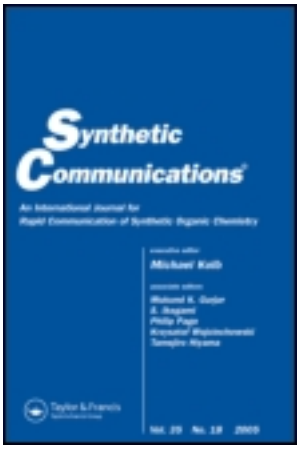

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Generalized Method for the Production of 1,3-Benzoxazine, 1,3-Benzothiazine, and Quinazoline Derivatives from 2-(Hydroxy, Thio, or Amino) Aromatic Acids Using Triphenylphosphine Thiocyanogen

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Generalized Method for the Production of 1,3-Benzoxazine, 1,3-Benzothiazine, and Quinazoline Derivatives from 2-(Hydroxy, Thio, or Amino) Aromatic Acids Using Triphenylphosphine Thiocyanogen

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Abstract: A modified one-pot method was developed for the synthesis of 1,3-benzoxazines, in which the preparation of unstable thiocyanogen was omitted. The method was found to be general for substituted (methyl, methoxy, halo, and hydroxy) 2-hydroxy benzoic acids and 2-hydroxy naphthoic acids. The method was extended to 2-thio, 2-amino, and *N*-methyl aminobenzoic acid with which the synthesis of 1,3-benzothiazine and quinazoline derivatives has been achieved, respectively. It was also found that 3-hydroxypyridine-2-carboxylic acid and 2-hydroxynicotinic acid using a modified method gave 2-thioxo-2,3-dihydro-4*H*-pyrido[2,3-*e*][1,3]oxazin-4-one and 2-thioxo-2,3-dihydro-4*H*-pyrido[3,2-*e*][1,3]oxazin-4-one, respectively. The structures of the new compounds were confirmed by the analysis of their IR, ^{1}H, and ^{13}C NMR spectra.

Keywords: Triphenylphosphine thiocyanogen, modified synthesis of 1,3-benzoxazines, 1,3-benzothiazine, quinazolines

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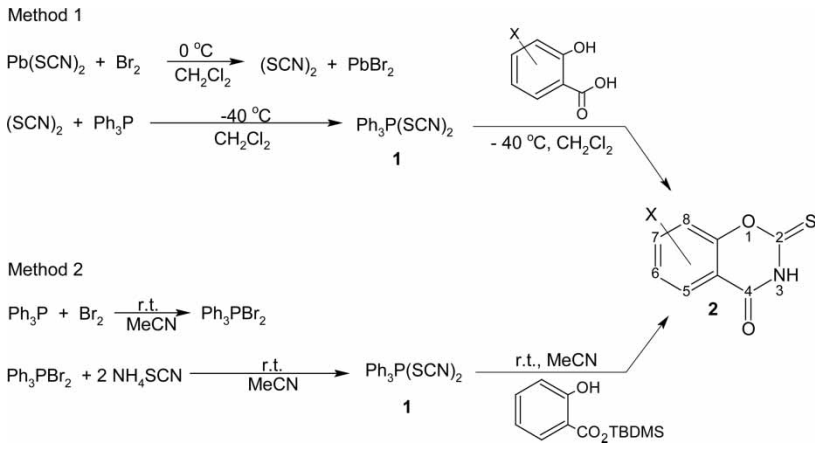
INTRODUCTION

Researchers have shown the significance of the title compounds in the development of antimicrobial, antiviral, and antifungal drugs.[1–3] Presence of a sulfur group in the C-2 position, which results in the 2-mercapto tautomer, provides a good leaving group for the reaction of morpholine (secondary amines) with the title compounds to give 2-morpholinyl antiatherosclerotic compounds.[4] The 2-mercapto tautomer also reacts with benzylamine (primary amines) to open the oxazine ring between positions 1 and 2 to give *N*-benzylthioureas, which have been found to possess antiviral, antiproliferation, and antibacterial properties.[5] Many methods (Scheme 1, methods 1 and 2) have been used in the synthesis of certain 1,3-oxazine derivatives. This has promoted the need for a general method to produce 1,3-oxazines and their related derivatives.

