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5-Bromobarbituric Acid : A Mild and Selective Monobrominating Agent Employed in the Synthesis of the Gastrin Antagonist GR174152

Robert Bright [a] , Steven J. Coote [a] , Stephen Freeman [a] , Doug Hayes [a] , Gordon Smith [a] & David Tapolczay [a]

[a] Process Research Department , Glaxo Wellcome Medicines Research Centre , Gunnels Wood Road STEVENAGE, Herts SG1 2NY

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5-BROMOBARBITURIC ACID : A MILD AND SELECTIVE MONOBROMINATING AGENT EMPLOYED IN THE SYNTHESIS OF THE GASTRIN ANTAGONIST GR174152

Robert Bright, Steven J Coote*, Stephen Freeman, Doug Hayes, Gordon Smith and David Tapolczay

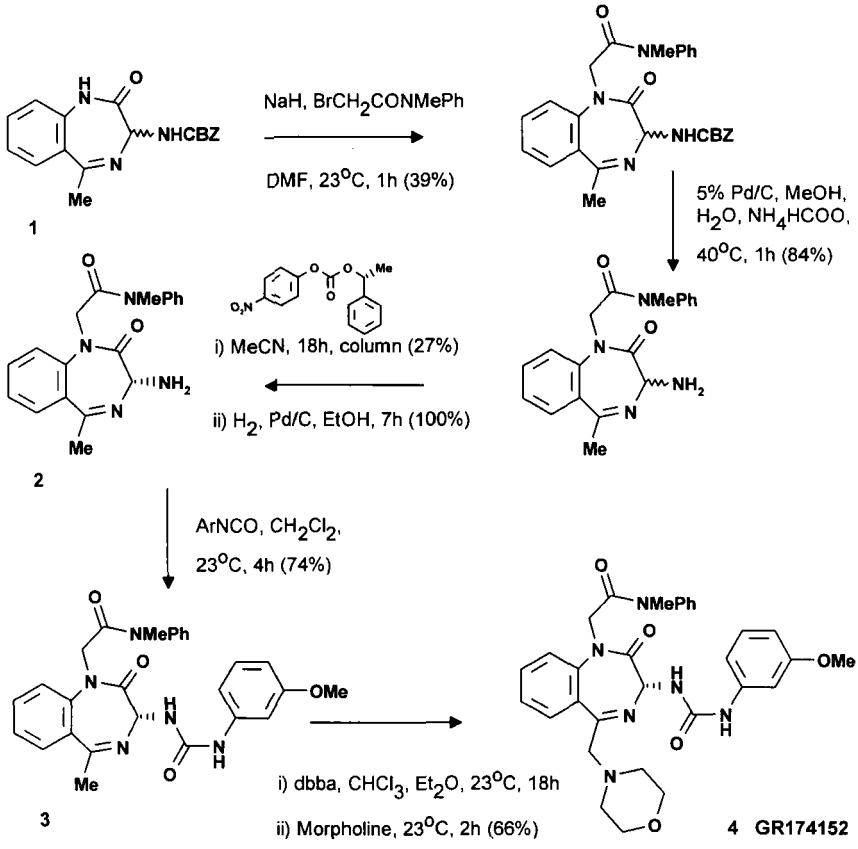
Process Research Department
GlaxoWellcome Medicines Research Centre
Gunnels Wood Road
STEVENAGE, Herts
SG1 2NY

5-Bromobarbituric acid (**5**) is a convenient reagent for the selective bromination of cyclic imine **3**. A facile, *in situ* synthesis of this reagent involving a disproportionation reaction between barbituric acid and dibromobarbituric acid is described.

The Gastrin antagonist GR174152[1] is a powerful suppressor of gastric acid secretion that may find use in the treatment of gastro-oesopheageal reflux disease (GORD). Our previously disclosed synthetic route[1] to this compound employs racemic 5-methyl-1,4-benzodiazepine **1** as a key intermediate[2] , the details of which are summarised below (scheme 1).

