Expedited Articles

N-3-Substituted Imidazoquinazolinones: Potent and Selective PDE5 Inhibitors as Potential Agents for Treatment of Erectile Dysfunction

David P. Rotella,*,† Zhong Sun,† Yeheng Zhu,† John Krupinski,‡ Ronald Pongrac,‡ Laurie Seliger,‡ Diane Normandin,‡ and John E. Macor†

Discovery Chemistry and Cardiovascular Drug Discovery, Bristol-Myers Squibb Pharmaceutical Research Institute, P.O. Box 5400, Princeton, New Jersey 08543-5400

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Phosphodiesterase type 5 (PDE5) inhibitors with improved PDE isozyme selectivity relative to sildenafil may result in agents for the treatment of male erectile dysfunction (MED) with a lower incidence of PDE-associated adverse effects. This paper describes the discovery of **14**, a PDE5 inhibitor with improved potency and selectivity in vitro compared to sildenafil. This compound shows activity in a functional assay of erectile function comparable to that of sildenafil.

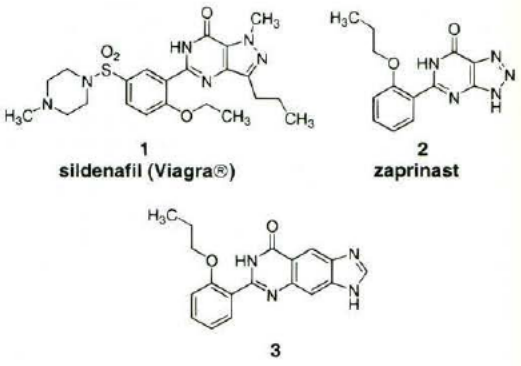
Introduction

The utility of sildenafil (**1**, Viagra; Chart 1) as an efficacious, orally active agent for the treatment of male erectile dysfunction (MED)[1] has created significant interest in the discovery of additional phosphodiesterase type 5 (PDE5) inhibitors.[2] PDE5 is the primary cGMP-hydrolyzing enzyme activity present in the corpus cavernosum, the smooth muscle in the penis which helps control vascular tone. When a man is sexually stimulated, nitric oxide is released from the cavernosal nerve. This activates soluble guanylyl cyclase in the corpus cavernosum, causing an increase in intracellular cGMP, which is normally hydrolyzed by PDE5. Inhibition of PDE5 elevates levels of the cyclic nucleotide, leading to enhanced relaxation of smooth muscle, increased arterial inflow, venous congestion, and ultimately an erection. Despite the efficacy of **1** as a treatment for MED, there are notable drawbacks associated with its use. Clinically significant adverse effects such as nausea, headache, cutaneous flushing, and visual disturbances have been noted, and their incidence is dose-dependent. Certain of these are thought to be due to nonspecific inhibition of other PDEs, specifically PDE1 and PDE6.[3,4] Thus, the identification of potent and more selective PDE5 inhibitors is of primary interest. This paper describes the discovery of an *N*-3-(fluorobenzyl)-imidazoquinazolinone that is more potent and selective in vitro as a PDE5 inhibitor compared to sildenafil. This compound demonstrates activity comparable to **1** in a functional assay of erectile dysfunction using rabbit corpus cavernosum tissue strips.

Results and Discussion

Using the prototypical PDE5 inhibitor zaprinast (**2**; Chart 1)[5] as a template, directed screening identified **3**

Chart 1



(Chart 1) as a moderately active but nonselective lead (Table 1). The potency of compound **3** was improved 10-fold by incorporation of an *N*-methylpiperazinesulfonamide in the pendant alkoxybenzene ring, leading to compound **7** (Scheme 1). This SAR observation was analogous to that described by Terrett et al.[1b] in the development of sildenafil. While this improved activity was encouraging, it was apparent that this modification did not enhance isozyme selectivity compared to sildenafil (Table 1).

In an attempt to improve the potency and selectivity of this series, modification of the imidazole ring was investigated. The synthesis of an *N*-3-benzyl derivative of **7** was carried out as shown in Scheme 2. Key to the synthesis of **11** was the selective formation of the imidazole ring in **9** that did not also lead to quinazolinone formation. This was achieved by stirring the diamine intermediate derived from **8** in formic acid overnight at room temperature. The formyl group on the amine *ortho* to the primary amide which also resulted from this transformation was cleaved by brief

* Corresponding author: David P. Rotella. Phone: 609-818-5398. Fax: 609-818-3450. E-mail: david.rotella@bms.com.
† Discovery Chemistry.
‡ Cardiovascular Drug Discovery.