Method 1 (Scheme 1) for the synthesis of 1,3-oxazines using substituted 2-hydroxybenzoic acids was reported in 1978.[6] Bromine was added to lead thiocyanate to produce thiocyanogen. Thiocyanogen was separated from the reaction mixture and allowed to react with triphenylphosphine at -40°C in dichloromethane to give triphenylphosphine thiocyanogen **1**. The reagent **1** was then allowed to react with 2-hydroxybenzoic acids to give the 1,3-oxazines. Several disadvantages were found with this method. Firstly, the separation of the thiocyanogen was difficult because this compound is highly susceptible to polymerization. Other disadvantages included the reaction conditions, where temperatures of -40°C were required and the reactions were poorly reproducible. Nine oxazines **2** were prepared using method 1 (Scheme 1) including where X = H, 6-Cl, 6-Br, 6-OH, 7-Me, 8-Me, 5/6-Ar, 6/7-Ar, and 7/8-Ar.

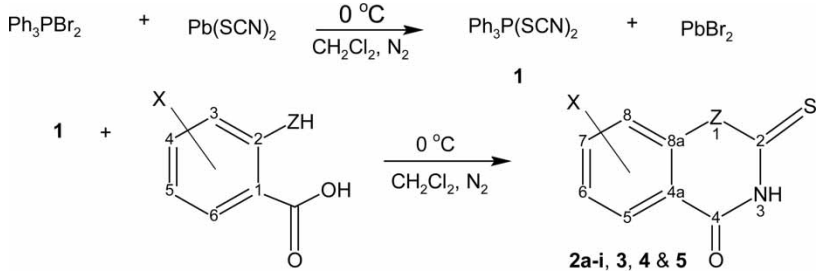


Scheme 1.

More recently a modified method (method 2, Scheme 1) was introduced[7] where bromine was added to triphenylphosphine, followed by the addition of ammonium thiocyanate, to produce triphenylphosphine thiocyanogen **1** at room temperature. Then, t-butyldimethylsilyl (TBDMS) or triisopropylsilyl (TIPS) salicylates were added to afford the 1,3-oxazine. In this method, a solution of ammonium thiocyanate in acetonitrile was added dropwise to a solution of the triphenylphosphine dibromide; however, both ammonium thiocyanate and triphenylphosphine dibromide are poorly soluble in acetonitrile. Furthermore, the extraction of the 1,3-oxazine (Scheme 1, method 2) was difficult because of interference by the by-product, ammonium bromide. This method also brought the need for an extra step in which the acid was converted to the silyl ester. This extra step was not only time consuming but also the t-butyldimethylsilyl salicyates are prone to hydrolysis,[8] leading to poor reproducibility. In method 2 (Scheme 1), only the oxazine **2** where X = H was prepared.

RESULTS AND DISCUSSION

The aim of this study was to generalize the one-pot method for the production of 1,3-oxazines from substituted 2-hydroxybenzoic acids. This has been achieved by simplifying the procedure. The reaction requires the addition of bromine to triphenylphosphine to give triphenylphosphine dibromide. Lead thiocyanate was then added to the reaction mixture, followed by a substituted 2-hydroxybenzoic acid, to produce a 1,3-oxazine (Scheme 2). The replacement of lead thiocyanate with ammonium thiocyanate was attempted because it would be advantageous to eliminate the use of lead thiocyanate, but it was found that the yield was decreased because of the difficult workup of the reaction mixture.



Scheme 2. Compound **2** (Z = O, **a** X = H; **b** X = 8-CH_3; **c** X = 8-OCH_3; **d** X = 7-OCH_3; **e** X = 8-Cl; **f** X = 7-Cl; **g** X = 6-Cl; **h** X = 7-OH; **i** X = 7-OH & 8-CH_3; Compound **3** Z = S, X = H; Compound **4** Z = NH, X = H; Compound **5** Z = NCH_3, X = H).

It was found that the yield of the 1,3-oxazines increased, and the workup was simplified, if the triphenylphosphine dibromide was first isolated and then used in the preparation of triphenylphosphine thiocyanogen (Scheme 2). Indeed, the use of the commercially available triphenylphosphine dibromide in the 1,3-oxazine synthesis improved the yield and the product purification. The best reaction temperature was found to be 0°C with the 1,3-oxazine yield decreasing if the temperature of the reaction was above 0°C.

It was found that this reaction was general for substituted 2-hydroxybenzoic acids, as well as 2-thio, 2-amino, and *N*-methylamino benzoic acids (Scheme 2). Furthermore, the reaction was successfully extended to 1-hydroxy-2-naphthoic acid, 3-hydroxy-2-naphthoic acid, 3-hydroxypyridine-2-carboxylic acid, and 2-hydroxynicotinic acid to produce the corresponding 1,3-oxazines **6**, **7**, **8** and **9**, respectively (Figure 1).