*To whom correspondence should be addressed

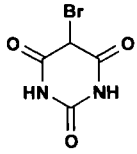
Scheme 1



The inefficient resolution procedure[3] to provide chiral amine **2** (requiring chromatographic separation of diastereoisomers), in addition to a relatively poor yield in the final bromination of the benzylic methyl group of cyclic imine **3**, prompted us to explore alternative routes to GR174152 that could be scaled up. In particular, we wished to focus upon the final bromination reaction and subsequent alkylation with morpholine which at best gave yields of approximately 60% for the overall conversion of **3** to **4**. In addition, our previously reported procedure[1] requires the use of large quantities of chloroform

as reaction solvent which, for environmental reasons, we wished to replace. We therefore chose to investigate this reaction more fully with a range of alternative brominating agents.

As a consequence of these investigations we wish to report the utility of monobromobarbituric acid **5** (mbba) as a more selective brominating agent of cyclic imine **3**. The suitability of this reagent for the bromination of other functionality is currently under investigation.

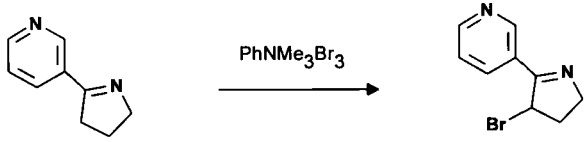


5

Results

Typical reagents that have been employed for the alpha bromination of ketones have also be utilised for the alpha bromination of imines. For example, phenyltrimethyl ammonium tribromide has been used to brominate cyclic imine **6**[4] (scheme 2) whilst NBS/AIBN has been used for bromination alpha to O-silylated oximes[5]

Scheme 2

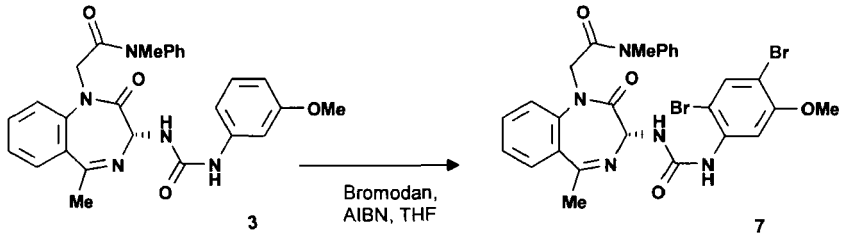


6

Attempted bromination of cyclic imine **3** under radical conditions (1,3-dibromo-5,5-dimethylhydantoin (bromodan)[6] or N-bromosuccinimide, AIBN,

THF), gave only aromatic ring bromination, presumably as a consequence of the presence of the activating methoxyl substituent to give dibromo derivative **7** (scheme 3). Use of pyridinium tribromide[7], phenyl trimethylammonium tribromide[8] or elemental bromine[9], all gave mixtures of polybrominated products.

