SYNTHESES OF SPIRO(OXAZOLIDINEDIONES): SPIRO[1*H*-ISOINDOLE-1,5'-OXAZOLIDINE]-2',3(2*H*),4'-TRIONES and SPIRO[1,2-BENZISOTHIAZOLE-3(2*H*),5'-OXAZOLIDINE]-2',4'-DIONE 1,1-DIOXIDES

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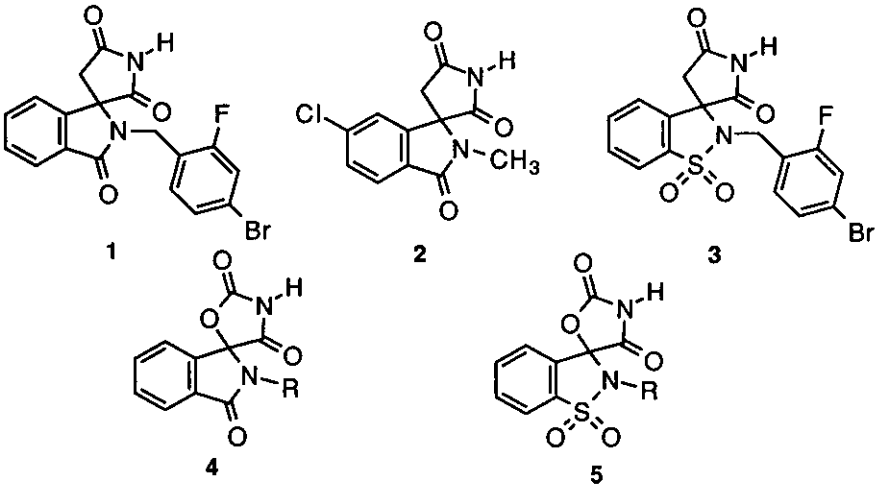
Abstract-Members of two novel families of spiro(oxazolidinediones) have been prepared. Spiro[1*H*-isoindole-1,5'-oxazolidine]-2', 3(2*H*),4'-triones (**4**) were synthesized from the corresponding 1-hydroxy-1-carboxyethylisoindol-3-one (**7**) or (**10**) or their primary amide derivatives (**14**). In turn **7** and **10** were prepared from 2-bromobenzoic acid amides (**6**) and (**9**). or from *N*-alkylated isoquinolin-1, 3, 4(2*H*)-triones (**12**). Spiro[1, 2-benzisothiazole-3(2*H*), 5'-oxazolidine]-2', 4'-dione 1,1-dioxides (**5**) were constructed from the appropriate 2,3-dihydro-3-hydroxy-1,2-benzisothiazole-3-carboxamide 1,1-dioxide (**17**). The immediate precursors to **14**, ethyl esters (**16**) and (**19**), were prepared from benzenesulfonamide (**15**), or from 2-bromobenzenesulfonamide (**18**).

Several members from two novel families of heterocyclic spirosuccinimides have recently been shown to possess antidiabetic activity. For instance, compounds (**1**) and (**3**) (the succinimide moiety spirofused to isoindolone or to benzisothiazole-1,1-dioxide rings, respectively) lowered plasma glucose levels in animal models of type 2 diabetes (insulin resistant mice).[1] Members of the former class, for example **2**, also possessed aldose reductase inhibitor activity and therefore have potential therapeutic value for the treatment of diabetic complications.[1] In an effort to improve upon these biological properties we wished to replace the succinimide moiety of **1**-**3** with other 5-membered cyclic imide-containing ring systems. This structural change had previously been explored in the area of aldose reductase inhibitors. For example, the hydantoin, succinimide, thiazolidine-2,4-dione and oxazolidine-2,4-dione ring systems could be interchanged without drastic alterations in the degree of inhibitor activity.[2] One modification we considered was the replacement of the succinimide ring by an oxazolidine-2,4-dione ring. The targets, shown by generic structures (**4**) and (**5**), were novel heterocyclic ring systems and therefore new procedures had to be developed to accomplish their synthesis. Herein, we report the syntheses of several members of these two classes of compounds.

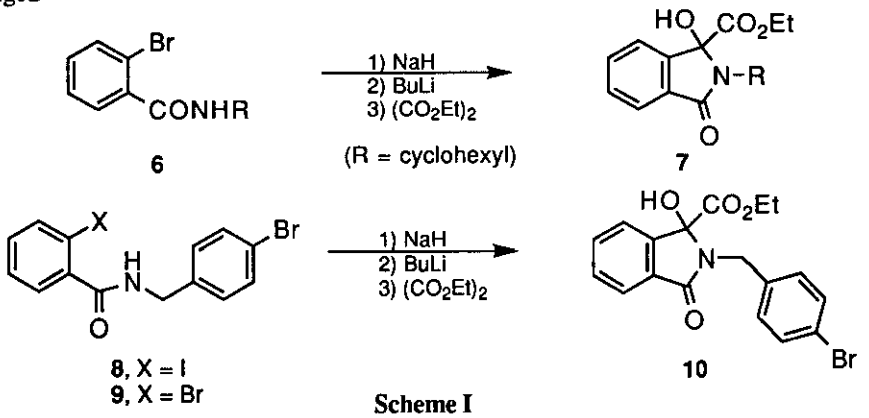
Syntheses of Spiro[1*H*-isoindole-1,5'-oxazolidine]-2',3(2*H*),4'-triones (4). We required synthesis procedures versatile enough to provide analogs of **4** or **5** such that the R group could be an alkyl, aryl or aralkyl unit. We were especially interested in obtaining compounds in which the R group was a *p*-halogenated benzyl moiety. We felt that the oxazolidindione ring of **4** could be constructed from an appropriate 1-hydroxy-1-carboxyisoindol-3-one derivative, such as **7** (Scheme I), so this became our initial target. In this regard, reaction



1 2 3 4 5

of a requisite alkyl-, aryl- or aralkylamine with the acid chloride derived from commercially available and inexpensive 2-bromobenzoic acid provided the amide (**6**). The intent was to do a metal-halogen exchange on **6** using n-butyllithium and react the generated aryllithium species with diethyl oxalate. However, there was evidence that metal-halogen exchange might be faster than the carboxamide hydrogen deprotonation[3,4] and therefore treatment of **6** with two equivalents of butyllithium might result in quenching the generated aryllithium species by the pendant secondary amide. In order to avoid this scenario, **6** was initially reacted with sodium hydride to effect amide deprotonation. The resultant sodium amide derivative of **6** was then cooled to -78°C and reacted with one equivalent of butyllithium. Addition of a large excess of diethyl oxalate, followed by warming to room temperature and dilute aqueous acid workup provided the desired 1-hydroxy-1-carboxyethylisoindol-3-one (**7**) (74%, R = cyclohexyl).

This protocol was very satisfactory for generating analogs of **7** with simple alkyl or aryl moieties. We also used this procedure in attempts to introduce *p*-bromobenzyl moieties as nitrogen R groups (Scheme I). Iodoamide (**8**) was initially prepared since aryl iodides are inherently more reactive toward metal-halogen exchange than are bromides.[5] Indeed compound (**8**) provided the desired isoindolone (**10**) in 65% yield. However, we also reasoned that the bromine ortho to the carboxamide moiety in dibromide (**9**), could be more readily exchanged



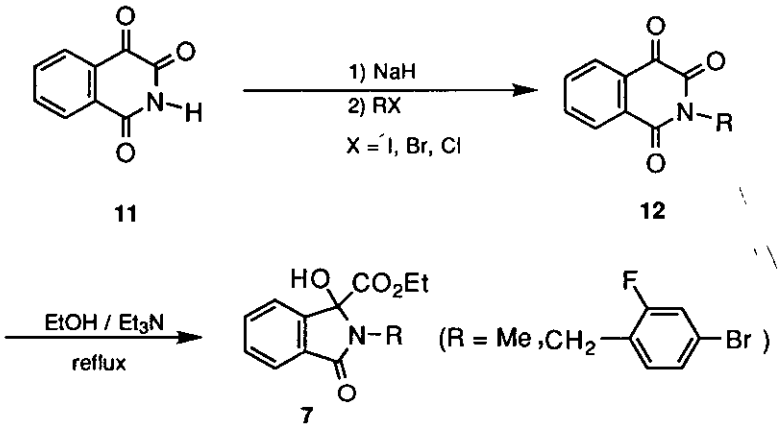
6 7

8, X = I
9, X = Br 10

Scheme I

with butyllithium than the *p*-bromobenzyl bromine due to inductive and chelation effects of the carboxamide group.[6] In fact, in most instances, the *o*-bromocarboxamide (**9**) provided the desired product (**10**) in yields similar to that seen for iodide (**8**). However, these reactions weren't always reproducible and there were occasions when significant amounts of byproducts, derived from metal-halogen exchange of the *p*-bromobenzyl halogen, also occurred.

