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Received February 12, 1996

Revised March 21, 1996

A series of new 1-phenyl-4(1*H*)-quinazolinones and 2,3-dihydro-1-phenyl-4(1*H*)-quinazolinones were synthesized and tested as cholecystokinin receptor ligands. All the compounds showed moderate affinity and 1-phenyl-4(1*H*)-quinazolinones resulted more effective towards the cholecystokinin-B receptor, meanwhile the dihydro derivatives were generally more effective towards the cholecystokinin-A receptor.

J. Heterocyclic Chem., **33**, 1163 (1996).

Cholecystokinin exerts a variety of actions on peripheral target tissues such as gall bladder contraction or pancreatic exocrine secretion and may function as a neurotransmitter or neuromodulator in the central nervous system [1,2]. These effects are mediated by at least two receptor subtypes designated cholecystokinin-A (predominantly distributed in the gastrointestinal tract) and cholecystokinin-B (predominantly distributed in the brain) [3]. In recent years specific and potent cholecystokinin-B antagonists, such as 1,5- [4-6] and 1,4-benzodiazepines [7], quinazolinones [8] and pyrazolidinones [9], have been developed. It is also well accepted [9,10] that the heterocyclic rings of the above structures appear to function primarily as scaffolding for the proper disposition of the aromatic domains. Based on this suggestion, as part of our ongoing study in the design of novel cholecystokinin-B receptor antagonists, we were intrigued by the prospect of applying similar design principles to 1-phenyl-4(1*H*)-quinazolinones **A** and 2,3-dihydro-1-phenyl-4(1*H*)-quinazolinones **B** (Figure 1).

Figure 1

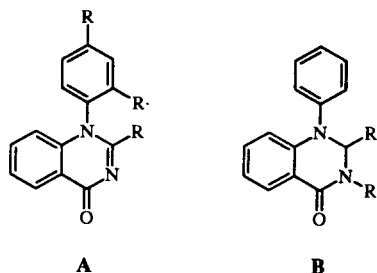
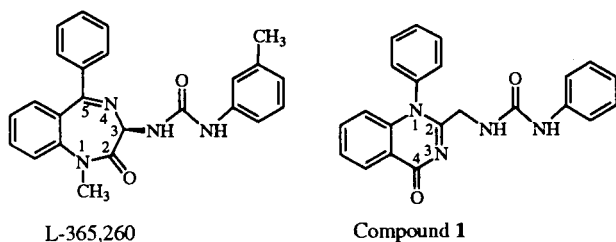
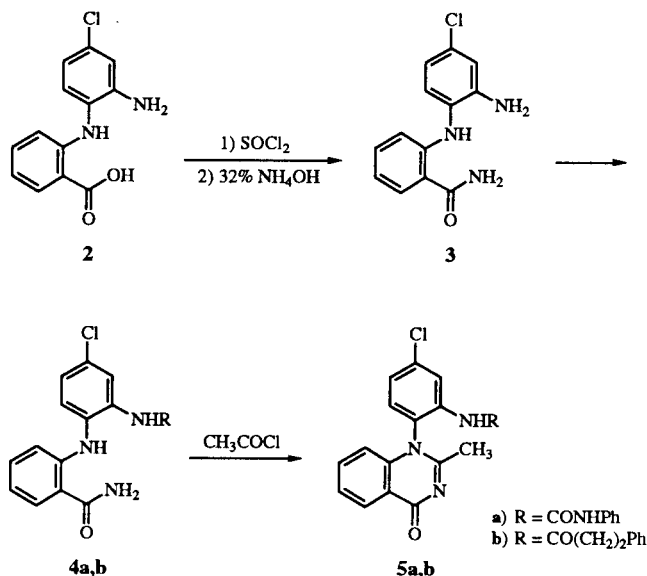


Figure 2

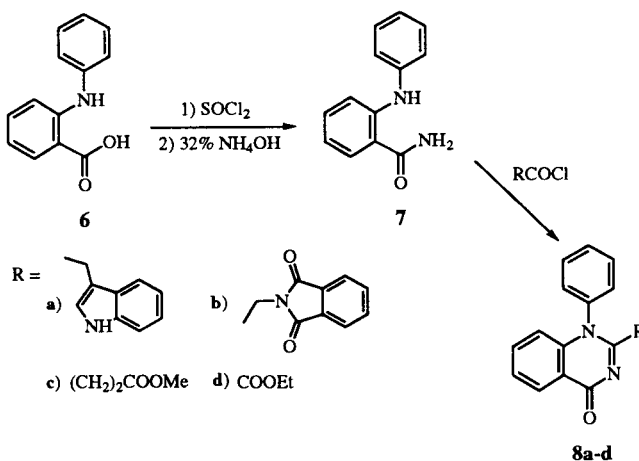


Thus, by using Sybyl 5.5 Tripos Associates Inc. [11], we compared the spatial orientation of the aromatic domains of the proposed 1-phenyl-4(1*H*)-quinazolinone

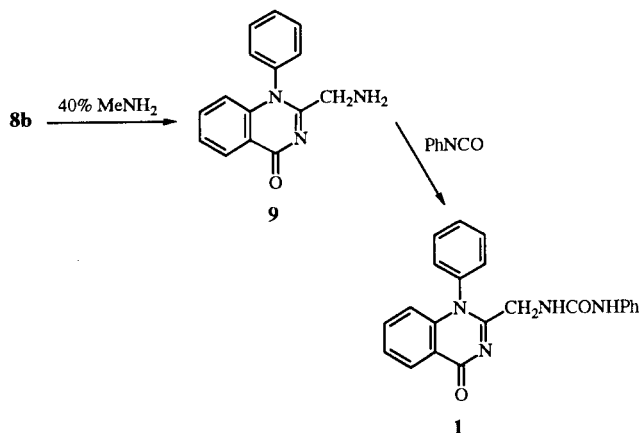
Scheme 1



Scheme 2



Scheme 3

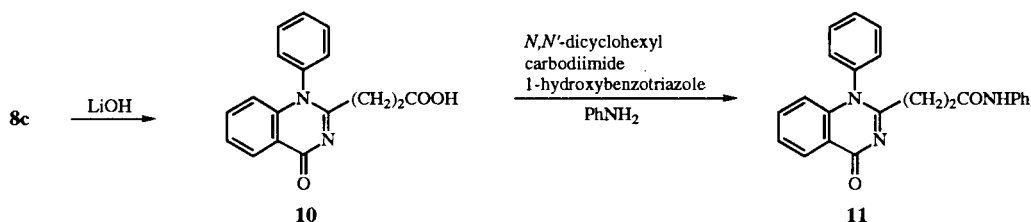


Synthesis.