Scheme 3

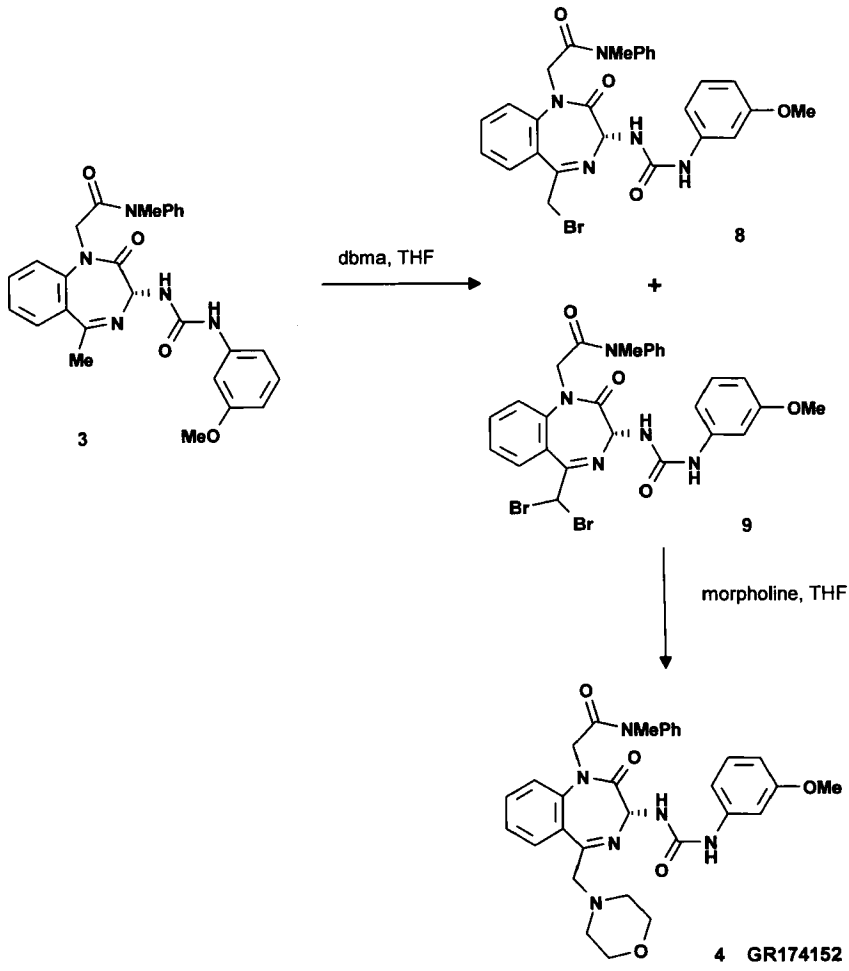


3 7

A report detailing the use of dibromo-Meldrum's acid (dbma) for the selective bromination of ketones[10] prompted us to investigate the use of this reagent for the bromination of cyclic imine **3**. Readily synthesised by direct bromination of Meldrum's acid with bromine[11] (65%th), this reagent gave bromination of the benzylic methyl group using THF as an alternative solvent. However, over bromination to give the benzylically dibrominated product **9** again proved to be a problem, as previously observed with our use of dibromobarbituric acid (dbba) **10** (scheme 4).

Having established that previously reported reagents employed for the alpha bromination of imines offered little or no advantage over the use of dbba (**10**), we elected to more fully investigate the original bromination reaction employing dbba (**10**). Reaction monitoring by hplc allowed us to quantify the progress of the bromination reaction with time, which revealed that relatively poor selectivity for the monobrominated derivative **8**[12] was achieved at early

Scheme 4



reaction times. However, as the reaction progressed, we observed that the ratio of **8** to **9** progressively improved with time until all of the brominating agent had been consumed, leaving approximately equal amounts of starting material **3** and dibrominated adduct **9** (Table 1).

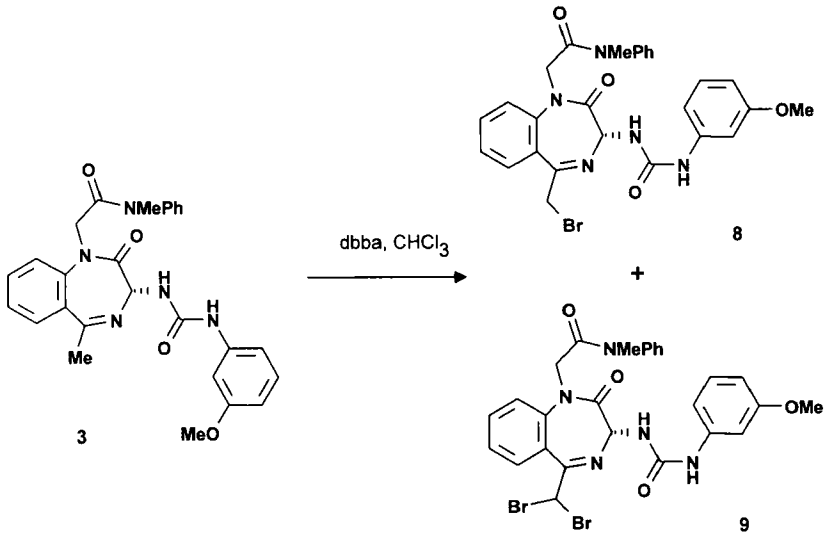


Table 1

Bromination of cyclic imine **3** with dbba (**10**) monitored by hplc

reaction time (h)	%SM (**3**)	%monobromo (**8**)	%dibromo (**9**)	ratio (**8**:**9**)
1	49.7	35.1	15.2	2.31:1
2	37.8	46.1	16.1	2.86:1
4	21.8	57.9	20.3	2.85:1
6	19.0	60.7	20.3	2.99:1
23	18.6	62.2	19.2	3.24:1

