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Benzhydrylquinazolinediones: Novel cytosolic phospholipase $A_2\alpha$ inhibitors with improved physicochemical properties

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ABSTRACT

The synthesis and optimization of a class of trisubstituted quinazoline-2,4(1*H*,3*H*)-dione $cPLA_2\alpha$ inhibitors are described. Utilizing pharmacophores that were found to be important in our indole series, we discovered inhibitors with reduced lipophilicity and improved aqueous solubility. These compounds are active in whole blood assays, and cell-based assay results indicate that prevention of arachidonic acid release arises from selective $cPLA_2\alpha$ inhibition.

1. Introduction

The cytosolic phospholipase A_2 ($cPLA_2$) family of enzymes is responsible for cleaving the sn-2 acyl bond of glycerophospholipids. One particular member, $cPLA_{2\alpha}$, is an 85 kDa, calcium-dependent, cytosolic lipase with selectivity for arachidonic acid (AA) and eicosapentenoic acid-containing glycerophospholipids.[1] AA release initiates the biosynthetic cascade that produces such inflammatory mediators as leukotrienes (LTs) via the lipoxygenase (5-LO) pathway, prostaglandins (PGs), thromboxanes (TXs) via the cyclooxygenase pathway, and platelet activating factor (PAF) which results from acylation of lyso-glycerophosphatidylcholine.[2] NSAIDS and COX-2 selective inhibitors reduce the pain and edema of osteo- (OA) and rheumatoid arthritis (RA) via suppression of PGs.[3] 5-LO and LT receptor antagonists have demonstrated the role of LTs in asthma. Inhibition of leukotriene production may also be beneficial in treating pain and the signs and symptoms of RA, and PGD_2 has been implicated in asthma through the agonism of both DP1 and CRTH2.[4] Therefore, $cPLA_{2\alpha}$ inhibitors, which will block both PG and LT production, are expected to be efficacious in these diseases and may be more effective than COX-2 inhibitors.

Validation for the role of $cPLA_{2\alpha}$ inhibition to combat inflammatory diseases comes from studies on gene-deficient mice bred into appropriate strains.[5–8] These animals are generally healthy, but a defect in labor induction and reduced fecundity is observed that is analogous to COX-1 and COX-2 deficiency.[9] These $cPLA_{2\alpha}$ deficient mice are resistant to disease in models for collagen-induced rheumatoid arthritis,[10] LPS-induced adult respiratory distress syndrome,[11] ova-induced anaphylaxis,[12] multiple sclerosis,[13] atherosclerosis,[14] stroke,[15] and colon cancer.[16,17] In addition to the listed diseases, there is a general need for the improved treatment of inflammatory disease as illustrated by its recent association with an increased risk for cancer,[18] heart attack,[19] chronic heart failure,[20] and morbidity.[21] A recent report describing a single human deficient in $cPLA_{2\alpha}$ activity (due to inheritance of two distinct inactivating alleles) has demonstrated the central role of $cPLA_{2\alpha}$ in AA release.[22]

The increased rate of cardiovascular complications in patients taking some COX-2 inhibitors may result from the selective inhibition of anti-thrombotic prostacyclin (PGI_2) without affecting prothrombotic TX.[23,24] In the case of classical, non-selective COX inhibitors, simultaneous inhibition of TX and PGI_2 provides cardiovascular benefits, especially for naproxen which is an effective inhibitor of COX-1 derived TX. However, the inhibition of gastric PGE_2 leads to an increased risk of gastrointestinal disorders. Inhibition of $cPLA_{2\alpha}$ would decrease the supply of AA which would in turn inhibit the formation of both TX and PGI_2. The further inhibition of pro-ulcerogenic LTB_4 should make it possible for $cPLA_{2\alpha}$

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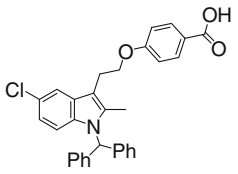
inhibitors to possess the desirable properties of selective and non-selective COX inhibitors. Notably, the $cPLA_{2\alpha}$ deficient human has a GI phenotype distinct from that associated with NSAID usage which is characterized by gastroduodenal ulcers and more subtle small intestinal ulcers. In contrast, all ulcers in this individual were localized to the small intestine, and there were no signs of gastroduodenal ulcers despite numerous endoscopies.[22]

A variety of $cPLA_{2\alpha}$ inhibitors have been reported in the literature (Fig. 1).[25] The structural motifs include activated ketones,[26–30] pyrrolidines,[31,32] indoles,[29,33–36] oxamides,[37,38] and triazinetriones.[39] Seno (Shionogi) has shown that thiazolidinedione-containing pyrrolidines, as exemplified by **1**, are potent $cPLA_{2\alpha}$ inhibitors.[31,32] Likely inspired by Merck-Frosst's success with arachidonyl trifluoromethyl ketone, Connolly et al. presented propanone **2**, an activated ketone with tunable electrophilicity, but without a metabolically-unstable unsaturated chain.[28] Kokotos has described 2-oxoamides (**3**) which are active in the rat-paw carrageenan edema model.[37,38] Lehr has recently reported on C-3 indole carboxylate compounds (**4**) which exhibit low nanomolar in vitro inhibition.[40] We have recently published the structures of WAY-196025 and Efipladib, indole-based $cPLA_{2\alpha}$ inhibitors which have nanomolar activity in the rat whole blood assay, and oral efficacy in several chronic and acute animal models.[35] With the exception of our indoles, the Shionogi compound is the only inhibitor from this group to display whole blood activity. Recent publications by Kokotos[41] and Lehr[40] provide an excellent summary of the field of $cPLA_{2\alpha}$ inhibitor research.

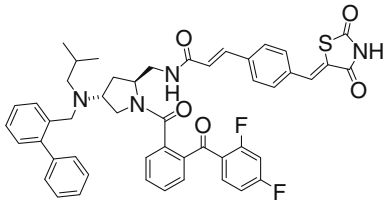


5

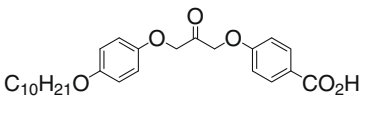
GLU IC_{50}= 3.0 μM

Although WAY-196025 is potent in whole blood assays and demonstrates in vivo efficacy, these indoles are large and lipophilic, and benefit from a lipid-based formulation to achieve modest bioavailability. Therefore, we initiated the pursuit of a second, unique, non-indole series that possessed improved physicochemical properties. Early efforts in our group to identify $cPLA_{2\alpha}$ inhibitors led to the discovery of 1,2,3-trisubstituted indole derivatives such as **5**.[42] Considerable improvements in potency were achieved with the inclusion of the N-1 benzhydryl, C-2 methyl, and C-3 tethered acid moieties. In spite of all efforts to find smaller lipophilic N-1 substituents and non-ionizable functionality, each of these groups contributed to the activity.

Our experiences with the indole SAR suggested that a reduction in molecular weight and lipophilicity could only come about by finding a new, more polar core. A HTS library using the GLU micelle assay noted here resulted in only two confirmed hits (data not



1



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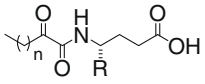

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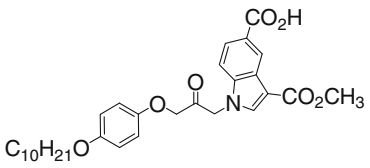

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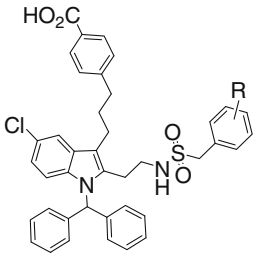
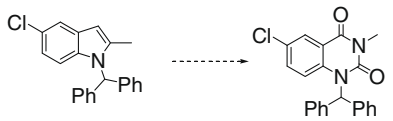


Compound	R	GLU IC_{50} (μM)	Rat WB IC_{50} (μM)	$plogD_{7.4}$
WAY-196025	2,6-di-Me	0.014	0.03	8.7
Efipladib	3,4-di-Cl	0.04	0.07	9.2

Figure 1. $cPLA_2$ inhibitors reported in the literature.



Δ plog P = - 2.9
Δ TPSA = + 39 Å^2
Δ Mol. Wt. = + 45

Figure 2. Comparison of calculated physical properties—indoles and quinazolinediones.

shown). Following initial optimization, the IC_{50}s in a human whole blood assay remained well in excess of 300 μM. Structure-driven drug design using our $cPLA_{2\alpha}$ X-ray crystal structure[43] was not possible because the active site conformation precluded the binding of an indole-based inhibitor. Furthermore, docking experiments with either the natural substrate or smaller molecules were not informative since an amphipathic helix covers the active site, and movement of the helix to allow binding alters the structure such that modeling was not predictive. After testing a number of heterocyclic cores that would allow for substituents to be spatially arranged in a manner similar to the 1,2,3-trisubstituted indoles, we found the quinazolinediones to be an excellent starting point. In principle, the quinazolinedione core provides novelty, greater inherent polarity, and the flexibility to utilize either N-1 or N-3 atoms in place of the N-1 indole position. Calculated properties for both substituted indole and quinazolinedione cores (Fig. 2) suggest that the desired polarity increase will be accompanied by increased polar surface area and molecular weight.

2. Chemistry

The synthesis of the N-1 benzhydryl quinazolinediones resulted from a four-step sequence starting from substituted anthranilic acids (Scheme 1). The acid was converted to the amide using standard EDCI coupling conditions followed by aniline alkylation with benzhydryl bromide. Exposure of the aminoamide to triphosgene and subsequent ester hydrolysis provided the quinazolinedione acids (see Fig. 3 for substitution key).

Similar chemistry starting from anthranilate esters was utilized to provide additional compounds (Schemes 2–4). An alternative approach involved sequential O-alkylation of commercially available 3-(2-chloroethyl)quinazoline-2,4(1*H*,3*H*)-dione followed by ester hydrolysis to provide the three atom-linked benzoic acid **27** (Scheme 5).

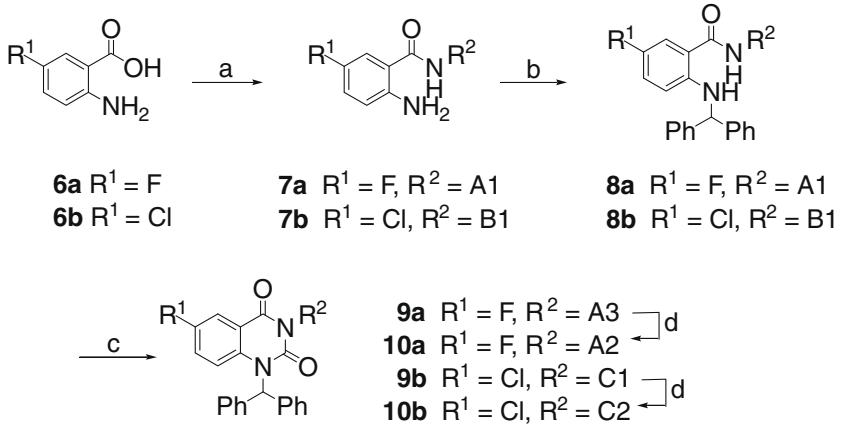
These routes proceeded without difficulty, but the inability to efficiently deliver N-3 diversity via imide alkylation after heterocycle formation, the occasionally observed instability of the N-1 benzhydryl group to basic ester hydrolysis conditions, and the absence of a common quinazolinedione intermediate greatly slowed progress. A careful examination of the alternative N-3 benzhydrylquinazolinediones revealed that N-1 substitution could be introduced late in the sequence and this would allow for the rapid, convergent synthesis of derivatives.