Compounds (**2a**, **2b**, **2g**, **3**, **4**, **5**, **6**, and **7**) were characterized by comparison of their physical data (mp, IR,^{1}H, and ^{13}C NMR spectra) with literature values.[6,9–14] The structures of the newly described 1,3-oxazines (**2c**–**f**, **h**, and **i**) were confirmed using IR, ^{1}H, and ^{13}C NMR spectroscopy. The infrared spectra of the new oxazines **2c**–**f**, **h**, and **i** showed a strong resemblance to those of the previously prepared oxazines **2a**, **2b**, **2g**, **3**, **4**, **5**, **6**, and **7**. The ^{1}H NMR spectra of the new oxazines **2c**–**f**, **h**, and **i** give strong support for the proposed structures.

The ^{13}C NMR chemical shift assignment for compounds **2c**–**f**, **h**, and **i** was achieved using the calculated value, starting from the previously reported chemical shifts of 1,3-oxazine **2a**[11] and substitution increments of the aromatic ring of **2c**, 8-OMe; **2d**, 7-OMe; **2e**, 8-Cl; **2f**, 7-Cl; **2h**, 7-OH; and **2i**, 7-OH and 8-Me.[15] The structures of the new heteroaromatic 1,3-oxazine structures **8** and **9** were confirmed by ^{1}H NMR and proton-decoupled ^{13}C NMR spectra as well as multinuclear two-dimensional NMR.

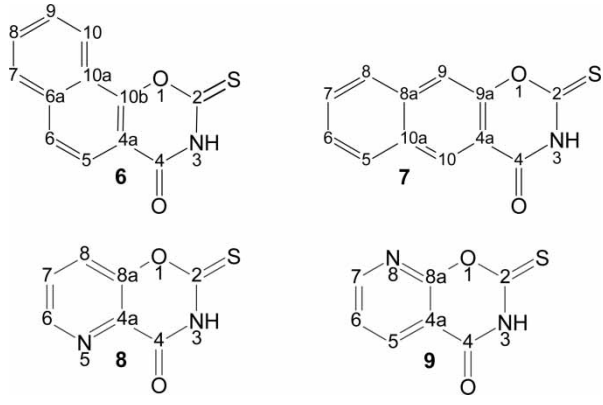
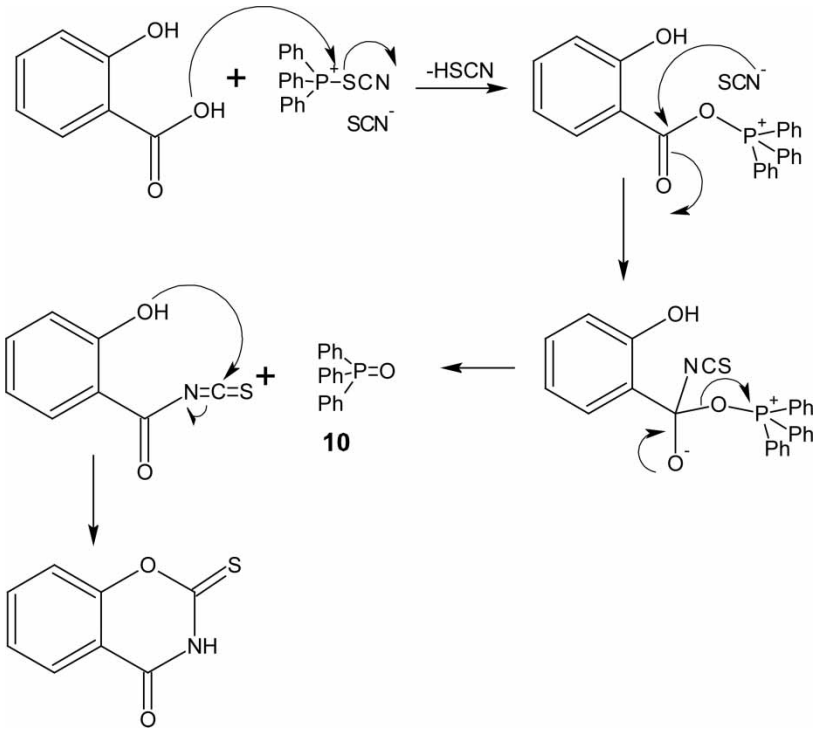


Figure 1. 1,3-Oxazines (**6**–**9**) prepared from 1-hydroxy-2-naphthoic acid, 3-hydroxypyridine-2-carboxylic acid and 2-hydroxynicotinic acid respectively.