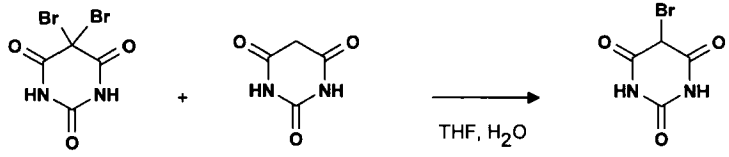
We were intrigued by the observation that the ratio of desired **8** to unwanted **9** improved as the reaction progressed. As only 0.5 moles of dbba (**10**) were present in the reaction mixture and more than 50% of desired monobrominated product (**8**) had been formed, we reasoned that monobromobarbituric acid (mbba)[13] (**5**) was likely to be formed as an intermediate in the reaction and that this compound itself was also likely to

function as a brominating agent[10,14]. Furthermore, we considered that mbba might be a more selective reagent (relative to dbba) for the bromination of the starting material in preference to bromination of the monobrominated product (**8**), thereby accounting for the improved selectivity observed in the bromination reaction with time.

To test this hypothesis we synthesised monobromobarbituric acid (**5**) by selective monobromination of barbituric acid (**11**) with bromine in water as previously reported[15]. However, in our hands (and those of others[16]) this method was not particularly efficient giving lower than expected yields of impure mbba (**5**).

As an alternative method, we investigated mono-debromination reactions of dbba (**10**), examples of which have been described in the literature[17]. During these investigations, we observed that an equimolar mixture of dbba (**10**) and barbituric acid (**11**) in aqueous THF underwent a disproportionation reaction at room temperature within 30 minutes to give mbba (**5**) (as judged by hplc) (scheme 5).

Scheme 5



10 **11** **5**

In support of our hypothesis, we were pleased to observe that direct bromination of cyclic imine **3** with mbba (**5**) in chloroform was considerably more selective in favour of the monobrominated product **8** (53:1). However, this reaction proved to be much slower at room temperature (70% complete after 48h)

than that employing dbba (**10**). In addition, environmental concerns over the use of chloroform on large scale prompted us to investigate the use of an alternative solvent.

Our new method for the generation of mbba (**5**) rendered THF an obvious choice of alternative solvent. Thus, disproportionation of equimolar amounts of barbituric acid (**11**) and dbba (**10**) in aqueous THF gave *in situ* generation of mbba (**5**) which was used to brominate cyclic imine **3** at 20-25°C. A single equivalent of mbba (**5**) did not prove sufficient to fully consume all of the starting material within 24h. Increasing the amount of brominating agent allowed more consumption of starting material within the same period of time, but at the expense of a compromise in selectivity. This selectivity could be improved by reducing the temperature of the reaction, but now at the expense of reducing the extent of reaction. As a compromise, we found that use of 1.2 equivalents of mbba (**5**) at room temperature left <2% of unreacted starting material (**3**) after 19h (Table 2). Subsequent displacement with morpholine followed by an acid/base extractive workup avoided the need for chromatographic purification and completed the synthesis of GR174152. Using these revised procedures we have now improved the yield for the conversion of cyclic imine **3** to the Gastrin antagonist GR174152 (**4**) to 82%.

Table 2

Bromination of cyclic imine **3** with mbba (**10**) (generated *in situ*)

reaction time (h)	%SM (**3**)	%monobromo (**8**)	%dibromo (**9**)	ratio (**8**:**9**)
3	10.0	81.3	8.7	9.3
19	1.9	88.4	9.7	9.1

5-Methyl-[18] and 5-isopropyl-[18,19] 5-bromobarbituric acids were prepared via direct bromination of the corresponding 5-alkyl barbituric acid with bromine

and their potential as alternative brominating agents of cyclic imine **3** was assessed. Although a high degree of selectivity for the monobrominated product **8** was obtained in both cases, a significant decrease in the rate of reaction was observed. Attempts at making the reaction catalytic in barbituric acid by slow addition of bromine to a mixture of cyclic imine **3** and barbituric acid (**11**) failed to give any of the desired benzylically brominated adduct (**8**).