The N-3 benzhydrylquinazolinediones were made from the substituted 2-nitrobenzoic acids through a five-step sequence involving amide coupling, nitro reduction, ring closure in the presence of triphosgene, N-1 alkylation, and ester hydrolysis (Scheme 6). Additional aromatic ring substitution was accessible through the use of commercially available anthranilic acids using a similar route (Scheme 7). A third method for synthesizing N-3 benzhydrylquinazolinediones involved isatoic anhydride aminolysis, ring closure, N-1 alkylation and ester hydrolysis (Scheme 8). Compounds **44a–d** were made from the N-3 benhydrylquinazolinedione via N-1 alkylation with the 1,4-dihaloolefin, phenol O-alkylation with methyl 4-hydroxybenzoate and ester hydrolysis (Scheme 9).

The earlier problems associated with introducing diversity via N-3 substitution had been addressed with the switch to N-3 benzhydryl derivatives, but the search for a convergent route to allow for efficient functionalization of the carbocyclic portion of the bicycle was more challenging. A variety of substituted isatoic anhydrides, 2-nitrobenzoic, and anthranilic acids were commercially available, but this required a new synthesis for each uniquely substituted heterocyclic core. Ideally, a common intermediate would be available which would enable the introduction of C-6 and C-7 diversity late in the synthetic sequence. Such an opportunity was realized when it was observed that the 7-fluoro substituent could be displaced with a variety of nucleophiles (Scheme 10). Nucleophilic aromatic substitution with oxygen, nitrogen, and sulfur nucleophiles in the presence of base followed by TFA-induced ester cleavage provided C-7 substituted analogs. Further diversification could be accomplished by sulfide oxidation or nitro reduction (Scheme 7). By using the more stable *tert*-butyl ester rather than the methyl ester, the final chromatographic purification could be performed readily on the ester.

3. Results and discussion

Prior work on the indole series clearly demonstrated that the linker between the acidic and the hydrophobic moieties need not include an electrophilic ketone to achieve $cPLA_{2\alpha}$ inhibition, but



6a R^1 = F
6b R^1 = Cl

7a R^1 = F, R^2 = A1
7b R^1 = Cl, R^2 = B1

8a R^1 = F, R^2 = A1
8b R^1 = Cl, R^2 = B1

9a R^1 = F, R^2 = A3
10a R^1 = F, R^2 = A2
9b R^1 = Cl, R^2 = C1
10b R^1 = Cl, R^2 = C2

Scheme 1. Reagents and conditions: (a) EDCI, amine, DMAP, DMF, rt; (b) DIEA, $BrCH(Ph)_2$, DCE, 55 °C; (c) triphosgene, THF, reflux; (d) NaOH, THF, H_2O, MeOH, 50 °C or TFA, DCM, rt.

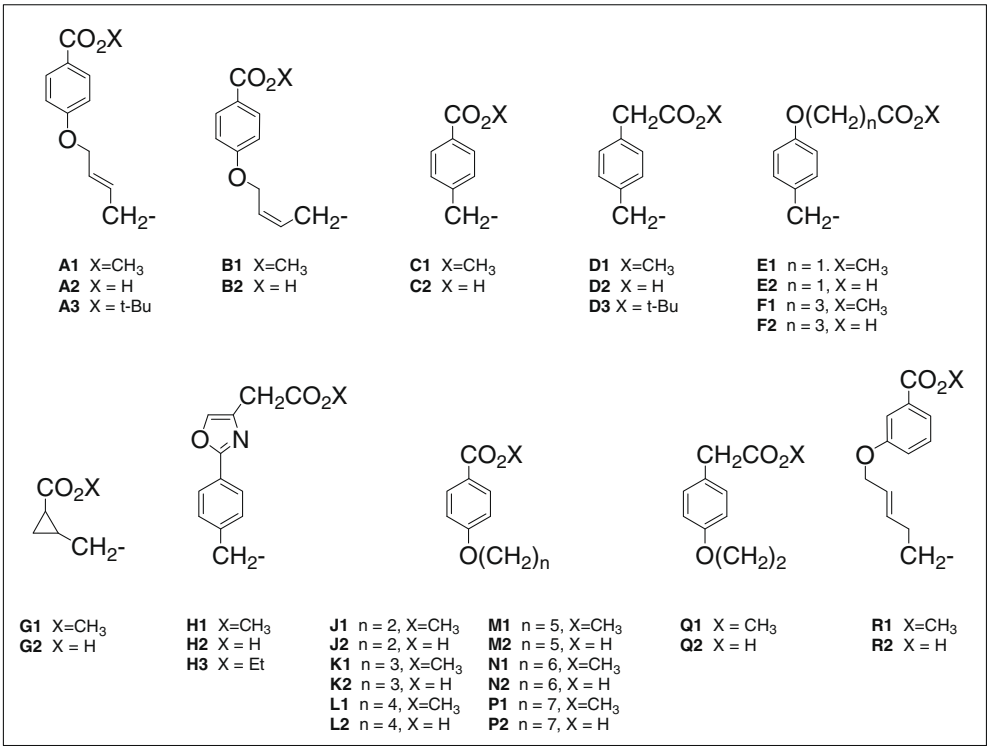
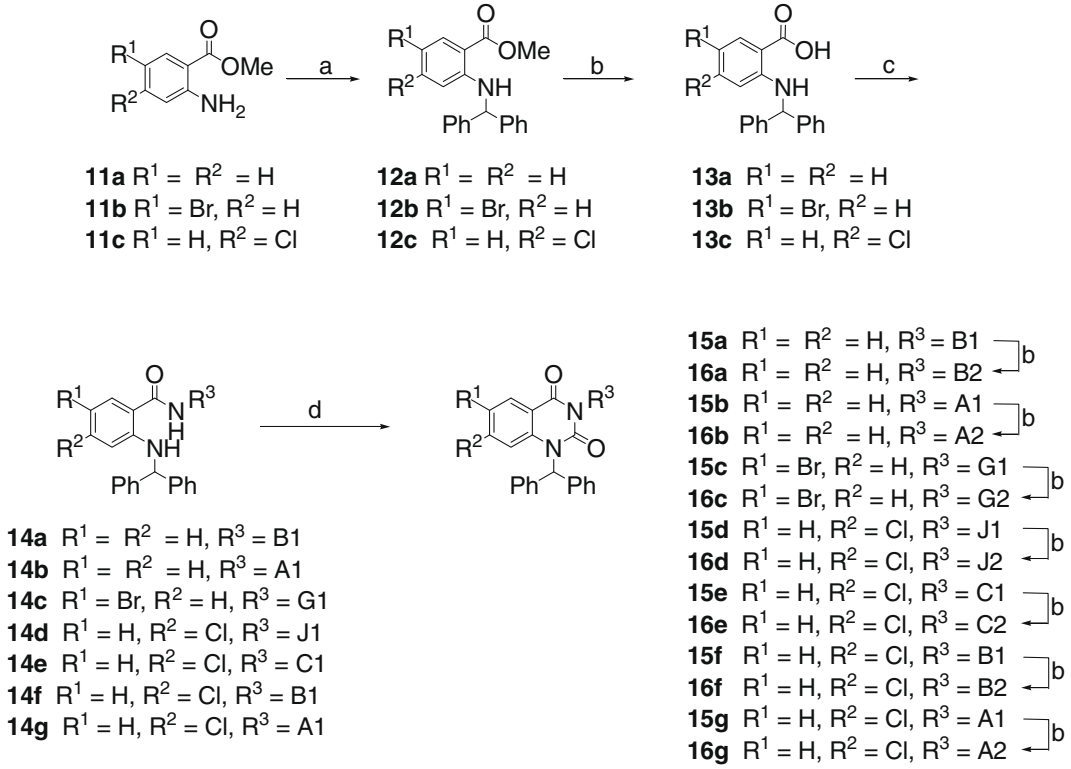
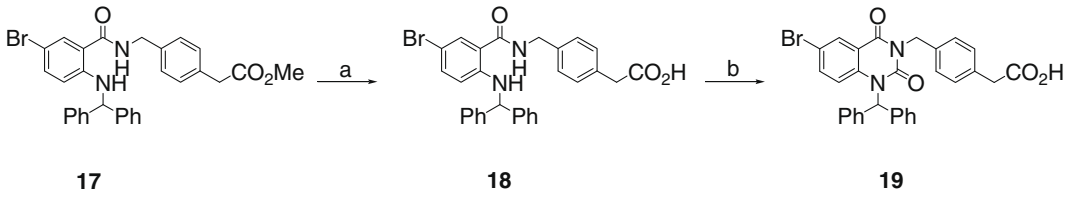


Figure 3. Quinazolinedione substitution key.

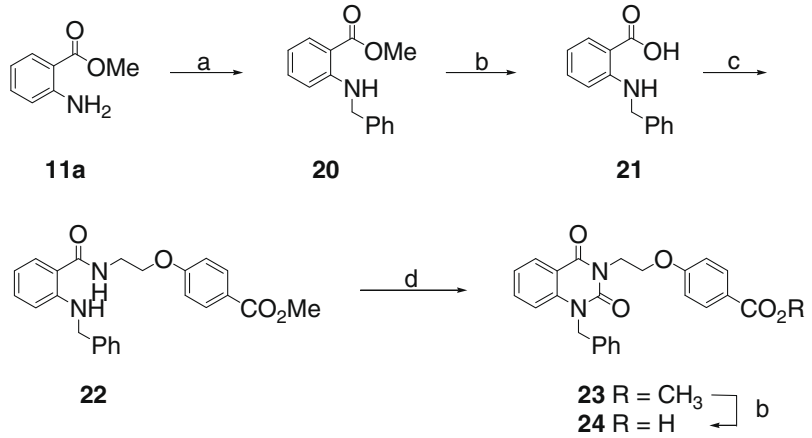
the results did indicate that the distance between these two moieties is important to activity.[33] The initial efforts to find quinazolinedione-based inhibitors began with the investigation of N-3 tethered carboxylic acids containing an N-1 benzhydryl group. (Table 1). As demonstrated by the comparison of **10b** and **16e**, the potency differences between 6- and 7-halogenated quinazolinediones were generally found to be negligible, but these compounds were more potent than 6,7-unsubstituted analogs (**16d**



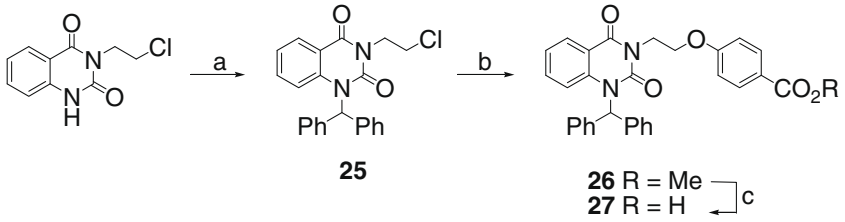
Scheme 2. Reagents and conditions: (a) DIEA, $BrCH(Ph)_2$; (b) NaOH, THF, H_2O, MeOH, 50 °C or TFA, DCM, rt; (c) EDCI, DMAP, DMF, rt; (d) triphosgene, THF, reflux.