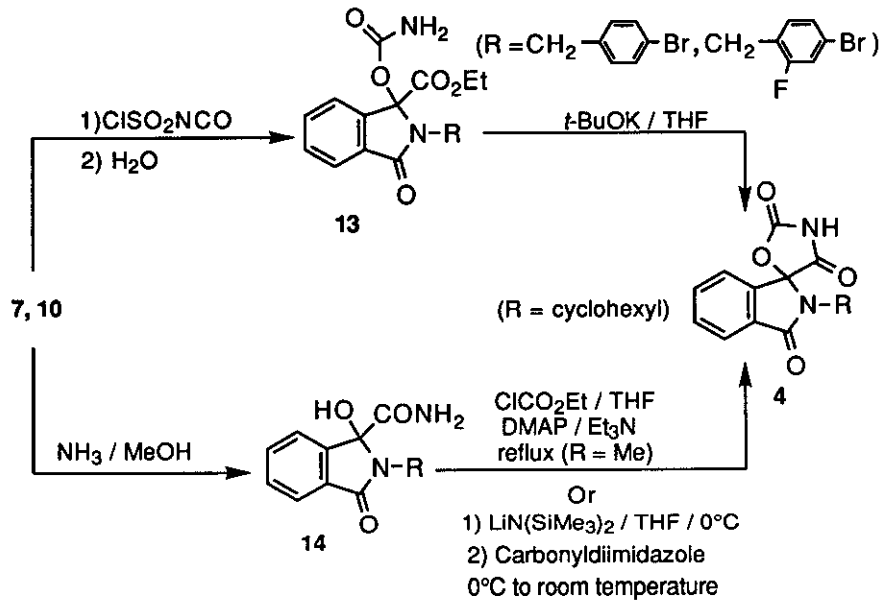
An alternate strategy for generating analogs of **7** that contain halobenzyl groups was developed in order to overcome the difficulties encountered using metal-halogen exchange (Scheme II). Peterson and Heitzer[7] had shown that the isoquinolin-1,3,4(2*H*)-trione (**11**) could undergo a facile rearrangement to the 1-hydroxy-1-carboethoxyisoindol-3-one (**7**) (R= H) in good yield upon reaction with triethylamine in ethanol at reflux temperatures. Indeed we found that various *N*-alkylated analogs of **11**, namely **12**, could also rearrange to *N*-alkylated analogs of **7** under the same conditions. The requisite starting material (**11**) and simple *N*-substituted derivatives of **12** could be prepared using established procedures.[7-10] In addition, we also found that N-substituted analogs of **12** could be directly synthesized from **11** *via* alkylation with an appropriate alkyl or aralkyl halide using sodium hydride as a base.



Scheme II

The construction of the spiro(oxazolidinedione) ring of **4** from **7** or **10** proved to be difficult using existing methods (Scheme III). For instance, one approach[11] involved formation of carbamate (**13**) from tertiary alcohol (**7**) or (**10**) using chlorosulfonyl isocyanate followed by potassium *t*-butoxide promoted cyclization. We found that reaction of this isocyanate with **7** or **10** proceeded smoothly to form the corresponding chlorosulfonylcarbamate. However upon aqueous workup to remove the chlorosulfonyl moiety, most of the desired carbamate (**13**) reverted to starting material, presumably through hydrolysis of a *N*-acyliminium ion intermediate.[12] The small amount of **13** that was obtained was cyclized successfully to **4**. However because of the problems in the first step, overall yields of **4** from **7** or **10** were low to moderate.

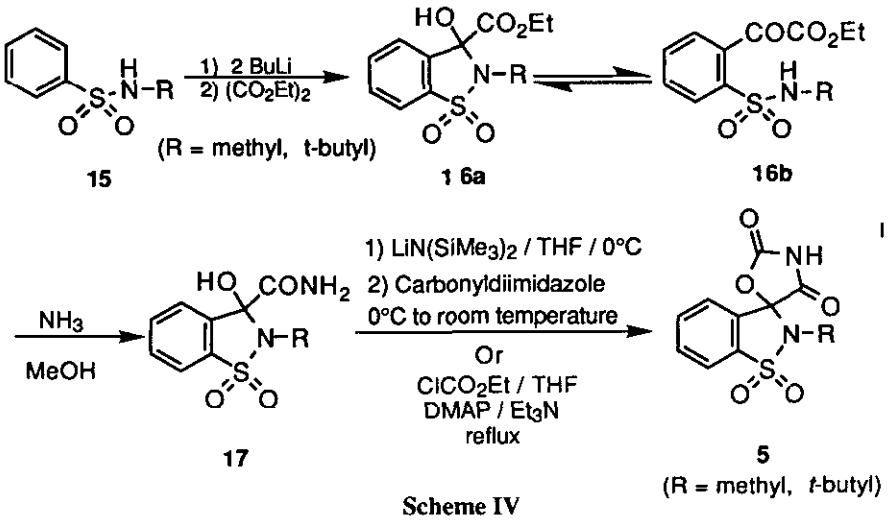
An alternate route to **4** proceeded *via* the primary carboxamide (**14**), which in turn was prepared from **7** under standard conditions (ammonia / MeOH). Treatment of **14** with ethyl chloroformate, triethylamine and DMAP in THF at reflux temperature led to oxazolidinedione (**4**) (R = Me), but again in low yields. Furthermore, these conditions failed totally when applied to more hindered substrates of **14**, such as R = isopropyl. We tried,



Scheme III

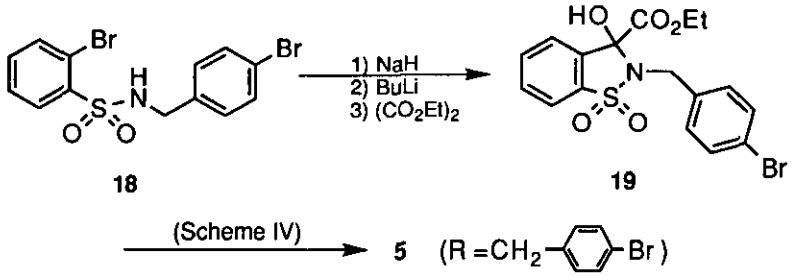
without success, other reagents to effect the transformation of **4** from **14**, including methyl cyanoformate / triethylamine, carbonyldiimidazole / DMAP, diethyl carbonate / KO*t*Bu. Resorting to conditions that were similar to one involved in the preparation of tetronic acids from α-hydroxyketones,[13] the amide (**14**) was treated with two equivalents of lithium bis(trimethylsilyl)amide in THF at 0°C, followed by excess carbonyldiimidazole and then warmed to room temperature. After workup and purification, the desired oxazolidinedione (**4**) (R = cyclohexyl) was obtained in 64% yield. This protocol was quite general and even analogs of **4** with bulky R groups such as *t*-butyl could be prepared in moderate to good yields.

Syntheses of Spiro[1, 2-benzisothiazole-3(2*H*), 5'-oxazolidine]-2', 4'-dione 1,1-Dioxides (5). Keeping in mind our efficient synthesis route to analogs of **4**, an obvious precursor for analogs of **5** would be the 3-hydroxy-3-carboxyethylbenzisothiazole derivative (**16**) (Scheme IV). Since simple secondary sulfonamides such as **15** underwent facile ortho-lithiation[14] they were attractive precursors for **16**. In fact various analogs of **15** could be treated with two or more equivalents of n-butyllithium at 0°C, cooled to -78°C and reacted with diethyl oxalate to provide the products **16** in good to excellent yield. Interestingly, ^{1}H nmr ($CDCl_3$) revealed that the solution structure of **16** varied with the size of the nitrogen R group. When R was small, such as a methyl moiety, compound (**16**) existed in the closed form (**16a**), which was characterized by a *N*-methyl singlet at δ 2.85, a sharp OH singlet at δ 4.74 and two doublets of quartets between δ 4.2 and 4.4 for the two hindered carboethoxy methylene protons. In contrast, when R was a *t*-butyl moiety, compound (**16**) existed in $CDCl_3$ solution in the open form (**16b**), which was characterized by a broad NH singlet at δ 5.00 and a two proton quartet at δ 4.40 for the unhindered carboethoxy methylene group. Other analogs of **16** showed equilibrium mixtures of open and closed forms. For instance **16**, R = isopropyl was a 4:1 mixture of closed (**16a**) and open (**16b**) forms.



