, 50 ml each time) and brine (50 ml), dried (magnesium sulfate), filtered and evaporated. Purification by column chromatography (silica gel-diethyl ether:hexane) provided **10**.

To **10** (5 mmol) dissolved in dry ethanol (25 ml) at 5 °C was added sodium ethoxide (0.37 g, 5.5 mmol). After 30 minutes water (100 ml) was slowly added followed by dropwise addition of 1.0 *N* hydrochloric acid (6 ml) with good stirring. After 30 minutes at 5 °C, the crystals were collected by filtration, washed with water, and dried at 40 °C under vacuum to give **1**.

The Following Compounds (**1a** to **1k**) were Prepared According to Method B, Reaction 2.

4-Hydroxy-*N*,1-dimethyl-6-(methylthio)-2-oxo-*N*-phenyl-1,2-dihydro-3-quinolinecarbothioamide (**1a**).

This compound was obtained as bright yellow crystals. Analytical data was identical to that obtained above by Method A.

4-Hydroxy-*N*,1-dimethyl-2-oxo-*N*-phenyl-6-(1*H*-pyrrol-1-yl)-1,2-dihydro-3-quinolinecarbothioamide (**1b**).

This compound was obtained as yellow crystals (water), mp 209 °C (dec.); ir (nujol) 3230, 1630, 1580, 1510 cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.46 (s, 3H), 3.75 (s, 3H), 6.27 (t, 2H, J=2.1 Hz), 7.17-7.39 (m, 5H), 7.35 (t, 2H, J=2.1 Hz), 7.44 (d, 1H, J=9.1 Hz), 7.78 (dd, 1H, J=9.1, 2.7 Hz), 7.89 (d, 1H, J=2.7 Hz), 11.04 (br s, 1H); ms: m/z 390 (M+1), 108.

Anal. Calcd. for $C_{22}H_{19}N_3O_2S$: C, 67.85; H, 4.92; N, 10.79. Found: C, 67.98; H, 4.79; N, 10.49.

6-Chloro-4-hydroxy-*N*,1-dimethyl-2-oxo-*N*-phenyl-1,2-dihydro-3-quinolinecarbothioamide (**1c**).

This compound was obtained as yellow crystals (water), mp 218 °C (dec.); ir (nujol) 3150, 1625, 1590, 1570, 1495, 1195, 1095 cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.42 (s, 3H), 3.74 (s, 3H), 7.17-7.49 (m, 6H), 7.55 (dd, 1H, J=9.0, 1.8 Hz), 7.81 (d, 1H, J=1.8 Hz), 11.15 (br s, 1H); ms: m/z 359 (M+1), 284.

Anal. Calcd. for $C_{18}H_{15}N_2ClO_2S$: C, 60.25; H, 4.21; N, 7.81. Found: C, 60.64; H, 4.07; N, 7.74.

6-Chloro-4-hydroxy-*N*-(4-methoxyphenyl)-*N*,1-dimethyl-2-oxo-1,2-dihydro-3-quinolinecarbothioamide (**1d**).

This compound was obtained as yellow-green crystals (water), mp 191 °C (dec.), ir (nujol) 3120, 1630, 1605, 1565 cm^{-1}, ^1H nmr (DMSO-d_6): δ 3.43 (s, 3H), 3.63 (s, 3H), 3.69 (s, 3H), 6.78 (d, 2H, J=8.9 Hz), 7.28 (d, 2H, J=8.9 Hz), 7.38 (d, 1H, J=9.1 Hz), 7.57 (dd, 1H, J=9.1, 2.4 Hz), 7.82 (d, 1H, J=2.4 Hz), 11.12 (s, 1H); ms: m/z 389 (M+1), 284, 138.

Anal. Calcd. for $C_{19}H_{17}ClN_2O_3S$: C, 58.69; H, 4.41; N, 7.20. Found: C, 59.06; H, 4.35; N, 7.21.

N-(4-Chlorophenyl)-4-hydroxy-6-methoxy-*N*-1-dimethyl-2-oxo-1,2-dihydro-3-quinolinecarbothioamide (**1e**).

This compound was obtained as yellow crystals (water), mp >290 °C, ir (nujol) 3350, 1620, 1580, 1305, 1220 cm^{-1}, ^1H nmr ($CDCl_3$): δ 3.31 (s, 3H), 3.89 (s, 3H), 3.94 (s, 3H), 6.98-7.30 (m, 6H), 7.50 (d, 1H, J=2.5 Hz), 9.69 (s, 1H); ms: m/z 389(M+1), 280, 142.

Anal. Calcd. for $C_{19}H_{17}ClN_2O_3S$: C, 58.69; H, 4.41; N, 7.20. Due to water traces, we were unable to obtain a better elemental analysis than the following: Found: C, 58.33; H, 4.55; N, 6.73.