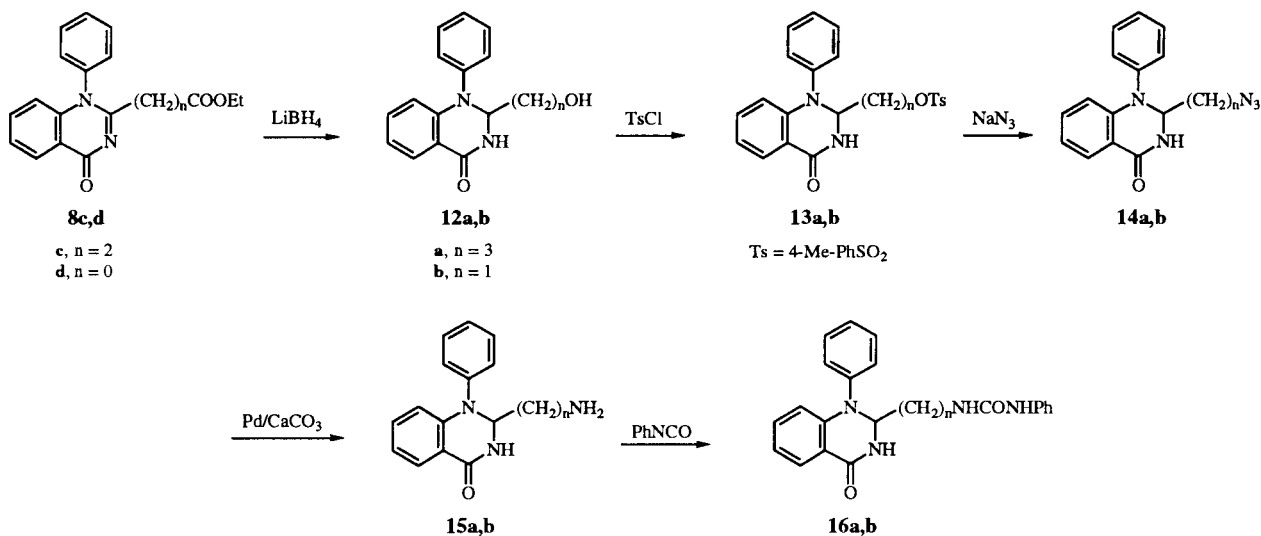
1-(2-Substituted-phenyl)-4(1*H*)-quinazolinones were prepared as outlined in Scheme 1 starting from *N*-(4-chloro-2-aminophenyl)anthranilic acid **2**. Thus, treatment of **2** with thionyl chloride at reflux, followed by addition of 32% ammonia, gave the corresponding benzamide **3** [12] in 85% yield. Further reaction with either phenyl isocyanate or 3-phenylpropionyl chloride afforded compounds **4a,b** in good yield. Cyclization reaction with acetyl chloride gave the quinazolinones **5a,b** in 80% and 90% yield respectively.

2-Substituted-1-phenyl-4(1*H*)-quinazolinones **8a-d** (Scheme 2) were obtained from the key benzamide **7**, which was in turn prepared by heating *N*-phenylantranilic acid **6** with thionyl chloride, followed by addi-

Scheme 4



Scheme 5

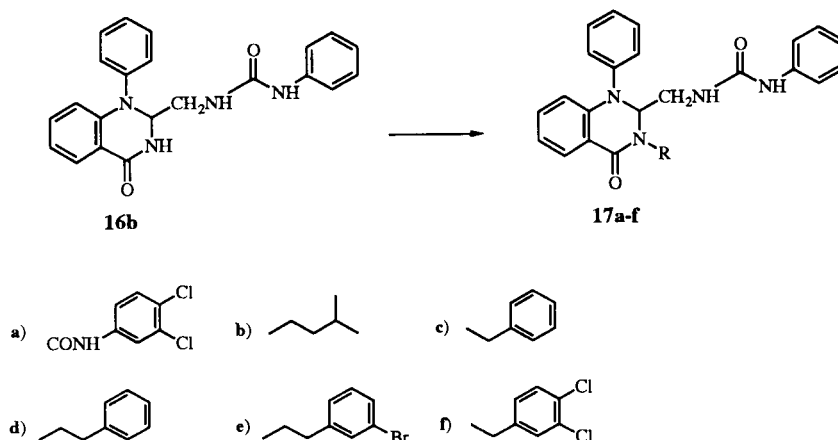


(1) and the 1,4-benzodiazepine L-365,260 [7]. We obtained a good overlap between the fused benzo rings, the 1-phenyl group of **1** and the 5-phenyl group of L-365,260 and between the aromatic substituent in the 2-position of **1** and the aromatic substituent in the 3-position of L-365,260 (Figure 2).

As a consequence, the synthesis of derivatives of general structures **A** and **B** was undertaken together with the *in vitro* evaluation of their affinity towards both cholecystokinin-B and cholecystokinin-A receptors.

tion of 32% ammonia. Compound **7** was then reacted with the desired acyl chloride to give compounds **8a-d** in good yield. The ureido compound **1** was prepared by deprotection of the phthalimido derivative **8b** with aqueous methylamine and reaction of the resulting amine **9** with phenyl isocyanate to afford the desired compound in 50% yield (Scheme 3). Hydrolysis of the ester **8c**, under aqueous basic conditions, gave the acid **10** which, upon activation with *N,N'*-dicyclohexylcarbodiimide and 1-hydroxybenzotriazole, was reacted with aniline to give the phenylaminocarbonyl compound **11** (Scheme 4).

Scheme 6



2,3-Dihydro-1-phenyl-4(1*H*)-quinazolinones were prepared as outlined in Scheme 5, starting from compounds **8c,d**. Thus, reduction of both imino and ester functions with lithium borohydride gave the 2,3-dihydroquinazolinones **12a,b** in good yield, as racemic mixtures, which were easily transformed into the tosyl derivatives **13a,b**. Nucleophilic substitution with sodium azide in dimethylformamide gave the azido compounds **14a,b**, which were hydrogenated to the amino compounds **15a,b** in good yield, using palladium on calcium carbonate as catalyst. Finally, amines **15a,b** were reacted with phenyl isocyanate to give the target molecules **16a,b**. 3-Substituted derivatives **17b-f** were synthesized by alkylation of the quinazolinone **16b** using sodium hydride and the appropriate alkyl halide, meanwhile the compound **17a** was obtained by reaction with 3,4-dichlorophenyl isocyanate (Scheme 6).

Biological Evaluation.

The *in vitro* cholecystokinin-B receptor binding assay was performed using guinea-pig cerebral cortex membrane, according to a modified procedure of Van Dijk *et al.* [13]; meanwhile the *in vitro* cholecystokinin-A receptor binding assay was performed using pancreas membrane according to a modified procedure of Innis [14]. In the 1-phenyl-4(1*H*)-quinazolinone series, maximal cholecystokinin-B receptor binding was observed for compound **1** (pK_i -B = 5.68) and all the compounds showed a very low affinity towards the cholecystokinin-A receptor. In the 2,3-dihydro-1-phenyl-4(1*H*)-quinazolinone series, the compounds showed a micromolar affinity towards both the cholecystokinin-B and cholecystokinin-A receptors. In general, a higher affinity was observed for the cholecystokinin-A receptor as shown by compounds **16a** (pK_i -A = 6.06) and **17a** (pK_i -A = 6.14).

Conclusions.