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Table 1. PDE5 IC_{50} and Selectivity Ratios for Other PDEs[a]

compd	PDE5 IC_{50} (nM)[b]	IC_{50} ratio PDE1/5	PDE2/5	PDE3/5	PDE4/5	PDE6/5
1	1.6 ± 0.5	140	>10^4	3500	2600	8
3	44 ± 19	200	360	300	100	1
7	5.3 ± 0.6	90	1300	5900	1600	2
11	5.3 ± 1.1	3400	>10^4	8800	600	20
14	0.48 ± 0.1	>10^5	>10^5	>10^5	4200	60

[a] Enzyme sources: PDE1, bovine heart; PDE2, rat kidney; PDE3, human platelet; PDE4, rat kidney; PDE5, human platelet; PDE6, bovine retina. [b] All IC_{50} determinations are averages based on 3 determinations; PDE5 values are represented as IC_{50} ± SD for at least 3 independent experiments.

treatment with acid, leading to **9** in good overall yield from dinitro intermediate **8**. Acylation of the aniline with acid chloride **12** gave piperazine **10**, which without purification was cyclized using potassium *tert*-butoxide in refluxing *tert*-butyl alcohol to furnish **11**. In vitro, **11** maintained PDE5 potency (relative to **7**) and also substantially improved the selectivity profile of the series (Table 1). Specifically, **11** was 20-fold selective for PDE6, 3400-fold selective for PDE1, and 600-fold selective for PDE4.

Compounds **7** and **11** were compared to **1** in a secondary in vitro assay to evaluate their functional effects on smooth muscle relaxation in rabbit cavernosal tissue strips.[6,7] This model measures potentiation of the normal smooth muscle relaxation process and reflects the indirect effect that a PDE5 inhibitor exerts on the target tissue. It is important to note that administration of sildenafil does not directly result in an erection (vide supra), rather an external stimulus is required to initiate the cascade. The data in Table 2 indicate that the unsubstituted benzimidazole **7** exhibited a dose-related effect and was as efficacious as sildenafil as measured by the potentiation of relaxation enhancement. The *N*-3-benzyl derivative **11** was less active than both **1** and **7**. We speculated that a contributing factor to this reduced activity was the significantly higher molecular weight of **11** (MW = 572), compared to either **1** (MW = 474) or **7** (MW = 482). This may reduce diffusion of the compound into smooth muscle cells of the corpus cavernosum where the drug must act.

Carboxamides offer an alternative, lower molecular weight handle for incorporation of potency-enhancing substituents in the alkoxybenzene moiety.[8] Making use of this variation, along with further optimization of the *N*-3-benzyl substituent, led to the synthesis of compound **14** (Scheme 3). Benzimidazole **9b** was coupled with 4-bromo-2-propoxybenzoic acid to furnish an intermediate amide, which was cyclized to afford **13**. Cyanide substitution, hydrolysis to the corresponding carboxylic acid, and amide formation afforded **14** in good yield.

Amide **14** displayed enhanced PDE5 potency (IC_{50} = 0.48 nM), compared to sildenafil and further improved the PDE selectivity profile of **11** (Table 1). Significant inhibition (PDE IC_{50} < 1 μM) of other PDEs is limited to PDE6. In this instance, compound **14** was 60-fold selective for PDE5, compared to less than 10-fold selective for sildenafil. Note that the improved selectivity of **14** can be attributed to both an increase in PDE5 potency and a decrease in affinity for PDE6 (Table 1). Evaluation of **14** (MW = 472) in rabbit corpus cavernosum tissue clearly showed a positive dose-related effect and improved efficacy compared to the higher molecular weight sulfonamide **11**. Compound **14** proved to be similar in efficacy to both **1** and **7** as measured by the increase in the relaxation integral relative to the control (Table 2). This information suggests that **14** is better able to penetrate cells in the target tissue, compared to **11**, but also shows that the improved in vitro potency relative to sildenafil did not lead to a measurable increase in functional efficacy. Nevertheless, the data in Table 2 indicate that this group of *N*-3-benzylbenzimidazoles is worthy of further study as potential agents for the treatment of MED.

Conclusion

In summary, we have identified a quinazolinone template that provides potent PDE5 inhibitors. Addition of a benzyl moiety at N-3 of this template confers substantial improvement in PDE selectivity and potency compared to sildenafil. This improved selectivity should translate into an improved PDE-related side effect profile in vivo, based on experience to date with sildenafil. In a functional assay of erectile function, the more selective PDE5 inhibitor **14** demonstrated activity comparable to sildenafil based on the ability of the compound to relax rabbit corpus cavernosum tissue. Additional studies with this series of molecules will be reported in due course.