The reasons for the apparent improvement in selectivity in the bromination of the benzylic methyl group of cyclic imine **3** offered by the use of monobromobarbituric acid (**5**) are not immediately clear to us. It appears likely that the significant difference in acidity between mbba (**5**) (pKa 0.26[20]) and dbba (**10**) (pKa 5.68[21]) may play a significant role in determining the selectivity of the bromination reaction in that these brominating agents will be ionised to differing extents by virtue of the imine nitrogen present in the substrate.

In conclusion, we have demonstrated an efficient and straightforward *in situ* synthesis of monobromobarbituric acid (**5**) involving a disproportionation reaction between equimolar amounts of dibromobarbituric acid (**10**) and barbituric acid (**11**). Monobromobarbituric acid (**5**) monobrominates cyclic imine **3** with a high degree of selectivity and in high yield, which offers a significant improvement over the use of dibromobarbituric acid (**10**). Other brominating agents appear to be less selective in achieving this transformation.

Further studies are underway to explore the range of functionality that may be selectively brominated using monobromobarbituric acid.

Experimental

(+)-2-{3-[3-(3-Methoxy-phenyl)-ureido]-5-morpholin-4-ylmethyl-2-oxo-2,3-dihydro-benzo[e][1,4]diazepin-1-yl}-N-methyl-N-phenyl-acetamide (GR

174152) (4) employing dibromobarbituric acid (10) as brominating agent[1]

A solution of 2-{3-[3-(3-Methoxy-phenyl)-ureido]-5-methyl-2-oxo-2,3-dihydro-benzo[e][1,4]diazepin-1-yl}-N-methyl-N-phenyl-acetamide (**3**) (cyclic imine) (189mg, 389μmol) in chloroform (8ml) and diethyl ether (3ml) was treated with 5,5-dibromobarbituric acid (**10**) (56mg, 196μmol) and the mixture was stirred at 23°C under nitrogen in the dark for 18h. Morpholine (68mg, 781μmol) was added and the mixture was stirred for a further 2h under nitrogen at 23°C. The reaction mixture was partitioned between ethyl acetate and phophate buffer (pH6.5) and the separated organic phase was dried (Na_2SO_4). Evaporation gave a residue that was purified by column chromatography eluting with ethyl acetate and then methanol-dichloromethane (1:20) to give the *title compound* as a white solid (147mg, 66%).

^{1}H NMR ($CDCl_3$) (400Mhz) : 2.51 (4H, m); 3.26 (3H, s); 3.51 (1H, d, J=13.9Hz); 3.61 (5H, m); 3.71 (3H, s); 4.27 (2H, q, J=16.9Hz); 5.49 (1H, d, J=8.2Hz); 6.54 (1H, dd, J=8.1Hz, J=2.6Hz); 6.76 (1H, dd, J=8.1Hz, J=1.1Hz); 6.99 (1H, d, J=8.1Hz); 7.09 (2H, s + t); 7.28 (5H, m); 7.41 (2H, m); 7.49 (1H, t, J=7.4Hz); 7.90 (1H, dd, J=8.1Hz, J=1.1Hz). TLC : Rf 0.35 (1:20, MeOH-DCM). IR (nujol mull) 3339; 1668; 1598; 1549; 1290; 1203; 1156; 1115; 771; 703cm^{-1}. MP 164-6°C decomp.

2-{3-[3-(4,6-Dibromo-3-methoxy-phenyl)-ureido]-5-morpholin-4-ylmethyl-2-oxo-2,3-dihydro-benzo[e][1,4]diazepin-1-yl}-N-methyl-N-phenyl-acetamide (7)

A solution of 2-{3-[3-(3-Methoxy-phenyl)-ureido]-5-methyl-2-oxo-2,3-dihydro-benzo[e][1,4]diazepin-1-yl}-N-methyl-N-phenyl-acetamide (**3**) (cyclic imine) (300mg, 620μmol) in anhydrous tetrahydrofuran (15ml) was treated with AIBN (5mg) and bromodan (95mg, 325μmol). The mixture was heated at reflux rapidly discharging the initial pale orange colouration. Upon cooling, tlc indicated approx 50% consumption of the starting material. Further portions of AIBN (5mg) and bromodan (95mg, 325μmol) were added and the mixture was

again heated to reflux. As previously observed, the initial pale orange colouration was rapidly discharged. Tlc indicated complete consumption of starting material. The reaction mixture was evaporated to a foam and purified by column chromatography eluting with ethyl acetate to give the *title compound* as a white solid (130mg, 33%).