A series of new 1-phenyl-4(1*H*)-quinazolinones and 2,3-

dihydro-1-phenyl-4(1*H*)-quinazolinones were synthesized following versatile synthetic pathways and the compounds were obtained in good overall yields. All the compounds were tested *in vitro* towards both cholecystokinin-A and cholecystokinin-B receptors. 1-Phenyl-4(1*H*)-quinazolinones showed a moderate affinity only towards cholecystokinin-B receptor, meanwhile for the 2,3-dihydro-1-phenyl-4(1*H*)-quinazolinones a higher affinity towards cholecystokinin-A receptor with respect to the cholecystokinin-B receptor was generally observed.

EXPERIMENTAL

The ir spectra were measured with a Bruker IFS48 spectrophotometer. The ^1H nmr spectra were obtained with a Varian VXR5000S (300 MHz) or a Varian Unity (400 MHz) with tetramethylsilane as an internal standard. The FAB-ms spectra were measured on a Fisons VG-4 instrument. Elemental analysis were performed on a CHNS-O EA-1108 Elemental Analyzer. Melting points were determined on a Buchi 510 apparatus. Column chromatography was carried out with Kieselgel 60 (230-400 mesh ASTM, Merck)

2-(2-Amino-4-chlorophenylamino)benzamide (3).

A mixture of *N*-(4-chloro-2-aminophenyl)anthranilic acid **2** (5 g, 19 mmol) and thionyl chloride (4 g, 34 mmol) in toluene (80 ml) was heated at reflux for 40 minutes. The mixture was allowed to cool to room temperature and added to a vigorously stirred solution of 32% ammonia in water (30 ml). The stirring was continued for 3 hours, then the precipitate formed was filtered off recovering the starting anthranilic acid **2** (2.1 g). The organic layer was washed with brine, dried over anhydrous sodium sulfate and evaporated *in vacuo*. The residue was purified by flash column chromatography on silica gel (cyclohexane/ethyl acetate 1:1 then 4:6 v/v) to afford **3** (1.7 g, 60%) as a yellow powder; ν max 3412, 3396, 3342, 3194 (NH, NH₂), 1672, 1657 (C=O) cm^{-1} ; ms: FAB m/z 261 (MH⁺); ^1H -nmr (300 MHz, deuteriochloroform): δ 3.90 (bs, 2H) 6.2-5.4

(bs, 2H) 6.63 (dd, 1H) 6.66-6.74 (m, 2H) 6.78 (m, 1H) 7.04 (d, 1H) 7.26 (dt, 1H) 7.44 (dd, 1H) 9.11 (bs, 1H).

Anal. Calcd. for $C_{13}H_{12}ClN_3O$: C, 59.66; H, 4.62; N, 16.06. Found: C, 59.88; H, 4.72; N, 16.00.

2-[4-Chloro-2-(3-phenylureido)phenylamino]benzamide (**4a**).

To a stirred solution of **3** (0.2 g, 0.76 mmole) in dry acetonitrile (5 ml) was added phenyl isocyanate (0.09 g, 0.76 mmole). A precipitate was observed immediately after the addition. After 3 hours, the white solid was collected and air-dried to yield **4a** (0.23 g, 80%), mp 218-220°; ir (nujol): ν max 3335-3256 (NH, NH₂), 1748, 1688 (C=O) cm^{-1} ; ms: FAB m/z 381 (MH⁺); ¹H-nmr (300 MHz, DMSO- d_6): δ 6.60 (d, 1H) 6.77 (t, 1H) 6.97 (t, 1H) 7.03 (dd, 1H) 7.18 (d, 1H) 7.27 (t, 3H) 7.42 (d, 2H) 7.77 (dd, 1H) 7.50 (bs, 1H) 8.18 (bs, 1H) 8.20 (d, 1H) 8.37 (bs, 1H) 9.33 (bs, 1H) 9.80 (bs, 1H).

Anal. Calcd. for $C_{20}H_{17}ClN_4O_2$: C, 63.08; H, 4.50; N, 14.71. Found: C, 63.12; H, 4.47; N, 14.76.

2-[4-Chloro-2-(3-phenylpropionylamino)phenylamino]benzamide (**4b**).

To a stirred solution of **3** (0.15 g, 0.57 mmole) in dry dichloromethane (5 ml) were added triethylamine (66 mg, 0.65 mmole) and 3-phenylpropionyl chloride (0.1 g, 0.65 mmole) and the stirring was continued for 1 hour. The reaction mixture was diluted with ethyl acetate, washed with 10% hydrochloric acid and a saturated solution of sodium chloride, dried over anhydrous sodium sulfate and evaporated *in vacuo*. The residue was purified by flash column chromatography on silica gel (cyclohexane/ethyl acetate 8:2 then 1:1 v/v) to afford **4b** (0.21 g, 93%) as a white powder, mp 161-163°; ir (nujol): ν max 3383, 3263, 3177 (NH, NH₂), 1664, 1651 (C=O) cm^{-1} ; ms: FAB m/z 395 (MH⁺); ¹H-nmr (300 MHz, DMSO- d_6): δ 2.59 (t, 2H) 2.88 (t, 1H) 6.79 (dt, 1H) 6.99 (d, 1H) 7.12-7.36 (m, 8H) 7.46 (s, 1H) 7.49 (d, 1H) 7.69 (dd, 1H) 8.04 (s, 1H) 9.56 (s, 1H) 9.83 (s, 1H).

Anal. Calcd. for $C_{22}H_{21}ClN_3O_2$: C, 66.91; H, 5.36; N, 10.64. Found: C, 67.01; H, 5.35; N, 10.43.

1-[4-Chloro-2-(3-phenylureido)phenyl]-2-methyl-4(1H)-quinazolinone (**5a**).

A mixture of **4a** (0.18 g, 0.47 mmole), acetyl chloride (0.15 g, 1.88 mmole) and 37% hydrochloric acid (0.01 ml) in acetic acid (10 ml) was stirred at room temperature for 24 hours. The resulting precipitate was dissolved with ethyl acetate, made basic with 10% sodium hydroxide and washed with saturated aqueous sodium chloride, dried over anhydrous sodium sulfate and evaporated *in vacuo*. The crude residue was triturated with ethyl acetate, affording compound **5a** (0.11 g, 52%) as a white powder; ir (nujol): ν max 3298 (NH), 1726 (C=O), 1628, 1600 (C=C, C=N) cm^{-1} ; ms: FAB m/z 405 (MH⁺); ¹H-nmr (300 MHz, DMSO- d_6): δ 2.15 (s, 3H) 6.59 (d, 1H) 6.97 (t, 1H) 7.24 (t, 2H) 7.28-7.38 (m, 3H) 7.47 (t, 1H) 7.55 (d, 1H) 7.64 (dt, 1H) 8.13 (dd, 1H) 8.25 (bs, 1H) 8.57 (d, 1H) 8.87 (bs, 1H).

Anal. Calcd. for $C_{22}H_{17}ClN_4O_2$: C, 65.26; H, 4.23; N, 13.84. Found: C, 65.56; H, 4.24; N, 13.83.

1-[4-Chloro-2-(3-phenylpropionylamino)phenyl]-2-methyl-4(1H)-quinazolinone (**5b**).

