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Reaction of $Ph_3P(SCN)_2$ with Further Orthohydroxy Carboxylic Acid Systems, Including Substituted β-Keto Acids: Synthesis of Novel 2-Thio-1,3-oxazines and Their Subsequent Transformation with Amines

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Reaction of $Ph_3P(SCN)_2$ with Further Orthohydroxy Carboxylic Acid Systems, Including Substituted β-Keto Acids: Synthesis of Novel 2-Thio-1,3-oxazines and Their Subsequent Transformation with Amines

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Abstract: We now report the first reaction of $Ph_3P(SCN)_2$ with 4,6-dihydroxy-5-methylisophthalic acid to give 10-methyl-2,8-dithio-1,3-oxazino-1,3-benzoxazine-4,6-dione. Also, the enol tautomer has been utilized in the reaction of β-keto acids with $Ph_3P(SCN)_2$ to give novel 2-thio-1,3-oxazines. Subsequent reaction of the 2-thio-1,3-oxazines with benzylamine resulted in opening of the oxazine ring and gave novel dibenzylamino-enamides, which could be cyclized to thiouracils. The reaction of 2-thio-1,3-oxazines with morpholine at low temperature led to the production of unstable 2-Mercapto-2-morpholino-1,3-oxazines. 2-Mercapto-2-morpholin-4-yl-2,3,5,6,7,8-hexahydro-4*H*-1,3-benzoxazin-4-one was observed to lose H_2S at room temperature to give 2-morpholin-4-yl-5,6,7,8-tetrahydro-4*H*-1,3-benzoxazin-4-one, which was subsequently tested and found to exhibit some antiplatelet activity.

Keywords: Dicarboxylic acid, β-keto acids, 2-morpholino-1,3-oxazines, 2-thio-1, 3-oxazines, thiouracils

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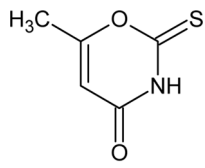
INTRODUCTION

The reaction of 2-hydroxy benzoic acids with $Ph_3P(SCN)_2$ to give 2-thio-1,3-benzoxazines has been reported earlier in our work[1] and also by others.[2] However, the reaction of other orthohydroxy carboxylic acid systems with $Ph_3P(SCN)_2$ is not covered in the literature. The synthesis of new 2-thio-1,3-oxazine analoges using the aid of $Ph_2P(SCN)_2$ is therefore one area that can be explored further.

Previously reported methods for the synthesis of 2-thio-1,3-oxazines **1** have been limited and have included the reaction of diketen and ammonia thiocyanate[3] and later the reaction of diketen and N,N-dimethylthiourea,[4] but the difficulty of producing other diketens[4] meant that only the 6-methyl-2-thio-1,3-oxazine **1a** (Fig. 1) could be easily prepared in this way.

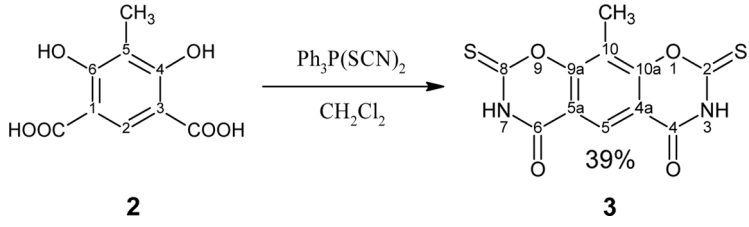
The subsequent reaction of **1a** with amines has also had little coverage in the literature. One reaction that has been reported, however, is the synthesis of 1-substituted-6-methylthiouracils from **1a** and primary amines.[5] Uracil derivatives have immense biological significance[6] and have been used as precursors for an array of biologically significant molecules.[7–9] Structurally similar 1,3-oxazine-2,4-diones and their *N*-alkyl derivatives have also reportedly been reacted with primary amines to give uracil derivatives,[4,10–13] with one group suggesting that the reaction proceeds via a 6-hydroxy intermediate.[11] The reaction of 6-methyl-1,3-oxazine-2,4-dione with aryl amines, however, saw the isolation of an open-chain urea derivative (with a mixture of imine and enamine tautomers), which was reported as an intermediate in uracil synthesis.[13]

Our earlier work has reported an efficient method for the production of 2-thio-1,3-benzoxazines using $Ph_3P(SCN)_2$.[1] In this article, we have extended our previously reported method[1] to include the use of 4,6-dihydroxy-5-methylisophthalic acid **2** for the synthesis of 10-methyl-2,8-dithio-1,3-oxazino-1,3-benzoxazine-4,6-dione **3** and the use of β-keto acids **4** for the synthesis of new 2-thio-1,3-oxazines **1**.



1a

Figure 1. 6-Methyl-2-thioxo-2,3-dihydro-4*H*-1,3-oxazin-4-one **1a**.



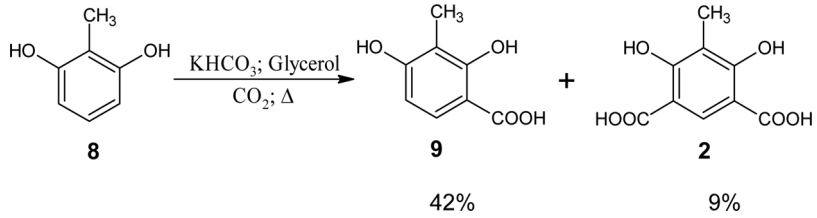
Scheme 1. Preparation of dicarboxylic acid **2** from 2-methylresorcinol **8**.

It has also been shown in past work that the 2-mercapto tautomer of 2-thio-1,3-benzoxazines can provide a good leaving group for the reaction with morpholine to give antiplatelet 2-morpholino-1,3-benzoxazine compounds.[14,15] Additionally, the reaction of 2-thio-1,3-benzoxazines with benzylamine has been found to lead to the opening of the oxazine ring between position 1 and 2.[14] This work explores the reaction of 2-thio-1,3-oxazines **1** with morpholine to produce 2-morpholino-1,3-oxazine **5**, as well as the reaction of **1** with benzylamine to produce dibenzylamino-enamides **6** and subsequent thiouracils **7**.

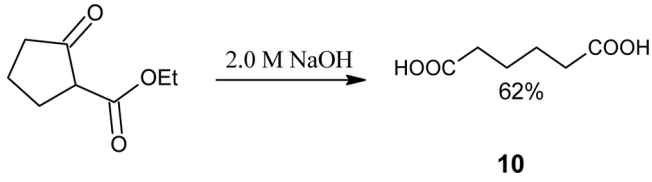
RESULTS AND DISCUSSION

In our earlier work, we reported the carboxylation of 2-methylresorcinol **8** to give 2,4-dihydroxy-3-methylbenzoic acid **9** (Scheme 1) which was then cyclized to the corresponding 2-thio-1,3-benzoxazine.[1] The carboxylation reaction of 2-methylresorcinol **8**, however, can also be found to give 4,6-dihydroxy-5-methylisophthalic acid **2** (Scheme 1) as a minor product.

The reaction of dicarboxylic acid **2** with $Ph_3P(SCN)_2$ was attempted to see if it would be possible to cyclize both orthohydroxy acid groups to give the 1,3-oxazine ring structure on either side of the aromatic ring.



Scheme 2. Preparation of dicarboxylic acid **2** from 2-methylresorcinal **9**.