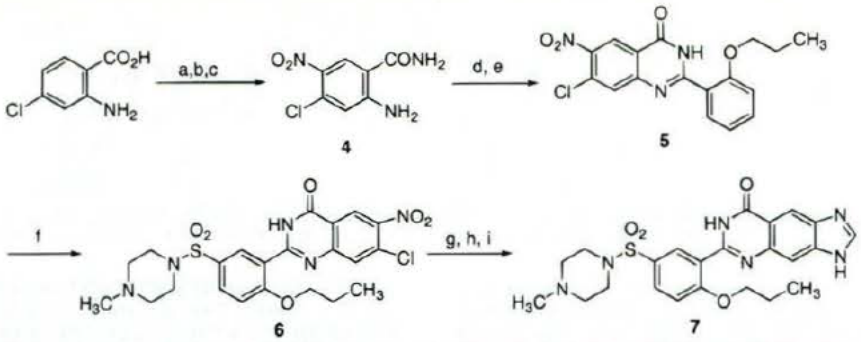
Experimental Section

General. NMR spectra were obtained at 400 MHz (^{1}H) and 100 MHz (^{13}C) on a Varian DRX-400 spectrometer. Chemical shifts are reported in ppm downfield from TMS as an internal standard. Thin-layer chromatography was carried out using 2.5 × 7.5-cm silica gel 60 (250 μM layer) plates with UV detection. Magnesium sulfate was employed to dry organic extracts prior to concentration by rotary evaporation. Flash chromatography was done using EM Science silica gel 60 (230−400 mesh). Standard solvents from EM Science were used as received. Anhydrous solvents from EM Science or Aldrich and all other commercially available reagents were used without further purification. Melting points were taken using a Thomas-Hoover MelTemp apparatus. Microanalysis was carried out by the Analytical Chemistry department at Bristol-Myers Squibb. Preparative HPLC was carried out on a Shimadzu LC8A system using a YMC ODS-A 30 × 250-mm column eluting with a 30-min linear gradient from 90% solvent A to 90% solvent B (solvent A: 90% water/10% MeOH with 0.1% TFA, solvent B: 90% MeOH/10% water with 0.1% TFA). Low-resolution mass spectra were recorded using an LC−MS system consisting of a Micromass ZMD mass spectrometer in electrospray (M + H) mode and a Shimadzu LC10AT HPLC using a YMC ODS-A 3 × 50-mm column using the same solvents as noted above in a 2-min linear gradient.

2-Amino-4-chloro-5-nitrobenzamide (4). 4-Chloroanthranilic acid (10.0 g, 56.5 mmol) was dissolved at room temperature with stirring in 190 mL of distilled water containing 8.98 g (84.7 mmol) Na_2CO_3. When the 4-chloroanthranilic acid was completely dissolved, a 20% w/v solution of phosgene in toluene (84 mL) was added dropwise via a dropping funnel over 45 min. The resulting suspension was stirred at room temperature overnight under nitrogen. The product was collected by filtration and washed well with water. The resulting gray-white solid was dried in a vacuum oven at 60 °C overnight to provide 7-chloro-1,4-dihydro-2*H*-3,1-benzoxazine-2,4-dione (10.3 g, 52.3 mmol, 93%): ^{1}H NMR (DMSO-d_6) δ 11.93 (br s, 1H), 7.17 (d, *J* = 1.5 Hz, 1H), 7.28 (dd, *J* = 1.6 and 8.2 Hz, 1H), 7.91 (d, *J* = 8.2 Hz, 1H).

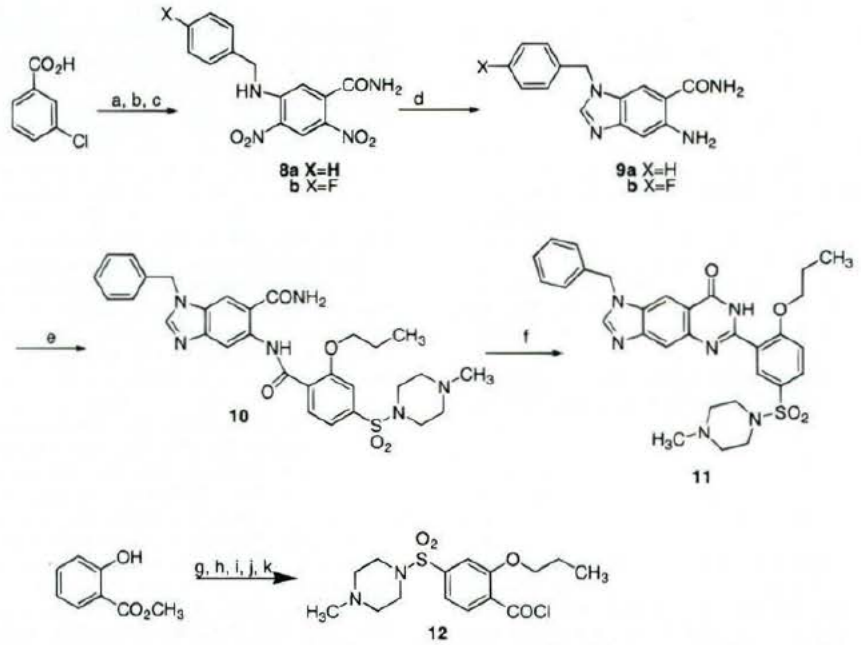
A portion of this material (5.1 g, 25.9 mmol) was added in portions over 40 min to a cold (0 °C) solution of concentrated (96−98%) sulfuric acid (15 mL) and concentrated (70%) nitric

Scheme 1[a]



[a] (a) Phosgene/$PhCH_3$/aq Na_2CO_3, rt 18 h, 93%; (b) HNO_3/H_2SO_4, 0 °C 1 h, 49%; (c) HOAc, NH_4OAc, 100 °C 3 h, 86%; (d) 2-propoxybenzoyl chloride/DMF/pyridine, 80 °C 2.5 h, 93%; (e) $NaOH/H_2O_2$, aq EtOH, reflux 2 h, 89%; (f) (i) chlorosulfonic acid, 0 °C to rt 4 h, (ii) 4-methylpiperazine, CH_2Cl_2, rt 2 h, 85%; (g) 2 M NH_3/EtOH, sealed tube, 130 °C overnight, 72%; (h) 40 psi H_2, EtOH/aq HCl, 10% Pd–C, rt overnight, 59%; (i) formic acid, reflux 3 h, 93%.