A mixture of **4b** (0.10 g, 0.25 mmole), acetyl chloride (0.077 g, 0.98 mmole) and 37% hydrochloric acid (0.005 ml) in acetic acid (5 ml) was stirred at room temperature for 24 hours. The reaction mixture was diluted with ethyl acetate, basified with

10% sodium hydroxide, washed with saturated aqueous sodium chloride, dried over anhydrous sodium sulfate and evaporated *in vacuo*. The residue was triturated in ethyl acetate/diethyl ether (1:2 v/v) to afford **5b** (0.032 g, 32%) as a white powder; ir (nujol): ν max 3161 (NH), 1704 (C=O) 1636, 1609 (C=C, C=N) cm^{-1} ; ms: FAB m/z 418 (MH⁺); ¹H-nmr (300 MHz, DMSO- d_6): δ 2.1 (s, 3H) 2.4 (m, 2H) 2.6 (m, 2H) 6.46 (d, 1H) 7.02 (dd, 2H) 7.208-7.23 (m, 3H) 7.43 (td, 1H) 7.44 (d, 1H) 7.57 (td, 1H) 7.60 (d, 1H) 8.08 (dd, 1H) 8.24 (d, 1H) 9.61 (s, 1H).

Anal. Calcd. for $C_{24}H_{20}ClN_3O_2$: C, 68.98; H, 4.82; N, 10.05. Found: C, 69.06; H, 4.62; N, 10.10.

2-Phenylaminobenzamide (**7**).

A mixture of *N*-phenylanthranilic acid **6** (10 g, 47 mmole) and thionyl chloride (5 ml, 70 mmole) in toluene (100 ml) was heated at reflux for 1 hour. The mixture was concentrated and added dropwise to a vigorously stirred solution of 32% ammonia in water (30 ml) cooled at 0°. The mixture was stirred for 3 hours, the precipitate which formed was filtered off, the organic layer was diluted with ethyl acetate and, after the usual work-up, the residue was purified by flash column chromatography on silica gel (cyclohexane/ethyl acetate 2:8 v/v) to afford **7** (6.5 g, 80%) as a yellow powder; ir (nujol): ν max 3468, 3350, 3331 (NH, NH₂), 1666 (C=O) cm^{-1} ; ¹H-nmr (300 MHz, deuteriochloroform): δ 5.6-6.0 (bs, 2H) 6.73 (dd, 1H) 7.02 (t, 1H) 7.20-7.3 (m, 6H) 7.45 (dd, 1H) 9.49 (bs, 1H).

Anal. Calcd. for $C_{13}H_{12}N_2O$: C, 73.56; H, 5.70; N, 13.20. Found: C, 73.66; H, 5.72; N, 13.40.

General Procedure for 2-Substituted-1-4(1H)-quinazolinone **8a,c**.

A mixture of **7** and the acyl chloride in dry dichloromethane was stirred at room temperature for 5 hours. In the case of **8c** the product precipitated as hydrochloride. The reaction mixture or the hydrochloride were diluted with ethyl acetate, washed with 5% sodium hydrogenocarbonate and brine, dried over anhydrous sodium sulfate and evaporated *in vacuo*. The residue was triturated in the appropriate organic solvent to yield the pure product. By using the above procedure, the following results were obtained.

2-(3-Indolylmethyl)-1-phenyl-4(1H)-quinazolinone (**8a**).

Compound **8a** was prepared from **7** (0.25 g, 1.12 mmole) and indole-3-acetyl chloride [15] (0.3 g, 1.62 mmole) in dichloromethane (4 ml), yielding 0.37 g (83%) as a cream colored powder from ethyl acetate; ir (nujol): ν max 3285, 3238 (NH), 1647 (C=O) 1609, 1600 (C=C, C=N) cm^{-1} ; ms: FAB m/z 352 (MH⁺); ¹H-nmr (300 MHz, deuteriochloroform): δ 4.0 (m, 2H) 6.50 (dd, 1H) 6.85 (d, 1H) 6.95 (dt, 1H) 7.02 (m, 2H) 7.11 (dt, 1H) 7.17 (d, 1H) 7.31 (d, 1H) 7.35-7.48 (m, 4H) 7.53 (m, 1H) 8.31 (bs, 1H) 8.38 (dd, 1H).

Anal. Calcd. for $C_{23}H_{17}N_3O$: C, 78.61; H, 4.88; N, 11.96. Found: C, 78.74; H, 4.86; N, 11.55.

2-(2-Methoxycarbonyl-ethyl)-1-phenyl-4(1H)-quinazolinone (**8c**).

Compound **8c** was prepared as hydrochloride from **7** (1.0 g, 4.7 mmole) and 3-carbomethoxypropionyl chloride (1.82 g, 12 mmole) in dichloromethane (20 ml), yielding 1.13 g (70%) as a white powder; ir (nujol): ν max 2727, 2667, 2575 (RNH⁺), 1732 (C=O ester), 1718 (C=O), 1616 (C=C) cm^{-1} ; ms: FAB m/z 309 (MH⁺); ¹H-nmr (300 MHz, DMSO- d_6): δ 2.76 (s, 4H) 3.54 (s,

3H) 6.65 (d, 1H) 7.6-7.82 (m, 7H) 8.23 (d, 1H).

Anal. Calcd. for $C_{18}H_{16}N_2O_3 \cdot HCl$: C, 62.70; H, 4.97; N, 8.12. Found: C, 62.54; H, 4.95; N, 8.31.

After basic work up, **8c** was isolated as a white powder (1 g, 100%); ir (nujol): ν max 1732 (C=O ester), 1655 (C=O), 1599 (C=C) cm^{-1} ; ms: FAB m/z 309 (MH⁺); ¹H-nmr (300 MHz, DMSO- d_6): δ 2.64 (t, 2H) 2.94 (t, 2H) 3.63 (s, 3H) 6.56 (d, 1H) 7.36-7.67 (m, 7H) 8.35 (dd, 1H).

Anal. Calcd. for $C_{18}H_{16}N_2O_3$: C, 70.12; H, 5.23; N, 9.09. Found: C, 70.19; H, 5.22; N, 8.98.

1-Phenyl-2-phthalimidomethyl-4(1H)-quinazolinone (**8b**).

To a solution of **7** (1.95 g, 9.18 mmol) in acetic acid (60 ml) were added phthalimidoyl acetyl chloride (6.5 g, 29 mmol) and 37% hydrochloric acid (8 ml) and the reaction mixture was stirred at room temperature for 20 hours. After the solution was concentrated *in vacuo*, the residue was dissolved in ethyl acetate, made basic with 10% sodium hydroxide and washed with saturated aqueous sodium chloride. The organic layer was dried over anhydrous sodium sulfate and evaporated *in vacuo*. The residue was purified by flash column chromatography on silica gel (cyclohexane/ethyl acetate 2:8 v/v) to afford **8b** (1.7 g, 50%) as a white powder; ir (nujol): ν max 1722, 1655 (C=O) cm^{-1} ; ms: FAB m/z 382 (MH⁺); ¹H-nmr (400 MHz, deuteriochloroform): δ 4.48 (s, 1H) 6.63 (d, 1H) 7.43 (m, 1H) 7.50-7.57 (m, 3H) 7.68-7.76 (m, 5H) 7.84-7.89 (m, 2H) 8.33 (m, 1H).