10

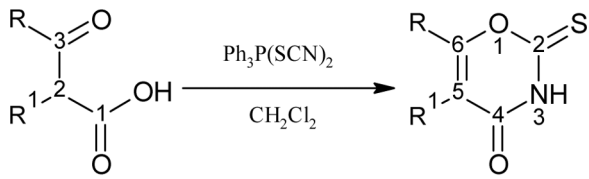
Scheme 3. Synthesis of adipic acid **10** from ethyl 2-oxocyclopentanecarboxylate.

A reaction was carried out using the conditions outlined earlier[1] with the ratio of reagent to acid increased to 2.5:1 to ensure cyclization would occur on both sides of the molecule (Scheme 2). On completion of the reaction and subsequent workup, the 10-methyl-2,8-dithio-1,3-oxazino-1,3-benzoxazine-4,6-dione **3** was isolated.

The synthesis of other 2-thio-1,3-oxazines **1** was also carried out using β-keto acids **4** as the starting material. In general, the β-keto acids **4** were prepared from their corresponding esters according to two separate methods, which were modified from previously reported procedures.[16,17] It is interesting to note, however, that the hydrolysis of ethyl 2-oxocyclopentane-carboxylate to give the corresponding β-keto acid **4d** required a decreased concentration of NaOH. With increased NaOH concentration, the formation of adipic acid **10** was favored in a retro Dieckmann reaction (Scheme 3).

Once isolated, the β-keto acids **4a**–**h** were then allowed to react with $Ph_3P(SCN)_2$ according to our earlier reported method[1] to give substituted 2-thio-1,3-oxazines **1a**–**h** (Scheme 4).

With the successful synthesis of the 2-thio-1,3-oxazines **1**, their reaction with amines (morpholine and benzylamine) was then explored. Our results showed that the reaction of 2-thio-1,3-oxazines **1** with



4 **1**

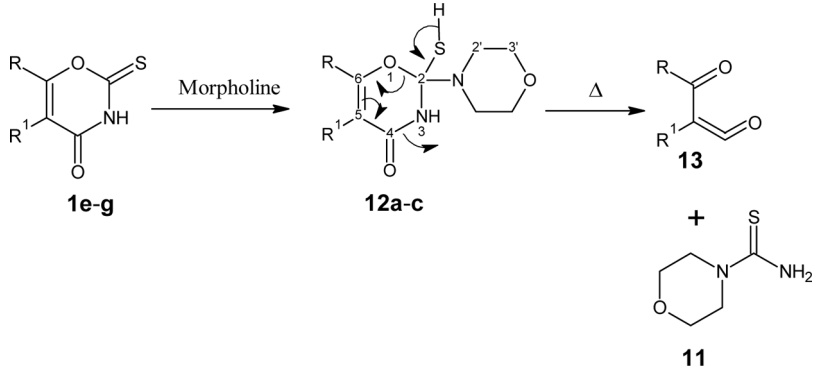
Scheme 4. Compounds **4** and **1**; **a**; $R = CH_3$, $R^1 = H$; **b**, $R = CH_2CH_3$, $R^1 = H$; **c**, $R = CH_2CH_2CH_3$, $R^1 = H$; **d**, $R/R^1 = (CH_2)_3$; **e**, $R/R^1 = (CH_2)_4$; **f**, $R = CH_3$, $R^1 = CH_2$ Ph; **g**, $R = CH_3$, $R^1 = CH_3$; **h**, $R = Ph$, $R^1 = H$. Note: Numbering is not according to the IUPAC convention.

morpholine requires much milder reaction conditions than those employed for the synthesis of 2-morpholino-1,3-benzoxazines.[15] The reaction of 2-thio-1,3-oxazine **1a** with morpholine did not give the expected 2-morpholino product when heated in dioxane and instead gave the 4-morpholinecarbothioamide **11**.

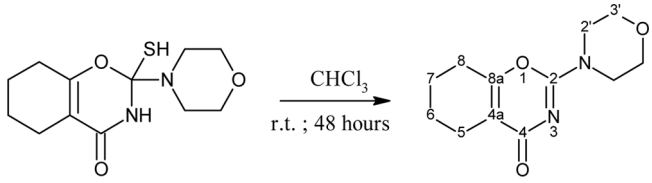
When compounds **1e**–**g** were allowed to react with morpholine while being cooled in ice, nucleophilic attack of morpholine took place on C-2 without any observed loss of H_2S to give the 2 mercapto-2-morpholino-1,3-oxazine analog **12** (Scheme 5).

After an attempt to recrystallize **12a** from toluene, the 4-morpholinecarbothioamide **11** was again isolated. This suggested that the 2-mercapto intermediate **12** was forming first during the reaction of **1** with morpholine. If the reaction was not kept cool, decomposition occured, leading to the formation of the unstable keten **13** and the 4-morpholinecarbothioamide **11** (Scheme 5). The keten **13** was not isolated. The 2-morpholino-1,3-oxazine **5** was isolated after **12a** was allowed to stir in chloroform at room temperature for 48 h (Scheme 6).

When observing the ^{1}H NMR of **12b** and **12c**, it was possible with time to see the degradation of the 2-mercapto-2-morpholine oxazines. However, multiple degradation products were seen for **12b** and **12c**, and we were not able to isolate their corresponding 2-morpholino-1,3-oxazine derivative of **5**. It is also interesting to note that it was only possible to isolate a pure sample of **12** when the starting 2-thio-1,3-oxazine **1** was substituted (other than H) at both C-5 and C-6. When **1b** (R^1=H) was allowed to react with morpholine in a similar manner, a solid was isolated, but it could not be precisely identified because the ^{1}H and



Scheme 5. Formation of 2-mercapto analog **12** followed by decomposition to give the keten **13** and 4-morpholinecarbothioamide **11**. Compounds **1** and **12**; **a**, $R/R^1 = (CH_2)_4$; **b**, $R = CH_3$, $R^1 = CH_2Ph$; **c**, $R = CH_3$, $R^1 = CH_3$.



12a **5**

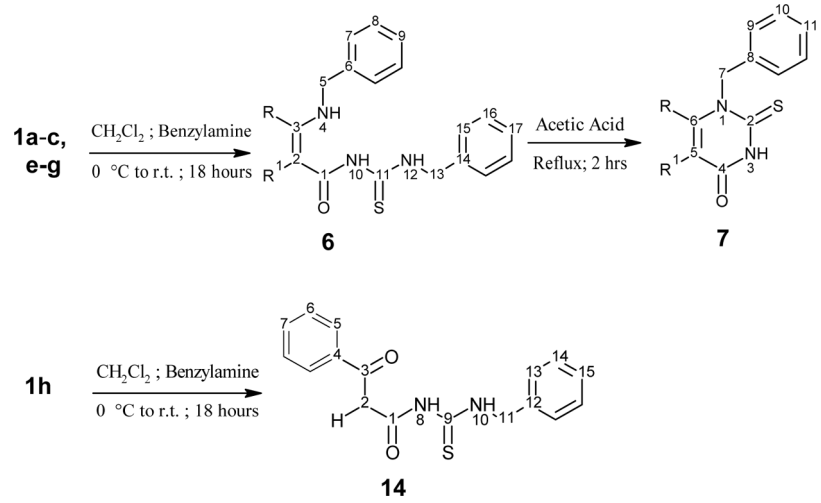
Scheme 6. Loss of H_2S from compound **12a** to give 2-morpholino compound **5**. Note: Numbering is not according to the IUPAC convention.