Scheme IV

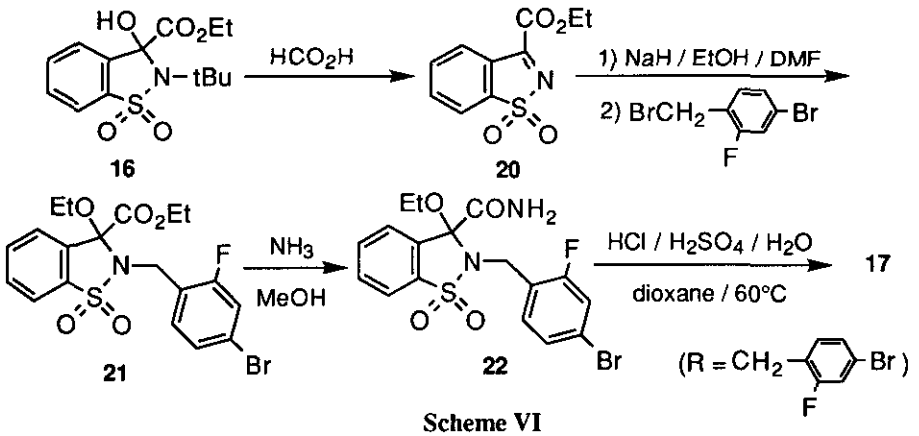
All analogs of **16** smoothly reacted with ammonia to produce the primary amide analogs (**17**). Then, using our preferred method, developed for analogs of **4**, (lithium bis(trimethylsilyl)amide followed by carbonyldiimidazole), **17** was converted to the target oxazolidinediones (**5**) in moderate to good yield, even in the case where R = *t*Bu. However, when R was a less sterically demanding group, the reagent combination ethyl chloroformate / DMAP / triethylamine could also be employed to prepare **5** from **17**, albeit in low yields. Although the procedures in Scheme IV, allowed us to readily access many analogs of **5**, the ortho-lithiation chemistry used in the production of **16** was not amenable to derivatives containing brominated or iodinated benzyl moieties on nitrogen. We therefore attempted a metal-halogen exchange procedure, similar to the one used in the synthesis of isoindolone congeners (**7**) and (**10**). Compound (**18**) (Scheme V) was prepared from 2-bromobenzenesulfonyl chloride and 4-bromobenzylamine and then reacted sequentially with sodium hydride, butyllithium and diethyl oxalate to produce the *p*-bromobenzyl containing analog (**19**) in 50% yield. Compound (**19**) could then be converted to **5** using the methods outlined in Scheme IV for analogs of **16**. Analogous to the isoindolone series, this protocol was not consistently reproducible and products from lithiation of the bromobenzyl moiety were obtained. Therefore we sought an additional route which did not involve ortho-lithiation or metal-halogen exchange.



Scheme V

In this regard, we envisioned that a derivative of **16a**, in which R is hydrogen, could be alkylated on the sulfonamide nitrogen with an appropriate benzyl bromide. A possible starting material for this alkylation precursor might be the *tert*-butyl derivative of **16** (R = *t*Bu). In fact, treatment of this latter compound with formic acid (Scheme VI) led to the formation of imino ester (**20**) in near quantitative yield via the formal loss of *t*-butyl alcohol. Next, **20** was reacted with one equivalent of sodium ethoxide in DMF. The ethoxide added to the carbon-nitrogen double bond of **20** to regenerate the tertiary oxygen function in the 3 position of the benzisothiazole ring. A sulfonamide anion was also generated in this process which was subsequently alkylated with 4-bromo-2-fluorobenzyl bromide to provide the desired adduct (**21**) in 68% yield after chromatographic purification. The primary amide (**22**) was then prepared by reaction of **21** with ammonia in methanol. Hydrolysis of **22** with aqueous acid proceeded *via* a *N*-acyliminium ion type intermediate[12] and led to formation of the tertiary-alcohol carboxamide (**17**) in 72% yield from **21**. The methods outlined in Scheme IV were then used to elaborate **17** (R = 4-bromo-2-fluorobenzyl) to the target spiro(oxazolidinedione) (**5**) (R = 4-bromo-2-fluorobenzyl).

The biological activity of derivatives of **4** and **5** closely paralleled their corresponding succinimide analogs.[1] For example, **4** (R = 4-bromobenzyl) and **5** (R = 4-bromo-2-fluorobenzyl) were approximately equipotent to **1** and **3** respectively with regard to their glucose lowering properties in insulin resistant mice. Also **4** (R = methyl) had very similar aldose reductase inhibitor activity (*in vitro*) to succinimide analog (**2**).



Scheme VI

EXPERIMENTAL

Melting points were determined on an Electrothermal capillary melting point apparatus and are not corrected. Proton magnetic resonance (^{1}H nmr) spectra were recorded at 200 MHz (Varian XL-200), 300 MHz (VXR-300), or at 400 MHz (Bruker AM-400 or VXR-400). Infrared spectra were obtained on either a Beckman Accu Lab 2 or a Perkin-Elmer model 781 spectrophotometer as KBr pellets, thin films on sodium chloride plates or as solutions in chloroform and are reported as reciprocal centimeters (cm^{-1}). Electron Impact (EI, IE = 70eV) and chemical ionization (CI, isobutane reagent gas) mass spectra were recorded on a Finnigan model 8230 spectrometer. Fast atom bombardment (FAB) were recorded on a Kratos ms50. Analyses (C, H, N) were carried out on a modified Perkin-Elmer model 240 CHN analyzer. Flash chromatography was carried out

according to the procedure of Still.[15] Thin layer analyses were done on E. Merck Silica Gel 60 F-254 plates of 0.25 mm thickness. Butyllithium (Aldrich, 2.5 N in hexanes) was titrated before use employing the phenylacetic acid method.[16] Diethyl oxalate (Aldrich) was fractionally distilled before use and stored under argon. Sodium hydride (Aldrich) was a 80% dispersion in mineral oil. Lithium bis(trimethylsilyl)amide (Aldrich) was a 1.0 N solution in hexanes. All other commercial reagents and solvents were used as received.

***N*-Cyclohexyl-2-bromobenzenecarboxamide (6, R = cyclohexyl).** Oxalyl chloride (2.40 ml, 27.4 mmol) was added dropwise to a suspension of 2-bromobenzoic acid (5.00 g, 24.9 mmol) and dimethylformamide (catalytic amount) in anhydrous methylene chloride (60 ml) at room temperature under a dry nitrogen atmosphere. Dissolution occurred within 10 min and the solution was stirred for 1 h. The solvent was removed and the amber oil was taken up in methylene chloride (50 ml) and added to a cold (0 to 5°C) solution of cyclohexylamine (3.13 ml, 27.4 mmol) and triethylamine (4.51 ml, 32.4 mmol) in anhydrous methylene chloride (50 ml) dropwise over a period of 40 min. The reaction mixture was stirred for 64 h, the solvent was removed, water (100 ml) was added to the residue and the resulting solid was filtered, washed with 0.5 N HCl (2 x 50 ml), water (50 ml), sat. aq. $NaHCO_3$ (2 x 50 ml), and water (50 ml). The white solid was dried to give the title compound (6.82 g, 97%): mp 126 - 127°C; nmr ($CDCl_3$, 200 MHz): δ 1.45 (m, 9H, CH_2), 2.05 (m, 2H, CH_2), 4.00 (m, 1H, NCH), 5.81 (br s, 1H, CONH), 7.28 (m, 2H, ArH), 7.53 (m, 2H, ArH); ir (KBr, cm^{-1}): 3280, 2930, 2850, 1640, 1530; ms (EI, m/z): 283 (7%), 282 (14%), 281 (44%), 202 (95%), 200 (95%), 185 (95%), 183 (100%), 157 (32%), 155 (32%); Anal. Calcd for $C_{13}H_{16}NOBr$: C, 55.33; H, 5.72; N, 4.96. Found: C, 55.46; H, 5.71; N, 4.79.

***N*-[(4-Bromophenyl)methyl]-2-bromobenzenecarboxamide (9).** Prepared from 2-bromobenzoic acid and 4-bromobenzylamine using the procedure for **6** (R = cyclohexyl) to provide the title compound as a white solid (78%): nmr ($CDCl_3$, 300MHz): δ 8.7-7.2 (m, 8H, ArH), 6.31 (m, 1H, NH), 4.60 (d, J = 8.0 Hz, CH_2); ms(CI): 2 Br present, 372 (MH+, 50%), 370 (MH+, 100%), 368 (MH+, 50%).