Anal. Calcd. for $C_{23}H_{15}N_3O_3$: C, 72.43; H, 3.96; N, 11.02. Found: C, 72.51; H, 4.02; N, 11.06.

2-Ethoxycarbonyl-1-phenyl-4(1H)-quinazolinone (**8d**) [12].

To a solution of **7** (4.00 g, 18.8 mmol) in acetic acid (30 ml) was added dropwise ethyl oxalyl chloride (5.76 ml, 56.5 mmol), at 0°. After being gradually warmed to room temperature, the mixture was stirred for 20 hours, then diluted with ethyl acetate, made basic with 10% sodium hydroxide and washed with saturated aqueous sodium chloride. The organic layer was dried over anhydrous sodium sulfate and evaporated *in vacuo*. The residue was triturated in ethyl acetate to yield **8d** as a white powder (3.3 g, 60%); ir (nujol): ν max 1744, 1663 (C=O), 1603, 1549 (C=C, C=N) cm^{-1} ; ms: FAB m/z 295 (MH⁺); ¹H-nmr (300 MHz, deuteriochloroform): δ 1.05 (t, 3H) 4.09 (q, 2H) 6.80 (d, 1H) 7.40-7.64 (m, 7H) 8.39 (dd, 1H).

Anal. Calcd. for $C_{17}H_{14}N_2O_3$: C, 69.40; H, 4.79; N, 9.52. Found: C, 69.33; H, 4.78; N, 9.40.

2-Aminomethyl 1-phenyl-4(1H)-quinazolinone (**9**).

To a solution of **8b** (1.4 g, 3.6 mmol) in ethanol 95% (160 ml) was added methylamine, 40% wt solution in water (1.28 ml, 14.4 mmol) and the reaction mixture was stirred at room temperature for 5 hours. After the solution was concentrated *in vacuo*, the residue was purified by flash column chromatography on silica gel (dichloromethane/methanol 9:1 v/v) to afford **9** (0.6 g, 66%) as a red colored powder; ir (nujol): ν max 3300 (NH), 1649 (C=O) cm^{-1} ; ms: FAB m/z 252 (MH⁺); ¹H-nmr (400 MHz, deuteriochloroform): δ 3.49 (s, 2H) 6.60 (dd, 1H) 7.32 (m, 2H) 7.64-7.71 (m, 3H) 7.45 (m, 1H) 7.52 (m, 1H) 8.39 (dd, 1H).

Anal. Calcd. for $C_{15}H_{13}N_3O$: C, 71.69; H, 5.21; N, 16.72. Found: C, 72.00; H, 5.29; N, 16.77.

1-Phenyl-2-phenylureidomethyl-4(1H)-quinazolinone (**1**).

To a solution of **9** (0.58 g, 2.3 mmol) in dry acetonitrile

(60 ml) was added dropwise phenyl isocyanate (0.38 ml, 3.4 mmol) and the reaction mixture was stirred at room temperature for 2 hours and a precipitate was observed during this time. Diethyl ether (15 ml) was added and the mixture stirred for 30 minutes.

The precipitate was filtered to give **1** (0.65 g, 88%) as a white powder; ir (nujol): ν max 3261, 3221 (NH), 1690, 1636 (C=O) cm^{-1} ; ms: FAB m/z 371 (MH⁺); ¹H-nmr (400 MHz, deuteriochloroform): δ 4.14 (d, 2H) 6.63 (d, 1H) 6.93 (t, 1H) 7.14-7.23 (m, 3H) 7.36-7.50 (m, 5H) 7.54 (td, 1H) 7.62-7.70 (m, 3H) 8.13 (bs, 1H) 8.35 (dd, 1H).

Anal. Calcd. for $C_{22}H_{18}N_4O_2$: C, 71.34; H, 4.89; N, 15.13. Found: C, 71.09; H, 4.90; N, 15.11.

2-(2-Carboxyethyl)-1-phenyl-4(1H)-quinazolinone (**10**).

To a solution of **8c** (0.56 g, 1.8 mmol) in dioxane/water (15 ml/5 ml) was added lithium hydroxide monohydrate (0.10 g, 2.34 mmol) and the reaction mixture was stirred at room temperature for 15 hours. The solution was acidified with 10% hydrochloric acid and, after the usual work-up the residue was purified by flash column chromatography on silica gel (dichloromethane/methanol 9:1 v/v, then 1:1 v/v) to afford **10** (0.40 g, 76%) as a white powder; ir (nujol): ν max 1728, (C=O) 1603, 1591 (C=C, C=N) cm^{-1} ; ms: FAB m/z 295 (MH⁺); ¹H-nmr (300 MHz, deuteriochloroform): δ 2.68 (m, 2H) 3.0 (m, 2H) 4.4-6.0 (bm, 1H+H₂O) 6.59 (d, 1H) 7.36-7.45 (m, 3H) 7.52 (dt, 1H) 7.60-7.72 (m, 3H) 8.33 (dd, 1H).

Anal. Calcd. for $C_{17}H_{14}N_2O_3$: C, 69.38; H, 4.79; N, 9.52. Found: C, 69.41; H, 4.80; N, 9.40.

1-Phenyl-2-(2-phenylaminocarbonyl)ethyl-4(1H)-quinazolinone (**11**).

To a solution of **10** (0.1 g, 0.35 mmol) in ethyl acetate (25 ml) and dichloromethane (10 ml) were added 1-hydroxybenzotriazole (0.06 g, 0.38 mmol) and *N,N'*-dicyclohexylcarbodiimide (0.082 g, 0.4 mmol) and the reaction mixture was stirred at room temperature for 2 hours. Aniline (0.1 ml, 1.1 mmol) then was added and the stirring was continued for a further 2 hours. After the usual work-up the residue was purified by flash column chromatography on silica gel (ethyl acetate) to afford a product which was crystallized from ethyl acetate (2 ml) to give the compound **11** (0.05 g, 40%) as a white powder; ir (nujol): ν max 1686, (C=O) 1637, 1607 (C=C, C=N) cm^{-1} ; ms: FAB m/z 370 (MH⁺); ¹H-nmr (300 MHz, deuteriochloroform): δ 2.78 (m, 2H) 2.93 (m, 2H) 6.57 (dd, 1H) 7.04 (t, 1H) 7.2-7.75 (m, 11H) 8.35 (dd, 1H) 9.00 (bs, 1H).

Anal. Calcd. for $C_{23}H_{19}N_3O_2$: C, 74.78; H, 5.18; N, 11.38. Found: C, 74.91; H, 5.11; N, 11.37.

General Procedure for 2,3-Dihydro-2-hydroxyalkyl-1-phenyl-4(1H)-quinazolinones **12a,b**.