^{13}C NMR showed rapid decomposition at room temperature to multiple products.

We also wanted to pursue the reaction of 2-thio-1,3-oxazines **1** with benzylamine. Therefore, we attempted the synthesis of 1-benzylthiouracil **7b** by heating **1e** to reflux with benzylamine in acetic acid for 4 h according to the earlier method.[13] No product could be isolated from this reaction, and the evolution of H_2S could be detected throughout the reaction. Applying excess benzylamine directly to the 2-thio-1,3-oxazine **1** and leaving it to stand at room temperature for 2 days was also tried, according to our earlier reported method.[15] It was observed, however, that upon addition of the excess benzylamine to the 2-thio-1,3-oxazine **1**, heat was evolved as the oxazine began to dissolve in the amine, and as a result no product was isolated from these reactions. One exception was noted when **1e** was allowed to stand at room temperature with excess benzylamine: the dibenzylamino **6d** was isolated.

When we cooled the 2-thio-1,3-oxazines **1a–c, e–g** before the addition of benzylamine (2 equivalents) and then stirred it at room temperature in dichloromethane overnight, the dibenzylamino analogs **6a–f** were isolated (Scheme 7). One exception was observed when 6-phenyl oxazine **1h** was allowed to react in a similar manner with benzylamine and a monobenzylamino product was isolated **14** (Scheme 7).

The reaction between 2-thio-1,3-oxazine **1e** and benzylamine was also attempted in an equimolar ratio, but the resulting solid contained the dibenzylamino product **6d** and some unreacted **1e**. Furthermore, we investigated whether the production of H_2O, as the dibenzylamino compound **6** is formed, would have any influence on the reaction yield. Consequently we performed one reaction with the inclusion of a 4 Å molecular sieve but found that no improvement in yield was achieved, suggesting that the production of water does not influence the outcome. The purified dibenzylamino analogs **6a, d–f** were heated to reflux in acetic acid for 2 h and gave the thiouracil **7a–d** (Scheme 7). When **14** was heated



Scheme 7. Compound **6**; **a**, $R = CH_3$, $R^1 = H$; **b**, $R = CH_2CH_3$, $R^1 = H$; **c**, $R = CH_2CH_2CH_3$, $R^1 = H$; **d**, $R/R^1 = (CH_2)_4$; **e**, $R = CH_3$, $R^1 = CH_2Ph$; **f**, $R = CH_3$, $R^1 = CH_3$. Compound **7**: **a**, $R = CH_3$, $R^1 = H$; **b**, $R/R^1 = (CH_2)_4$; **c**, $R = CH_3$, $R^1 = CH_2Ph$; **d**, $R = CH_3$, $R^1 = CH_3$. Note: Numbering is not according to the IUPAC convention.

to reflux in acetic acid, however, 80% of the monobenzylamino analog **14** was recovered unchanged.

Given that we were able to isolate the dibenzylamino intermediates **6** prior to the formation of the thiouracil **7**, it would appear that the mechanism for the transformation of 2-thio-1,3-oxazines to thiouracils most closely resembles the mechanism outlined by Singh and co-workers[13] in their work with 1,3-oxazine-2,4-diones and aryl amines. The ^{1}H NMR of **6**, however, showed that only the enamine tautomer was present as none of the imine was detected. The isolation of the dibenzylamino intermediate **6** is also evidence that the formation of the thiouracil **7** from the reaction of 2-thio-1,3-oxazines **1** with benzylamine does not proceed via the 6-hydroxy intermediate as was suggested for 6-methyl-1,3-oxazine-2,4-diones.[11]

It is interesting to note that higher yields were observed for **7b–d** in comparison to **7a**, which may suggest that the presence of substituent groups other than hydrogen at C-5 and C-6 positions in the 2-thio-1,3-oxazine ring **1** might play some part in the progress of the reaction. The corresponding 2-thio-1,3-oxazines **1e–g**, which contained a substituent other than hydrogen at the C-5 and C-6 positions, were also found to give a slightly more stable reaction product **12** from their reaction with

morpholine. In particular, it was noticed that **1e**, which most closely resembles the 2-thio-1,3-benzoxazines, gave the most stable reaction products with both morpholine and benzylamine.

Overall, it appears to be evident from this work that unlike 2-thio-1,3-benzoxazines, the 2-thio-1,3-oxazine compounds **1** require much milder temperatures for their reaction with amines. However, it would appear that it is the 2-thio group that is influencing the stability of the reaction products because the 2-oxo analog yields 1-substituted uracils[4,10,12,13,18] when heated with primary amines.

With the exception of the 2-mercapto analogs **12**, all newly described compounds were confirmed using CHN microanalysis and IR, ^{1}H NMR, and ^{13}C NMR spectroscopy. 2-Mercapto analogs **12** were confirmed using IR, ^{1}H NMR, and ^{13}C NMR spectroscopy. Assignment of the carbon-13 chemical shifts for C-2 and C-4 of the oxazine rings were made using the aid of previously reported oxazine ring chemical shifts.[19] Recorded carbon-13 chemical shifts for the reaction products of 2-thio-1,3-benzoxazine with morpholine and benzylamine[19] were also used where appropriate as well as the ^{13}C NMR spectra of the parent esters.[20] Experimental data for 4-morpholinecarbothioamide **11** agreed with previously reported literature values.[21]

The structural similarities between the 2-morpholino-1,3-oxazine **5** and our earlier reported antiplatelet 2-morpholino-1,3-benzoxazines[15] led us to test **5** to see if it would exhibit antiplatelet properties. Therefore compound **5** was tested in accordance with our earlier reported methods[15] against both adenosine triphosphate (ADP)- and collagen-induced platelet aggregation. Although the results of the antiplatelet tests showed that **5** did exert some inhibition of platelet aggregation, the IC_{50} values were much higher than that shown for the 2-morpholino-1,3-benzoxazines.[15] Compound **5** was seen to be most active against ADP-induced platelet aggregation with an IC_{50} of $98 \pm 5.0\,\mu M$. The IC_{50} of **5** against collagen-induced platelet aggregation was found to be more than $130\,\mu M$.

CONCLUSION

In conclusion, we have shown that further orthohydroxy carboxylic acid systems including the enol form of β-keto acids can be successfully utilized in the synthesis of 2-thio-1,3-oxazines **1**, extending the use of $Ph_3P(SCN)_2$. Furthermore, we have shown that, in the presence of amines, the 2-thio-1,3-oxazines **1** require much milder reaction conditions compared to 2-thio-1,3-benzoxazines. The reaction of 2-thio-1,3-oxazine **1** with morpholine gave the unstable 2-mercapto-2-morpholino analog **12**,

with the successful elimination of H_2S from **12a**, giving the 2-morpholino analog **5**. The reaction of 2-thio-1,3-oxazines **1** with benzylamine led to the synthesis of thiouracil **7** via a dibenzylamino intermediate **6**.