Ethyl 2-Cyclohexyl-2,3-dihydro-1-hydroxy-3-oxo-1*H*-isoindole-1-carboxylate (7, R = cyclohexyl). Sodium hydride (1.34 g, 44.6 mmol) was added to a solution of **6** (R = cyclohexyl, 6.28 g, 22.3 mmol) in anhydrous tetrahydrofuran (47 ml) at room temperature under a dry nitrogen atmosphere. The suspension was heated at 54°C for 1 h then cooled to -78°C. A solution of butyllithium (9.37 ml, 23.4 mmol) in hexanes was added over a period of 37 min. After stirring an additional 25 min, diethyl oxalate (15.2 ml, 111.5 mmol) was added. The reaction was stirred at -78°C for 2 min and then at ambient temperature for 14 min. It was then quenched quickly with 5% aq. HCl (110 ml) to pH 1. The reaction mixture was poured into water (400 ml) and the dark insoluble oil was extracted with ether (400 ml). The extract was dried with brine (100 ml) and silica gel (60 ml) was added. The solvent was removed and the adsorbate was flash chromatographed (80 / 20 petroleum ether / ethyl acetate) to provide the title compound (5.00 g, 74%): mp 94 - 95°C; nmr ($CDCl_3$, 200 MHz): δ 1.14 (t, J = 7 Hz, 3H, $COOCH_2CH_3$), 1.33 (m, 3H, CH_2), 1.95 (m, 7H, CH_2), 3.51 (m, 1H, NCH), 4.20 (m, 2H, $COOCH_2CH_3$), 4.63 (s, 1H, OH), 7.32 (m, 1H, ArH), 7.52 (septet, 2H, ArH), 7.75 (m, 1H, ArH); ir (KBr, cm^{-1}): 3220 broad band, 2960, 2935, 2850, 1750, 1685, 1670; ms(+CI, m/z): 304 (100%), 286 (15%), 216 (8%), 81 (14%), 79 (18%), 73 (43%); Anal. Calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.01; H, 6.91; N, 4.35.

Ethyl 2-[(4-Bromophenyl)methyl]-2,3-dihydro-1-hydroxy-3-oxo-1*H*-isoindole-1-carboxylic Acid (10). Compound (9) (6.02 g, 16.30 mmol) was added to a stirred, room temperature suspension of sodium hydride (0.98 g, 32.7 mmol) in dry THF (40 ml) under a dry N_2 atmosphere. After gas evolution subsided, the suspension was heated in a 55°C oil bath for 15 min. The reaction mixture was cooled to -78°C and butyllithium (6.63 ml, 16.30 mmol, 2.46 M solution in hexane) was added dropwise over a 30 min period. The reaction mixture was stirred an additional 30 min at -78°C and diethyl oxalate (11.0 ml, 81.5 mmol) was added. After 1 min at -78°C, the cold bath was removed and the reaction mixture was warmed to room temperature. After 15 min, the reaction mixture was cautiously quenched with 5% aqueous HCl (80 ml). The reaction mixture was added to water (400 ml) and extracted with ether (400 ml). The ether phase was washed with brine, dried ($MgSO_4$) and concentrated. The solid residue was recrystallized from toluene to provide 1.87 g of a white solid. The toluene mother liquor was flash chromatographed (gradient: 98:2 to 96:4 CH_2Cl_2 : MeCN) to provide an additional 1.93 g of a white solid. Total yield of the title compound 3.80 g (60%): mp 136-138°C; nmr ($CDCl_3$, 400 MHz): δ 7.85-7.89 (m, 1H, ArH), 7.53-7.60 (m, 2H, ArH), 7.37-7.43 (m, 3H, ArH), 7.26 (d, J = 8.4 Hz, 2H, ArH), 4.86 (d, J = 15.3 Hz, 1H, NCH_2), 4.36 (d, J = 15.3 Hz, 1H, NCH_2), 3.87 (dq, J = 7.2, 10.7 Hz, 1H, OCH_2), 3.53 (dq, J = 7.2, 10.7 Hz, 1H, OCH_2), 0.87 (t, J = 7.2 Hz, OCH_3); ir (KBr, cm^{-1}): 3400, 1750, 1690; ms(CI): 390 (100%, MH+), 392 (98%, MH+); Anal. Calcd for $C_{18}H_{16}NO_4Br$: C, 55.40; H, 4.13; N, 3.59. Found: C, 55.50; H, 4.27; N, 3.48.

2-[(4-Bromo-2-fluorophenyl)methyl]-1,3,4-trioxo-1,2,3,4-tetrahydroisoquinoline, (12, R = (4-bromo-2-fluorophenyl)methyl). Sodium hydride (0.68 g, 22.6 mmol) was added to a stirred, room temperature solution of 1,3,4-trioxo-1,2,3,4-tetrahydroisoquinoline (**11**[9], 3.05 g, 17.4 mmol) in dry DMF (21 ml) under a dry N_2 atmosphere. After 20 min, 4-bromo-2-fluorobenzyl bromide (4.66 g, 17.4 mmol) was added. After an additional 1 h 20 min the reaction mixture was quenched with saturated aqueous NH_4Cl (50 ml) and water was added to the mixture. The resulting solid was filtered from the reaction mixture, washed with water (80 ml) and then triturated with petroleum ether (3 X 30 ml) to provide the title compound as an off white solid (5.02 g, 80%): mp 158-161°C; nmr ($CDCl_3$, 300MHz): δ 8.34 (dd, J = 1.5, 8.0 Hz, 1H , ArH), 8.22 (dd, J = 1.5, 8.0 Hz, 1H, ArH), 7.88 (m, 2H, ArH), 7.24 (m, 3H, ArH), 5.27 (s, 2H, CH_2); ir (KBr, cm^{-1}): 1730, 1705, 1670; ms(EI, m/z): 363 (3.3%, M), 361 (4.0%, M), 336 (10%), 334 (10%), 189 (30%), 187 (30%), 160 (100%).

Ethyl 2,3-Dihydro-1-hydroxy-2-methyl-3-oxo-1H-isoindole-1-carboxylate (7, R = methyl). A stirred suspension of 2-methyl-1,3,4-trioxo-1,2,3,4-tetrahydroisoquinoline (**12**, R = methyl[9], 3.65 g, 19.3 mmol) and triethylamine (1.1 ml) in absolute ethanol (46 ml) was heated to reflux under a dry nitrogen atmosphere for 1 h. The ethanol was removed and the residue was partitioned between water and ethyl acetate. The ethyl acetate layer was separated and concentrated. The residual oil was treated with a petroleum ether / ether mixture to give a powdery solid which was collected by filtration. The solid was washed with petroleum ether and dried *in vacuo* to give the title compound as a red-brown solid (3.65 g, 80%): mp 75-77°C; nmr ($CDCl_3$, 200 MHz): δ 1.17 (t, 3H,J = 7 Hz, CH_2CH_3), 2.95 (s, 3H, NCH_3), 4.21 (m, 2H, CH_2CH_3), 4.64 (s, 1H, OH), 7.51 (m, 4H, ArH), 7.82 (m, 1H, ArH); ir (KBr, cm^{-1}): 3280, 1738, 1688; ms (EI, m/z): 235 (2%), 163 (45%), 162 (100%), 161 (16%), 133 (34%) 104 (24%), 77 (26%); Anal. Calcd for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.93. Found: C, 60.97; H, 5.51; N, 5.98.

Ethyl 2-[(4-Bromo-2-fluorophenyl)methyl]-2,3-dihydro-1-hydroxy-3-oxo-1*H*-isoindole-1-carboxylate (7, R = (4-bromo-2-fluorophenyl)methyl). A suspension of **12** (R = (4-bromo-2-fluorophenyl)methyl, 4.94 g, 13.6 mmol), triethylamine (0.78 ml) and absolute ethanol (32 ml) was heated to reflux temperatures for 10 min. The cooled reaction mixture was concentrated, treated with water (100 ml) and the solid residue was filtered. The solid was washed with water, triturated with ether (20 ml) and dried in vacuo to provide the title compound as a light green solid (4.70 g, 85%): nmr ($CDCl_3$, 300 mHz): δ 7.86 (m, 1H, ArH), 7.59 (m, 2H, ArH), 7.38 (m, 2H, ArH), 7.23 (m, 2H, ArH), 4.68 (dd, J = 7.5, 16.5 Hz, 2H, NCH_2), 3.95 (dq, J = 7.0, 10.5 Hz, OCH_2), 3.74 (dq, J = 7.0, 10.5, OCH_2), 0.95 (t, J = 7.0, CH_3).