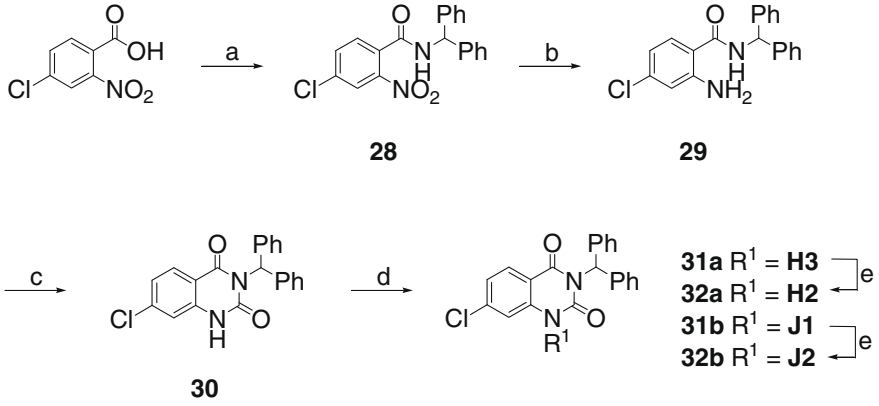
Scheme 3. Reagents and conditions: (a) NaOH, THF, H_2O, MeOH, 50 °C; (b) triphosgene, THF, reflux.



Scheme 4. Reagents and conditions: (a) DIEA, BnBr, DCE, 55 °C; (b) NaOH, THF, H_2O, MeOH, 50 °C; (c) EDCI, DMAP, amine, rt; (d) triphosgene, THF, reflux.

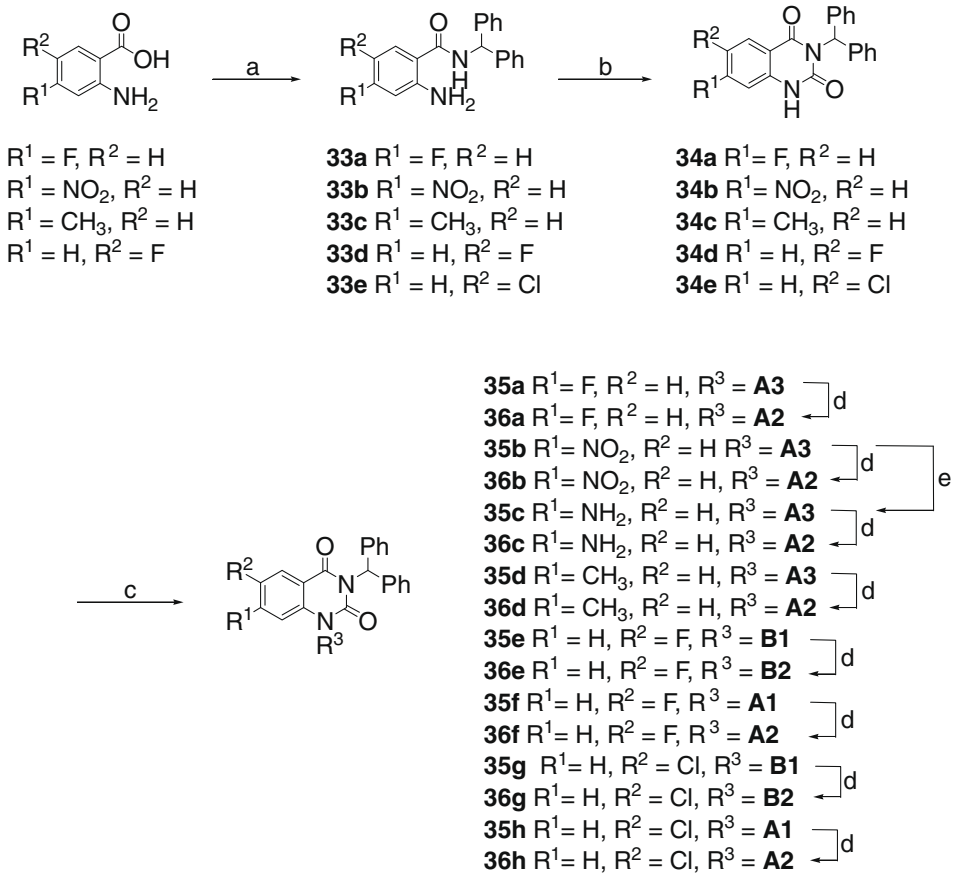


Scheme 5. Reagents and conditions: (a) DIEA, $BrCH(Ph)_2$, DCE, 55 °C (b) NaH, methyl 4-hydroxybenzoate, DMF; (c) NaOH, THF, H_2O, MeOH, 50 °C.

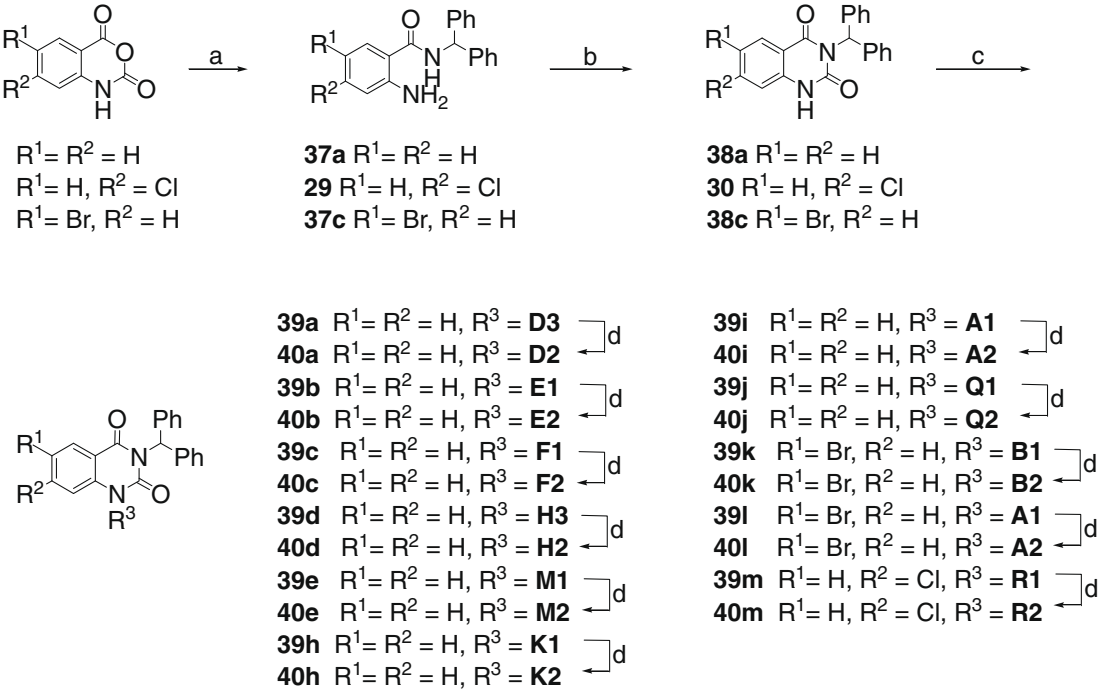


Scheme 6. Reagents and conditions: (a) EDCI, DMAP, $NH_2CH(Ph)_2$, DMF, rt; (b) $SnCl_2{\cdot}2H_2O$, EtOH, 80 °C; (c) triphosgene, THF, reflux; (d) NaH, RX, DMF; (e) NaOH, THF, H_2O, MeOH, 50 °C.

vs **27**). With the addition of a one-carbon spacer between the aromatic ring and the acid of **10b**, a sevenfold potency gain was realized with phenylacetic acid **19**. When the ether linker spanning the heterocycle and the benzoic acid was extended from one (**10b**) to three atoms (**16d**), potency was improved by a factor of 20. Replacing the phenyl group of **10b** with the trans-substituted cyclopropyl ring decreased potency. In the case of an unsaturated 5-atom linker, the potency was sensitive to olefin geometry as shown by the comparison of **16f** and **16g**. These data are consistent with the results from the indole series,[33] and suggest that linker length,

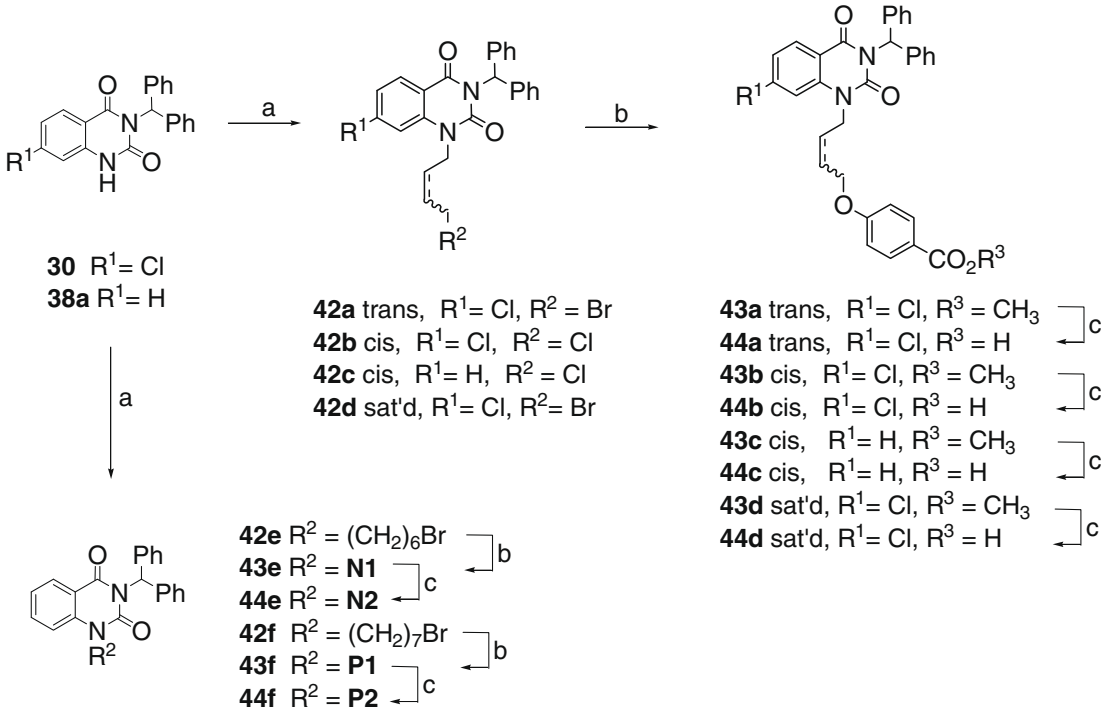


Scheme 7. Reagents and conditions: (a) EDCI, $NH_2CH(Ph)_2$, DMAP, DMF, rt; (b) triphosgene, THF, reflux; (c) NaH, R^3X, DMF; (d) NaOH, THF, H_2O, MeOH, 50 °C or TFA, DCM; (e) $SnCl_2{\cdot}2H_2O$, EtOH, 80 °C.