The spectra of compound **8** showed the correct number of signals. Assignment of the carbon-13 chemical shifts was made as follows: (d_6DMSO) δ 181.5 and 156.5 were assigned to C-2 and C-4, respectively, by analogy to the corresponding carbons in compound **2a**.[11] The assignment of the pyridine ring carbons C-4a, C-6, C-7, C-8, and C-8a was accomplished using the corresponding aromatic ring carbons chemical shifts of 1,3-oxazine **2a** and the nitrogen insertion effect. (Starting from 128.5 as the carbon chemical shift for benzene ring and the use of pyridine C-2, C-3, and C-4 carbon chemical shifts allowed the calculation of the nitrogen insertion effect increments, with the increments being +21.7, −4.6 and +7.4, respectively.) The observed/calculated values for the oxazine **8** are C-4a 133.2/137.3 (quaternary carbon); C-6 147.9/147.9 (CH); C-7 130.3/131.9 (CH); C-8 125.1/123.8 (CH); and C-8a 153.5/150.7 (quaternary carbon). Similarly, the ^{13}C NMR spectra of compound **9** also showed the correct number of signals and their assignment was achieved in a similar manner to that outlined for compound **8** (see Experimental).

The proposed reaction mechanism for 1,3-oxazine synthesis is shown in Scheme 3. Confirmation of the proposed reaction mechanism was possible



Scheme 3.

after the isolation and identification of the by-product triphenylphosphine oxide **10** (see Experimental).

EXPERIMENTAL

Infrared spectra were obtained using a Perkin Elmer FT-IR spectrometer. ^{1}H NMR and ^{13}C NMR spectra were obtained using a Bruker UX NMR spectrometer at 300 MHz and 75.5 MHz, respectively, and HSQC two-dimensional NMR were obtained. All ^{1}H and ^{13}C NMR spectral results are recorded as chemical shifts (δ) and are relative to the internal TMS. 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 corrected to $\pm 1^{\circ}$C.

Starting Materials

All acids (with the exception of 2,4-dihydroxy-3-methylbenzoic acid), lead thiocyanate, triphenylphosphine, and triphenylphosphine dichloride were purchased from Aldrich Chemical Company and were used as received. Bromine was purchased from BDH laboratory supplies and used as received. Triphenylphosphine dibromide was purchased from Strem Chemicals (USA) and also used as received.

2,4-Dihydroxy-3-methylbenzoic acid was prepared from 2-methylresorcinol[16] to give the acid in 42% yield after recrystalization from ethanol/water, mp 205–206°C (lit. mp 204–206°C); ν_{max} (KBr) 3500–3300 and 3250–2500w (OH), 1646 and 1622s (C=O) cm^{-1}; ^{1}H (d_6-DMSO) δ 14.9, (s, 1H, COOH), 11.6 (s, 1H, 2-OH), 10.2 (s, 1H, 4-OH), 7.5 (d, 1H, $J = 8.6$ Hz, 6-H), 6.4 (d, 1H, $J = 8.6$ Hz, 5-H), 1.9 (s, 3H, 3-CH_3); ^{13}C (d_6-DMSO) δ 103.9 (C-1), 161.5 and 161.6 (C-2 and C-4), 110.2 (C-3), 107.0 (C-5), 128.5 (C-6), 172.6 (COOH), 7.8 (CH_3).

Synthesis of 1,3-Benzoxazines

General Method

Triphenylphosphine dibromide (5 mmol) was weighed out under nitrogen into a three-necked, round-bottomed flask containing a stirring bar. Dry dichloromethane (20 mL) was then added to the flask and the flask was placed into an ice bath. The reaction vessel was equipped with a nitrogen gas inlet with bubbling tube as well as a dropping funnel. The other side arm was fitted with a calcium chloride drying tube. A suspension of lead thiocyanate (6 mmol) in dry dichloromethane (40 mL) was then added slowly via the

dropping funnel with stirring. A suspension of 2-hydroxy aromatic/heteroaromatic acid (4 mmol) in dry dichloromethane (20 mL) was then added to the reaction mixture. The flask was stoppered and the mixture left to stir while slowly warming to room temperature. The reaction mixture was stirred at room temperature for 30 min and then heated at reflux for 3 h. Some of the acids required the reagent to be in a greater excess and/or needed a longer reaction time. (Any variation from this general method is specified with the following details of the prepared oxazine.)