Scheme 2[a]



[a] (a) H_2SO_4/KNO_3, 40–145 °C, 45%; (b) (i) $(COCl)_2$, CH_2Cl_2, cat. DMF, 1 h, (ii) NH_4OH, acetone, 0 °C 45 min, 75%; (c) (X)-benzylamine, THF, Et_3N, reflux 1–2 h, 81–84%; (d) (i) 25 psi H_2, PtO_2, MeOH, 3–5 h; (ii) formic acid, rt overnight, (iii) 10% aq HCl/EtOH, rt 3 h, 90–93%; (e) 5-[(4-methylpiperazinyl)sulfonyl]-2-propoxybenzoyl chloride, pyridine/DMF, 75 °C 1–2 h; (f) tBuOK–tBuOH, reflux 2 h, 39% (two steps); (g) propyl iodide, K_2CO_3/DMF, rt overnight; (h) $HSO_3Cl/SOCl_2$, 0 °C 30 min, 28% net; (i) 4-methylpiperazine, triethylamine, CH_2Cl_2, 0 °C 1.5 h, 100%; (j) LiOH, THF–H_2O, reflux 16 h, 96%; (k) $(COCl)_2$, CH_2Cl_2, cat. DMF, 2 h.

Table 2. Rabbit Corpus Cavernosum Functional Assay

	% control relaxation integral	
compd	30 nM[a]	300 nM[a]
1	150 ± 20	220 ± 25
7	140 ± 10	210 ± 30
11	120 ± 10	150 ± 13
14	140 ± 12	190 ± 32

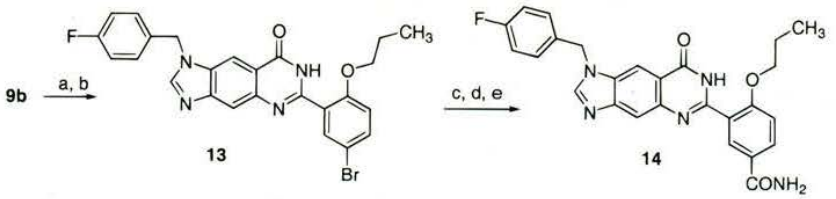
[a] Control (untreated) response = 100%.

acid (15 mL). The reaction was stirred at 0 °C for 1 h, then filtered through a sintered glass funnel. The filtrate was cautiously poured into crushed ice (250 g) to precipitate a yellow-tan solid. This solid was washed well with water and dried overnight in a vacuum oven (60 °C) to furnish 7-chloro-1,4-dihydro-6-nitro-2*H*-3,1-benzoxazine-2,4-dione (3.09 g, 12.7 mmol, 49%): ^{1}H NMR (DMSO-d_6) δ 12.30 (br s, 1H), 7.28 (s, 1H), 8.53 (s, 1H).

This product (6.5 g, 26.8 mmol) was suspended in glacial acetic acid (70 mL). Ammonium acetate (6.2 g, 80.6 mmol) was added, and the resulting mixture was heated to 100 °C with stirring for 3 h. After cooling to room temperature, the brown solution was poured into distilled water (200 mL) to precipitate a yellow solid which was collected by filtration and washed well with water and ether. This material was first air-dried, then dried overnight under high vacuum to provide **4** (4.9 g, 23.0 mmol, 86%): ^{1}H NMR (DMSO-d_6) δ 6.92 (s, 1H), 7.49 (br s, 1H), 7.89 (br s, 2H), 8.22 (br s, 1H), 8.53 (s, 1H).

7-Chloro-6-nitro-2-(2-propoxyphenyl)-4(3*H*)-quinazolinone (5). Compound **4** (3.50 g, 16.3 mmol) was dissolved in pyridine at room temperature (1 mol equiv). *o*-Propoxybenzoyl chloride (4.51 g, 22.8 mmol) was partially dissolved in a small quantity (<10 mL) of DMF, and this mixture was added to the pyridine solution. The resulting brown solution was heated to 80 °C for 2.5 h. The reaction mixture was cooled to room temperature and poured into distilled water to precipitate a

Scheme 3[a]



[a] (a) 2-Propoxy-4-bromobenzoic acid, HOBt, EDAC, cat. DMAP, DMF, 4 h; (b) tBuOK, tBuOH, reflux 2 h, 82%; (c) CuCN, *N*-methylpyrrolidinone, reflux 18 h, 91%; (d) NaOH, EtOH, reflux 5 h, 75%; (e) NH_3/THF, EDAC, HOBt, cat. DMAP, pyridine, 82%.

brown solid. This suspension was stirred at room temperature overnight. In the morning, the solid was collected by filtration and washed with water, 10% HCl, and then ether. The product (4-chloro-2-[(2-propoxybenzoyl)amino]-5-nitrobenzamide) was obtained in 93% yield (5.70 g, 15.2 mmol) after drying in a vacuum oven: mp 177−178 °C; ^{1}H NMR (DMSO-d_6) δ 9.04 (s, 1H), 8.55 (s, 2H), 8.05 (s, 1H), 7.88 (d, J = 6.5 Hz, 1H), 7.59 (apparent t, J = 6.2 Hz, 1H), 7.23 (d, J = 6.5 Hz, 1H), 7.10 (apparent t, J = 6.2 Hz, 1H), 4.19 (t, J = 7.2 Hz, 2H), 1.84 (m, 2H), 0.92 (t, J = 7.4 Hz, 3H).