4-Hydroxy-6-methoxy-*N*,1-dimethyl-2-oxo-*N*-[3-(trifluoromethyl)phenyl]-1,2-dihydro-3-quinolinecarbothioamide (**1f**).

This compound was obtained as yellow crystals (water), mp 193-195 °C, ir (nujol) 3150, 1615, 1580 cm^{-1}, ^1H nmr (DMSO-d_6): δ 3.39 (s, 3H), 3.76 (s, 3H), 3.78 (s, 3H), 7.17 (dd, 1H, J=10.0, 2.6 Hz), 7.20-7.30 (m, 2H), 7.40-7.54 (m, 2H), 7.60-7.70 (m, 1H), 7.76 (s, 1H), 10.93 (br s, 1H); ms: m/z 423 (M+1), 280, 176.

Anal. Calcd. for $C_{20}H_{17}F_3N_2O_3S$: C, 56.87; H, 4.06; N, 6.63. Found: C, 56.87; H, 4.14; N, 6.53.

N-(4-Chlorophenyl)-4-hydroxy-*N*-1-dimethyl-2-oxo-6-(trifluoromethoxy)-1,2-dihydro-3-quinolinecarbothioamide (**1g**).

This compound was obtained as yellow crystals (water), mp 290 °C (dec.); ir (nujol) 1625, 1580, 1460, 1380, 1250 cm^{-1}; ^1H nmr ($CDCl_3$): δ 3.33 (s, 3H), 3.89 (s, 3H), 7.07-7.60 (m, 6H), 7.92 (s, 1H), 9.78 (br s, 1H); ms: m/z 443 (M+1).

Anal. Calcd. for $C_{19}H_{14}ClF_3N_2O_3S$: C, 51.53; H, 3.19; N, 6.33. Found: C, 51.71; H, 2.97; N, 5.99.

6-Chloro-*N*-(4-chlorophenyl)-4-hydroxy-*N*-1,8-trimethyl-2-oxo-1,2-dihydro-3-quinolinecarbothioamide (**1h**).

This compound was obtained as yellow crystals (water), mp 285-290 °C; ir (nujol) 1620, 1570, 1480 cm^{-1}, ^1H nmr (DMSO-d_6): δ 2.50 (s, 3H), 3.38 (s, 3H), 3.89 (s, 3H), 7.05 (d, 2H, J=8.0 Hz), 7.16 (d, 2H, J=8.0 Hz), 7.26-7.30 (m, 1H), 7.70 (s, 1H), 10.91 (br s, 1H); ms: m/z 407 (M+1).

Anal. Calcd. for $C_{19}H_{16}Cl_2N_2O_2S \bullet {}^1/_2H_2O$: C, 54.82; H, 4.12; N, 6.73. Found: C, 54.96; H, 4.21; N, 6.39.

6-Chloro-4-hydroxy-*N*,1-dimethyl-2-oxo-*N*-[3-(trifluoromethyl)phenyl]-1,2-dihydro-3-quinolinecarbothioamide (**1i**).

This compound was obtained as yellow crystals (water), mp >290 °C, ir (nujol) 3350, 1607, 1580 cm^{-1}, ^1H nmr (DMSO-d_6): δ 3.41 (s, 3H), 3.77 (s, 3H), 7.38-7.82 (m, 7H), 11.29 (s, 1H); ms: m/z 427 (M+1), 284, 176.

Anal. Calcd. for $C_{19}H_{14}ClF_3N_2O_2S \bullet H_2O$: C, 51.30; H, 3.63; N, 6.30. Found: C, 51.29; H, 3.65; N, 6.18.

6-Chloro-4-hydroxy-*N*,1-dimethyl-2-oxo-*N*-(2-thienyl)-1,2-dihydro-3-quinolinecarbothioamide (**1j**).

This compound was obtained as white crystals (water), mp 199-201 °C, ir (nujol) 3200, 3090, 1620, 1590 cm^{-1}, ^1H nmr (DMSO-d_6): δ 3.47 (s, 3H), 3.74 (s, 3H), 6.76 (dd, 1H, J=5.5, 3.7 Hz), 6.99 (dd, 1H, J=3.7, 1.4 Hz), 7.24 (dd, 1H, J=5.5, 1.4 Hz), 7.42 (d, 1H, J=9.1 Hz), 7.59 (dd, 1H, J=9.1, 2.4 Hz), 7.85 (d, 1H, J=2.4 Hz), 11.25 (s, 1H); ms: m/z 365 (M+1), 284, 114.

Anal. Calcd. for $C_{16}H_{13}ClN_2O_2S_2$: C, 52.67; H, 3.59; N, 7.68. Found: C, 52.80; H, 3.55; N, 7.51.