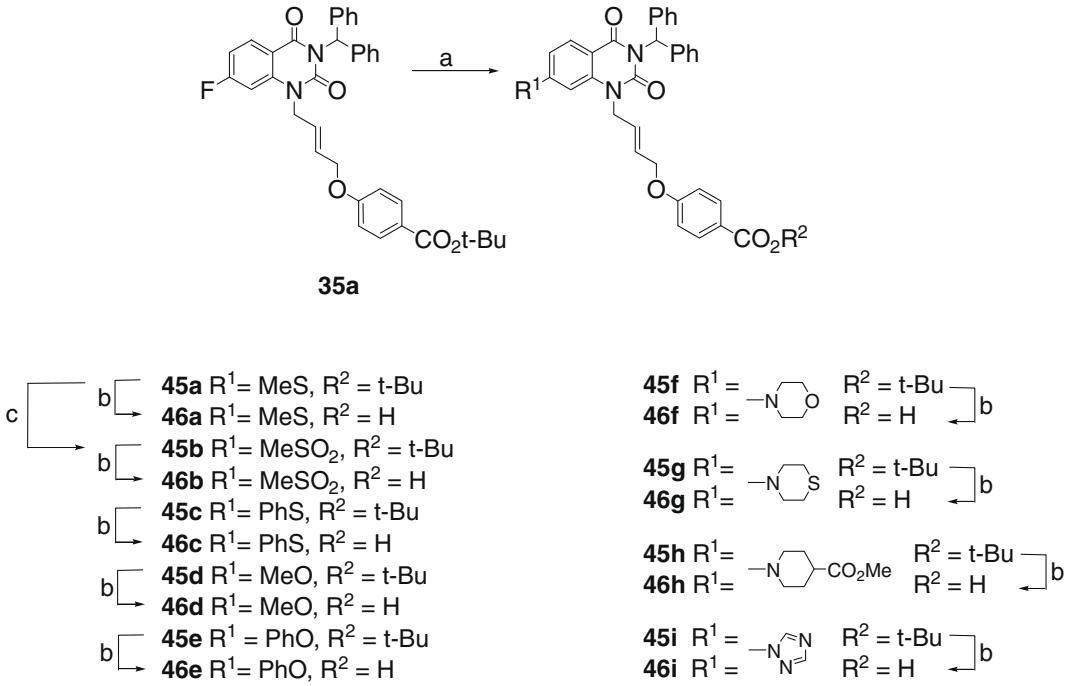


Scheme 8. Reagents and conditions: (a) $NH_2CH(Ph)_2$, CH_3CN, reflux, 48 h; (b) triphosgene, THF, reflux; (c) NaH, R^3X, DMF; (d) NaOH, THF, H_2O, MeOH, 50 °C or TFA, DCM.

linker flexibility and the placement of the phenyl ring dramatically affect potency. The fact that **16d** and **16g** are equipotent indicates that there may be more than one site on the enzyme capable of accommodating an interaction with the carboxylate, and the dra-



Scheme 9. Reagants and conditions: (a) NaH, RX, DMF; (b) NaH, methyl 4-hydroxy-benzoate, DMF; (c) NaOH, THF, H_2O, MeOH, 50 °C.



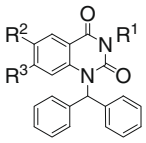
Scheme 10. Reagents and conditions: (a) nucleophile, DMF, 60 °C, 16 h; (b) TFA, DCM; (c) mCPBA, DCM.

matic difference between **16f** and **16g** suggests that linker length and configuration can affect this interaction.

The departure from indoles to quinazolinediones provided an opportunity to start with a more polar core, and the elimination of one of the phenyl rings of the benzhydryl group would address our general goal of reducing lipophilicity. As shown in Table 2, consistent with the parent indoles, considerable activity is lost in the quinazolinedione series upon converting the benzhydryl to a benzyl group.

From this initial SAR exploration of the N-1 benzhydrylquinazolinediones, a comparison with the analogous indole-based $cPLA_{2\alpha}$ inhibitor **5** is possible (Table 3). Quinazolinedione **16d** does have a slightly higher molecular weight, but the desired reduction in lipophilicity has been achieved while maintaining activity in the GLU micelle assay.[33] Indole **5** is slightly more active in the cell-based MC-9 selectivity assay[33,44] which measures the inhibition of both LTB_4 and $PGF_{2\alpha}$ production. A $cPLA_{2\alpha}$ inhibitor would affect the biosynthesis of these inflammatory mediators, but similar results could

Table 1
N-3 linked carboxylic acids



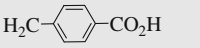
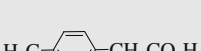
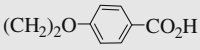
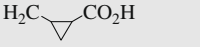
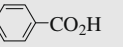
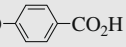
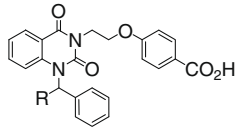
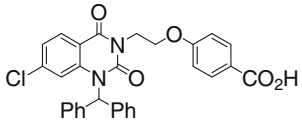
Compound	R^1	R^2	R^3	GLU IC_{50} (μM)
10b		Cl	H	90
16e		H	Cl	80
19		Br	H	12
16d		H	Cl	4
27		H	H	10
16c		Br	H	120
16f	*cis* - $CH_2CH{=}CHCH_2O$ 	H	Cl	60
16g	*trans* - $CH_2CH{=}CHCH_2O$ 	H	Cl	4.5

Table 2
N-1 benzyl–benzhydryl comparison

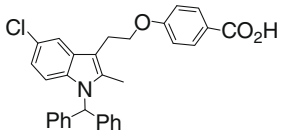


Compound	R	GLU IC_{50} (μM)
24	H	>100
27	Ph	10

Table 3
Quinazolinedione–indole comparison



16d



5

Compound	Mol. wt	plog $D_{7.4}$	GLU IC_{50} (μM)	MC-9 (% Inhib, 5 μM)		
				LTB_4	$PGF_{2\alpha}$	$PGF_{2\alpha}$ AA feed[a]
16d	527	3.3	4	93	61	0
5	496	6.1	3	96	81	−8

[a] Exogenous arachidonic acid added to cells.

arise from a dual inhibitor acting on both the 5-LO and COX pathways. Upon addition of exogenous AA to the cells, the role of $cPLA_{2\alpha}$ is bypassed and the lack of $PGF_{2\alpha}$ inhibition is indicative of a selective $cPLA_{2\alpha}$ inhibitor that does not affect the activity of downstream enzymes in the PG biosynthetic pathway. These promising early results indicate that reduced lipophilicity is possible while maintaining activity and target selectivity in enzymatic and cell-based assays.

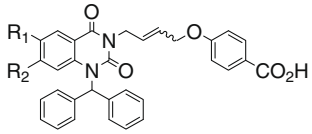
The *trans*-5-atom (butenyloxy) linker provided one of the most potent N-1 benzhydryl-quinazolinediones, and this result was followed-up to determine whether the preference for *trans*- over *cis*-five atom-linked benzoic acids was consistent (Table 4). These additional examples further demonstrate the effect of the *trans* linker and the relatively minor influence of C-6 and C-7 core substitution. Compounds **16d** (Table 1) and **16g** are equipotent, but the extended linker of the latter apparently contributes to a notable improvement in aqueous solubility (1 vs 28 μg/mL, pH 7.4).

The early SAR in the project largely consisted of indoles containing an N-1 benzhydryl group and a *para*-substituted phenyl ring containing a carboxylic acid linked to C-3 through a one-carbon linker.[42] Similarly functionalized N-3 benzhydryl-quinazolinediones were also examined (Table 5). The acids linked to the phenyl ring with one, two, or four atoms were relatively inactive as was the compound (**40d**) containing an oxazole spacer between the phenyl ring and the acid.

Some of the more active compounds in the N-1 benzhydrylquinazolinedione series have an oxygen containing linker between the core heterocycle and the benzoic acid, and this seemed to be an appropriate region for N-3 benzhydrylquinazolinedione SAR exploration (Table 6). Lengthening the three-atom linker of **32b** by one carbon atom resulted in a fivefold loss in activity. The addition of two carbon atoms to **32b** resulted in a fourfold improvement. As shown by the data resulting from further chain lengthening, the five-atom linker, as also observed in the case of the N-1 benzhydryl-quinazolinediones, provided the optimal distance between the core and the acid (**44d**).

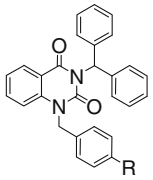
In the N-1 benzhydrylquinazolinedione series, the most active compound (**16g**) contains a *trans* olefin-containing five atom linker (four carbons plus oxygen), and it was approximately 10-fold more potent than **16f** which has the corresponding *cis* linker (Table 1). This trend is also consistent across a variety of N-3 benzhydryl analogs (Table 7). Compound **44d**, which has a saturated linker, is equipotent to *trans* analog **44a**. These *trans*-linked benzoic acids were the first non-indole $cPLA_{2\alpha}$ inhibitors to exhibit low micro-

Table 4
N-3 linker olefin geometry



Compound	R^1	R^2	Olefin	GLU IC_{50} (μM)	$Solubility_{7.4}$ (μg/mL)
16a	H	H	Cis	25	37
16b	H	H	Trans	2	51
10a	F	H	Trans	5.6	42
16f	H	Cl	Cis	60	51
16g	H	Cl	Trans	4.5	28

Table 5
N-1 benzyl-linked carboxylic acids



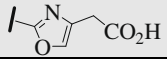
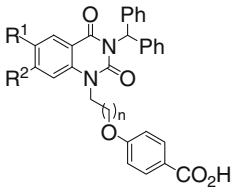
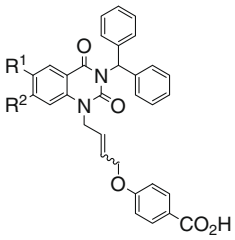
Compound	R	GLU IC_{50} (μM)
40a	CH_2CO_2H	260
40b	OCH_2CO_2H	360
40c	$O(CH_2)_3CO_2H$	40
40d		140

Table 6
N-1 linked benzoic acid SAR



Compound	*n*	R^1	R^2	GLU IC_{50} (μM)
32b	1	H	Cl	10
40h	2	H	H	50
44d	3	Cl	H	2.5
40e	4	H	H	30
44e	5	H	H	47
44f	6	H	H	71

Table 7
N-1 linker olefin geometry SAR



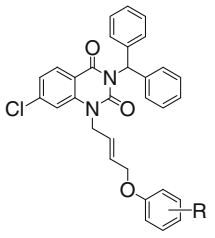
Compound	R^1	R^2	Olefin	GLU IC_{50} (μM)
44c	H	H	Cis	44
40i			Trans	3
36e	F	H	Cis	40
36f			Trans	6
36a	H	F	Trans	1.4
36g	Cl	H	Cis	40
36h			Trans	10
40k	Br	H	Cis	30
40l			Trans	9
44b	H	Cl	Cis	30
44a			Trans	1
44d			Satd	2.5

molar activity in the rat whole blood assay (**40i**: IC_{50} = 14 μM; **36a** (6 μM); **44a** (11 μM). Like the N-1-benzhydryl analogs, the potency of these compounds varies minimally with respect to C-6 and C-7 substitution. One of the goals of this non-indole effort was to discover inhibitors that had improved physical properties. When compared to both the indoles and the *cis*-linked acids, the *trans*-linked quinazolinediones **40i** (55 μg/mL), **36f** (53 μg/mL), and **44a** (25 μg/mL) have considerably improved aqueous solubility (pH 7.4).