EXPERIMENTAL

Infrared spectra were obtained using a Perkin-Elmer FT-IR spectrometer. ^{1}H NMR and ^{13}C NMR spectra were obtained at 293 K using a Bruker AC 200 NMR spectrometer with Techmag upgrade at 200 MHz and 50 MHz, respectively. All ^{1}H and ^{13}C NMR spectral results are recorded as chemical shifts (δ) with chemical shifts recorded in $CDCl_3$ relative to the internal TMS (0 ppm) and 77.0 ppm respectively. Chemical shifts recorded in d_6-DMSO are relative to 2.5 ppm and 39.5 ppm respectively. Chemical shifts recorded in d_6-acetone are relative to 2.05 ppm and 29.8 ppm respectively. Microanalysis was measured by CMAS (Chemical and Microanalytical Services), Australia. Melting-point determinations were carried out using a Stuart Scientific (SMP3) melting-point apparatus, and all melting points are uncorrected. Aldrich silica gel, 200–400 mesh, 60 Å, was used for column chromatography. All esters were purchased from Aldrich Chemical Company and were used as received (with the exception of ethyl acetoacetate, which was purchased from BDH Laboratory Supplies and used as received).

Synthesis of 4,6-Dihydroxy-5-methylisophthalic Acid 2

The carboxylation of 2-methylresorcinol **8** as outlined in the earlier synthesis of **9**[1] gave compound **2** (9%) as a minor product after recrystallization from ethanol/water. Mp 174 °C decomp. (loss of CO_2 observed above this temperature). Found: C, 50.89; H, 3.75. $C_9H_8O_6$ requires C, 50.95; H, 3.80%. IR(KBr) 3280–2380w (OH), 1652 (C=O) cm^{-1}; ^{1}H NMR (d_6-DMSO) δ 12.1 (bs, 2H, COOH), 8.2 (s, 1H, H-2), 5.1 (bs, 2H exchangeable with H_2O, 2 × OH), 2.0 (s, 3H, CH_3). ^{13}C NMR (d_6-DMSO) δ 171.9 (COOH), 164.4 (C-4/C-6), 131.2 (C-2), 111.1 (C-5), 105.0 (C-1/C-3), 7.4 (CH_3).

General Methods for the Synthesis of β-Keto Acids

Method 1

A mixture of the appropriate ester (40 mmol) in 1.5 M aq. NaOH (40 mL) was stirred at ambient temperature overnight. The reaction mixture was

extracted with 3×15 mL of ether, and the aqueous layer was cooled in ice before the addition of sulphuric acid (3.6 mL) diluted in water (10 mL). The mixture was saturated with NaCl before being extracted with 4×20 mL of ether. The combined organics were dried over Mg_2SO_4 before the ether was evaporated off in vacuo at ambient temperature. The residual ether was removed by freeze drying the resulting oil to give **4a**–**c**, **e**.

Method 2

A mixture of the appropriate ester (40 mmol) in 1.0 M aq. NaOH (80 mL) was stirred at ambient temperature overnight in the presence of ethanol (1–2 mL), which promoted the formation of a homogeneous solution. The reaction mixture was extracted with 3×20 mL of ether, and the aqueous layer was cooled in ice before being strongly acidified with conc. HCl. The oily acids (**4f** and **4g**) were extracted from the aqueous layer using 4×20 mL of ether, and the combined organics were washed with saturated brine (40 ml) before being dried over Mg_2SO_4. The ether was evaporated off in vacuo at ambient temperature, and residual ether was removed by freeze drying. The precipitated acid (**4h**) was collected by vacuum filtration using cold water to wash before being freeze dried.

Note: ethyl 2-oxocyclopentanecarboxylate was allowed to react with NaOH (0.8 M), in the absence of ethanol, for 4 days at ambient temperature in a modification to method 2 to give **4d**.

Experimental data for the prepared β-keto acids **4** agreed with previously reported literature values[16,17,22,23] where available. Similarly, the melting point, IR, ^{1}H NMR, and ^{13}C NMR spectroscopic data obtained for adipic acid **10** agreed with previously reported data.[24,25]

General Method for the Synthesis of 2-Thio-1,3-oxazines

4,6-Dihydroxy-5-methylbenzene-1,3-dicarboxylic acid **2** or β-keto acids **4a**–**h** were allowed to react with $Ph_3P(SCN)_2$ according to the general method (reported earlier[1] in greater detail) to produce **3** and **1a**–**h**.

Triphenylphosphine dibromide (5 mmol) was weighed out under nitrogen into a three-necked, round-bottomed flask. Dry dichloromethane (20 mL) was then added, and the flask was placed into an ice bath. The reaction vessel was fitted with a nitrogen gas inlet with bubbling tube, calcium chloride drying tube, and a dropping funnel. A suspension of lead thiocyanate (6 mmol) in dry dichloromethane (40 mL) was added slowly with stirring, followed by the addition of acid (4 mmol)

in dry dichloromethane (20 mL). The mixture was allowed to warm to room temperature and then stir for 30 min before being heated at reflux for 3 h. The reaction mixture was filtered, and the filtrate evaporated off under reduced pressure. Toluene was used to dissolve any oil, and the resulting solid was collected by vacuum filtration.

10-Methyl-2,8-dithioxo-2,3,7,8-tetrahydro-4*H*,6*H*-[1,3]oxazino[5,6-*g*][1,3]benzoxazine-4,6-dione 3

4,6-Dihydroxy-5-methylisophthalic acid **2** (2 mmol) was allowed to react with $Ph_3P(SCN)_2$ according to the conditions outlined previously. On completion of the reaction, the initial $PbBr_2$ filter cake was collected and hot filtered using acetone. The acetone filtrate was evaporated to dryness under reduced pressure, and toluene was used to triturate the any oil that accompanied the resulting solid. The crude solid was collected by filtration and recrystallized from 1,4-dioxane to give **3** (39%). Mp 290 °C decomp. Found C, 47.20; H, 3.65; N, 7.24; $C_{11}H_6N_2O_4S_2 + 1$ molecule of 1,4-dioxane requires C, 47.11; H, 3.69; N, 7.33%. IR(KBr) 3080w and 2905w (NH), 1737 (C=O), 1254 (C=S) cm^{-1}; ^1H NMR (350 K d_6-DMSO) δ 8.3 (s, 1H, H-5), 3.4 (bs, 2H, 2 × NH exchangeable with H_2O), 2.4 (s, 3H, CH_3). ^{13}C NMR (350 K d_6-DMSO) δ 180.8 (C-2), 156.9 (C-4), 156.2 (C-10a), 123.2 (C-5), 113.0 (C-10), 112.8 (C-4a), 7.9 (CH_3).

6-Methyl-2-thioxo-2,3-dihydro-4*H*-1,3-oxazin-4-one 1a

3-Oxobutanoic acid **5a** was allowed to react with $Ph_3P(SCN)_2$ to give **1a** (84%) and recrystallized from toluene. Mp 194 °C decomp. (lit.[26] 201–203 °C); IR (KBr) 3200w and 3083w (NH), 1722 s and1693s (CO), 1247 s (CS) cm^{-1}; ^1H NMR (d_6-DMSO) δ 13.3 (br s, 1H, NH), 6.1 (s, 1H, H-5), 2.2 (s, 3H, CH_3); ^{13}C NMR (d_6-DMSO) δ 182.8 (C-2), 168.6 (C-4), 158.7 (C-6), 103.4 (C-5), 18.7 (CH_3).