N-(*tert*-Butyl)-6-chloro-4-hydroxy-1-methyl-2-oxo-*N*-phenyl-1,2-dihydro-3-quinolinecarbothioamide (**1k**).

This compound was obtained as yellow crystals (water), mp 198-204 °C, ir (nujol) 1620, 1545, 1455, 1370 cm^{-1}, ^1H nmr ($CDCl_3$): δ 1.57 (s, 9H), 3.75 (s, 3H), 6.64 (d, 1H, J=9.1 Hz), 6.96-7.12 (m, 5H), 7.26-7.33 (m, 1H), 7.59-7.65 (m, 2H); ms: m/z 150 (PhNHtBu+1).

Anal. Calcd. for $C_{21}H_{21}ClN_2O_2S \bullet {}^1/_3H_2O$: C, 61.98; H, 5.37; N, 6.88. Found: C, 62.03; H, 5.35; N, 6.70.

The Following Compounds (**10a** to **10k**) were Prepared According to Method B, Reaction 1.

These synthetic intermediates were usually oils or amorphous solids and thus elemental analyses were not obtained.

Ethyl 2-{Methyl-[2-(methyl-phenyl-thiocarbamoyl)-acetyl]-amino}-5-(methylthio)-benzoate (**10a**).

This compound was obtained as a light green oil, ir (nujol): 2990, 2940, 1720, 1655, 1595 cm^{-1}; ms: m/z 417 (M+1); ^1H nmr ($CDCl_3$): δ 1.20 (t, 3H, J=7.1 Hz), 2.51 (s, 3H), 3.12 (s, 3H), 3.32 (d, 1H, J=15.2 Hz), 3.42 (d, 1H, J=15.2 Hz), 3.71 (s, 3H), 4.19 (q, 2H, J=7.1 Hz), 7.05 (d, 1H, J=8.3 Hz), 7.10-7.50 (m, 6H), 7.70 (d, 1H, J=2.3 Hz).

Ethyl 2-{Methyl-[2-(methyl-phenyl-thiocarbamoyl)-acetyl]-amino}-5-pyrrol-1-yl-benzoate (**10b**).

This compound was obtained as a light green foam, ir (nujol) 1720, 1710, 1655 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.14 (t, 3H, J=7.1 Hz), 2.99 (s, 3H), 3.24 (d, 1H, J=15.4 Hz), 3.31 (d, 1H, J=15.4 Hz), 3.59 (s, 3H), 4.18 (m, 2H), 6.32 (t, 2H, J=2.2 Hz), 7.07 (d, 1H, J=8.4 Hz), 7.21 (m, 2H), 7.40-7.51 (m, 5H), 7.81-7.92 (m, 2H); ms: m/z 436 (M+1).

Ethyl 5-Chloro-2-{methyl-[2-(methyl-phenyl-thiocarbamoyl)-acetyl]-amino}-benzoate (**10c**).

This compound was obtained as a thick, green oil, ir (neat) 1720, 1710, 1690 cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.20 (t, 3H, J=7.1 Hz), 3.12 (s, 3H), 3.35 (s, 2H), 3.71 (s, 3H), 4.20 (m, 2H), 7.15 (d, 1H, J=8.4 Hz), 7.17-7.44 (m, 5H), 7.49 (dd, 1H, J=8.4, 2.6 Hz), 7.87 (d, 1H, J=2.6 Hz); ms: m/z 405 (M+1), 192, 108.

Ethyl 5-Chloro-2-({2-[(4-methoxyphenyl)-methyl-thiocarbamoyl]-acetyl}-methylamino)-benzoate (**10d**).

This compound was obtained as a yellow foam, ir (nujol) 1720, 1655, 1605 cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.22 (t, 3H, J=7.1 Hz), 3.14 (s, 3H), 3.36 (s, 2H), 3.68 (s, 3H), 3.85 (s, 3H), 4.22 (q, 2H, J=7.1 Hz), 6.82-6.99 (m, 2H), 7.01-7.30 (m, 2H), 7.21 (d, 1H, J=8.4 Hz), 7.51 (dd, 1H, J=8.4, 2.5 Hz), 7.88 (d, 1H, J=2.5 Hz); ms: m/z 435 (M+1), 222, 138.

Ethyl 2-({2-[(4-Chlorophenyl)-methyl-thiocarbamoyl]-acetyl}-methylamino)-5-methoxy-benzoate (**10e**).