2-[(4-Bromophenyl)methyl]spiro[1*H*-isoindole-1,5'-oxazolidine]-2',3(2*H*),4'-trione, (4, R = (4-bromophenyl)methyl). Chlorosulphonylisocyanate (0.3 ml, 3.45 mmol) was added to a stirred, 0 to 5°C solution of **10** (1.20 g, 3.07 mmol) in dry THF (15 ml) under a dry N_2 atmosphere. After 16 min, a solution of saturated aqueous sodium sulfite (7 ml) and a solution of saturated aqueous sodium bicarbonate (7 ml) were added simultaneously, the ice bath was removed and the reaction mixture was stirred for 12 min. After carefully acidifying with 10% aqueous HCl the reaction mixture was added to water (100 ml) and extracted with ethyl acetate (100 ml). The organic phase was washed with saturated aqueous sodium bicarbonate (100 ml), brine (100 ml), dried ($MgSO_4$) and concentrated to provide the title compound as an impure white solid (1.24 g) which contained the carbamate (**14**) (R = (4-bromophenyl)methyl). Potassium *tert*-butoxide (319 mg, 2.84 mmol) was added to a stirred 0 to 5°C solution of this solid in dry THF (10 ml) under a dry N_2 atmosphere. The reaction mixture was heated in a 50°C oil bath for 5 min, then cooled to 0 to 5°C and acidified with 10% HCl. This mixture was diluted with water (100 ml) and extracted with ethyl acetate (100 ml). The ethyl acetate phase was concentrated and ether (60 ml) was added. The ether phase was then partitioned with dilute aqueous sodium bicarbonate (60 ml). The bicarbonate phase was acidified with 10% aqueous HCl and extracted with ethyl acetate (100 ml). The ethyl acetate phase was washed with brine (100 ml) and silica gel (10 ml) was added to it. The mixture was concentrated and the adsorbate was flash chromatographed (9:1, ethyl acetate : isopropanol) to provide the title compound as a white solid [523 mg, 44% from **11**: mp 198-200°C; nmr (DMSO-d_6, 400 MHz): δ 12.90 (br s, 1H, NH), 7.89 (m, 2H, ArH), 7.75 (m, 2H, ArH), 7.51 (d, J = 8.3 Hz, 2H, ArH), 7.25 (d, J = 8.3 Hz, 2H, ArH), 4.70 (d, J = 16.0 Hz, 1H, CH_2), 4.54 (d, J = 16.0 Hz, 1H, CH_2); ir (KBr, cm^{-1}): 3440, 2750, 1890, 1840, 1760, 1710; ms (CI, m/z): 389 (10%, MH+), 387 (9%, MH+), 219 (24%) 179 (100%); Anal. Calcd for $C_{17}H_{11}N_2O_4Br$: C, 52.74; H, 2.86; N, 7.24. Found: C, 52.39; H, 3.10; N, 7.07.

2-[(4-Bromo-2-fluorophenyl)methyl]spiro[1*H*-isoindole-1,5'-oxazolidine]-2', 3(2*H*),4'-trione, (4, R = (4-bromo-2-fluorophenyl)methyl). Prepared from **7** (R = (4-bromo-2-fluorophenyl)methyl) using the procedure for **4** (R = (4-bromophenyl)methyl) to provide the title compound as a white solid (11%): mp 172-177°C (decomp.); nmr (DMSO-d_6, 400 MHz): δ 12.90 (br s, 1H NH), 7.95 (dd, J = 2.6, 8.7 Hz, 1H, ArH), 7.68 (m, 2H, ArH), 7.45 (dd, J = 2.9, 5.7 Hz, 1H, ArH), 7.38 (t, J = 8.0, 1H, ArH), 7.25 (m, 2H, ArH), 4.81 (d, J = 15.9 Hz, 1H, CH_2), 4.67 (d, J = 16.0 Hz, 1H, CH_2); ir (KBr, cm^{-1}): 3440, 2740, 1830, 1760, 1700; ms(+FAB): 407 (22%, MH+), 405 (21%, MH+), 232 (30%) 91 (100%); Anal. Calcd for $C_{17}H_{10}N_2O_4BrF$:C, 50.39; H, 2.49; N, 6.91. Found: C, 50.35; H, 2.55; N, 6.65.

2,3-Dihydro-1-hydroxy-2-methyl-3-oxo-1*H*-isoindole-1-carboxamide (14, R = methyl). Compound (**7**) (R = methyl, 3.15 g, 13.4 mmol] was added to a cold (0-5°C) saturated solution of ammonia in methanol (100

in a pressure bottle. The bottle was sealed and the mixture was stirred at room temperature for 3 h. The solvent was evaporated and the residue was taken up in methylene chloride and concentrated (to remove traces of methanol) o provide the title compound as a red solid (2.68 g, 97%): mp 223-228°C; nmr (DMSO-d_6, 200 MHz): δ 2.79 (s, 3H, NC$\underline{H}_3$), 7.23 (s, 1H, O$\underline{H}$), 7.58 (m, 5H, Ar$\underline{H}$ and N$\underline{H}$), 7.88 (s, 1H, N$\underline{H}$); ir (KBr, cm^{-1}): 3500-3000 broad band, 1680, 1650; ms (+FAB, m/z): 207 (0.6%, MH+), 163 (21%), 162(100%), 133 (34%), 105 (18%), 77 (27%).

2-Cyclohexyl-2,3-dihydro-1-hydroxy-3-oxo-1*H*-isoindole-1-carboxamide (14, R = cyclohexyl). Compound (7) (R = cyclohexyl, 4.90 g, 16.2 mmol) was added to a cold (5°C) saturated solution of ammonia in anhydrous methanol (125 ml) and was stirred at room temperature, in a sealed pressure bottle, for 21 h. The methanol was removed. The white solid product was triturated with ether (50 ml), petroleum ether (100 ml), and ether again (35 ml), and dried *in vacuo* at 40°C to give the title compound (4.00 g, 90%): mp 225-229°C; nmr (DMSO-d_6, 200 MHz): δ 1.25 (m, 3H, C$\underline{H}_2$), 1.70 (m, 5H, C$\underline{H}_2$), 2.05 (m, 2H, C$\underline{H}_2$), 3.31 (m, 1H, NC$\underline{H}$), 7.25 (s, 1H, O$\underline{H}$), 7.54 (m, 5H, Ar$\underline{H}$ and N$\underline{H}$), 7.85 (s, 1H, N$\underline{H}$); ir (KBr, cm^{-1}): 3420 broad band, 2930, 2850, 1685, 1670; ms (EI, m/z): 231 (5%), 230 (28%), 229 (2%), 149 (14%), 148 (73%), 130 (100%), 102 (32%), 77 (37%); Anal. Calcd for $C_{15}H_{18}N_2O_3$: C, 65.68; H, 6.61; N, 10.21. Found: C, 65.51; H, 6.58; N, 9.98.

2-Methylspiro[1*H*-isoindole-1,5'-oxazolidine]-2',3(2*H*),4'-trione, (4, R = methyl]. Ethyl chloroformate (1.27 ml, 13.0 mmol) was added dropwise over a 20 min period to a cold (0 to 5°C), mechanically stirred suspension of **14** (R = methyl, 2.50 g, 12.1 mmol), triethylamine (2.02 ml, 14.2 mmol), and 4-dimethylaminopyridine (0.30 g, 2.42 mmol) in anhydrous tetrahydrofuran (35 ml) under a dry nitrogen atmosphere. The reaction mixture was warmed slowly to 70°C and heated there for 2.5 h; then cooled in an ice bath and acidified with 10% HCl to pH = 1. It was then diluted with water (200 ml) and immediately extracted with ethyl acetate (1 x 200 ml, 1x80 ml).The extracts were combined and concentrated. The residue was partitioned between dilute aqueous $NaHCO_3$ (280 ml) and ether (200 ml). The ether layer was discarded. The solid material that was suspended in the aqueous phase was removed by filtration. A final extraction with ethyl acetate (80 ml) was performed before carefully acidifying the cold (0 to 5°C) aqueous phase with concentrated HCl. The resultant fine white solid was filtered, washed with water and dried *in vacuo* at 108°C to give the title compound (0.83 g, 29%): mp 280-312°C (decomp.); nmr (DMSO-d_6, 400 MHz): δ 2.90 (s, 3H, NC$\underline{H}_3$), 7.73 (m, 2H, Ar$\underline{H}$), 7.83 (m, 1H, Ar$\underline{H}$), 7.96 (m, 1H, Ar$\underline{H}$), 13.0 (br s, 1H, N$\underline{H}$); ir (KBr, cm^{-1}): 3600-3300 broad band, 3600-2800 broad band, 1835, 1755, 1700; ms (EI, m/z): 232 (42%), 161 (100%), 117 (77%), 104 (42%), 76 (50%); Anal. Calcd for $C_{11}H_8N_2O_4$: C, 56.90; H, 3.47; N, 12.06. Found: C, 56.77; H, 3.58; N, 11.68.