Like the indole $cPLA_{2\alpha}$ inhibitors, the level of quinazolinedione activity depends on the benzhydryl group and an appropriately spaced benzoic acid. Previous results in the indole series have shown that the *para*-substituted aromatic ring is significantly more active than the corresponding *meta*-acid.[33,34] In the case of the N-3 benzhydryl-quinazolinediones, *para*-acid **44a** is two orders of magnitude more potent than the *meta* analog **40m** (Table 8).

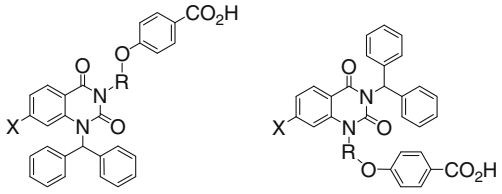
The switch from N-1 to N-3 benzhydrylquinazolinediones was made based on synthetic considerations, but a comparison between the two series is nonetheless worthwhile. In the case of the three and five atom-linked benzoic acids (Table 9), the activity differences between N-1 and N-3 substitution are nominal, and the *trans*-butenyloxy-linked benzoic acid is consistently more potent than the *cis* isomer in both the N-1 and N-3 benzhydrylquinazolinediones.

Table 8
The effect of carboxylic acid placement



Compound	R	GLU IC_{50} (μM)
40m	*m*-CO_2H	100
44a	*p*-CO_2H	1

Table 9
Regioisomeric quinazolinedione comparison

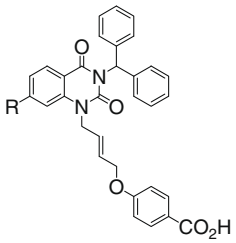


A B

Series	Compound	X	R	GLU IC_{50} (μM)
A	**27**	H	CH_2CH_2	10
B	**32b**	Cl		10
A	**16a**	H	*cis*-$CH_2CH{=}CHCH_2$	25
B	**44c**	H		44
A	**16b**	H	*trans*-$CH_2CH{=}CHCH_2$	2
B	**40i**	H		3

The early stages of quinazolinedione SAR exploration were heavily influenced by the experience gained from the indole $cPLA_{2\alpha}$ inhibitors. Isolated enzyme and whole blood activities have been reduced to low micromolar levels, but the increased polarity of the quinazolinedione core has just modestly improved upon the physicochemical properties of the lead indole series. The limited variety of C-6 and C-7 quinazolinedione substitution has generally made little or no contribution to the potency, and as such, this presented an opportunity to introduce polar functionality. As shown in Table 10, a series of C-7 substituted compounds were examined with the purpose of exploring the possibility of improving upon the physicochemical properties of the lead N-3 benzhydrylquinazolinedione series. There is no discernable correlation between activity and either C-7 substituent size, polarity or electronegativity. The relationship between plog *D* and solubility is more apparent; the compounds of greatest polarity have the best aqueous solubility (**46b**, **46i**, and **36c**), and the least polar compounds (**46c** and **46e**) have the poorest solubility. The quinazolinediones with the best membrane permeability, as measured in a PAMPA[45] assay, have plog *D* values in the 2.5–3.5 range. The poor permeability of high plog *D* compounds **46c** and **46e** is most likely the result of low solubility. Of the three most soluble, polar compounds (**46b**, **46i**, and **36c**), **46i** is distinguished by its enzymatic activity and good permeability. In the case of **46b** and **36c**, there is a measurable difference in both activity and permeability, and a comparison of **46b** and **46i** shows that good activity can be achieved with lower plog *D*. The low correlation between activity and polarity further corroborates our previous findings from the indole series: the GLU micelle assay provides enzyme inhibition data that is not skewed by the possible existence of non-specific, hydrophobic interactions.[33]

Table 10
C-7 aromatic substitution



Compound	R	GLU IC_{50} (μM)	Solubility$_{7.4}$ (μg/mL)	plog $D_{7.4}$	PAMPA$_{7.4}$ ($\times 10^{-6}$ cm/s)
46a	CH_3S	2	26	3.2	4.5
46b	CH_3SO_2	15	>100	1.4	0.3
46c	PhS	2.1	0	4.8	0
46d	CH_3O	3	40	2.8	1.8
46e	PhO	1.6	15	4.8	0
46f		2.2	48	2.5	1.0
46g		2.4	–	3.6	–
46h		1.8	30	3.3	1.0
46i		1.1	>100	1.4	1.6
36a	F	1.4	–	2.9	–
36b	NO_2	1	34	2.4	2.6
36c	NH_2	9	>100	1.7	0.4
36d	CH_3	2.8	40	3.2	2.0

Table 11
Secondary assays

Compound	Rat WB IC_{50} (μM)	MC-9 (% Inhib, 5 μM)		
		LTB_4	$PGF_{2\alpha}$	$PGF_{2\alpha}$ AA feed[a]
16b	12	98	61	−15
40i	14	97	52	−476
36a	6	99	83	−27
44a	11	98	99	−45
46d	9	99	74	−98
46i	11	100	102	−28
36b	13	97	30	−12

[a] Exogenous arachidonic acid added to cells.

A subset of N-1 and N-3 quinazolinediones were tested in the rat whole blood and MC-9 assays (Table 11). These compounds maintain activity in this assay, with ~5–10-fold loss in potency when compared to the enzymatic assay data. All of the compounds inhibited COX-1 dependent $PGF_2\alpha$ production in the MC-9 assay, and the inhibition was lost when exogenous AA was added to bypass $cPLA_2\alpha$. These data indicate that the inhibitors are acting on $cPLA_2\alpha$ to block AA release. Interestingly, the quinazolinediones inhibited LTB_4 to a greater extent than $PGF_2\alpha$, suggesting some additional inhibition of the 5-LO pathway. A similar bias toward inhibition of LTB_4 was observed when **46i** was assayed in human blood. Dual inhibition of $cPLA_2\alpha$ and 5-LO pathways would not be seen as a liability. Inhibitors blocking multiple AA processing enzymes are known in the literature, and subtle changes can shift the relative potency dramatically.[46] We continue to explore this series with the expectation, but not the requirement, that 5-LO inhibition will be minimized.

4. Conclusions

A novel, second series of $cPLA_2\alpha$ inhibitors were developed utilizing SAR data gathered from an earlier indole series. Good activity in the quinazolinedione series requires the presence of a tethered benzoic acid and a benzhydryl group. The appropriate length and geometry of this tether is of critical importance as is the *para*-substituted benzoic acid. The incorporation of polar C-7 functionality provides $cPLA_2\alpha$ selective compounds with low micromolar activity in both enzymatic and whole blood assays. Furthermore, this substitution provides water-soluble compounds with plog *D* and clog *P* values below 2 and 5, respectively. As exemplified by the dearth of polar, low molecular weight $cPLA_2\alpha$ inhibitors reported in the literature, the quinazolinediones represent a positive step toward the discovery of drug-like inhibitors.

5. Experimental

All solvents and reagents were used as obtained. ^1H and ^{13}C NMR spectra were recorded at 300 MHz on a Varian Gemini 2000 or a 400 MHz Bruker AV-400 spectrometer using TMS (δ 0.0) as a reference. Low resolution mass spectra were obtained using a Micromass Platform Electrospray Ionization Quadrapole mass spectrometer. High resolution mass spectra were obtained using a Bruker (Billerica, MA) APEXIII Fourier transform ion cyclotron resonance (FT-ICR) mass spectrometer equipped with an actively shielded 7 Tesla superconducting magnet (Magnex Scientific Ltd, UK) and an external Bruker APOLLO electrospray ionization (ESI) source. Flash chromatography was performed using EM Science 230–400 mesh silica gel or Biotage flash columns packed with KP-SIL 60 Angstrom silica gel. Thin-layer chromatography (TLC) was performed using EMD 250 μm prescored Silica Gel 60 F_{254} plates.

5.1. General procedure for amide coupling

A mixture of acid (1.0 mmol), amine (1.5 equiv), EDCI (1.2 equiv), and DMAP (5 mol %) in DMF (5 mL) was stirred at rt for 5 h. The mixture was diluted with EtOAc, washed with water (3 × 100 mL), dried over $MgSO_4$, evaporated, and flash chromatographed (EtOAc–hexanes) to afford the amide.

5.2. General procedure for aniline alkylation

A mixture of aniline (1.0 mmol), (bromomethylene)dibenzene (1.4 equiv), and DIEA (1.1 equiv) in DCE (5 mL) was heated at 55 °C for 16 h. The solvent was removed by evaporation and the residue was flash chromatographed (EtOAc–hexanes) to afford the aniline.

5.3. General procedure for quinazolinedione cyclization

A mixture of amino-amide (1.0 mmol) and triphosgene (5 equiv) in THF was heated at reflux for 20 h. The cooled solution was partitioned between EtOAc and satd aq $NaHCO_3$. The organic layer was washed with brine, dried over $MgSO_4$, and flash chromatographed (EtOAc–hexanes) to afford the quinazolinedione.

5.4. General procedure for basic ester hydrolysis

A solution of ester (1.0 mmol) and either NaOH or LiOH (3.0 mmol) was dissolved in a mixture of THF, MeOH, and water (2:1:1 5 mL), and was heated at 50 °C until the starting material was consumed as determined by TLC. The cooled solution was acidified with 1 N HCl, diluted with ethyl acetate, washed with water and brine, dried, filtered, evaporated, and flash chromatographed (EtOAc–hexanes) to afford the carboxylic acid.