6-Ethyl-2-thioxo-2,3-dihydro-4*H*-1,3-oxazin-4-one 1b

Similarly 3-oxopentanoic acid **5b** was allowed to react with $Ph_3P(SCN)_2$ to give **1b** (83%) and recrystallized from toluene. Mp 148–150 °C; IR (KBr) 3187w and 3072w (NH), 1684 s (CO), 1293 s (CS) cm^{-1}; ^1H NMR ($CDCl_3$) δ 10.6 (br s, 1H, NH), 5.9 (s, 1H, H-5), 2.6 (q, 2H, J=8.0 Hz, CH_2CH_3), 1.3 (t, 3H, J=8.0 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$) δ 181.7 (C-2), 173.9 (C-4), 159.2 (C-6), 101.6 (C-5), 26.4 (CH_2CH_3),

10.0 (CH_2CH_3). Anal. calcd for $C_6H_7NO_2S$: C, 45.85; H, 4.49; N, 8.91. Found: C, 45.77; H, 4.45; N, 8.86%.

6-Propyl-2-thioxo-2,3-dihydro-4*H*-1,3-oxazin-4-one 1c

3-Oxohexanoic acid **5c** was allowed to react with $Ph_3P(SCN)_2$ to give **1c** (57%) and recrystallized from toluene. Mp 123–126 °C; IR (KBr) 3185w and 3094w (NH), 1703 s and 1678 s (CO), 1259 s (CS) cm^{-1}; ^1H NMR ($CDCl_3$) δ 10.4 (br s, 1H, NH), 5.9 (s, 1H, H-5), 2.5 (t, 2H, J=8.0 Hz, CH_2C-O), 1.7 (sextet, 2H, J=8.0 Hz, CH_2CH_3), 1.0 (t, 3H, J=8.0 Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ 181.7 (C-2), 172.7 (C-4), 159.3 (C-6), 102.4 (C-5), 34.9 (CH_2 C-O), 19.3 (CH_2CH_3), 13.3 (CH_3). Anal. calcd for $C_7H_9NO_2S$: C, 49.10; H, 5.30; N, 8.18. Found: 49.19; H, 5.24; N, 8.21%.

2-Thioxo-2,3,6,7-tetrahydrocyclopenta[*e*][1,3]oxazin-4(5*H*)-one 1d

Similarly, 2-oxocyclopentanecarboxylic acid **5d** was allowed to react with $Ph_3P(SCN)_2$ to give **1d** (48%) and recrystallized from toluene. Mp 176–179 °C decomp.; IR (KBr) 3179w and 3070w (NH), 1685 s (CO), 1220 s (CS) cm^{-1}; ^1H NMR ($CDCl_3$) δ 10.1 (br s, 1H, NH), 2.9–2.7 (m, 4H, $CH_2CH_2CH_2$), 2.2–2.1 (m, 2H, $CH_2CH_2CH_2$); ^{13}C NMR ($CDCl_3$) δ 182.4 (C-2), 171.8 (C-4), 157.6 (C-6), 115.0 (C-5), 31.2 (CH_2C-O), 25.2 (CH_2C-C=O), 19.3 ($CH_2CH_2CH_2$). Anal. calcd. for $C_7H_7NO_2S$: C, 49.69; H, 4.17; N, 8.28. Found: 49.71; H, 4.15; N, 8.21%.

2-Thioxo-2,3,5,6,7,8-hexahydro-4*H*-1,3-benzoxazin-4-one 1e

2-Oxocyclohexanecarboxylic acid **5e** was allowed to react with $Ph_3P(SCN)_2$ to give **1e** (67%) and recrystallized from toluene. Mp 182–184 °C; IR(KBr) 3179w and 3079w (NH), 1674 s (CO), 1219 s (CS) cm^{-1}; ^1H NMR ($CDCl_3$) δ 10.3 (br s, 1H, NH), 2.5–2.4 [br m, 4H, $(CH_2)_2$], 1.9–1.7 [br m, 4H, $(CH_2)_2$]; ^{13}C NMR ($CDCl_3$) δ 181.6 (C-2), 166.5 (C-4), 159.2 (C-6), 112.2 (C-5), 26.9 (CH_2C-O), 21.3/20.8/20.2 [$(CH_2)_3$]. Anal. calcd. for $C_8H_9NO_2S$: C, 52.44; H, 4.95; N, 7.64. Found: C, 52.31; H, 4.86; N, 7.59%.

5-Benzyl-6-methyl-2-thioxo-2,3-dihydro-4*H*-1,3-oxazin-4-one 1f

Similarly, 2-benzyl-3-oxobutanoic acid **5f** was allowed to react with $Ph_3P(SCN)_2$ (stirred for 7 h at 0 °C and then allowed to warm to rt overnight

before being heated). The crude oil was triturated with ether and gave **1f** plus triphenylphosphine oxide. The crude solid was purified by column chromatography on silica using dichloromethane and ethyl acetate (9:1) as eluent, which gave the oxazine **1f** (60%), and recrystallized from toluene. Mp 136–138 °C; IR (KBr) 3178w and 3085w (NH), 1672 s (CO), 1237 s (CS) cm^{-1}; ^1H NMR ($CDCl_3$) δ 10.6 (br s, 1H, NH), 7.3–7.1 (m, 5H, Ar), 3.7 (s, 2H, CH_2Ph), 2.3 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 181.1 (C-2), 165.5 (C-4), 159.4 (C-6), 137.4 (*C*-Ar), 128.7, 128.2 (*C*H-Ar-o,m), 126.8 (*C*H-Ar-p), 114.3 (C-5), 29.6 (*C*H_2Ph), 17.5 (*C*H_3). Anal. calcd. for $C_{12}H_{11}NO_2S$: C, 61.78; H, 4.75; N, 6.00. Found: C, 61.69; H, 4.70; N, 5.94%.

5,6-Dimethyl-2-thioxo-2,3-dihydro-4*H*-1,3-oxazin-4-one 1g

2-Methyl-3-oxo-butanoic acid **5g** was allowed to react with $Ph_3P(SCN)_2$ (2 mmol of acid was used and the reaction was stirred for 6 h at 0 °C, then allowed to warm to rt overnight before being heated) to give **1g** (63%); it was recrystallized from toluene. Mp 192–194 °C; IR (KBr) 3188w and 3089w (NH), 1708s (CO), 1235s (CS) cm^{-1}; ^1H NMR (d_6-acetone) δ 11.9 (br s, 1H, NH), 2.3 (s, 3H, 6-CH_3), 1.9 (s, 3H, 5-CH_3); ^{13}C NMR (d_6-acetone) δ 183.2 (C-2), 164.4 (C-4), 160.0 (C-6), 111.2 (C-5), 17.1 (6-*C*H_3), 9.4 (5-*C*H_3). Anal. calcd. for $C_6H_7NO_2S$: C, 45.85; H, 4.49; N, 8.91. Found: C, 45.90; H, 4.52; N, 8.96%.

6-Phenyl-2-thioxo-2,3-dihydro-4*H*-1,3-oxazin-4-one 1h

3-Oxo-3-phenylpropanoic acid **5h** was allowed to react with $Ph_3P(SCN)_2$ (2 mmol of acid was used, and the reaction was stirred for 6 h at 0 °C, then allowed to warm to rt overnight before being heated) to give **1h** (62%); it was recrystallized from toluene, mp 196–199 °C decomp.; IR (KBr) 3176w and 3062w (NH), 1679 s (CO), 1256 s (CS) cm^{-1}; ^1H NMR (d_6-acetone) δ 12.1 (br s, 1H, NH), 8.0–7.9 (m, 2H, C*H*-Ar-o), 7.7–7.6 (m, 3H, C*H*-Ar-m,p), 6.7 (s, 1H, H-5); ^{13}C NMR (d_6-DMSO) δ 182.5 (C-2), 164.3 (C-4), 159.3 (C-6), 132.8 (*C*H-Ar-p), 129.4, 126.4 (*C*H-Ar-o,m), 128.7 (*C*-Ar), 100.6 (C-5). Anal. calcd. for $C_{10}H_7NO_2S$: C, 58.52; H, 3.44; N, 6.82. Found: C, 58.57; H, 3.42; N, 6.81%.