2-Cyclohexylspiro[1*H*-isoindole-1,5'-oxazolidine]-2', 3(2*H*),4'-trione, (4, R = cyclohexyl). Lithium bis(trimethylsilyl)amide (30.1 ml, 30.1 mmol) was added dropwise to a cold (0 to 5°C), mechanically stirred suspension of **14** (R = cyclohexyl, 3.93 g, 14.3 mmol) in anhydrous tetrahydrofuran (41 ml) over a 17 min period under a dry nitrogen atmosphere. During the addition, dissolution occurred and shortly thereafter a precipitate reformed. After stirring an additional 27 min at 0 to 5°C, a solution of 1,1'-carbonyldiimidazole (5.80 g, 35.8 mmol) in anhydrous tetrahydrofuran (101 ml) was added dropwise over a period of 9 min. After stirring an additional 20 min, the ice bath was removed and the reaction mixture was stirred at ambient temperature for 21 h. The reaction mixture was cooled to 0 to 5°C and 10% aq HCl (80 ml) was added. The reaction mixture was added to water (200 ml) and more 10% HCl (40 ml) was added. The organics were

extracted with ethyl acetate (300 ml) and the solvent was removed. A solution of saturated aqueous $NaHCO_3$ (190 ml) and water (100 ml) was added to the concentrate which was then partitioned with ether (200 ml). The layers were separated and the aqueous phase was washed with ether (200 ml). The aqueous phase was cooled in an ice bath and carefully acidified with concentrated HCl. The white solid precipitate was collected, washed well with water (100 ml), and petroleum ether (100 ml) and dried *in vacuo* at 80°C to give the title compound (2.73 g, 63%); nmr (DMSO-d_6, 400 MHz): δ 1.10 (m, 1H, CH_2). 1.30 (m, 2H, CH_2), 1.58 (m, 1H, CH_2), 1.67 (s, 4H, CH_2), 1.90 (m, 2H, CH_2), 3.47 (m, 1H, NCH), 7.71 (m, 2H, ArH), 7.78 (m, 1H, ArH), 7.85 (m, 1H, ArH), 13.2 (br s, 1H, NH); ir (KBr, cm^{-1}): 3450 broad band, 2940, 2725, 1830, 1765, 1690; ms (+FAB, m/z): 301 (30%, MH+), 217 (23%), 109 (23%), 91 (100%), 73 (41%), 57 (39%), 47 (30%); Anal. Calcd for $C_{16}H_{16}N_2O_4$: C, 63.99; H, 5.37; N, 9.33. Found: C, 63.92; H, 5.41; N, 9.27.

***N*-1,1-Dimethylethylbenzenesulfonamide (15, R = *t*Bu).** Benzenesulfonyl chloride (3.0 ml, 23.51 mmol) was added to a cold (0 to 5°C) solution of *tert*-butylamine (3.7 ml, 35.26 mmol), triethylamine (6.6 ml, 47.02 mmol), 4-dimethylaminopyridine (0.570 g, 4.70 mmol) and methylene chloride (22 ml) under a dry nitrogen atmosphere. After stirring for 2 h the methylene chloride was removed and the reaction mixture was partitioned between 2N HCl (120 ml) and ether (250 ml). The ether phase was washed with brine, dried over $MgSO_4$, concentrated, and dried *in vacuo* to give the title compound as a white solid, (4.61 g, 92 %): nmr ($CDCl_3$, 300 MHz): δ 1.23 (s, 9 H, $C(CH_3)_3$), 7.51 (m, 3H, ArH), 7.90 (m, 2H, ArH).

***N*-Methylbenzenesulfonamide (15, R = Me).** Benzenesulfonyl chloride (5.0 ml, 39.18 mmol) was added to a stirred, cold (0 to 5°C), diphasic mixture of aqueous methylamine (40% solution, 7.5 ml, 98 mmol), dimethylaminopyridine (0.96 g, 7.84 mmol) and methylene chloride (30 ml). After 35 min, more methylene chloride (40 ml) was added and the reaction mixture was washed with 10% aqueous HCl (3 x 30 ml). The methylene chloride phase was dried (MgSO4) and concentrated to provide the title compound as an oil, (6.01 g, 90%): nmr ($CDCl_3$, 300 MHz): δ 2.67 (d, 3H, J = 5.4 Hz, NCH_3), 4.40 (m, 1H, NH), 7.57 (m, 3H, ArH), 7.88 (d, 2H, J = 6.7 Hz, ArH).

Ethyl 2-[1,1-Dimethylethyl]-2,3-dihydro-3-hydroxy-1,2-benzisothiazole-3-carboxylate 1,1-Dioxide (16, R = *t* Bu). Butyllithium (16.14 ml, 40.36 mmol) was added dropwise over a 20 minute period to a cold (0 to 5°C), mechanically stirred solution of **15** (R = *t*Bu) (4.2 g, 19.69 mmol) in anhydrous tetrahydrofuran (118 ml) under a dry nitrogen atmosphere. After stirring an additional 25 min at 0 to 5°C a precipitate formed. The suspension was cooled further to -78°C and diethyl oxalate was added. The cooling bath was removed and the suspension was stirred at ambient temperature for 17 min and dissolution occurred. The reaction was quenched with 5% HCl (40 ml) and added to water (200 ml).The organics were extracted with ether (200 ml). The ether phase was washed with brine (200 ml) and silica gel (50 ml) was added. The solvent was removed and the adsorbate was flash chromatographed (7 : 3 petroleum ether : ethyl acetate) to give the title compound as an off white solid, (5.51 g, 89%): mp 93-95°C; nmr ($CDCl_3$, 300 MHz): δ 1.27 (s, 9H, $C(CH_3)_3$), 1.41 (t, 3H, J= 7.0 Hz, CH_2CH_3), 4.41 (d, 2H, J = 7.0 Hz, CH_2CH_3), 5.01 (s, 1H, SO_2NH), 7.64 (m, 3H, ArH), 8.03 (m, 1H, ArH); ir (KBr, cm^{-1}): 3400, 3285, 1735, 1705; ms (CI, m/z): 314 (18%), 258 (65%), 240 (100%), 241 (18%); Anal. Calcd for $C_{14}H_{19}NO_5S$: C, 53.66; H, 6.11; N, 4.47. Found: C, 53.75; H, 6.11; N, 4.34.

Ethyl 2,3-Dihydro-3-hydroxy-2-methyl-1,2-benzisothiazole-3-carboxylate 1,1-Dioxide (16, R = Me). Prepared from **15** (R = methyl) using the procedure for **16** (R = *t*-Bu) to provide the title compound as an off white solid (83%): mp 116-118°C; nmr ($CDCl_3$, 300 MHz): δ 1.23 (t, 3H, J = 7 Hz, CH_2CH_3), 2.85 (s, 3H,

NCH_3), 4.24 (dq, 1H. J = 10.7, 7.0 Hz, CH_2CH_3), 4.33 (dq, 1H, J = 10.7, 7.0 Hz, CH_2CH_3), 4.74 (s, 1H, OH), 7.50 (m, 1H, ArH), 7.68 (m, 2H, ArH), 7.87 (m, 1H, ArH): ms (CI, m/z): 272 (22%, MH+), 254 (100%), 226 (44%): Anal. Calcd for $C_{11}H_{13}NO_5S$: C, 48.70; H, 4.83; N, 5.16. Found: C, 48.49; H, 4.72; N, 5.01.

2-[1,1-Dimethylethyl]-2,3-dihydro-3-hydroxy-1,2-benzisothiazole-3-carboxamide 1,1-Dioxide (17, R = *t*-Bu). Ester (**16**) (R = *t*-Bu) (2.5 g, 7.98 mmol) was added to a saturated solution of ammonia in methanol in a pressure bottle. The bottle was sealed and stirred at 0°C for 25 min before warming to room temperature. After stirring one h the solvent was removed and the resulting solid was triturated with ether and filtered to give the title compound as an off white solid, (2.15 g, 95%): mp 139.5-140.5°C; nmr (DMSO-d_6, 300 MHz): δ 1.51 (s, 9H, $(CH_3)_3$), 7.68 (m, 6H, ArH and NH_2), 7.90 (s, 1H, OH); ir (KBr, cm^{-1}): 3420, 3310, 1685, 1595; ms (+FAB, m/z): 307 (70%, MNa+), 285 (20%, MH+), 229 (40%), 212 (100%); Anal. Calcd for $C_{12}H_{16}N_2O_4S$: C, 50.69; H, 5.67; N, 9.85. Found: C, 50.71; H, 5.66; N, 59.59.

2,3-Dihydro-3-hydroxy-2-methyl-1,2-benzisothiazole-3-carboxamide 1,1-Dioxide (17, R = methyl). Prepared from **16** (R = methyl) using the procedure for **17** (R = *t*-Bu) to provide the title compound as a white solid (96%): mp 215-216°C; nmr (DMSO-d_6, 300 MHz): δ 2.68 (s, 3H, NCH_3), 7.6-7.9 (m, 7 H, ArH, NH_2, OH); ms (CI, m/z): 243 (14%, MH+), 225 (100%), 198 (14%); Anal. Calcd for $C_9H_{10}N_2O_4S$: C, 44.62; H, 4.16; N, 11.56. Found: C, 44.46; H, 4.18; N, 11.36.