5.5. General procedure for phenol alkylation

To a solution of phenol (1.0 mmol) in DMF (5 mL) was added 60% NaH (1.1 equiv). After 10 min at rt, the halide (1.0 equiv)

was added dropwise as a DMF (2 mL) solution, and the reaction was stirred overnight. The reaction was quenched with water, extracted with EtOAc, washed with water, 1 N NaOH, and brine, dried, filtered, evaporated, and flash chromatographed (EtOAc–hexanes) to afford the ether.

5.6. General procedure for isatoic anhydride aminolysis

A solution of isatoic anhydride (1 mmol) and diphenylmethanamine (1.5 equiv) in ACN (10 mL) was heated at reflux for 48 h. The solution was diluted with EtOAc (50 mL), washed with H_2O, 10% aq HCl, and brine, dried, filtered, and evaporated to provide the crude aminoamide.

5.7. General procedure for N-1 quinazolinedione alkylation

To a solution of quinazolinsdione (1.0 mmol) in DMF (5 mL) was added 60% NaH (1.1 equiv). After 10 min at rt, the halide (1.0 equiv) was added dropwise as a DMF (2 mL) solution, and the reaction was stirred at room temperature for 3 h and then for 2 h at 100 °C. The reaction was quenched with water, extracted with EtOAc, washed with water and brine, dried, filtered, evaporated, and flash chromatographed (EtOAc–hexanes) to afford the N-1 alkylated quinazolinedione.

5.8. General procedure for nitro reduction

A suspension of the nitro compound (1 mmol) and tin chloride dihydrate (4.8 equiv) in ethanol (10 mL) was stirred at 80 °C for 1.5 h. To the cooled solution was added Celite and solid $NaHCO_3$ (10 equiv) followed by the dropwise addition of water until all acid is neutralized. The suspension is filtered, diluted with EtOAc, washed with brine, dried, filtered, evaporated, and flash chromatographed (EtOAc–hexanes) to provide the aniline.

5.9. General procedure for acidic ester hydrolysis

A solution of *tert*-butyl ester (1 mmol), and triethylsilane (5 equiv) in DCM (5 mL) and trifluoroacetic acid (5 mL) was stirred at room temperature for 2 h. The solution was evaporated and flash chromatographed (EtOAc–hexanes) to provide the carboxylic acid.

5.10. General procedure for nucleophilic aromatic substitution

A solution of **35a** (200 mg, 0.34 mmol) and nucleophile (3–5 equiv) in DMF was heated at 60 °C for 16 h. The solution was diluted with ethyl acetate, washed with water and brine, dried, filtered, and flash chromatographed (EtOAc–hexanes) to provide the N-7 functionalized quinazolinedione.

5.10.1. *tert*-Butyl 4-({(2*E*)-4-[(2-amino-5-fluorobenzoyl)amino]but-2-en-1-yl}oxy)benzoate (7a)

The general amide coupling procedure was followed utilizing acid **6a** and methyl 4-{[(2*E*)-4-aminobut-2-en-1-yl]oxy}benzoate (0.74 g, 13%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.57 (s, 9H), 4.02–4.15 (m, 2H), 4.48–4.57 (m, 2H), 5.93 (d, J = 4.0 Hz, 2H), 6.47–6.53 (m, 1H), 6.70–6.80 (m, 1H), 6.88 (d, J = 9.0 Hz, 2H), 6.90–7.02 (m, 1H), 7.12 (dd, J = 9.0, 3.3 Hz, 1H), 7.91 (d, J = 8.8 Hz, 2H).

5.10.2. *tert*-Butyl 4-{[(2*E*)-4-({2-[(diphenylmethyl)amino]-5-fluorobenzoyl}amino)but-2-en-1-yl]oxy}benzoate (8a)

The general aniline alkylation procedure was followed utilizing **7a** (110 mg, 58%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.58 (s, 9H), 4.06 (br s, 2H), 4.54 (d, J = 3.5 Hz, 2H), 5.55 (s, 1H), 5.93 (d, J = 4.0 Hz, 2H), 6.58–6.70 (m, 2H), 6.80–6.97 (m, 3H), 7.17–7.32 (m, 10H), 7.93 (d, J = 8.5 Hz, 2H).

5.10.3. *tert*-Butyl 4-({(2*E*)-4-[1-(diphenylmethyl)-6-fluoro-2,4-dioxo-1,4-dihydroquinazolin-3(2*H*)-yl]but-2-en-1-yl}oxy)benzoate (9a)

The general quinazolinedione cyclization procedure was followed utilizing **8a** (342 mg, 53%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.57 (s, 9H), 4.56 (s, 2H), 4.79 (s, 2H), 6.03 (s, 2H), 6.87 (d, J = 8.8 Hz, 2H), 7.00–7.10 (m, 2H), 7.22–7.42 (m, 10H), 7.90 (d, J = 8.8 Hz, 2H).

5.10.4. 4-({(2*E*)-4-[1-(Diphenylmethyl)-6-fluoro-2,4-dioxo-1,4-dihydroquinazolin-3(2*H*)-yl]but-2-en-1-yl}oxy)benzoic acid (10a)

The general acidic ester hydrolysis conditions were followed utilizing **9a** (141 mg, 91%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.60 (br s, 2H), 4.81 (br s, 2H), 6.03 (br s, 2H), 6.93 (d, J = 9.0 Hz, 2H), 7.00–7.15 (m, 2H), 7.25–7.42 (m, 10H), 7.74 (s, 1H), 7.87 (dd, J = 7.9, 2.2 Hz, 1H), 8.02 (d, J = 8.9 Hz, 2H); ^{13}C NMR (DMSO-d_6) 169.26, 159.99, 159.32, 158.57, 156.16, 150.22, 137.18, 136.21, 130.65, 128.74, 128.50, 128.01, 127.56, 127.50, 127.33, 126.77, 122.02, 121.78, 119.24, 119.16, 117.25, 117.18, 113.30, 113.11, 67.19, 61.56, 42.56; HRMS: $C_{32}H_{25}FN_2O_5$ requires $(M+1)^+$ at m/z 537.1820; found, 537.1824.

5.10.5. Methyl 4-({[(2-amino-5-chlorophenyl)carbonyl]amino}-methyl)benzoate (7b)

The general amide coupling procedure was followed utilizing acid **6b** and methyl 4-(aminomethyl)benzoate (2.2 g, 73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.91 (s, 3H), 4.64 (d, J = 6.1 Hz, 2H), 5.54 (s, 2H), 6.40–6.53 (m, 1H), 6.63 (d, J = 8.8 Hz, 1H), 7.16 (dd, J = 8.7, 2.4 Hz, 1H), 7.31 (d, J = 2.5 Hz, 1H), 7.39 (d, J = 8.6 Hz, 2H), 8.01 (d, J = 8.3 Hz, 2H).

5.10.6. Methyl 4-[({5-chloro-2-[(diphenylmethyl)amino]benzoyl}amino)methyl]benzoate (8b)

The general aniline alkylation procedure was followed utilizing **7b** (3.91 g, 62%, white solid). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.95 (s, 3H), 4.65 (d, J = 5.77 Hz, 2H), 5.59 (d, J = 5.22 Hz, 1H), 6.40–6.46 (m, 1H), 6.52 (d, J = 9.07 Hz, 1H), 7.13 (dd, J = 8.93, 2.33 Hz, 1H), 7.21–7.44 (m, 13H), 8.05 (d, J = 8.52 Hz, 2H), 8.35 (d, J = 4.12 Hz, 1H).

5.10.7. Methyl 4-{[6-chloro-1-(diphenylmethyl)-2,4-dioxo-1,4-dihydroquinazolin-3(2*H*)-yl]methyl}benzoate (9b)

The general quinazolinedione cyclization procedure was followed utilizing **8b** (549 mg, 50%, white solid). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.93 (s, 3H), 5.37 (s, 2H), 7.06 (d, J = 9.07 Hz, 1H), 7.23–7.45 (m, 11H), 7.54 (d, J = 8.52 Hz, 2H), 7.73 (s, 1H), 8.01 (d, J = 8.24 Hz, 2H), 8.21 (d, J = 2.47 Hz, 1H).

5.10.8. 4-{[6-Chloro-1-(diphenylmethyl)-2,4-dioxo-1,4-dihydroquinazolin-3(2*H*)-yl]methyl}benzoic acid (10b)

The general basic ester hydrolysis conditions were followed utilizing ester **9b** (0.17 g, 49%, white solid). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.39 (s, 2H), 7.07 (d, J = 9.34 Hz, 1H), 7.22–7.41 (m, 11H), 7.57 (d, J = 8.24 Hz, 2H), 7.73 (s, 1H), 8.08 (d, J = 8.24 Hz, 2H), 8.22 (d, J = 2.47 Hz, 1H); ^{13}C NMR (DMSO-d_6) 167.18, 160.18, 150.42, 141.48, 138.61, 137.09, 134.16, 130.23, 129.37, 128.47, 128.04, 127.52, 127.32, 127.13, 127.02, 118.90, 117.34, 61.90, 44.54; HRMS: $C_{29}H_{21}ClN_2O_4$ requires $(M+1)^+$ at m/z 497.1262; found, 497.1268.

5.10.9. Methyl 2-[(diphenylmethyl)amino]benzoate (12a)

The general aniline alkylation procedure was followed utilizing **11a** (75%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.81 (s, 3H), 5.86 (d,

J = 6.3 Hz, 1H), 6.56–6.66 (m, 2H), 7.02–7.10 (m, 1H), 7.16–7.45 (m, 10H), 8.23 (d, *J* = 7.8 Hz, 1H), 8.50 (d, *J* = 6.3 Hz, 1H).

5.10.10. 2-[(Diphenylmethyl)amino]benzoic acid (13a)

The general basic ester hydrolysis conditions were followed utilizing ester **12a** (84%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.65 (d, *J* = 3.0 Hz, 1H), 6.54–6.63 (m, 2H), 7.25–7.38 (m, 11H), 7.97 (d, *J* = 7.8 Hz, 1H), 8.31 (br s, 1H).

5.10.11. Methyl 4-{[(2*Z*)-4-({2-[(diphenylmethyl)amino]benzoyl}amino)but-2-en-1-yl]oxy}benzoate (14a)

The general amide coupling procedure was followed utilizing acid **13a** and *cis*-4-(4-amino-but-2-enyloxy) benzoate (63 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.89 (s, 3H), 4.13 (t, *J* = 6.0 Hz, 2H), 4.72 (d, *J* = 5.7 Hz, 2H), 5.58 (d, *J* = 6.0 Hz, 1H), 5.74–5.94 (m, 2H), 6.14–6.20 (m, 1H), 6.50–6.55 (m, 2H), 6.92 (d, *J* = 9.0 Hz, 2H), 7.12–7.40 (m, 12H), 7.98 (d, *J* = 9.0 Hz, 2H), 8.40 (d, *J* = 5.7 Hz, 1H).