The reaction mixture was then filtered and the filter cake was washed with dichloromethane. The initial waste solid collected was hot filtered with acetone or acetic acid to ensure all of the product had been extracted. All the filtrates were evaporated to dryness in vacuo and toluene was used to dissolve any oil which accompanied the solid product. The products were collected and recrystallized from a suitable solvent. The use of triphenylphosphine dichloride was explored with results being comparable to the use of triphenylphosphine dibromide.

Isolation of triphenylphosphine oxide **10** was achieved when the residual mother liquor oil, collected from the reaction to prepare **2a**, was applied to a silica-gel column and eluted with acetone. The solid recovered was identified by melting point and comparison of the IR spectrum to the known spectrum.

2-Thioxo-2,3-dihydro-4*H*-1,3-benzoxazin-4-one 2a. Salicylic acid was allowed to react with **1** as described in the general method to give **2a** with the solid collected from the mother liquor and the acetone hot-filtration wash of the initial waste solid combined and recrystallized from toluene, 80% yield, mp 247–249°C (lit. mp 246–247°C), ^{1}H (d_6-DMSO) δ 13.5 (s, 1H, NH), 7.9 (d, 1H, $J = 7.5$ Hz, H-5), 7.8 (t, 1H, $J = 7.5$ Hz, H-7), 7.5 (d, 1H, $J = 7.5$ Hz, H-8), 7.4 (t, 1H, $J = 7.5$ Hz, H-6).

8-Methyl-2-thioxo-2,3-dihydro-4*H*-1,3-benzoxazin-4-one 2b. Similarly, the general method was used for the reaction of 3-methylsalicylic acid with **1** to give **2b** with the solid collected from the mother liquor (no solid collected from the acetone hot-filtration wash of the initial waste solid), then recrystallized from $CHCl_3$, 68% yield, mp 216–218°C (lit. mp 213°C), ^{1}H (d_6-DMSO) δ 13.5 (s, 1H, NH), 7.8 (d, 1H, $J = 7.1$ Hz, H-5), 7.7 (d, 1H, $J = 7.1$ Hz, H-7), 7.4 (t, 1H, $J = 7.1$ Hz, H-6), 2.4 (s, 3H, 8-CH_3).

8-Methoxy-2-thioxo-2,3-dihydro-4*H*-1,3-benzoxazin-4-one 2c. 3-Methoxysalicylic acid was allowed to react with **1** as described in the general method to give **2c.** The solid from the mother liquor and the acetone hot-filtration wash of the initial waste solid were then combined and recrystallized from toluene, 84% yield, mp 243–246°C; (found C, 51.73; H, 3.49; N, 6.75; $C_9H_7NO_3S$ requires C, 51.66; H, 3.37; N, 6.69); ν_{max} (KBr) 3191w and 3087w (N–H), 1718s (4–C═O), 1618m (C═C), 1222s (C═S) cm^{-1}; ^{1}H

(d_6-DMSO) δ 13.5 (s, 1H, NH), 7.5–7.4 (m, 3H, Ar), 3.9 (s, 3H, 8-OCH_3); ^{13}C (d_6-DMSO) δ 181.6 (C-2), 157.5 (C-4), 116.5 (C-4a), 117.3 (C-5), 126.3 (C-6), 118.8 (C-7), 146.5 (C-8), 145.4 (C-8a), 56.8 (8-OCH_3).

7-Methoxy-2-thioxo-2,3-dihydro-4*H*-1,3-benzoxazin-4-one 2d. 4-Methoxysalicylic acid was allowed to react with **1** as described in the general method to give **2d** with the solid from the mother liquor (no solid collected from the acetone hot-filtration wash of the initial waste solid), then recrystallized from toluene, 97% yield, mp 213–215°C (found C, 51.78; H, 3.38; N, 6.75; $C_9H_7NO_3S$ requires C, 51.66; H, 3.37; N, 6.69); ν_{max} (KBr) 3203w and 3119w (N–H), 1723s (4–C=O), 1625s (C=C), 1180s (C=S) cm^{-1}; ^{1}H (d_6-DMSO) δ 13.4 (s, 1H, NH), 7.9 (d, 1H, $J = 8.3$ Hz, 5-H), 7.1 (s, 1H, 8-H), 7.0 (d, 1H, $J = 8.3$ Hz, 6-H), 3.9 (s, 3H, 7-OCH_3); ^{13}C (d_6-DMSO) δ 182.2 (C-2), 157.2 (C-4 and C-8a), 108.3 (C-4a), 128.2 (C-5), 114.3 (C-6), 165.7 (C-7), 100.3 (C-8), 56.5 (7-OCH_3).