To a suspension of lithium borohydride (2 equivalents) in dry tetrahydrofuran at 0°, was added dropwise a solution of compound **8** in tetrahydrofuran and the reaction mixture was stirred for 1 hour. After the usual work-up the residue was triturated in the appropriate organic solvent to yield the pure product. By using the above procedure, the following results were obtained.

2,3-Dihydro-2-(3-hydroxypropyl)-1-phenyl-4(1H)-quinazolinone (**12a**).

Compound **12a** was prepared from **8c** (0.2 g, 0.65 mmol), yielding 0.11 g (60%) as a white powder from ethyl acetate; ir

(*n*ujol): ν max 3470 (NH) 3500-3000 (OH) 1655 (C=O), 1605 (C=C) cm^{-1} ; ms: FAB m/z 283 (MH^+); ^1H -nmr (300 MHz, deuteriochloroform): δ 1.64-1.87 (m, 2H) 1.87-2.1 (m, 2H) 3.67 (m, 2H) 5.23 (m, 1H) 6.85 (d, 1H) 6.99 (td, 1H) 7.12-7.23 (m, 4H) 7.24-7.4 (m, 2H) 7.99 (dd, 1H).

Anal. Calcd. for $\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}_2$: C, 72.31; H, 6.42; N, 9.92. Found: C, 72.25; H, 6.46; N, 9.89.

2,3-Dihydro-2-hydroxymethyl-1-phenyl-4(1*H*)-quinazolinone (12*b*).

Compound 12*b* was prepared from 8*d* (1 g, 3.4 mmole), yielding 0.72 g (84%) as a white powder from ethyl acetate; ir (*n*ujol): ν max 3217, 3238 (NH, OH), 1643 (C=O) 1605, 1593 (C=C) cm^{-1} ; ms: FAB m/z 255 (MH^+); ^1H -nmr (300 MHz, DMSO- d_6): δ 3.36-3.44, 3.46-3.56 (m, 2H) 4.83 (m, 1H) 5.28 (t, 1H) 6.9-7.0 (m, 2H) 7.08 (t, 1H) 7.24-7.4 (m, 5H) 7.77 (dd, 1H) 8.26 (d, 1H).

Anal. Calcd. for $\text{C}_{15}\text{H}_{14}\text{N}_2\text{O}_2$: C, 70.85; H, 5.55; N, 11.42. Found: C, 70.90; H, 5.53; N, 11.36.

General Procedure for 2,3-Dihydro-2-methyl-*p*-toluenesulfonyloxyalkyl-1-phenyl-4(1*H*)-quinazolinones 13*a,b*.

To a suspension of 12 in pyridine was added toluene-4-sulfonyl chloride (1.5 eq) and the reaction mixture was stirred for 24 hours. After dilution with ethyl acetate, the solution was washed with a 1*M* solution of hydrochloric acid and saturated aqueous sodium chloride, dried over anhydrous sodium sulfate and evaporated *in vacuo*. The residue was purified by flash column chromatography on silica gel (cyclohexane/ethyl acetate 8:2 v/v, then 1:1 v/v) to afford the pure product. By using the above procedure, the following results were obtained.

2,3-Dihydro-2-(3-methyl-*p*-toluenesulfonyloxypropyl)-1-phenyl-4(1*H*)-quinazolinone (13*a*).

Compound 13*a* was prepared from 12*a* (0.11 g, 0.39 mmole), yielding 0.1 g (60%) as a white powder; ir (*n*ujol): ν max 1666 (C=O), 1609 (C=C) cm^{-1} ; ms: FAB m/z 437 (MH^+); ^1H -nmr (300 MHz, deuteriochloroform): δ 1.87 (bs, 4H) 2.44 (s, 3H) 4.03 (m, 2H) 5.04 (bs, 1H) 6.74 (bs, 1H) 6.86 (d, 1H) 7.03 (t, 1H) 7.07 (d, 2H) 7.15 (t, 1H) 7.31-7.4 (m, 5H) 7.74 (d, 2H) 7.98 (dd, 1H).

Anal. Calcd. for $\text{C}_{24}\text{H}_{24}\text{N}_2\text{O}_4\text{S}$: C, 66.04; H, 5.54; N, 6.42. Found: C, 65.99; H, 5.58; N, 6.40.

2,3-Dihydro-2-methyl-*p*-toluenesulfonyloxymethyl-1-phenyl-4(1*H*)-quinazolinone (13*b*).

Compound 13*b* was prepared from 12*b* (0.72 g, 2.81 mmole), yielding 0.99 g, 86% as a white powder; ir (*n*ujol): ν max 3194 (NH), 1672 (C=O) 1607, 1595 (C=C) cm^{-1} ; ms: FAB m/z 409 (MH^+); ^1H -nmr (300 MHz, DMSO- d_6): δ 2.42 (s, 3H) 4.07 (dd, 1H) 4.22 (dd, 1H) 5.27 (m, 1H) 6.67 (bs, 1H) 6.83 (d, 1H) 7.00 (t, 1H) 7.14-7.20 (m, 3H) 7.26-7.4 (m, 5H) 7.72 (d, 2H) 7.91 (dd, 1H).

Anal. Calcd. for $\text{C}_{22}\text{H}_{20}\text{N}_2\text{O}_4\text{S}$: C, 64.69; H, 4.93; N, 6.86. Found: C, 64.92; H, 4.92; N, 6.88.

General Procedure for 2,3-Dihydro-2-azidoalkyl-1-phenyl-4(1*H*)-quinazolinones 14*a,b*.

A solution of compound 13 and sodium azide (1.1 eq) in DMF was heated at reflux for 8 hours. After the usual work-up the residue was purified by flash column chromatography on silica gel chromatography on silica gel (cyclohexane/ethyl acetate 1:1

v/v) to afford the pure product. By using the above procedure, the following results were obtained.

2-(3-Azidopropyl)-2,3-dihydro-1-phenyl-4(1*H*)-quinazolinone (14*a*).

Compound 14*a* was prepared from 13*a* (0.1 g, 0.23 mmole), yielding 0.07 g (99%) as an oil; ir (*n*ujol): ν max 2097 (N_3) 1668 (C=O), 1607-1595 (C=C) cm^{-1} ; ms: FAB m/z 308 (MH^+); ^1H -nmr (300 MHz, deuteriochloroform): δ 1.75-2.3 (m, 4H) 3.35 (t, 2H) 5.10 (m, 1H) 6.75 (d, 1H) 6.90 (d, 1H) 7.05 (td, 1H) 7.12-7.2 (m, 6H) 7.3-7.4 (m, 2H) 8.3 (dd, 1H).

Anal. Calcd. for $\text{C}_{17}\text{H}_{17}\text{N}_5\text{O}$: C, 66.42; H, 5.57; N, 22.78. Found: C, 66.44; H, 5.55; N, 22.88.

2-Azidomethyl-2,3-dihydro-1-phenyl-4(1*H*)-quinazolinone (14*b*).