General Method for the Synthesis of 2-Mercapto-2-morpholino-1,3-oxazines

2-Thio-1,3-oxazine **1** (1 mmol) was dissolved in dry dichloromethane (2 mL) and cooled in an ice/water bath. Morpholine (1 mmol) in dry

dichloromethane (1 mL) was added dropwise with stirring. The reaction was continued at 0–5 °C for 2 h, then the solvent was evaporated off in vacuo (ice/water bath); ether was added to the resulting oil, and the mixture was left overnight at 4 °C. The precipitated solid was collected by vacuum filtration and safely stored at 4 °C for several days.

2-Mercapto-2-morpholin-4-yl-2,3,5,6,7,8-hexahydro-4*H*-1,3-benzoxazin-4-one 12a

Compound **1e** was allowed to react with morpholine (1.25 mmol) according to the general method to give **12a** (70%); IR (KBr) 2540w (SH), 1661 s (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.1 (br s, 2H, NH & SH), 3.8 (t, 4H, J=4.6 Hz, H-3′), 3.0 (t, 4H, J=4.6 Hz, H-2′), 2.5–2.3 [m, 4H, (CH_2)$_2$], 1.9–1.7 [m, 4H, (CH_2)$_2$]; ^{13}C NMR ($CDCl_3$) δ 185.4 (C-2), 165.6/165.3 (C-4/C-6), 112.1 (C-5), 65.0 (C-3′), 43.9 (C-2′), 26.5 (CH$_2$C-O), 21.3/21.1/20.4 [(CH$_2$)$_3$].

5-Benzyl-2-mercapto-6-methyl-2-morpholin-4-yl-2,3-dihydro-4*H*-1,3-oxazin-4-one 12b

Similarly **1f** was allowed to react with morpholine according to the general method to give **12b** (56%), IR (KBr) 2455w (SH), 1654 s (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.3–7.2 (m, 5H, Ar), 6.8 (br s, 2H, NH and SH), 3.8 (t, 4H, J=4.0 Hz, H-3′), 3.7 (s, 2H, CH_2 Ph), 3.0 (t, 4H, J=4.0 Hz, H-2′), 2.3 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 185.4 (C-2), 165.4/165.3 (C-4/C-6), 138.4 (*C*-Ar), 128.6, 127.8 (*C*H-Ar-o,m), 126.4 (*C*H-Ar-p), 114.1 (C-5), 65.2 (C-3′), 44.1 (C-2′), 29.9 (CH$_2$ Ph), 17.3 (CH$_3$).

2-Mercapto-5,6-dimethyl-2-morpholin-4-yl-2,3-dihydro-4*H*-1,3-oxazin-4-one 12c

Compound **1g** was allowed to react with morpholine according to the general method to give **12c** (29%); IR (KBr) 2628w (SH), 1666 s (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.4 (br s, 2H, NH and SH), 3.8 (t, 4H, J=4.8 Hz, H-3′), 3.0 (t, 4H, J=4.8 Hz, H-2′), 2.3 (s, 3H, 6-CH_3), 1.9 (s, 3H, 5-CH_3); ^{13}C NMR ($CDCl_3$) δ 185.2 (C-2), 165.5 (C-4), 163.4 (C-6), 110.7 (C-5), 65.3 (C-3′), 44.1 (C-2′), 16.9 (6-CH$_3$), 9.6 (5-CH$_3$).

Synthesis of 2-Morpholin-4-yl-5,6,7,8-tetrahydro-4*H*-1,3-benzoxazin-4-one 5

Compound **12a** (0.18 g, 0.67 mmol) was dissolved in chloroform (4 mL) and stirred at room temperature for 48 h. On completion of the reaction,

the chloroform was evaporated off in vacuo, and cyclohexane (25 mL) was added. The reaction mixture was heated to boiling, and minimal toluene was added to aid in dissolving of the oily material. The mixture was hot filtered to a fresh flask containing cyclohexane, leaving a small amount of oily material still undissolved. The fresh cyclohexane was then concentrated down with heat and allowed to cool. Compound **5** crystallized out of the cyclohexane (27 mg, 17%) as white crystals; mp 132–135 °C (lit.[27] 129–130 °C); IR (KBr) 1686 m (CO), 1559 s (CN) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.8–3.6 (br m, 8H, H-2′ & H-3′), 2.5–2.3 [br m, 4H, (CH_2)$_2$], 1.9–1.7 [m, 4H, (CH_2)$_2$]; ^{13}C NMR ($CDCl_3$) δ 169.1 (C-2), 159.3 (C-4), 157.2 (C-8a), 113.7 (C-4a), 66.2 (C-3′), 44.1 (C-2′), 26.1 (C-8), 21.7, 21.0 [(CH_2)$_3$].

General Method for the Reaction of 1,3-Oxazines with Benzylamine

2-Thio-1,3-oxazine **1** (1 mmol) was dissolved in dry dichloromethane (4 mL) and cooled in an ice/water bath. Benzylamine (2 mmol) in dry dichloromethane (1 mL) was added dropwise with stirring and the reaction mixture was allowed to return to room temperature and stir at ambient temperature for 18 h. The dichloromethane was evaporated off in vacuo, and the reaction mixture was triturated with diethyl ether. The resulting solid was collected by vacuum filtration.

(2*Z*)-3-(Benzylamino)-*N*-[(benzylamino)carbonothioyl]but-2-enamide 6a

6-Methyl-2-thioxo-2,3-dihydro-4*H*-1,3-oxazin-4-one **1a** was allowed to react with benzylamine according to the general method to give **6a** (51%); and recrystallized from abs. EtOH. Mp 116–117 °C; IR (KBr) 3264w (NH), 1623 m (CO), 1173 s (CS) cm^{-1}; ^1H NMR ($CDCl_3$) δ 11.0 (br s, 1H, H-12), 9.5 (br s, 1H, H-4), 8.0 (br s, 1H, H-10), 7.4–7.2 (m, 10H, Ar), 4.9 (d, 2H, J=6.0 Hz, H-13), 4.44 (d, 2H, J=6.0 Hz, H-5), 4.36 (s, 1H, H-2), 2.0 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 180.9 (C-11), 168.7 (C-1), 164.5 (C-3), 137.7/137.0 (C-6/C-14), 128.9, 128.6, 127.7, 127.6, 127.5, 126.6 (*C*H-Ar), 84.6 (C-2), 49.3 (C-13), 47.0 (C-5), 19.6 (*C*H$_3$). Anal. calcd. for $C_{19}H_{21}N_3OS$: C, 67.23; H, 6.24; N, 12.38. Found: C, 67.21; H, 6.26; N, 12.35%.