5.10.12. Methyl 4-({(2*Z*)-4-[1-(diphenylmethyl)-2,4-dioxo-1,4-dihydroquinazolin-3(2*H*)-yl]but-2-en-1-yl}oxy)benzoate (15a)

The general quinazolinedione cyclization procedure was followed utilizing aminoamide **14a** (21%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.89 (s, 3H), 4.86 (d, *J* = 6.3 Hz, 2H), 4.92 (d, *J* = 6.3 Hz, 2H), 5.78–5.97 (m, 2H), 7.00 (d, *J* = 9.3 Hz, 2H), 7.05–7.23 (m, 2H), 7.26–7.45 (m, 11H), 7.74 (s, 1H), 7.97 (d, *J* = 9.3 Hz, 2H), 8.23 (d, *J* = 8.8 Hz, 1H).

5.10.13. 4-({(2*Z*)-4-[1-(Diphenylmethyl)-2,4-dioxo-1,4-dihydroquinazolin-3(2*H*)-yl]but-2-en-1-yl}oxy)benzoic acid (16a)

The general basic ester hydrolysis conditions were followed utilizing ester **15a** (94%, hexane/$CHCl_3$ trituration). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.70 (d, *J* = 5.4 Hz, 2H), 4.86 (d, *J* = 5.4 Hz, 2H), 5.63–5.85 (m, 2H), 7.04 (d, *J* = 9.0 Hz, 2H), 7.15–7.55 (m, 13H), 7.60 (s, 1H), 7.86 (d, *J* = 8.8 Hz, 2H), 8.10 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (DMSO-d_6) 169.82, 160.80, 158.69, 150.61, 139.45, 137.30, 134.24, 133.18, 130.54, 128.70, 128.46, 128.09, 128.02, 127.42, 122.94, 116.83, 115.75, 112.86, 63.66, 61.20, 28.98; HRMS: $C_{32}H_{26}N_2O_5$ requires $(M+1)^+$ at *m/z* 519.1914; found, 519.1915.

5.10.14. Methyl 4-{[(2*E*)-4-({2-[(diphenylmethyl)amino]benzoyl}amino)but-2-en-1-yl]oxy}benzoate (14b)

The general amide coupling procedure was followed utilizing acid **13a** and *trans*-4-(4-amino-but-2-enyloxy) benzoate (76%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.88 (s, 3H), 4.05–4.13 (m, 2H), 4.57 (d, *J* = 2.6 Hz, 2H), 5.59 (d, *J* = 5.4 Hz, 1H), 5.86–6.02 (m, 2H), 6.15–6.24 (m, 1H), 6.52–6.62 (m, 2H), 7.14–7.40 (m, 11H), 7.97 (d, *J* = 8.7 Hz, 2H), 8.38 (d, *J* = 5.4 Hz, 1H).

5.10.15. Methyl 4-({(2*E*)-4-[1-(Diphenylmethyl)-2,4-dioxo-1,4-dihydroquinazolin-3(2*H*)-yl]but-2-en-1-yl}oxy)benzoate (15b)

The general quinazolinedione cyclization procedure was followed utilizing aminamide **14b** (65%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.87 (s, 3H), 4.53–4.59 (m, 2H), 4.78–4.82 (m, 2H), 6.00–6.05 (m, 2H), 6.91 (d, *J* = 8.7 Hz, 2H), 7.05–7.20 (m, 2H), 7.25–7.40 (m, 11H), 7.71 (br s, 1H), 7.95–8.00 (m, 2H), 8.22 (d, *J* = 7.5 Hz, 1H).

5.10.16. 4-({(2*E*)-4-[1-(Diphenylmethyl)-2,4-dioxo-1,4-dihydroquinazolin-3(2*H*)-yl]but-2-en-1-yl}oxy)benzoic acid (16b)

The general basic ester hydrolysis conditions were followed utilizing ester **15b** (80%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.57–4.66 (m, 4H), 5.75–6.00 (m, 2H), 6.99 (d, *J* = 8.7 Hz, 2H), 7.19–7.40 (m, 12H), 7.47–7.58 (m, 2H), 7.85 (d, *J* = 8.7 Hz, 2H), 8.09 (dd, *J* = 7.7, 2.0 Hz, 1H); ^{13}C NMR (DMSO-d_6) 169.77, 160.70, 158.74, 150.45, 139.55, 137.39, 134.33, 133.19, 130.52, 128.47, 128.13, 128.00, 127.55, 127.42, 126.93, 122.97, 116.74, 115.67, 112.80, 67.14, 62.51, 61.32, 42.33, 37.12, 28.99; HRMS: $C_{32}H_{26}N_2O_5$ requires $(M+1)^+$ at *m/z* 519.1914; found, 519.1917.

5.10.17. Methyl 5-bromo-2-[(diphenylmethyl)amino]benzoate (12b)

The general aniline alkylation procedure was followed utilizing **11b** (0.94 g, 60%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.85 (s, 3H), 5.59 (d, *J* = 5.6 Hz, 1H), 6.42 (d, *J* = 9.1 Hz, 1H), 7.19–7.42 (m, 10H), 8.03 (d, *J* = 2.5 Hz, 1H), 8.44 (d, *J* = 5.3 Hz, 1H).

5.10.18. 5-Bromo-2-[(diphenylmethyl)amino]benzoic acid (13b)

The general basic ester hydrolysis conditions were followed utilizing ester **12b** (95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 5.61 (d, *J* = 5.1 Hz, 1H), 6.45 (d, *J* = 9.1 Hz, 1H), 7.22–7.40 (m, 11H), 8.08 (d, *J* = 2.5 Hz, 1H), 8.28 (d, *J* = 4.8 Hz, 1H).

5.10.19. Ethyl 2-[({5-bromo-2-[(diphenylmethyl)amino]benzoyl}amino)-methyl]cyclopropanecarboxylate (14c)

The general amide coupling procedure was followed utilizing acid **13b** and *trans*-methyl 2-(aminomethyl)cyclopropane-carboxylate (1.19 g, 52%). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 0.85–0.96 (m, 1H), 1.21–1.28 (m, 1H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.56–1.66 (m, 1H), 1.66–1.79 (m, 1H), 3.24–3.44 (m, 2H), 4.15 (q, *J* = 7.0 Hz, 2H), 5.56 (d, *J* = 4.9 Hz, 1H), 6.36 (t, *J* = 5.2 Hz, 1H), 6.44 (d, *J* = 8.8 Hz, 1H), 7.17–7.43 (m, 12H), 7.49 (d, *J* = 2.2 Hz, 1H), 8.34 (d, *J* = 4.9 Hz, 1H).

5.10.20. Ethyl 2-{[6-bromo-1-(diphenylmethyl)-2,4-dioxo-1,4-dihydroquinazolin-3(2*H*)-yl]methyl}cyclopropanecarboxylate (15c)

The general quinazolinedione cyclization procedure was followed utilizing aminoamide **14c** (231 mg, 44%). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 0.99–1.09 (m, 1H), 1.22–1.29 (m, 1H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.67–1.75 (m, 1H), 1.77–1.90 (m, 1H), 3.68 (d, *J* = 5.5 Hz, 2H), 4.17 (q, *J* = 7.0 Hz, 2H), 6.83 (d, *J* = 9.1 Hz, 1H), 7.25–7.45 (m, 11H), 8.20 (d, *J* = 2.2 Hz, 1H).

5.10.21. 2-{[6-Bromo-1-(diphenylmethyl)-2,4-dioxo-1,4-dihydroquinazolin-3(2*H*)-yl]methyl}cyclopropanecarboxylic acid (16c)

The general basic ester hydrolysis conditions were followed utilizing ester **15c** (188 mg, 86%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.92–1.02 (m, 2H), 1.58–1.73 (m, 2H), 3.87–4.01 (m, 2H), 7.18 (d, *J* = 9.1 Hz, 1H), 7.28–7.43 (m, 10H), 7.55 (s, 1H), 7.70 (dd, *J* = 9.1, 2.5 Hz, 1H), 8.15 (d, *J* = 2.5 Hz, 1H), 12.13 (s, 1H); HRMS: $C_{26}H_{21}BrN_2O_4$ requires $(M+1)^+$ at *m/z* 505.0758; found, 505.0762.

5.10.22. Methyl 4-[2-({4-chloro-2-[(diphenylmethyl)amino]benzoyl}amino)ethoxy]benzoate (14d)

The general amide coupling procedure was followed utilizing acid **13c** and methyl 4-(2-aminoethoxy)benzoate (1.04 g, 53%, white solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.81 (dd, *J* = 5.56 Hz, 2H), 3.89 (s, 3H), 4.16 (t, *J* = 5.18 Hz, 2H), 5.55 (d, *J* = 5.81 Hz, 1H), 6.47 (t, *J* = 5.43 Hz, 1H), 6.52 (s, 1H), 6.55 (d, *J* = 2.02 Hz, 1H), 6.92 (d, *J* = 9.09 Hz, 2H), 7.31 (m, 11H), 7.99 (d, *J* = 9.09 Hz, 2H), 8.57 (d, *J* = 5.81 Hz, 1H).

5.10.23. Methyl 4-{2-[7-chloro-1-(diphenylmethyl)-2,4-dioxo-1,4-dihydroquinazolin-3(2*H*)-yl]ethoxy}benzoate (15d)

The general quinazolinedione cyclization procedure was followed utilizing aminoamide **14d** (506 mg, 65%, of white solid).

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.90 (s, 3H), 4.36 (t, J = 5.91 Hz, 2H), 4.60 (t, J = 5.91 Hz, 2H), 6.90 (d, J = 8.79 Hz, 2H), 7.14 (s, 1H), 7.13–7.17 (m, 1H), 7.24–7.42 (m, 10H), 7.64 (s, 1H), 7.97 (d, J = 9.07 Hz, 2H), 8.17 (d, J = 7.97 Hz, 1H).

5.10.24. 4-{2-[7-Chloro-1-(diphenylmethyl)-2,4-dioxo-1,4-dihydroquinazolin-3(2*H*)-yl]ethoxy}benzoic acid (16d)

The general basic ester hydrolysis conditions were followed utilizing ester **15d** (0.14 g, 60%, white solid). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.38 (t, J = 5.8 Hz, 2H), 4.61 (t, J = 5.8 Hz, 2H), 6.93 (d, J = 8.8 Hz, 2H), 7.14 (s, 1H), 7.15–7.17 (m, 1H), 7.25–7.43 (m, 10H), 7.64 (s, 1H), 8.04 (d, J = 9.1 Hz, 2H), 8.18 (d, J = 8.24 Hz, 1H); ^{13}C NMR (DMSO-d_6) 169.52, 160.47, 158.70, 150.47, 140.64, 138.97, 137.08, 133.41, 130.52, 130.04, 128.48, 127.98, 127.52, 123.14, 116.13, 114.62, 112.67, 66.98, 63.83, 61.58, 25.09. HRMS: $C_{30}H_{23}ClN_2O_5$ requires $(M+1)^+$ at m/z 527.1368; found, 527.1370.