^{1}H NMR (DMSO-d_6) (400Mhz) : 2.39 (3H, s); 3.18 (3H, s); 3.72 (3H, s); 4.29 (2H, s); 5.11 (1H, d, J=7.4Hz); 7.36 (1h, t,J=7.8Hz); 7.46 (6H, m); 7.60 (1H, t,J=7.8Hz); 7.73 (1H, s); 7.75 (1H, d, J=7.7Hz); 7.89 (1H, s); 8.50 (1H, s). ^{13}C NMR (DMSO-d_6) : 24.8; 25.1; 37.3; 50.3; 56.3; 67.4; 102.5; 103.3; 105.5; 122.7; 125.3; 127.3; 128.2; 130.0; 130.7; 131.7; 134.7; 138.4; 140.3; 142.7; 154.2; 154.9; 156.1; 166.8; 179.3. Mass spectrum : MH^+ = 642 (splitting pattern indicates the presence of two bromine atoms)

Dibromo-Meldrum's acid[11]

A solution of Meldrum's acid (14.4g, 100mmol) in 2M sodium hydroxide solution (100ml) was cooled to *ca* 5°C and treated with bromine (32.0g, 10.3mmol) over a period of 10 minutes giving an increase in temperature of approx 15°C. The resultant yellow granular solid was stirred at 0-5°C for a further 30 minutes and the slurry was filtered and washed with cold (5°C) water (2x30ml). The crude product was dissolved in dichloromethane (200ml) and washed with water. The organic phase was dried ($MgSO_4$) and evaporated to leave the *title compound* as an oil that crystallised upon standing (19.75g, 65%).

(+)-2-{3-[3-(3-Methoxy-phenyl)-ureido]-5-morpholin-4-ylmethyl-2-oxo-2,3-dihydro-benzo[e][1,4]diazepin-1-yl}-N-methyl-N-phenyl-acetamide (GR 174152) (4) employing dibromo-Meldrum's acid as brominating agent

A solution of 2-{3-[3-(3-Methoxy-phenyl)-ureido]-5-methyl-2-oxo-2,3-dihydro-benzo[e][1,4]diazepin-1-yl}-N-methyl-N-phenyl-acetamide (**3**) (cyclic imine) (1.69g, 3.48mmol) in anhydrous THF (75ml) was treated with dibromo-

Meldrum's acid (552mg, 1.83mmol) and the solution was stirred at 20-25°C under nitrogen for 21h. Morpholine (0.61ml, 7.0mmol) was added to the reaction mixture and stirring was continued at 20-25°C overnight giving precipitation of what was believed to be morpholine hydrobromide (the prolonged reaction time was employed for convenience, the reaction being essentially complete within 2 hours of morpholine addition). The reaction mixture was evaporated to dryness to leave a yellow foam that was purified by column chromatography eluting with a mixture of methanol and ethyl acetate (1:50) to give the *title compound* as a white solid (1.40g, 70%).

5,5-Dibromobarbituric acid (9)[14, 15]

A suspension of barbituric acid (**11**) (375g, 2.93mol) in water (938ml) at 20-25°C was treated dropwise with bromine (936g, 5.86mol) over a period of 70 minutes giving a slight exotherm. At the end of the addition the orange/yellow colouration persisted. The reaction mixture was stirred for a further 2.5h whilst cooling to *ca* 5°C. The precipitated solid was collected by filtration, washed with cold (5°C) water and dried in vacuo at 40°C to give the *title compound* as an amorphous white powder (743g, 89%).