Compound 14*b* was prepared from 13*b* (1.2 g, 2.9 mmole), yielding 0.57 g (70%) as a white powder, ir (*n*ujol): ν max 2102 (N_3), 1670 (C=O) 1609, 1600 (C=C) cm^{-1} ; ms: FAB m/z 280 (MH^+); ^1H -nmr (300 MHz, DMSO- d_6): δ 3.33 (dd, 1H) 3.70 (dd, 1H) 5.14 (m, 1H) 7.0-7.54 (m, 8H) 8.05 (d, 1H) 9.5 (bs, 1H).

Anal. Calcd. for $\text{C}_{15}\text{H}_{13}\text{N}_5\text{O}$: C, 64.50; H, 4.69; N, 25.08. Found: C, 64.47; H, 4.68; N, 25.12.

General Procedure for 2-Aminoalkyl-2,3-dihydro-1-phenyl-4(1*H*)-quinazolinones 15*a,b*.

A solution of compound 14 in ethanol was hydrogenated at 1 atmosphere for 4 hours, using 10% Pd/CaCO₃ (10%) as catalyst. After filtration over Celite, the residue was purified by flash column chromatography on silica gel chromatography on silica gel (dichloromethane/methanol 7:3 v/v) to afford the pure product. By using the above procedure, the following results were obtained.

2-(3-Aminopropyl)-2,3-dihydro-1-phenyl-4(1*H*)-quinazolinones (15*a*).

Compound 15*a* was prepared from 14*a* (0.065 g, 0.21 mmole), yielding 0.04 g (68%) as a white powder; ir (*n*ujol): ν max 3357 (NH_2) 1664 (C=O), 1595 (C=C) cm^{-1} ; ms: FAB m/z 282 (MH^+); ^1H -nmr (300 MHz, deuteriochloroform): δ 1.64 (m, 2H) 1.88 (m, 2H) 2.7 (t, 2H) 5.10 (t, 1H) 6.86 (d, 1H) 6.98 (t, 1H) 7.14-7.15 (m, 3H) 7.29 (m, 1H) 7.31 (m, 2H) 7.97 (d, 1H).

Anal. Calcd. for $\text{C}_{17}\text{H}_{19}\text{N}_3\text{O}$: C, 72.57; H, 6.81; N, 14.94. Found: C, 72.49; H, 6.86; N, 14.99.

2-Aminomethyl-2,3-dihydro-1-phenyl-4(1*H*)-quinazolinone (15*b*).

Compound 15*b* was prepared from 14*b* (1.1 g, 3.87 mmole), yielding 0.65 g (66%) as a white powder; ir (*n*ujol): ν max 3412 (NH_2), 1666 (C=O) 1609 (C=C) cm^{-1} ; ms: FAB m/z 254 (MH^+); ^1H -nmr (300 MHz, DMSO- d_6): δ 2.99 (m, 2H) 5.00 (m, 1H) 6.80-6.90 (broad, 1H) 6.86 (d, 1H) 7.01 (t, 1H) 7.14-7.40 (m, 6H) 8.01 (dd, 1H).

Anal. Calcd. for $\text{C}_{15}\text{H}_{15}\text{N}_3\text{O}$: C, 71.12; H, 5.97; N, 16.59. Found: C, 71.37; H, 5.98; N, 16.63.

General Procedure for 2,3-Dihydro-2-phenylureidoalkyl-1-phenyl-4(1*H*)-quinazolinones 16*a,b*.

To a solution of 15 in acetonitrile was added phenylisocyanate (1.4 eq) and the reaction mixture was stirred for 30 minutes. Compound 16*a* precipitated and was collected after filtration and air-dried meanwhile the solution containing the compound 16*b* was evaporated *in vacuo* and the residue was purified by

flash column chromatography on silica gel (cyclohexane/ethyl acetate 7:3 v/v) to afford the pure product. By using the above procedure, the following results were obtained.

2,3-Dihydro-2-(3-phenylureidopropyl)-1-phenyl-4(1*H*)-quinazolinone (**16a**).

Compound **16a** was prepared from **15a** (0.04 g, 0.14 mmole), yielding 0.04 g (70%) as a white powder; ir (nujol): ν max 3302 (NH), 1680 (C=O amide), 1634 (C=O), 1609 (C=C) cm^{-1} ; ms: FAB m/z 401 (MH^+); ^1H -nmr (300 MHz, DMSO- d_6): δ 1.56 (m, 2H) 1.69 (m, 2H) 3.05 (m, 2H) 4.99 (m, 1H) 6.10 (t, 1H) 6.85 (t, 1H) 6.89 (d, 1H) 7.00 (t, 1H) 7.08 (t, 1H) 7.15 (td, 2H) 7.20 (d, 2H) 7.34-7.35 (m, 5H) 7.81 (d, 1H) 8.36 (s, 1H) 8.45 (d, 1H).

Anal. Calcd. for $\text{C}_{24}\text{H}_{24}\text{N}_4\text{O}_2$: C, 71.98; H, 6.04; N, 13.99. Found: C, 71.89; H, 6.06; N, 13.40.

2,3-Dihydro-2-phenylureidomethyl-1-phenyl-4(1*H*)-quinazolinone (**16b**).

Compound **16b** was prepared from **15b** (0.24 g, 0.93 mmole), yielding 0.32 g (93%) as a white powder; ir (nujol): ν max 3314-3398 (NH), 1653, 1607 (C=O) 1551 (C=C) cm^{-1} ; ms: FAB m/z 373 (MH^+); ^1H -nmr (300 MHz, deuteriochloroform): δ 3.15-3.24 (m, 1H) 3.76-3.84 (m, 1H) 5.1-5.2 (m, 1H) 6.36 (bt, 1H) 6.83 (t, 1H) 6.94 (d, 2H) 7.08-7.18 (m, 3H) 7.2-7.32 (m, 5H) 7.79 (bs, 1H) 7.90 (dd, 1H) 7.95 (d, 1H).

Anal. Calcd. for $\text{C}_{22}\text{H}_{20}\text{N}_4\text{O}_2$: C, 70.95; H, 5.41; N, 15.04. Found: C, 70.92; H, 5.42; N, 15.08.

General Procedure for 3-Substituted-2,3-dihydro-2-phenylureidomethyl-1-phenyl-4(1*H*)-quinazolinones **17b-f**.

To a solution of **16b** in DMF at 0° , was added sodium hydride (1.0 eq) and the reaction mixture was stirred for 45 minutes, then the alkyl halide was added and the stirring was continued at room temperature. After the usual work-up the crude residue was purified by flash column chromatography on silica gel (cyclohexane/ethyl acetate) to afford the pure product. By using the above procedure, the following results were obtained.

2,3-Dihydro-3-(3-methylbutyl)-2-phenylureidomethyl-1-phenyl-4(1*H*)-quinazolinone (**17b**).

Compound **17b** was prepared from **16b** (0.15 g, 0.4 mmole) and 1-bromo-3-methylbutane (57.5 ml, 0.48 mmole) for 5 hours, yielding 0.085 g (48%) as a white powder; ir (nujol): ν max 1653, 1628 (C=O) cm^{-1} ; ms: FAB m/z 443 (MH^+); ^1H -nmr (400 MHz, deuteriochloroform): δ 0.61 (d, 3H) 0.74 (d, 3H) 1.18-1.38 (m, 3H) 3.03 (m, 1H) 3.45 (m, 1H) 3.74 (m, 1H) 4.14 (m, 1H) 5.34 (dd, 1H) 6.23 (t, 1H) 6.98-7.08 (m, 3H) 7.13 (m, 1H) 7.21-7.44 (m, 9H) 7.73 (s, 1H) 7.96 (dd, 1H).