8-Chloro-2-thioxo-2,3-dihydro-4*H*-1,3-benzoxazin-4-one 2e. The general method was used for the reaction of 3-chlorosalicylic acid with **1** to give **2e** with the solid collected from the mother liquor (no solid from acetone hot-filtration wash of the initial waste solid), then recrystallized from toluene, 48% yield, mp 220–223°C (found C, 45.02; H, 1.78; N, 6.47; $C_8H_4ClNO_2S$ requires C, 44.98; H, 1.89; N, 6.56); ν_{max} (KBr) 3195w and 3098w (N–H), 1693s (4–C=O), 1606m (C=C), 1175m (C=S) cm^{-1}; ^{1}H (d_6-DMSO) δ 13.6 (s, 1, NH), 8.0 (d, 1H, $J = 7.6$ Hz, H-5), 7.9 (d, 1H, $J = 7.6$ Hz, H-7), 7.5 (t, 1H, $J = 7.6$ Hz, H-6); ^{13}C (d_6-DMSO) δ 181.1 (C-2), 157.1 (C-4), 117.6 (C-4a), 125.7 (C-5), 126.6 (C-6), 136.2 (C-7), 119.6 (C-8), 151.2 (C-8a).

7-Chloro-2-thioxo-2,3-dihydro-4*H*-1,3-benzoxazin-4-one 2f. 4-Chlorosalicylic acid was allowed to react with **1** to give **2f** as described in the general method with the mother liquor solid (no solid obtained from the acetone hot-filtration wash of the initial waste solid), then recrystallized from toluene, 90% yield, mp 194°C (found C, 45.01; H, 1.75; N, 6.47; $C_8H_4ClNO_2S$ requires C, 44.98; H, 1.89; N, 6.56); ν_{max} (KBr) 3198w and 3085w (N–H), 1718s (4–C=O), 1611m (C=C), 1165s (C=S) cm^{-1}; ^{1}H (d_6-DMSO) δ 13.6 (s, 1H, NH), 7.9 (d, 1H, $J = 8.2$ Hz, H-5), 7.7 (s, 1H, H-8), 7.5 (d, 1H, $J = 8.2$ Hz, H-6); ^{13}C (d_6-DMSO) δ 181.7 (C-2), 156.9 (C-4), 114.8 (C-4a), 128.4 (C-5), 126.5 (C-6), 140.8 (C-7), 116.6 (C-8), 155.7 (C-8a).

6-Chloro-2-thioxo-2,3-dihydro-4*H*-1,3-benzoxazin-4-one 2g. The general method was used for the reaction of 5-chlorosalicylic acid with **1** to give **2g.** The mother liquor solid and the solid obtained from the acetone hot-filtration of the initial waste solid were then combined and recrystallized from toluene, 79% yield, mp 239–242°C (lit. mp 235°C), ^{1}H (d_6-DMSO) δ 13.6 (s, 1H, NH), 7.9 (s, 1H, H-5), 7.9 (d, 1H, $J = 8.8$ Hz, H-7), 7.6 (d, 1H, $J = 8.8$ Hz, H-8).

7-Hydroxy-2-thioxo-2,3-dihydro-4*H*-1,3-benzoxazin-4-one 2h. 2,4-Dihydroxybenzoic acid was allowed to react with **1** as described in the general method to give **2h**, then the solid collected from the mother liquor and the acetone hot-filtration wash of the initial waste solid were combined and recrystallized from dioxane/dichloromethane (dissolved in minimum hot dioxane and precipitated after the addition of cold dichloromethane), 90% yield, mp 245°C decomp. (found C, 49.17; H, 2.49; N, 7.20; $C_8H_5NO_3S$ requires C, 49.23; H, 2.58; N, 7.18); ν_{max} (KBr) 3200–2700b (O-H), 3255w and 3078 w (N–H), 1686s (4–C═O), 1626m (C═C), 1180m (C═S) cm^{-1}; ^1H (d_6-DMSO) δ 13.3 (s, 1H, NH), 11.2 (s, 1H, 7-OH), 7.8 (d, 1H, $J = 8.6$ Hz, H-5), 6.9 (d, 1H, $J = 8.6$ Hz, H-6), 6.7 (s, 1H, H-8); ^{13}C (d_6-DMSO) δ 182.3 (C-2), 157.2 (C-4 and C-8a), 107.0 (C-4a), 128.6 (C-5), 114.9 (C-6), 164.8 (C-7), 101.6 (C-8).