IR (nujol mull) 3309; 3195; 1769; 1754; 1735; 1715; 1698cm^{-1}. Water content by Karl; Fischer analysis : 0.2% H_2O. Analysis : Found : C, 16.9; H, 0.7; N, 9.9; Br, 55.4. $C_4H_2N_2O_3Br_2$ requires : C, 16.8; H, 0.7; N, 9.8; Br, 55.9%. MP 235°C (decomp.) (lit[22] 234°C).

5-Bromobarbituric acid (5)[15]

A suspension of barbituric acid (5.0g, 39mmol) in water (75ml) was heated to 50-54°C and treated dropwise with bromine (1.6ml, 31.0mmol). After complete addition, the suspension was cooled to <5°C and the resultant solid was collected by filtration, washed with water (2 x 10ml) and dried in vacuo at 40°C to give the *title compound* as a white amorphous solid (4.94g, 61%).

Analysis : Found : C, 25.1; H, 1.2; N, 14.6; Br, 34.8. $C_4H_3N_2O_3Br$ requires : C, 23.2; H, 1.5; N, 13.5; Br, 38.6%. MP 214°C (lit[15] 212-215°C).

***In situ* generation of 5-bromobarbituric acid (5)**

A slurry of dibromobarbituric acid (**10**) (2.86g, 10.0mmol) and barbituric acid (**11**) (1.28g, 10.0mmol) in tetrahydrofuran (30ml) was treated with water (1.5ml) giving rise to complete solution. The solution was stirred at 20-25°C for 30 minutes after which time only a single component was apparent in the reaction mixture by hplc analysis which coeluted with an authentic sample of 5-bromobarbituric acid (**5**) prepared by a literature procedure[15].

Bromination of cyclic imine (3) using 5-bromobarbituric acid (5) in chloroform.

A solution of 2-{3-[3-(3-Methoxy-phenyl)-ureido]-5-methyl-2-oxo-2,3-dihydro-benzo[e][1,4]diazepin-1-yl}-N-methyl-N-phenyl-acetamide (**3**) (cyclic imine) (500mg, 1.03mmol) in chloroform (15ml) was treated with 5-bromobarbituric acid (**5**) (213mg, 1.03mmol) and the solution was stirred at 20-25°C under nitrogen for 24h. Hplc analysis after this period of time revealed 40% of starting material (**3**) remaining, 58.9% of monobrominated adduct (**8**) and 1.1% of dibrominated adduct (**9**).

(+)-2-{3-[3-(3-Methoxy-phenyl)-ureido]-5-morpholin-4-ylmethyl-2-oxo-2,3-dihydro-benzo[e][1,4]diazepin-1-yl}-N-methyl-N-phenyl-acetamide (GR 174152) (4) employing 5-bromobarbituric acid (5) (generated *in situ*) as brominating agent

A mixture of dibromobarbituric acid (**10**) (1.91g, 6.7mmol) and barbituric acid (**11**) (860mg, 6.7mmol) in THF (110ml) was treated with water (5ml) and stirred at 23°C for 5 minutes. 2-{3-[3-(3-Methoxy-phenyl)-ureido]-5-methyl-2-oxo-2,3-dihydro-benzo[e][1,4]diazepin-1-yl}-N-methyl-N-phenyl-acetamide (**3**) (cyclic imine) (5.0g, 10.3mmol) was added and the clear solution was stirred at

23°C under nitrogen for 21h, giving some turbidity during this time. Morpholine (3.0ml, 34.5mmol) was added and the mixture was stirred at 23°C under nitrogen for a further 2h. Water (50ml) and ethyl acetate (50ml) was added and the batch was reduced in volume to 100ml by evaporation. A further portion of ethyl acetate (50ml) was added and the batch volume was again reduced to about 100ml by evaporation. The organic phase was separated and the aqueous pahse was extracted with ethyl acetate (50ml). The combined organic phases were extracted with two portions of 0.5M citric acid solution (50ml and 25ml) and the combined acidic extracts were backwashed with a further portion of ethyl acetate (25ml). The aqueous phase was overlayered with ethyl acetate (50ml) and the pH was adjusted to pH6-7 using solid potassium carbonate. The reaction mixture was transferred to a separator and the product was re-extracted with ethyl acetate (25ml) and washed with water (25ml). Evaporation gave the *title compound* as a white solid (4.82g, 82%).

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