(2*Z*)-3-(Benzylamino)-*N*-[(benzylamino)carbonothioyl]pent-2-enamide 6b

6-Ethyl-2-thioxo-2,3-dihydro-4*H*-1,3-oxazin-4-one **1b** was allowed to react with benzylamine according to the general method to give **6b**

(73%) and recrystallized from abs. EtOH. Mp 128–130 °C; IR (KBr) 3216w (NH), 1627 m (CO), 1182 s (CS) cm^{-1}; ^1H NMR ($CDCl_3$) δ 11.0 (br s, 1H, H-12), 9.5 (t, 1H, J=6.4 Hz, H-4), 8.2 (br s, 1H, H-10), 7.4–7.2 (m, 10H, Ar), 4.9 (d, 2H, J=5.4 Hz, H-13), 4.5 (d, 2H, J=6.4 Hz, H-5), 4.4 (s, 1H, H-2), 2.3 (q, 2H, J=7.5 Hz, CH_2 CH_3), 1.1 (t, 3H, J=7.5 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$) δ 181.0 (C-11), 169.5/169.0 (C-1/C-3), 137.8/137.1 (C-6/C-14), 128.9, 128.7, 127.7, 127.6, 127.5, 126.6 (*C*H-Ar), 82.7 (C-2), 49.3 (C-13), 46.5 (C-5), 25.4 (CH_2CH_3), 12.1 (CH_2CH_3). Anal. calcd. for $C_{20}H_{23}N_3OS$: C, 67.96; H, 6.56; N, 11.89. Found: C, 68.05; H, 6.60; N, 11.91%.

(2*Z*)-3-(Benzylamino)-*N*-[(benzylamino)carbonothioyl]hex-2-enamide 6c

6-Propyl-2-thioxo-2,3-dihydro-4*H*-1,3-oxazin-4-one **1c** was allowed to react with benzylamine according to the general method to give **6c** (48%) and recrystallized from abs. EtOH. Mp 105–106 °C; IR (KBr) 3214w (NH), 1628 m (CO), 1172 s (CS) cm^{-1}; ^1H NMR ($CDCl_3$) δ 11.0 (br s, 1H, H-12), 9.5 (br s, 1H, H-4), 8.0 (br s, 1H, H-10), 7.3–7.2 (m, 10H, Ar), 4.9 (d, 2H, J=5.5 Hz, H-13), 4.44 (d, 2H, J=6.4 Hz, H-5), 4.37 (s, 1H, H-2), 2.2 (t, 2H, J=7.7 Hz, $CH_2CH_2CH_3$), 1.6–1.5 (m, 2H, $CH_2CH_2CH_3$), 1.0 (t, 3H, J=7.3 Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ 181.0 (C-11), 168.9/168.2 (C-1/C-3), 137.9/137.1 (C-6/C-14), 128.8, 128.6, 127.7, 127.6, 127.5, 126.7 (*C*H-Ar), 83.7 (C-2), 49.3 (C-13), 46.6 (C-5), 34.3 ($CH_2CH_2CH_3$), 21.2 ($CH_2CH_2CH_3$), 13.8 (CH_3). Anal. Calcd for $C_{21}H_{25}N_3OS$: C, 68.63; H, 6.86; N, 11.43. Found: C, 68.63; H, 6.96; N, 11.37%.

N-[(Benzylamino)carbonothioyl]-2-(benzylamino)cyclohex-1-ene-1-carboxamide 6d

2-Thioxo-2,3,5,6,7,8-hexahydro-4*H*-1,3-benzoxazin-4-one **1e** was allowed to react with benzylamine according to the general method to give **6d** (53%) and recrystallized from abs. EtOH. Mp 115–116 °C; IR (KBr) 3442w and 3181w (NH), 1619 m (CO), 1169 m (CS) cm^{-1}; ^1H NMR ($CDCl_3$) δ 11.3 (br s, 1H, H-12), 10.2 (t, 1H, J=6.1 Hz, H-4), 8.2 (br s, 1H, H-10), 7.3–7.2 (m, 10H, Ar), 4.9 (d, 2H, J=5.4 Hz, H-13), 4.4 (d, 2H, J=6.1 Hz, H-5), 2.4–2.2 (bm, 4H, $(CH_2)_2$), 1.7–1.5 (bm, 4H, $(CH_2)_2$); ^{13}C NMR ($CDCl_3$) δ 181.0 (C-11), 169.3 (C-1), 163.3 (C-3), 138.3/137.0 (C-6/C-14) 128.8, 128.6, 127.7, 127.5, 127.4, 126.6 (*C*H-Ar), 88.9 (C-2), 49.4 (C-13), 46.2 (C-5), 26.7 (CH_2C-N), 23.9, 22.3, 21.5 [$(CH_2)_3$]. Anal. calcd. for $C_{22}H_{25}N_3OS$: C, 69.62; H, 6.64; N, 11.07. Found: C, 69.56; H, 6.61; N, 11.12%.

(2*Z*)-3-(Benzylamino)-2-benzyl-*N*-[(benzylamino)carbonothioyl]but-2-enamide 6e

5-Benzyl-6-methyl-2-thioxo-2,3-dihydro-4*H*-1,3-oxazin-4-one **1f** was allowed to react with benzylamine according to the general method to give **6e** (70%) and recrystallized from abs. EtOH. Mp 141–143 °C; IR (KBr) 3425w and 3170 (NH), 1618 m (CO), 1167 s (CS) cm^{-1}; ^1H NMR ($CDCl_3$) δ 11.2 (br s, 1H, H-12), 10.7 (br s, 1H, H-4), 8.1 (br s, 1H, H-10), 7.3–7.2 (m, 15H, Ar), 4.8 (d, 2H, *J*=5.3 Hz, H-13), 4.5 (d, 2H, *J*=6.0 Hz, H-5), 3.6 (s, 2H, CCH_2Ph), 2.0 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 181.0 (C-11), 169.5 (C-1), 164.6 (C-3), 138.8/138.0/137.0 (C-6/C-14/*C*-Ar), 129.0, 128.9, 128.6, 127.8, 127.6, 127.5, 127.4, 126.9, 126.6 (CH-Ar), 90.5 (C-2), 49.4 (C-13), 47.5 (C-5), 33.0 (CCH_2Ph), 16.0 (CH_3). Anal. calcd. for $C_{26}H_{27}N_3OS$: C, 72.69; H, 6.34; N, 9.78. Found: 72.70; H, 6.44; N, 9.83%.

(2*Z*)-3-(Benzylamino)-*N*-[(benzylamino)carbonothioyl]-2-methylbut-2-enamide 6f

5,6-Dimethyl-2-thioxo-2,3-dihydro-4*H*-1,3-oxazin-4-one **1g** was allowed to react with benzylamine according to the general method to give **6f** (69%) and recrystallized from abs. EtOH. Mp 137–138 °C; IR (KBr) 3449w and 3178 (NH), 1621 m (CO), 1170 s (CS) cm^{-1}; ^1H NMR ($CDCl_3$) δ 11.3 (br s, 1H, H-12), 10.5 (br s, 1H, H-4), 8.2 (br s, 1H, H-10), 7.4–7.2 (m, 10H, Ar), 4.9 (d, 2H, *J*=5.5 Hz, H-13), 4.5 (d, 2H, *J*=6.2 Hz, H-5), 2.0 (s, 3H, 3-CH_3), 1.9 (s, 3H, 2-CH_3); ^{13}C NMR ($CDCl_3$) δ 181.0 (C-11), 169.2 (C-1), 163.1 (C-3), 138.2/136.9 (C-6/C-14), 128.7, 128.6, 127.6, 127.4, 127.3, 126.5 (CH-Ar), 86.5 (C-2), 49.3 (C-13), 47.2 (C-5), 16.0 (3-CH_3), 13.0 (2-CH_3). Anal. calcd. for $C_{20}H_{23}N_3OS$: 67.96; H, 6.56; N, 11.89. Found: C, 68.05; H, 6.63; N, 11.82%.