This compound was obtained as a yellow oil, ir (neat) 1720, 1655, 1285, 1220; ^1H nmr ($CDCl_3$): δ 1.25 (t, 3H, J=7.1 Hz), 3.11 (s, 3H), 3.31 (d, 1H, J=15.0 Hz), 3.34 (d, 1H, J=15.0 Hz), 3.69 (s, 3H), 3.85 (s, 3H), 4.20 (q, 2H, J=7.1 Hz), 6.98-7.27 (m, 4H), 7.37-7.49 (m, 3H); ms: m/z 435 (M+1), 142.

Ethyl 5-Methoxy-2-(methyl-{2-[methyl-(3-trifluoromethyl-phenyl)thiocarbamoyl]-acetyl}-amino)-benzoate (**10f**).

This compound was obtained as a yellow oil, ir (neat) 1720, 1655, 1495, 1330 cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.20 (t, 3H, J=7.1 Hz), 3.09 (s, 3H), 3.37 (s, 2H), 3.71 (s, 3H), 3.84 (s, 3H), 4.18 (q, 2H, J=7.1 Hz), 6.99-7.10 (m, 2H), 7.30-7.61 (m, 5H); ms: m/z 469 (M+1), 176.

Ethyl 2-({2-[(4-Chlorophenyl)-methyl-thiocarbamoyl]-acetyl}-methylamino)-5-trifluoromethoxy-benzoate (**10g**).

This compound was obtained as a yellow oil, ^1H nmr ($CDCl_3$): δ 1.25 (t, 3H, J=7.1 Hz), 3.15 (s, 3H), 3.36 (s, 2H), 3.68 (s, 3H), 4.21 (q, 2H, J=7.1 Hz), 7.15-7.50 (m, 6H), 7.75 (s, 1H); ms: m/z 489(M+1), 142.

Ethyl 5-Chloro-2-({2-[(4-chlorophenyl)-methyl-thiocarbamoyl]-acetyl}-methylamino)-3-methyl-benzoate (**10h**).

This compound was obtained as yellow crystals (diethyl ether/hexane), mp 160-161 °C, ir (nujol) 1725, 1655, 1280, 1175 cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.25 (t, 3H, J=7.1 Hz), 2.23 (s, 3H), 3.06 (s, 3H), 3.17 (d, 1H, J=15.0 Hz), 3.32 (d, 1H, J=15.0 Hz), 3.71 (s, 3H), 4.09-4.20 (m, 2H), 7.26-7.43 (m, 5H), 7.69 (d, 1H, J=2.5 Hz); ms: m/z 453 (M+1), 142.

Ethyl 5-Chloro-2-(methyl-{2-[methyl-(3-trifluoromethyl-phenyl)thiocarbamoyl]-acetyl}-amino)-benzoate (**10i**).

This compound was obtained as a yellow oil, ir (neat) 2970, 1720, 1655, 1592 cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.20 (t, 3H, J=7.1 Hz), 3.11 (s, 3H), 3.35 (s, 2H), 3.71 (s, 3H), 4.18 (q, 2H, J=7.1 Hz), 7.11-7.19 (m, 1H), 7.47-7.65 (m, 5H), 7.88 (d, 1H, J=2.4 Hz); ms: m/z 473 (M+1).

Ethyl 5-Chloro-2-{methyl-[2-(methyl-thiophen-2-yl-thiocarbamoyl)-acetyl]-amino}-benzoate (**10j**).

This compound was obtained as a yellow-green waxy solid, ir (neat) 3100, 1720, 1670, 1595, 1535 cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.28 (t, 3H, J=7.1 Hz), 3.15 (s, 3H), 3.50 (s, 2H), 3.71 (s, 3H), 4.25 (q, 2H, J=7.1 Hz), 6.92 (dd, 1H, J=5.4, 3.6 Hz), 6.98 (dd, 1H, J=3.6, 1.4 Hz), 7.17 (d, 1H, J=8.4 Hz), 7.23 (dd, 1H, J=5.4, 1.4 Hz), 7.50 (dd, 1H, J=8.4, 2.5 Hz), 7.91 (d, 1H, J=2.5 Hz); ms: m/z 411 (M+1), 129.

Ethyl 2-{[2-(*tert*-Butyl-phenyl-thiocarbamoyl)-acetyl]-methylamino}-5-chlorobenzoate (**10k**).

This compound was obtained as a yellow oil, ^1H nmr ($CDCl_3$): δ 1.25 (t, 3H, J=7.1 Hz), 1.26 (s, 9H), 2.98 (d, 1H, J=16.1 Hz), 3.23 (d, 1H, J=16.1 Hz), 3.71 (s, 3H), 4.20 (q, 2H, J=7.1 Hz), 6.99-7.07 (m, 1H), 7.14-7.53 (m, 5H), 7.58 (dd, 1H, J=8.5, 2.5 Hz), 8.00 (d, 1H, J=2.5 Hz); ms: m/z 447 (M+1).

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