This material was suspended in absolute ethanol (15 mL ethanol), and water was added (7 mL). Sodium hydroxide (0.73 g, 18.2 mmol) was then added, followed by 0.86 mL (0.26 g, 7.6 mmol) of 30% (w/v) aqueous hydrogen peroxide. The reaction mixture was then heated to reflux, and the starting material gradually dissolved. When the starting material was consumed as determined by TLC analysis (generally in less than 2 h), the reaction was cooled to room temperature and concentrated by rotary evaporation to furnish a yellow-brown solid which was washed with water and triturated with ether to provide an 89% yield (4.38 g, 12.2 mmol) of **5**: mp 178−181 °C; ^{1}H NMR (DMSO-d_6) δ 8.80 (s, 1H), 8.59 (apparent d, J = 8 Hz, 1H), 7.91 (s, 1H), 7.57 (apparent t, J = 8 Hz, 1H), 7.19 (apparent t, J = 7.4 Hz, 1H), 7.09 (d, J = 8 Hz, 1H), 4.24 (t, J = 6.5 Hz, 2H), 2.04 (m, 2H), 1.18 (t, J = 7.4 Hz, 3H).

1-[[3-(7-Chloro-3,4-dihydro-6-nitro-4-oxo-2-quinazolinyl)propoxyphenyl]sulfonyl]-4-methylpiperazine (6). Chlorosulfonic acid (10 mL) was cooled to 0 °C in ice under nitrogen. Compound **5** (0.81 g, 2.3 mmol) was added portionwise over 20−30 min. The reaction was stirred at 0 °C for 5 h then, very cautiously, poured slowly into crushed ice. The resulting yellow precipitate was collected by filtration, washed thoroughly with water and sucked dry with a water aspirator. This material was used without further purification for sulfonamide formation. The resulting sulfonyl chloride was partially dissolved in 20 mL of methylene chloride/2 mL of THF. Triethylamine (0.31 g, 3.04 mmol, 423 μL) was added. This was followed by 0.24 g (264 μL, 2.39 mmol) of 4-methylpiperazine. The reaction mixture was stirred at room temperature for 2 h then diluted with additional methylene chloride and washed twice with water, dried over magnesium sulfate and concentrated to furnish the product as a yellow solid in 72% yield (0.86 g, 1.66 mmol): mp 225−228 °C; LRMS [MH$^+$] 522; ^{1}H NMR ($CDCl_3$) δ 8.94 (d, 1H, J = 2.4 Hz), 8.79 (s, 1H), 7.98 (s, 1H), 7.92 (dd, 1H, J = 2.4, 8.7 Hz), 7.22 (d, 1 H, J = 8.7 Hz), 4.32 (t, 2H, J = 6.6 Hz), 3.08−3.12 (m, 4H), 2.43−2.56 (m, 4H), 2.28 (s, 3H), 2.05−2.10 (m, 2H), 1.40 (t, 2H, J = 7.2 Hz), 1.19 (t, 3H, J = 7.2 Hz).

1-[[3-(7,8-Dihydro-8-oxo-1*H*-imidazo[4,5-*g*]quinazolin-6-yl)-4-propoxyphenyl]sulfonyl]-4-methylpiperazine (7). Compound **6** (0.65 g, 1.24 mmol) was suspended in equal volumes of absolute ethanol and 28% aqueous ammonium hydroxide in a pressure bottle (total volume 25 mL) with a stirring bar. After the bottled was tightly sealed, the contents were heated at 140 °C overnight. The reaction mixture was cooled to room temperature, and the resulting suspension was diluted with water. The resulting mixture was filtered to afford a bright yellow solid. This solid was washed with water, ethanol, and ether to provide 1-[[3-(7-amino-3,4-dihydro-6-nitro-4-oxo-2-quinazolinyl)-4-propoxyphenyl]sulfonyl]-4-methylpiperazine (0.44 g, 0.87 mmol, 70% yield): mp 270−271 °C; LRMS [MH$^+$] 503; ^{1}H NMR (DMSO-d_6) δ 8.75 (s, 1H), 7.94 (d, 1H, J = 2.3 Hz), 7.86 (dd, 1h, J = 2.3, 8.6 Hz), 7.72 (s, 1H), 7.41 (d, 1H, J = 8.7 Hz), 7.12 (s, 1H), 4.13 (t, 2H, J = 6.2 Hz), 2.90 (br s, 4H), 2.37 (br s, 4H), 2.15 (s, 3H), 1.71−1.77 (m, 2H), 0.95 (t, 3H, J = 6.2 Hz).