7-Hydroxy-8-methyl-2-thioxo-2,3-dihydro-4*H*-1,3-benzoxazin-4-one 2i: 2,4-Dihydroxy-3-methylbenzoic acid was allowed to react with **1** as described in the general method to give **2i.** The solid from the mother liquor and the acetone hot-filtration wash of the initial waste solid were then combined and recrystallized from ethyl acetate, 86% yield, mp 250°C decomp. (found C, 51.69; H, 3.40; N, 6.63; $C_9H_7NO_3S$ requires C, 51.67; H, 3.37; N, 6.69); ν_{max} (KBr) 3188w and 3085w (N–H), 3250–2900b (O-H); 1664s (4–C═O), 1619m (C═C), 1223m (C═S) cm^{-1}; ^1H (d_6-DMSO) δ 13.3 (s, 1H, NH), 11.1 (s, 1H, 7-OH), 7.7 (d, 1H, $J = 8.4$ Hz, H-5), 6.9 (d, 1H, $J = 8.4$ Hz, H-6), 2.1 (s, 3H, 8-CH_3); ^{13}C (d_6-DMSO) δ 182.3 (C-2), 155.1 (C-4), 106.9 (C-4a), 125.3 (C-5), 113.6 (C-6), 162.6 (C-7), 110.5 (C-8), 157.6 (C-8a), 8.1 (8–CH_3).

2-Thioxo-2,3-dihydro-4*H*-1,3-benzothiazin-4-one 3. Thiosalicylic acid was allowed to react with **1** as described in the general method to give **3**, then the solid from the mother liquor and the acetone hot-filtration wash of the initial waste solid were combined and recrystallized from acetonitrile, 55% yield, mp 234–235°C (lit. mp 232–233°C), ^1H (d_6-DMSO) δ 13.6 (s, 1H, NH), 8.2 (d, 1H, $J = 7.6$ Hz, H-5), 7.8 (t, 1H, $J = 7.6$ Hz, H-7), 7.6 (t, 1H, $J = 7.6$ Hz, H-6), 7.5 (d, 1H, $J = 7.6$ Hz, H-8); ^{13}C (d_6-DMSO) δ 192.8 (C-2), 160.5 (C-4), 122.4 (C-4a), 130.0 (C-5/C-6), 128.4 (C-6/C-5), 134.6 (C-7), 123.4 (C-8), 137.0 (C-8a).

2-Thioxo-2,3-dihydroquinazolin-4(1*H*)-one 4. Anthranilic acid was allowed to react with **1** as described in the general method and then left to stir at room temperature overnight to give **4.** The solid from the mother liquor and the acetic acid hot-filtration wash of the initial waste solid were then combined and recrystallized from acetonitrile, 70% yield, mp 294–296°C (lit. mp 295–296°C), ^1H (d_6-DMSO) δ 12.6 (bs, 2H, 2 x NH), 7.9 (d, 1H, $J = 7.7$ Hz, H-5), 7.7 (t, 1H, $J = 7.7$ Hz, H-7), 7.3 (m, 2H, H-8 and H-6).

1-Methyl-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one 5. *N*-Methylanthranilic acid (3.3 mmol) was allowed to react with **1** as described in the general method and then left to stir at room temperature overnight to give **5.** The solid from the mother liquor and the acetone hot-filtration wash of the initial waste solid were then combined and recrystallized from methanol, 81% yield, mp 255–257°C (lit. mp 253°C); ν_{max} (KBr) 3196w and 3082w (N–H), 1690s (4–C═O), 1610m (C═C), 1202m (C═S) cm^{-1}; ^1H (d_6-DMSO) δ 12.6 (s, 1H, NH), 8.0 (d, 1H, $J = 7.6$ Hz, H-5), 7.8 (t, 1H, $J = 7.6$ Hz, H-7), 7.6 (d, 1H, $J = 7.6$ Hz, H-8), 7.4 (t, 1H, $J = 7.6$ Hz, H-6), 4.0 (s, 3H, N–CH_3); ^{13}C (d_6-DMSO) δ 175.4 (C-2), 157.4 (C-4), 117.2 (C-4a), 126.5 (C-5), 123.7 (C-6), 134.8 (C-7), 115.5 (C-8), 140.8 (C-8a) 36.0 (N–CH_3).