Anal. Calcd. for $\text{C}_{27}\text{H}_{30}\text{N}_4\text{O}_2$: C, 73.28; H, 6.83; N, 12.66. Found: C, 73.51; H, 6.82; N, 12.61.

3-Benzyl-2,3-dihydro-2-phenylureidomethyl-1-phenyl-4(1*H*)-quinazolinone (**17c**).

Compound **17c** was prepared from **16b** (0.08 g, 0.21 mmole) and benzyl bromide (25 ml, 0.21 mmole) for 6 hours, yielding 0.067 g (69%) as a white powder; ir (nujol): ν max 3393 (NH), 1697, 1626 (C=O), 1609 (C=C) cm^{-1} ; ms: FAB m/z 463 (MH^+); ^1H -nmr (400 MHz, deuteriochloroform): δ 3.50-3.66 (m, 2H) 4.24 (d, 1H) 5.26 (t, 1H) 5.42 (d, 1H) 5.78 (bt, 1H) 7.00-7.10 (m, 12H) 7.18-7.40 (m, 7H) 8.05 (dd, 1H).

Anal. Calcd. for $\text{C}_{29}\text{H}_{26}\text{N}_4\text{O}_2$: C, 75.30; H, 5.66; N, 12.11. Found: C, 75.41; H, 5.70; N, 12.15.

2,3-Dihydro-2-phenylureidomethyl-1-phenyl-3-(2-phenylethyl)-4(1*H*)-quinazolinone (**17d**).

Compound **17d** was prepared from **16b** (0.10 g, 0.27 mmole) and (2-bromoethyl)benzene (67 ml, 0.62 mmole) for 24 hours, yielding 0.034 g (23%) as white powder; ir (nujol): ν max 3329, 3192 (NH), 1700-1600 (C=O) cm^{-1} ; ms: FAB m/z 477 (MH^+); ^1H -nmr (400 MHz, deuteriochloroform): δ 2.73 (m, 2H) 3.24 (m, 1H) 3.36 (m, 1H) 3.73 (m, 1H) 4.34 (m, 1H) 5.20 (dd, 1H) 6.25 (t, 1H) 6.90-7.43 (m, 18H) 7.79 (bs, 1H) 7.88 (dd, 1H).

Anal. Calcd. for $\text{C}_{30}\text{H}_{28}\text{N}_4\text{O}_2$: C, 75.60; H, 5.92; N, 11.76. Found: C, 75.54; H, 5.94; N, 11.72.

3-(3-Bromobenzyl)-2,3-dihydro-2-phenylureidomethyl-1-phenyl-4(1*H*)-quinazolinone (**17e**).

Compound **17e** was prepared from **16b** (0.14 g, 0.38 mmole) and 3-bromobenzyl bromide (0.113 g, 0.45 mmole) for 3 hours, yielding 0.085 g (42%) as a white powder; ir (nujol): ν max 3350, 3186 (NH), 1626 (C=O) cm^{-1} ; ms: FAB m/z 541, 543 (MH^+); ^1H -nmr (400 MHz, deuteriochloroform): δ 3.55 (m, 1H) 3.60 (m, 1H) 34.11 (d, 1H) 5.26 (t, 1H) 5.45 (d, 1H) 5.84 (t, 1H) 6.87-7.42 (m, 18H) 8.03 (dd, 1H).

Anal. Calcd. for $\text{C}_{29}\text{H}_{25}\text{BrN}_4\text{O}_2$: C, 64.32; H, 4.65; N, 10.35. Found: C, 64.28; H, 4.66; N, 10.32.

3-(3,4-Dichlorobenzyl)-2,3-dihydro-2-phenylureidomethyl-1-phenyl-4(1*H*)-quinazolinone (**17f**).

Compound **17f** was prepared from **16b** (0.20 g, 0.54 mmoles) and 3,4-dichlorobenzyl bromide (97 ml, 0.70 mmole) for 4 hours, yielding 0.19 g (66%) as a white powder; ir (nujol): ν max 3420, 3317 (NH), 1693 (C=O) cm^{-1} ; ms: FAB m/z 531 (MH^+); ^1H -nmr (400 MHz, deuteriochloroform): δ 3.31 (m, 1H) 3.36 (m, 1H) 4.04 (d, 1H) 5.25 (t, 1H) 5.39 (d, 1H) 5.56 (t, 1H) 6.88 (m, 2H) 6.95 (d, 1H) 7.02 (d, 1H) 7.05-7.15 (m, 5H) 7.21 (t, 2H) 7.28-7.36 (m, 4H), 7.3 (td, 1H), 8.05 (dd, 1H).

Anal. Calcd. for $\text{C}_{29}\text{H}_{24}\text{Cl}_2\text{N}_4\text{O}_2$: C, 65.54; H, 4.55; N, 10.54. Found: C, 65.50; H, 4.54; N, 10.62.

3-(3,4-Dichlorophenylaminocarbonyl)-2,3-dihydro-2-phenylureidomethyl-1-phenyl-4(1*H*)-quinazolinone (**17a**).

A solution of **16b** (0.095 g, 0.25 mmole) and 3,4-dichlorophenylisocyanate (0.71 g, 0.38 mmole) in acetonitrile (15 ml) was heated at reflux for 6 hours. The solvent was evaporated *in vacuo* and the residue was purified by flash column chromatography on silica gel (dichloromethane/diethyl ether 8:2 v/v) to afford **17a** (0.068 g, 49%) as a white powder; ir (nujol): ν max 1709, 1653 (C=O) cm^{-1} ; ms: FAB m/z 560 (MH^+); ^1H -nmr (400 MHz, deuteriochloroform): δ 3.56 (m, 1H) 3.84 (m, 1H) 5.07 (m, 1H) 6.56 (bs, 1H) 6.59 (dd, 1H) 7.04-7.38 (m, 14H) 7.46 (m, 1H) 7.79 (d, 1H) 8.10 (dd, 1H) 11.75 (s, 1H).

Anal. Calcd. for $\text{C}_{29}\text{H}_{23}\text{Cl}_2\text{N}_5\text{O}_3$: C, 62.15; H, 4.14; N, 12.50. Found: C, 62.10; H, 4.13; N, 12.58.

Acknowledgements.

We thank Ms. B. Oliosi and Dr. F. Van Amsterdam for the cholecystokinin receptor binding assay, Dr. A. Feriani and Dr. A. M. Capelli for the Computational Chemistry, Mr. A. Piccolboni for the microanalyses, Dr. O. Curcuruto and Dr. M. Hamdan for the Mass Spectra and Mrs. M. Passarini, Dr. C. Marchioro, Dr. A. Orlandi, R. Upton, Mrs. N. Case, Dr. S. Provera for the ir and ^1H nmr spectra.

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