2-(1,1-Dimethylethyl)spiro[1,2-benzisothiazole-3(2*H*), 5'-oxazolidine]-2', 4'-dione 1,1-Dioxide (5, R = *t*Bu). Lithium bis(trimethylsilyl)amide (14.76 ml, 14.76 mmol) was added dropwise to a 0 to 5°C, mechanically stirred suspension of **17** (R = *t*Bu) (2.0 g, 7.03 mmol) in tetrahydrofuran (18 ml) over a 10 min period under a dry nitrogen atmosphere. Dissolution occurred. After stirring an additional 30 min at 0 to 5°C, a solution of carbonyldiimidazole (2.85 g, 17.58 mmol) in tetrahydrofuran (55 ml) was added dropwise over a 6 min period immediately giving a suspension which was stirred at room temperature for 17.5 h. The reaction mixture was cooled to 0 to 5°C and 10% HCl (45 ml) was added, the mixture was poured into water (120 ml) and more 10% HCl (20 ml) was added. The organics were extracted with ethyl acetate (200 ml) and the solvent was removed. Saturated aqueous $NaHCO_3$ (85 ml) and water (60 ml) were added to the concentrate which was then partitioned with ether (200 ml). The layers were separated and the aqueous phase was extracted with ether (2 x 100 ml). The aqueous phase was cooled in an ice bath and carefully acidified with concentrated HCl. The semisolid which precipitated was extracted with ethyl acetate (200 ml). The ethyl acetate phase was washed with brine, dried over $MgSO_4$ and concentrated to give a foamy solid (1.31 g, 60%). This solid was stirred as a suspension in petroleum ether (300 ml) for 45 h then filtered and dried *in vacuo* to give the title compound as a white solid (1.19 g, 55%): mp 135-136°C; nmr (DMSO-d_6, 400 MHz): δ 1.55 (s, 9H, $(CH_3)_3$), 7.86 (m, 3H, ArH), 8.05 (m, 1H, ArH), 13.25 (br s, 1H, NH); ir (KBr, cm^{-1}): 3250, 1835, 1775; ms (+FAB, m/z): 311 (5%, MH+), 255 (50%), 211 (27%), 157 (15%), 57 (90%); Anal. Calcd for $C_{13}H_{14}N_2O_5S$: C, 50.32; H, 4.55; N, 9.03. Found: C, 50.34; H, 4.53; N, 8.88.

2-Methylspiro[1,2-benzisothiazole-3(2*H*), 5'-oxazolidine]-2', 4'-dione 1,1-Dioxide (5, R = methyl). Prepared from **17** (R = methyl) using the procedure for **5** (R = *t*Bu) to provide the title compound as a white solid (92%): mp 290-300°C (decomp.); nmr (DMSO-d_6, 400 MHz): δ 2.84 (s, 3H, NCH_3), 7.89 (m, 2H, ArH), 8.02 (m, 1H, ArH), 8.15 (m, 1H, ArH), 7.89 (m, 2H, ArH),13.5 (br s ,1H, OH); ms (CI, m/z): 269 (100%, MH+); Anal. Calcd for $C_{10}H_8N_2O_5S$: C, 44.78; H, 3.01 N, 10.44. Found: C, 44.70; H, 2.92; N, 10.61.

***N*-[(4-Bromophenyl)methyl]-2-bromobenzenesulfonamide (18).** 2-Bromobenzenesulfonyl chloride (5.9 g, 23.5 mmol) was added dropwise to a stirred 0°C suspension of 2-bromobenzylamine hydrochloride (4.79 g, 19.6 mmol), pyridine (7.9 ml., 97.9 mmol) and 4-dimethylaminopyridine (0.23 g, 1.96 mmol) in dichloromethane (10 ml). The reaction mixture was then stirred at room temperature for 1h, then triethylamine (2.73 ml, 19.6 mmol) was then added at 0°C. After stirring overnight at room temperature, the reaction was diluted with dichloromethane (100 ml) then washed with water (50 ml), 0.5 N HCl (2 x 50 ml), water (50 ml), sat. aq. $NaHCO_3$ (2 x 50 ml) and water (50 ml). The dichloromethane solution was dried ($MgSO_4$) and silica gel (80 ml) was added. The solution was concentrated and the adsorbate was flash chromatographed (4:1 petroleum ether : ethyl acetate) to provide the title compound as a white solid (5.92 g, 75%): mp 108-110°C; nmr ($CDCl_3$, 300 MHz): δ 8.08 (m, 1H, ArH), 7.70 (m, 1H, ArH), 7.55-7.30 (m, 4H, ArH), 7.08 (d, 2H, J = 7.5 Hz, ArH), 5.42 (t, 1H, J = 8.1 Hz, NH), 4.07 (d, 2H, J = 8.1 Hz, CH_2); Anal. Cacld for $C_{13}H_{11}NO_2Br_2S$: C, 38.54; H, 2.74; N, 3.46. Found: C, 38.75; H, 2.64; N, 3.32.

Ethyl 2-[(4-Bromophenyl)methyl]-2,3-dihydro-3-hydroxy-1,2-benzisothiazole-3-carboxylate 1,1-Dioxide (19). Sodium hydride (0.44 g, 14.81 mmol) was added to a stirred, room temperature solution of **18** (5.0 g, 12.34 mmol) in tetrahydrofuran under a dry nitrogen atmosphere. After foaming subsided, the reaction mixture was heated in a 50°C oil bath for 5 min, then cooled to -78°C whereupon an additional amount of THF was added (45 ml). Butyllithium (5.0 ml, 12.34 mmol, 2.46 M solution in hexane) was added over a 25 min period. After an additional 20 min, diethyl oxalate (8.4 ml, 61.8 mmol) was added and the cold bath was removed. The reaction mixture was allowed to warm over a 25 min period, then quenched carefully with 5% HCl. The reaction mixture was then quickly added to water (400 ml) and extracted with ether (400 ml). The ether phase was washed with brine (200 ml) and silica gel (30 ml) was added. The reaction mixture was concentrated and the adsorbate was flash chromatographed (gradient, 4:1 to 7:3 to 3:2 to 1:1 petroleum ether : ethyl acetate) to provide the title compound as a white solid (2.61 g, 50%): mp 152-153°C; nmr ($CDCl_3$, 400 MHz): δ 7.90 (m, 1H, ArH), 7.68 (m, 2H, ArH), 7.46 (m, 2H, ArH), 7.36 (m, 3H, ArH), 4.90 (s, 1H, OH), 4.56 (d, 1H, J = 16.0 Hz, NCH_2), 4.35 (d, 1H, J = 16.0 Hz, NCH_2), 3.92 (dq, 1H, J = 10.6, 7.1 Hz, OCH_2), 3.70 (dq, 1H, J = 10.6, 7.1 Hz, OCH_2), 1.01 (t, 3H, J = 7.1 Hz, OCH_2CH_3); ir (KBr, cm^{-1}): 3440, 1725; ms (EI): 379, 381 (M-EtOH, 2%), 352, 354 (8%), 315, 317 (11%), 169, 171 (100%); Anal. Cacld for $C_{17}H_{16}NO_5BrS$: C, 52.74; H, 2.86; N, 7.24. Found: C, 52.39; H, 3.10; N, 7.07.

2-[(4-Bromophenyl)methyl]-2,3-dihydro-3-hydroxy-1,2-benzisothiazole-3-carboxamide 1,1-Dioxide (17, R = (4-Bromophenyl)methyl). This compound was prepared from **19** using the procedure for compound **17** (R = *t*Bu) to provide the title compound as a white solid (97%): mp 166-168°C; nmr (DMSO-d_6, 300 MHz): δ 7.90-7.30 (m, 10H, ArH, NH_2, OH), 4.40 (d, 1H, J = 16.1 Hz, NCH_2), 4.13 (d, 1H, J = 16.1 Hz, NCH_2); ir (KBr, cm^{-1}): 3470, 3230, 1695; ms (+FAB): 421, 423 (MNa+, 10%), 397, 399 (MH+, 10%), 381, 383 (20%).