This material was partially dissolved in 5 mL of 10% aqueous HCl and added to a suspension of 10% palladium on charcoal (50 wt %) in absolute ethanol (20 mL) in a Parr bottle. The mixture was hydrogenated on a Parr shaker at room temperature under 40 psi H_2 overnight. The suspension was filtered through Celite and the cake washed well with ethanol. The filtrate was evaporated to provide 1-[[3-(6,7-diamino-3,4-dihydro-4-oxo-2-quinazolinyl)-4-propoxyphenyl]sulfonyl]-4-methylpiperazine as the hydrochloride salt (0.21 g, 0.44 mmol, 50% yield). This material was used without further purification: LRMS [MH$^+$] 473; ^{1}H NMR (CD_3OD) δ 8.22 (s, 1H), 8.18 (d, 1H, J = 8.6 Hz), 8.00 (s, 1H), 7.58 (d, 1H, J = 8.6 Hz), 7.15 (s, 1H), 4.24 (t, 2H, J = 6.2 Hz), 3.94 (br d, 4H, J = 8.2 Hz, D_2O exchangeable), 3.24 (m, 4H), 2.85−3.05 (m, 7H), 1.80−1.93 (m, 2H), 1.00 (t, 3H, J = 6.2 Hz).

This diamine (0.20 g, 0.39 mmol) was dissolved in 10 mL of concentrated formic acid and heated to reflux under nitrogen. The reaction was followed by HPLC, and generally conversion to product was complete in 2 h or less. The reaction was cooled to room temperature and formic acid was removed in vacuo. Residual water was azeotropically removed with ethanol leaving a light brown to reddish brown solid. The solid was dissolved in 10% aqueous HCl and washed with three portions of ethyl acetate. The pH of the water layer was adjusted to 12 with sodium hydroxide solution and extracted five times with ethyl acetate. The collected organic extracts were washed twice with brine, dried and concentrated. Further purification was accomplished by dissolving this material in 20 mL of EtOAc, which was cooled in ice before HCl gas was passed through the solution to deposit fine tan needles of the hydrochloride salt of the product (0.14 g, 0.26 mmol, 66% yield): mp (free base) 164−167 °C; LRMS [MH$^+$] 483; ^{1}H NMR (CD_3OD) δ 9.59 (s, 1H), 8.66 (s, 1H), 8.22 (d, 1H, J = 2.4 Hz), 8.17 (s, 1H), 7.96 (dd, 1H, J = 2.4, 8.7 Hz), 7.40 (d, 1H, J = 8.7 Hz), 4.16 (t, 2H, J = 6.3 Hz), 3.87 (br d, 2H, J = 12.8 Hz), 3.50 (br d, 2H, J = 12.8 Hz), 3.1−3.2 (m, partially obscured by MeOH, 2H), 2.8−2.92 (m, 5H), 1.75−1.88 (m, 2H), 0.95 (t, 3H, J = 7.4 Hz). Anal. Calcd for $C_{23}H_{27}ClN_6O_4S$: C, 53.22; H, 5.24; Cl, 6.83; N, 16.19; S, 6.18. Found: C, 53.20; H, 5.25; Cl, 6.79; N, 16.14.

2,4-Dinitro-5-chlorobenzoic Acid. 3-Chlorobenzoic acid (12.5 g, 80 mmol) was dissolved in 145 mL of concentrated sulfuric acid with stirring, while warming to 40 °C. Potassium nitrate (8.0 g, 78 mmol) was added in divided portions over 30 min. The reaction mixture was then warmed to 100 °C and an additional 14 g of potassium nitrate was added over 20 min. The reaction mixture was warmed to 145 °C and held at this temperature for 15 min. The reaction was cooled to room temperature and poured into 1 kg of ice to precipitate a faintly yellow solid. This material was collected by filtration and washed with water. The resulting solid was then suspended in 500 mL of distilled water and stirred at room temperature for 45 min. The undissolved solid was collected by filtration and dried under high vacuum to obtain 8.9 g (36%) yield of product as a faintly yellow solid: ^{1}H NMR (acetone-d_6) δ 8.76 (s, 1H), 8.26, (s, 1H).

2,4-Dinitro-5-chlorobenzamide. 2,4-Dinitro-5-chloroben-

zoic acid (7.00 g, 28.4 mmol) was suspended in 40 mL of thionyl chloride containing 3 drops of DMF. The suspension was warmed to reflux for 4 h. After cooling to room temperature, solvent was removed by rotary evaporation leaving a golden yellow liquid. This was diluted with 30 mL of acetone and added dropwise over 20 min to a 0 °C solution of 20 mL of concentrated ammonium hydroxide. The reaction was stirred at 0 °C for 30 min, then poured into 250 g of ice. The yellow orange precipitate was collected by filtration and washed well with water. The solid was dried first by water aspirator then under high vacuum to furnish 5.9 g (24 mmol, 84% yield) of product: ^{1}H NMR (acetone-d_6) δ 8.75 (s, 1H), 8.25 (s, 1H); mp 201–203 °C.