2-Thioxo-2,3-dihydro-4*H*-naphtho[2,1-*e*][1,3]oxazin-4-one 6. 1-Hydroxy-2-naphthoic acid was allowed to react with **1** as outlined in the general method and then left to stir at room temperature overnight to give **6.** The solid from the mother liquor and the acetone hot filtration wash of the initial waste solid were then combined and recrystallized from acetic acid, 76% yield, mp 245°C decomp. (lit. mp 242°C); ν_{max} (KBr) 3187w and 3079w (N–H), 1684s (4–C═O), 1636m (C═C), 1209m (C═S) cm^{-1}; ^1H (d_6-DMSO) δ 14.9 (s, 1H, NH), 8.4–7.8 (m, 6H, Ar).

2-Thioxo-2,3-dihydro-4*H*-naphtho[2,3-*e*][1,3]oxazin-4-one 7. 3-Hydroxy-2-naphthoic acid was allowed to react with **1** as described in the general method and then left to stir at room temperature overnight to give **7.** The solid from the mother liquor and the acetic acid hot-filtration wash of the initial waste solid were then combined and recrystallized from ethanol, 70% yield, mp 250°C decomp. (lit. mp 248°C); ν_{max} (KBr) 3188w and 3084w (N–H), 1695s (4–C═O), 1634m (C═C), 1215s (C═S) cm^{-1}; ^1H (d_6-DMSO) δ 14.9 (s, 1H, NH), 8.7 (s, 1H, H-10), 8.2 (d, 1H, $J = 7.1$ Hz, H-5/H-8), 8.1 (d, 1H, $J = 7.1$ Hz, H-8/H-5), 8.0 (s, 1H, H-9), 7.7 (t, 1H, $J = 7.1$ Hz, H-6/H-7), 7.6 (t, 1H, $J = 7.1$ Hz, H-7/H-6).

2-Thioxo-2,3-dihydro-4*H*-pyrido[2,3-*e*][1,3]oxazin-4-one 8. 3-Hydroxypicolinic acid (2 mmol) was allowed to react with **1** as outlined in the general method and then left to stir at room temperature overnight to give **8.** The solid from the mother liquor and the acetic acid hot-filtration wash of the initial waste solid were then combined and recrystallized from ethyl acetate, 70% yield, mp 198°C decomp. (found C, 46.70; H, 2.16; N, 15.62; $C_7H_4N_2O_2S$ requires C, 46.66; H, 2.24; N, 15.55); ν_{max} (KBr) 3210w and 3119w (N–H), 1711s (4–C═O), 1605w (C═C), 1585w (C═N), 1232s (C═S) cm^{-1}; ^1H (d_6-DMSO) δ 13.7 (s, 1H, NH), 8.7 (s (broad-nitrogen quadruple coupling), 1H, H-6), 8.0 (d, 1H, $J = 8.1$ Hz, H-8) 7.8 (dd, 1H, $J_{H7,H6} = 8.1$ Hz, $J_{H7,H8} = 8.1$ Hz, H-7); ^{13}C (d_6-DMSO) δ 181.5 (C-2), 156.5 (C-4), 133.2 (C-4a), 147.9 (C-6), 130.3 (C-7), 125.1 (C-8), 153.5 (C-8a).

2-Thioxo-2,3-dihydro-4*H*-pyrido[3,2-*e*][1,3]oxazin-4-one 9. 2-Hydroxynicotinic acid (2 mmol) was allowed to react with **1** as outlined in the general method and then left to stir at room temperature overnight to give **9.** The solid from the mother liquor and the acetone hot-filtration wash of the initial waste solid were then combined and recrystallized from toluene, 97% yield, mp 209–211°C; (found C, 46.62; H, 2.23; N, 15.61; $C_7H_4N_2O_2S$ requires C, 46.66; H, 2.24; N, 15.55); ν_{max} (KBr) 3203w and 3101w (N–H), 1698s (4–C═O), 1610m (C═C), 1587m (C═N), 1212m (C═S) cm^{-1}; ^1H (d_6-DMSO) δ 13.6 (s, 1H, NH), 8.7 (d, 1H, $J = 6.7$ Hz, H-7), 8.4 (d, 1H, $J = 6.7$ Hz, H-5), 7.6 (dd, 1H, $J_{H6,H7} = 6.7$ Hz, $J_{H6,H5} = 6.7$ Hz, H-6); ^{13}C (d_6-DMSO) δ 181.9 (C-2), 160.0 (C-4), 111.7 (C-4a), 137.4 (C-5), 123.0 (C-6), 154.4 (C-7), 158.2 (C-8a).

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