N-[(benzylamino)carbonothioyl]-3-oxo-3-phenylpropanamide 14

6-Phenyl-2-thioxo-2,3-dihydro-4*H*-1,3-oxazin-4-one **1h** was allowed to react with benzylamine according to the general method to give **14** (53%) and recrystallized from abs. EtOH. Mp 171–173 °C; IR (KBr) 3189w (NH), 1705s (CO), 1677s (CO), 1166s (CS) cm^{-1}; ^1H NMR (d_6-DMSO) δ 11.5 (br s, 0.8H, H-8 keto), 11.3 (br s, 0.2H, H-8 enol), 10.9 (t, 0.8H, *J*=5.3 Hz, H-10 keto), 10.8 (br s, 0.2H, H-10 enol), 8.0–7.3 (m, 10H, Ar), 6.2 (s, 0.2H, H-2 enol), 4.8 (d, 2H, *J*=5.3 Hz, H-11),

4.3 (s, 1.8H, H-2 keto); ^{13}C NMR (d_6-DMSO) δ 194.1 (C-3), 180.2 (C-9), 169.2 (C-1), 137.4/136.0 (C-4/C-12), 134.0 (C-7), 129.0/128.6/128.4/127.7 (C-5/C-6/C-13/C-14), 127.5 (C-15), 48.0 (C-2 & C-11) [171.3 (C-3 enol) 129.1, 128.4, 127.1, 125.9 (Ar-enol), 89.1 (C-2 enol)]. Anal. calcd. for $C_{17}H_{16}N_2O_2S$: C, 65.36; H, 5.16; N, 8.97. Found: C, 65.28; H, 5.20; N, 9.03%.

General Method for the Synthesis of Thiouracils

Dibenzylamino compound **6** (0.2 g) was heated to reflux in acetic acid (3 mL) for 2 h before being cooled, and the acetic acid evaporated off in vacuo. The oily reaction mixture was triturated with diethyl ether, and the resulting solid was collected by vacuum filtration and recrystallized from the appropriate solvent.

1-Benzyl-6-methyl-2-thioxo-2,3-dihydropyrimidin-4(1*H*)-one 7a

A suspension of **6a** was heated to reflux in acetic acid according to the general method to give **7a** (28%) and recrystallized from abs. EtOH. Mp 211–212 °C; IR (KBr) 3178w and 3081w (NH), 1654 s (CO), 1192 m (CS) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.9 (br s, 1H, NH), 7.4–7.2 (m, 5H, Ar), 5.9 (s, 1H, H-5), 5.7 (s, 2H, H-7), 2.2 (s, 3H, C*H*$_3$); ^{13}C NMR ($CDCl_3$) δ 178.4 (C-2), 159.4 (C-4), 154.9 (C-6), 134.6 (C-8), 129.1/125.8 (C-9/C-10), 127.9 (C-11), 107.6 (C-5), 53.3 (C-7), 21.3 (*C*H$_3$). Anal. calcd. for $C_{12}H_{12}N_2OS$: C, 62.04; H, 5.21; N, 12.06. Found: 61.96; H, 5.33; N, 12.15%.

1-Benzyl-2-thioxo-2,3,5,6,7,8-hexahydroquinazolin-4(1*H*)-one 7b

A suspension of **6d** was heated to reflux in acetic acid according to the general method to give **7b** (67%) and recrystallized from abs. EtOH. Mp 241–242 °C; IR (KBr) 3163w and 3059w (NH), 1663 s (CO), 1172 s (CS) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.8 (br s, 1H, NH), 7.4–7.2 (m, 5H, Ar), 5.8 (br s, 2H, H-7), 2.6–2.3 [br m, 4H, (C*H*$_2$)$_2$], 1.8–1.5 [br m, 4H, (C*H*$_2$)$_2$]; ^{13}C NMR ($CDCl_3$) δ 176.7 (C-2), 159.5 (C-4), 151.1 (C-6), 135.0 (C-8), 129.0/125.6 (C-9/C-10), 127.7 (C-11), 116.3 (C-5), 52.6 (C-7), 27.2 (*C*H$_2$C-N), 22.1, 21.8, 20.2 [(*C*H$_2$)$_3$]. Anal. calcd. for $C_{15}H_{16}N_2OS$: C, 66.15; H, 5.92; N, 10.29. Found: C, 66.23; H, 6.07; N, 10.24%.

1,5-Dibenzyl-6-methyl-2-thioxo-2,3-dihydropyrimidin-4(1*H*)-one 7c

A suspension of **6e** was heated to reflux in acetic acid according to the general method to give **7c** (52%) and recrystallized from methanol. Mp 164–165 °C; IR (KBr) 3160w and 3060w (NH), 1663 s (CO), 1218 m (CS) cm^{-1}; ^1H NMR ($CDCl_3$) δ 10.1 (br s, 1H, NH), 7.4–7.2 (m, 10H, Ar), 5.8 (br s, 2H, H-7), 3.8 (s, 2H, CCH_2 Ph), 2.2 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 177.0 (C-2), 159.6 (C-4), 151.6 (C-6), 138.4/134.8 (C-8/*C*-Ar), 129.1/128.6/128.0/125.7 (C-9/C-10/*C*H-Ar-o,m), 127.8/126.5 (C-11/*C*H-Ar-p), 118.0 (C-5), 54.1 (C-7), 31.1 (CCH_2Ph), 17.7 (CH_3). Anal. calcd. for $C_{19}H_{18}N_2OS$: C, 70.78; H, 5.63; N, 8.69. Found: 70.71; H, 5.65; N, 8.75%.

1-Benzyl-5,6-dimethyl-2-thioxo-2,3-dihydropyrimidin-4(1*H*)-one 7d

A suspension of **6f** was heated to reflux in acetic acid according to the general method to give **7d** (63%) and recrystallized from methanol. Mp 221–223 °C; IR (KBr) 3161w and 3052w (NH), 1656 s (CO), 1235 m (CS) cm^{-1}; ^1H NMR ($CDCl_3$) δ 10.1 (br s, 1H, NH), 7.4–7.2 (m, 5H, Ar), 5.8 (br s, 2H, H-7), 2.2 (s, 3H, 6-CH_3), 2.0 (s, 3H, 5-CH_3); ^{13}C NMR ($CDCl_3$) δ 176.7 (C-2), 159.7 (C-4), 149.9 (C-6), 134.9 (C-8), 129.1/125.8 (C-9/C-10), 127.8 (C-11), 114.7 (C-5), 54.2 (C-7), 17.5 (6-*C*H_3), 11.5 (5-*C*H_3). Anal. calcd. for $C_{13}H_{14}N_2OS$: C, 63.39; H, 5.73; N, 11.37. Found: C, 63.22; H, 5.74; N, 11.21%.

Platelet Aggregometry

The test compound was dissolved in ethanol, and antiplatelet evaluation was carried out according to our earlier reported procedure.[15] Platelet aggregation was determined by the optical method in a two-channel platelet aggregometer (Chrono-Log). The agonists used were ADP (final concentration 10 μM) and collagen (final concentration 4 μg/mL). The concentration of the compound at which the aggregation was inhibited by 50% (IC_{50}) was determined as the average of multiple determinations (three or more) where platelet aggregation was reduced by 50%. La Trobe University Human Ethics Committee approval was obtained (HREC Number 06–16).

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