General Procedure for Preparation of 5-Benzylamino-2,4-dinitrobenzamides. 2,4-Dinitro-5-chlorobenzamide (2.00–14.25 mmol) was suspended in 15–70 mL of THF and 1.2 equiv of triethylamine was added, followed by 1.2 equiv of the appropriate benzylamine. The reaction was heated to reflux until TLC indicated starting material had been consumed. The cooled reaction mixture was filtered and the filtrate was concentrated in vacuo leaving a solid which was triturated with ether. This solid was collected by filtration, washed with ether and dried affording the product.

5-[(Phenylmethyl)amino]-2,4-dinitrobenzamide (8a): 95% yield; mp 143–146 °C; ^{1}H NMR (acetone) δ 9.21 (br s, 1H), 8.90 (s, 1H), 7.31–7.49 (m, 5H), 7.13 (s, 1H), 7.02 (br s, 1H), 4.90 (d, 2H, J = 6 Hz).

5-[[(4-Fluorophenyl)methyl]amino]-2,4-dinitrobenzamide (8b): 81% yield; mp 178–180 °C; ^{1}H NMR (DMSO) δ 9.44 (br t 1H, exchangeable with D_2O), 8.72 (s, 1H), 8.35 (br s, 2H, exchangeable with D_2O), 7.40–7.44 (m, 2H), 7.15–7.21 (m, 2H), 7.02 (s, 1H), 4.75 (d, 2H, J = 6.3 Hz).

General Procedure for Synthesis of 5-Amino-1-[(phenylmethyl)amino]-1*H*-benzimidazole-6-carboxamides. The appropriate 5-benzylamino-2,4-dinitrobenzamide (**8a** or **8b** from above) (0.50–3.5 g) was partially dissolved in methanol (20–200 mL) containing 25 wt % platinum oxide. Hydrogen was introduced using a balloon and the flask was evacuated and filled several times before leaving the suspension stirring under an atmosphere of hydrogen at room temperature. The mixture was stirred until HPLC analysis showed consumption of starting material and conversion to the desired diamine product (typically 5 h). The suspension was filtered through Celite and the filter cake was washed with methanol. The filtrate was concentrated to furnish the crude diamine. This material was then dissolved in concentrated (96%) formic acid and stirred at room temperature overnight. Formic acid was removed at room temperature under vacuum, leaving a brown solid. This material was dissolved in absolute ethanol (10–50 mL) and 10% aqueous HCl (3–10 mL) and stirred at room temperature for 3 h. Solvent was removed by rotary evaporation to furnish the product as the hydrochloride salt. This material was sufficiently pure for further transformation. The yield stated is the net for this three-step sequence.

5-Amino-1-[(phenylmethyl)amino]-1*H*-benzimidazole-6-carboxamide (9a): 90% yield; LRMS [MH$^+$] 267; ^{1}H NMR (CD_3OD) δ 9.68 (s, 1H), 8.55 (s, 1H), 7.98 (s, 1H), 7.40–7.52 (m, 5H), 5.81 (s, 2H).

5-Amino-1-[[(4-fluorophenyl)methyl]amino]-1*H*-benzimidazole-6-carboxamide (9b): 93% yield; LRMS [MH$^+$] 286; ^{1}H NMR (CD_3OD) δ 9,73 (s, 1H), 8.64 (s, 1H), 7.60–7.68 (m, 2H), 7.19 (apparent t, 2H, J = 8.5 Hz), 5.83 (s, 2H).

5-[(4-Methyl-4-piperazinyl)sulfonyl]-2-propoxybenzoic Acid, Lithium Salt. To a solution of methyl salicyclate (25.00 g, 0.16 mol) in 200 mL of DMF were added potassium carbonate (34.00 g, 0.25 mol) and 1-iodopropane (84.00 g, 0.49 mol). The mixture was stirred at room temperature for 24 h. The reaction was diluted with 400 mL of water and extracted with 5 × 100 mL of ether. The combined organic extracts were washed twice with brine, dried and concentrated to give a faintly yellow liquid that contained the product, methyl-2-propoxybenzoic acid and excess 1-iodopropane. This mixture was added dropwise at 0 °C to a mixture of 35 mL of chlorosulfonic acid and 10 mL of thionyl chloride over 30 min. The dark red reaction was allowed to slowly warm to room temperature overnight. The mixture was cautiously poured over 1 kg of ice and stirred to deposit a yellow solid that was recrystallized from cyclohexane to furnish 13.00 g (0.045 mol, 28% yield) of the corresponding sulfonyl chloride: mp 58–59 °C; ^{13}C NMR ($CDCl_3$) δ 164.7, 163.9, 135.6, 132.7, 131.8, 121.5, 113.6, 71.6, 52.9, 22.6, 10.7.