2-[(4-Bromophenyl)methyl]spiro[1,2-benzisothiazole-3(2*H*), 5'-oxazolidine]-2', 4'-dione 1,1-Dioxide (5, R = (4-Bromophenyl)methyl). Ethyl chloroformate (0.31 ml, 3.24 mmol) was added dropwise to a 0°C, stirred suspension of **17** (R = (4-bromophenyl)methyl) (1.15 g, 2.90 mmol), triethylamine (0.49 ml, 3.48 mmol), dimethylaminopyridine (70 mg, 0.58 mmol) and tetrahydrofuran (7.5 ml). The resultant suspension was stirred at room temperature for 1.5 h then heated in a 70°C oil bath for 2.5 h. The suspension was then cooled in an ice bath and acidified with 10% HCl. Water (50 ml) and ethyl acetate (50 ml) were added and the layers were

shaken then separated. The ethyl acetate layer was concentrated then 5% aqueous $NaHCO_3$ (70 ml) and ether (70 ml) were added. The layers were separated and the $NaHCO_3$ layer was extracted with more ether (40 ml). The $NaHCO_3$ layer was cooled in an ice bath and carefully acidified with concentrated HCl. The resultant solid was filtered, washed with water and dried *in vacuo* to provide the title compound as a white solid (0.37 g, 30%): mp 220-260°C (decomp.); nmr (DMSO-d_6, 400 MHz): δ 13.10 (broad s, 1H, NH), 8.20 (m, 1H, ArH), 7.98 (m, 1H, ArH), 7.91 (m, 2H, ArH), 7.55 (m, 2H, ArH), 7.35 (m, 2H, ArH), 4.57 (d, 1H, J = 16.2 Hz, NCH_2), 4.52 (d, 1H, J = 16.2 Hz, NCH_2); ir (KBr, cm^{-1}): 3000-3700, 1835, 1770; ms (+FAB): 423, 425 (MH+, 10%), 169, 171 (30%); Anal. Calcd for $C_{16}H_{11}N_2O_5BrS$: C, 45.40; H, 2.62; N, 6.62. Found: C, 45.65 H, 2.64; N, 6.88.

Ethyl 1,2-Benzoisothiazole-3-carboxylate 1,1-Dioxide (20). Formic acid (25 ml) was added to **16** (R = t Bu) (2.45 g, 7.82 mmol) and the suspension was stirred at room temperature under a dry nitrogen atmosphere. After 5 min dissolution occurred. After 20 h the solution was concentrated and the resultant solid was dissolved in CH_2Cl_2 and concentrated (three times) to remove traces of formic acid. This afforded the title compound as a white solid (1.85 g, 98%). A small portion of this material was further purified by flash chromatography (7:3 petroleum ether: ethyl acetate): mp 114-115°C; nmr ($CDCl_3$, 300 MHz): δ 8.32 (dd, 1H, J = 1.1, 3.1 Hz, ArH), 7.96 (dd, 1H, J = 1.1, 3.1 Hz, ArH), 7.79 (m, 2H, ArH), 4.55 (q, 2H, J = 7.2 Hz , CH_2), 1.49 (t, 3H, J = 7.2 Hz , CH_3); ir (KBr, cm^{-1}): 1735, 1555; ms (EI, m/z): 239 (M, 3%), 195 (20%), 102 (100%); Anal. Calcd for $C_{10}H_9NO_4S$: C, 50.20; H, 3.79; N, 5.85. Found: C, 49.92 H, 3.84; N, 5.69.

Ethyl 2-[(4-Bromo-2-fluorophenyl)methyl]-2,3-dihydro-3-ethoxy-1,2-benzisothiazole-3-carboxylate 1,1-Dioxide (21). Sodium hydride (0.21 g, 7.02 mmol) was added to a stirred, room temperature solution of **20** (1.40 g, 5.85 mmol) and dry ethanol (0.38 ml, 6.44 mmol) in DMF (8 ml). An exotherm resulted and after 10 min, 4-bromo-2-fluorobenzyl bromide (1.72 g, 6.44 mmol) was added. After 2 h, the reaction mixture was added to an aqueous solution consisting of 10% aq. HCl (25 ml) and water (125 ml). This was extracted with ether (150 ml) and the ether extract was washed with brine (150 ml) and silica gel (25 ml) was added to it. The ether was removed and the silica adsorbate was flash chromatographed (7:3 petroleum ether : ethyl acetate) to provide the title compound as an oil (1.89 g, 68%): nmr ($CDCl_3$, 300 MHz): δ 7.89 (m, 1H, ArH), 7.70 (m, 2H, ArH), 7.55 (m, 2H, ArH), 7.26 (m, 2H, ArH), 4.60 (d, 1H, J = 16.7 Hz, NCH_2), 4.50 (d, 1H, J = 16.7 Hz, NCH_2), 4.05 (m, 2H, CO_2CH_2), 3.22 (m, 1H, OCH_2), 2.94 (m, 1H, OCH_2), 1.11 (t, 3H, J = 7.3 Hz, CH_3), 1.05 (t, 3H, J = 7.3 Hz, CH_3); ir (neat, cm^{-1}): 1750; ms (+FAB): 472, 474 (MH+, 5%), 426, 428 (35%), 187, 189 (100%).

2-[(4-Bromo-2-fluorophenyl)methyl]-2,3-dihydro-3-ethoxy-1,2-benzisothiazole-3-carboxamide 1,1-Dioxide (22). Compound **21** (1.89 g, 4.00 mmol) was added to a saturated solution of ammonia in methanol at 0°C . This solution was stirred at room temperature for 4 h then the solvent was removed and the resulting solid was dissolved in CH_2Cl_2 and concentrated to remove traces of methanol to give the title compound as a white solid, (1.77 g, 100%): mp 175-177°C; nmr (DMSO-d_6, 300 MHz): δ 8.00-7.40 (m, 9H, ArH, NH_2), 4.51 (d, 1H, J = 16.1 Hz, NCH_2), 4.23 (d, 1H, J = 16.1 Hz, NCH_2), 3.01 (m, 1H, OCH_2), 2.82 (m, 1H, OCH_2), 0.84 (t, 3H, J = 7.2 Hz, CH_3); ir (KBr, cm^{-1}): 1710; ms (+FAB): 465, 466 (MNa+, 25%), 399, 401 (15%), 187, 189 (100%). Anal. Calcd for $C_{17}H_{16}N_2O_4BrFS$: C, 46.06; H, 3.64; N, 6.32. Found: C, 46.03 H, 3.65; N, 6.22.

2-[(4-Bromo-2-fluorophenyl)methyl]-2,3-dihydro-3-hydroxy-1,2-benzisothiazole-3-carboxamide 1,1-Dioxide (17, R = (4-Bromo-2-fluorophenyl)methyl). A mixture of **22** (1.73 g, 3.90 mmol), 1,4-dioxane (15 ml), 10% aq. HCl (5 ml) and conc. H_2SO_4 (1 ml) were heated with stirring in a 60°C oil bath for 5 h. The mixture was cooled to room temperature and added to water (200 ml). The water phase was extracted with ethyl acetate (200 ml) and these extracts were washed with sat. aq. $NaHCO_3$ (4 x 100 ml), dried ($MgSO_4$) and concentrated to provide the title compound as a white solid (1.16 g, 72%): mp 182-184°C: nmr (DMSO-d_6, 300 MHz): δ 8.0-7.3 (m, 10H, ArH, OH, NH_2), 4.54 (d, 1H, J = 16.7 Hz, NCH_2), 4.24 (d, 1H, J = 16.7 Hz, NCH_2); ir (KBr, cm^{-1}): 3450, 3340, 1695; ms (+FAB): 437, 439 (MNa+, 10%), 415, 417 (MH+, 5%), 399, 401 (10%); Anal. Calcd for $C_{15}H_{10}N_2O_4BrFS$: C, 43.49; H, 2.91 N, 6.75. Found: C, 43.33 H, 2.91; N, 6.36.

2-[(4-Bromo-2-fluorophenyl)methyl]spiro[1,2-benzisothiazole-3(2*H*), 5'-oxazolidine]-2', 4'-dione 1,1-Dioxide (5, R = (4-Bromo-2-fluorophenyl)methyl). Prepared from **17** (R = (4-bromo-2-fluorophenyl)methyl according to the procedure for **5** (R = *t*Bu) to provide the title compound as a white solid (70%): mp 269-270°C (decomp.); nmr (DMSO-d_6, 400 MHz): δ 13.05 (br s, 1H, NH), 8.19 (m, 1H, ArH), 7.96 (m, 1H, ArH), 7.91 (m, 2H, ArH), 7.57 (dd, 1H,, J = 1.8, 9.8 Hz, ArH), 7.45 (dd, 1H, J = 1.8, 8.3 Hz, ArH), 7.38 (t, 1H, J = 8.3 Hz, ArH), 4.58 (d, 1H, J = 15.6 Hz, NCH_2), 4.53 (d, 1H, J = 15.6 Hz, NCH_2); ir (KBr, cm^{-1}): 3150-3600, 1830, 1765; ms (+FAB): 463, 465 (MNa+, 10%), 441, 443 (MH+, 10%); Anal. Cacld for $C_{16}H_{10}N_2O_5BrFS$: C, 43.55; H, 2.29; N, 6.35. Found: C, 43.42 H, 2.43; N, 6.15.

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