1.3 g of this compound (6.23 mmol) was dissolved in 20 mL of methylene chloride and cooled to 0 °C in ice; 0.82 g (8.10 mmol) of triethylamine was added, followed by 0.69 g (6.86 mmol) of 4-methylpiperazine. The reaction was stirred in ice for 1.5 h, then diluted with 50 mL of methylene chloride and washed twice with water and dried. The organic phase was concentrated in vacuo leaving a clear colorless oil which partially solidified under vacuum to give 2.21 g (6.23 mmol, 100% yield) of the desired sulfonamide: ^{1}H NMR ($CDCl_3$) δ 8.15 (d, 1H, J = 2.5 Hz), 7.81 (dd, 1H, J = 2.5, 8.9 Hz), 7.05 (d, 1H, J = 8.9 Hz), 4.07 (t, 2H, J = 6.4 Hz), 3.90 (s, 3H), 3.03 (br apparent s, 4H), 2.47 (apparent t, 4H, J = 4.8 Hz), 2.26 (s, 3H), 1.86–1.91 (m, 2H), 1.09 (t, 3H, J = 7.3 Hz).

This ester was dissolved in 45 mL of THF with 5 mL of water and 0.27 g (6.23 mmol) of lithium hydroxide monohydrate. The solution was heated to reflux overnight and in the morning, solvents were removed in vacuo leaving the product as a white solid (2.17 g, 6.23 mmol, 100%): ^{1}H NMR (D_2O) δ 7.62 (dd, 1H, J = 2.5, 8.7 Hz), 7.57 (d, 1H, 2.5 Hz), 7.09 (d, 1H, J = 8.7 Hz), 3.97 (t, 2H, J = 6.5 Hz), 2.89 (br s, 4H), 2.38 (br, s, 4H), 2.06 (s, 3H), 1.60–1.69 (m, 2H), 0.84 (t, 3H, J = 7.5 Hz).

1-[[3-[7,8-Dihydro-8-oxo-1-(phenylmethyl)-1*H*-imidazo[4,5-*g*]quinazolin-6-yl]-4-propoxyphenyl]sulfonyl]-4-methylpiperazine (11). 5-[(4-Methyl-4-piperazinyl)sulfonyl]-2-propoxybenzoic acid, lithium salt (1.4 g, 3.9 mmol) was dissolved in 20 mL of methylene chloride containing 3 drops of DMF at 0 °C. Oxalyl chloride (0.70 g, 5.11 mmol, 0.48 mL) was added dropwise over 20 min. The cold bath was removed and the reaction stirred at room temperature for 2 h. Solvents were removed on a rotary evaporator and the residue was suspended in 25 mL of pyridine and 2 mL of DMF. To this was added **9a** (0.91 g, 3 mmol) and the reaction was heated to 75 °C for 30 min. The reaction was poured into cold water and extracted with methylene chloride (4 × 25 mL). The organic extract was washed with water and brine and dried, then concentrated in vacuo to afford a dark brown semisolid (1.2 g) that was used without further purification for the next reaction.

This crude material was suspended in 15 mL of dry *tert*-butyl alcohol and 4.4 mL of KOtBu (1.0 M in tBuOH) was added. The solution was heated to reflux under argon for 45 min. Water (25 mL) was added to the reaction to precipitate a brown solid that was collected by filtration, washed with water and dried to furnish 0.45 g (0.78 mmol, 39% yield) of product: mp 125–127 °C; ^{1}H NMR (CD_3OD) δ 8.63 (s, 1H), 8.32 (s, 1H), 8.25 (d, 1H, J = 2.3 Hz), 7.90 (d, 1H, J = 2.3 Hz), 7.88 (d, 1H, J = 2.4 Hz), 7.29–7.39 (m, 5H), 5.60 (d, 2H, J = 13 Hz), 4.19 (t, 2H, J = 6.3 Hz), 3.07 (br s, 4H), 2.51 (m, 4H), 1.81–1.90 (m, 2H), 1.03 (t, 3H, J = 7.4 Hz). An analytical sample was obtained following preparative HPLC. Anal. Calcd for $C_{30}H_{32}N_6O_4S\cdot1.3H_2O$: C, 51.73; H, 4.97; N, 11.10; S, 4.24. Found: C, 51.52; H, 5.00; N, 11.09; S, 4.52.

1-[3-[1-[(4-Fluorophenyl)methyl]-7,8-dihydro-8-oxo-1*H*-imidazo[4,5-*g*]quinazolin-6-yl]-4-propoxyphenyl]carboxamide (14). 2-Propoxy-4-bromobenzoic acid (2.60 g, 10.0 mmol) was dissolved in 25 mL of pyridine. To this were added **9b** (3.20 g, 10 mmol), EDAC (2.30 g, 12 mmol), DMAP (0.18 g 1.5 mmol) and HOBt (1.84 g, 12 mmol). The reaction was stirred at room temperature for 2 h. Most of the pyridine was removed in vacuo and 50 mL of water was added to precipitate the product which was collected by filtration, washed with water and dried to afford 4.57 g of material which was used without further purification. This material was cyclized as described above for the preparation of **11** to furnish compound **13** as a beige solid in 82% yield (3.47 g): mp 295–297 °C; LCMS [MH$^+$] 508; HPLC (YMC S5 ODS 4.6 × 50-mm column,

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