5.10.25. Methyl 4-chloro-2-[(diphenylmethyl)amino]benzoate (12c)

The general aniline alkylation procedure was followed utilizing **11c** (91%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.84 (s, 3H), 5.59 (d, J = 5.8 Hz, 1H), 6.52–6.57 (m, 2H), 7.22–7.37 (m, 10H), 7.84 (d, J = 8.1 Hz, 1H), 8.55–8.60 (m, 1H).

5.10.26. 4-Chloro-2-[(diphenylmethyl)amino]benzoic acid (13c)

The general basic ester hydrolysis conditions were followed utilizing ester **12c** (98%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 5.93 (d, J = 6.6 Hz, 1H), 6.58–6.66 (m, 2H), 7.22–7.31 (m, 2H), 7.32–7.45 (m, 8H), 7.82 (d, J = 8.1 Hz, 1H), 8.82 (d, J = 6.6 Hz, 1H), 13.03 (s, 1H).

5.10.27. Methyl 4-{[({4-chloro-2-[(diphenylmethyl)amino]phenyl}carbonyl)amino]methyl}benzoate (14e)

The general amide coupling procedure was followed utilizing acid **13c** and methyl 4-(aminomethyl)benzoate (0.11 g, 52%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.84 (s, 3H), 4.52 (d, J = 5.8 Hz, 2H), 5.84 (d, J = 6.3 Hz, 1H), 6.59 (d, J = 2.0 Hz, 1H), 6.64 (dd, J = 8.3, 2.0 Hz, 1H), 7.19–7.28 (m, 2H), 7.30–7.41 (m, 7H), 7.45 (d, J = 8.3 Hz, 2H), 7.72 (d, J = 8.3 Hz, 1H), 7.93 (d, J = 8.3 Hz, 2H), 9.02 (d, J = 6.6 Hz, 1H), 9.15 (t, J = 6.2 Hz, 1H).

5.10.28. Methyl 4-{[7-chloro-1-(diphenylmethyl)-2,4-dioxo-1,4-dihydroquinazolin-3(2*H*)-yl]methyl}benzoate (15e)

The general quinazolinedione cyclization procedure was followed utilizing **14e** (350 mg, 71%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.84 (s, 3H), 5.18 (s, 2H), 7.29–7.43 (m, 12H), 7.48 (s, 1H), 7.88 (d, J = 8.6 Hz, 2H), 8.10 (d, J = 8.3 Hz, 1H).

5.10.29. 4-{[7-Chloro-1-(diphenylmethyl)-2,4-dioxo-1,4-dihydroquinazolin-3(2*H*)-yl]methyl}benzoic acid (16e)

The general basic ester hydrolysis conditions were followed utilizing ester **15e** (140 mg, 91%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 5.17 (s, 2H), 7.28–7.42 (m, 14H), 7.48 (s, 1H), 7.85 (d, J = 8.1 Hz, 2H), 8.10 (d, J = 8.6 Hz, 1H); HRMS: $C_{29}H_{21}ClN_2O_4$ requires $(M+1)^+$ at m/z 497.1262; found, 497.1268.

5.10.30. Methyl 4-{[(2*Z*)-4-({4-chloro-2-[(diphenylmethyl)amino]benzoyl}amino)but-2-en-1-yl]oxy}benzoate (14f)

The general amide coupling procedure was followed utilizing acid **13c** and *cis*-4-(4-amino-but-2-enyloxy) benzoate (78 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.88 (s, 3H), 4.12 (t, J = 6.0 Hz, 2H), 4.71 (d, J = 5.7 Hz, 2H), 5.54 (d, J = 6.0 Hz, 1H), 5.75–5.95 (m, 2H), 6.11 (br s, 1H), 6.50–6.54 (m, 2H), 6.92 (d, J = 9.0 Hz, 2H), 7.19–7.40 (m, 11H), 7.97 (d, J = 9.0 Hz, 2H), 8.59 (d, J = 6.0 Hz, 1H).

5.10.31. Methyl 4-({(2*Z*)-4-[7-chloro-1-(diphenylmethyl)-2,4-dioxo-1,4-dihydroquinazolin-3(2*H*)-yl]but-2-en-1-yl}oxy)benzoate (15f)

The general quinazolinedione cyclization procedure was followed utilizing aminoamide **14f** (72%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.89 (s, 3H), 4.81 (d, J = 6.2 Hz, 2H), 4.90 (d, J = 6.0 Hz, 2H), 5.76–5.95 (m, 2H), 6.96 (d, J = 9.0 Hz, 2H), 7.08–7.14 (m, 2H), 7.25–7.44 (m, 10H), 7.67 (s, 1H), 7.96 (d, J = 9.0 Hz, 2H), 8.13 (d, J = 9.0 Hz, 1H).

5.10.32. 4-({(2*Z*)-4-[7-Chloro-1-(diphenylmethyl)-2,4-dioxo-1,4-dihydroquinazolin-3(2*H*)-yl]but-2-en-1-yl}oxy)benzoic acid (16f)

The general basic ester hydrolysis conditions were followed utilizing ester **15f** (33%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.66 (d, J = 6.6 Hz, 2H), 4.84 (d, J = 6.6 Hz, 2H), 5.61–5.72 (m, 1H), 5.74–5.85 (m, 1H), 7.03 (d, J = 8.7 Hz, 2H), 7.22–7.43 (m, 13H), 7.54 (br s, 1H), 7.87 (d, J = 8.7 Hz, 2H), 8.09 (d, J = 8.4 Hz, 1H); ^{13}C NMR (DMSO-d_6) 169.66, 160.20, 158.78, 150.37, 140.64, 138.87, 137.07, 132.91, 130.56, 130.02, 129.05, 128.73, 128.52, 128.01, 127.57, 127.30, 123.11, 116.25, 114.79, 112.92, 63.67, 62.12, 61.59, 28.86. HRMS: $C_{32}H_{25}ClN_2O_5$ requires $(M+1)^+$ at m/z 553.1525; found, 553.1525.

5.10.33. Methyl 4-{[(2*E*)-4-({4-chloro-2-[(diphenylmethyl)amino]benzoyl}amino)but-2-en-1-yl]oxy}benzoate (14g)

The general amide coupling procedure was followed utilizing acid **13c** and *trans*-4-(4-amino-but-2-enyloxy) benzoate (76%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.89 (s, 3H), 4.03–4.10 (m, 2H), 4.57–4.60 (m, 2H), 5.55 (d, J = 6.0 Hz, 1H), 5.89–5.95 (m, 2H), 6.10–6.16 (m, 1H), 6.50–6.57 (m, 2H), 6.90 (d, J = 9.0 Hz, 2H), 7.20–7.42 (m, 13H), 7.98 (d, J = 9.0 Hz, 2H), 8.57 (d, J = 6.0 Hz, 1H).

5.10.34. Methyl 4-({(2*E*)-4-[7-chloro-1-(diphenylmethyl)-2,4-dioxo-1,4-dihydroquinazolin-3(2*H*)-yl]but-2-en-1-yl}oxy)benzoate (15g)

The general quinazolinedione cyclization procedure was followed utilizing aminoamide **14g** (32%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.87 (s, 3H), 4.54–4.58 (m, 2H), 4.74–4.78 (m, 2H), 5.98–6.03 (m, 2H), 6.86–6.94 (m, 2H), 7.09–7.14 (m, 2H), 7.24–7.40 (m, 10H), 7.64 (s, 1H), 7.93–8.00 (m, 2H), 8.13 (d, J = 8.0 Hz, 1H).

5.10.35. 4-({(2*E*)-4-[7-Chloro-1-(diphenylmethyl)-2,4-dioxo-1,4-dihydroquinazolin-3(2*H*)-yl]but-2-en-1-yl}oxy)benzoic acid (16g)

The general basic ester hydrolysis conditions were followed utilizing ester **15g** (80%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.57 (br s, 4H), 5.74–5.97 (m, 2H), 6.99 (d, J = 9.0 Hz. 2H), 7.24–7.44 (m, 12H), 7.51 (s, 1H), 7.86 (d, J = 9.0 Hz, 2H), 8.08 (d, J = 8.3 Hz, 1H); ^{13}C NMR (DMSO-d_6) 169.59, 160.10, 158.82, 150.18, 140.73, 138.97, 137.15, 132.88, 130.53, 130.05, 128.51, 127.98, 127.61, 127.56, 127.19, 123.14, 116.16, 114.69, 112.85, 67.13, 61.69, 42.39, 28.84; HRMS: $C_{32}H_{25}ClN_2O_5$ requires $(M+1)^+$ at m/z 553.1525; found, 553.1530.

5.10.36. Methyl {4-[({5-bromo-2-[(diphenylmethyl)amino]benzoyl}-amino)methyl]phenyl}acetate (17)

The general amide coupling procedure was followed utilizing acid **13b** and methyl [4-(aminomethyl)phenyl]acetate (380 mg, 47%). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 3.59–3.66 (m, 2H), 3.66–3.74 (m, 3H), 4.48–4.60 (m, 2H), 5.49–5.61 (m, 1H), 6.33–6.51 (m, 1H), 7.16–7.42 (m, 17H), 7.46–7.57 (m, J = 2.2 Hz, 1H), 8.38–8.51 (m, 1H).

5.10.37. {4-[({5-Bromo-2-[(diphenylmethyl)amino]benzoyl}amino)methyl]phenyl}acetic acid (18)

The general basic ester hydrolysis conditions were followed utilizing ester **17** (321 mg, 93%). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 3.51–3.60 (m, 2H), 4.45–4.63 (m, 2H), 5.52–5.65 (m, 1H), 6.30–6.47 (m, 1H), 7.21–7.45 (m, 17H), 7.46–7.57 (m, J = 2.2 Hz, 1H), 8.35–8.48 (m, 1H).

5.10.38. (4-{[6-Bromo-1-(diphenylmethyl)-2,4-dioxo-1,4-dihydroquinazolin-3(2*H*)-yl]methyl}phenyl)acetic acid (19)

The general quinazolinedione cyclization procedure was followed utilizing aminoamide **18** (115 mg, 50%). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 3.64 (s, 2H), 5.31 (s, 2H), 6.97 (d, J = 9.1 Hz, 1H), 7.22–7.42 (m, 14H), 7.50 (d, J = 8.0 Hz, 2H), 7.76 (s, 1H), 8.34 (d, J = 2.5 Hz, 1H); HRMS: $C_{30}H_{23}BrN_2O_4$ requires $(M+1)^+$ at m/z 555.0914; found, 555.0921.

5.10.39. Methyl 2-(benzylamino)benzoate (20)

A solution of methyl 2-aminobenzoate (10 g, 66 mmol), benzyl bromide, and potassium carbonate (22.8 g, 2.5 equiv) in acetone (200 mL) was heated at reflux for 18 h. The solution was filtered, evaporated, and flash chromatographed (5% EtOAc/hexanes) to provide **20** (8.5 g, 53%, amber oil). ^{1}H NMR (400 MHz, chloroform-*d*) δ ppm 3.86 (s, 3H), 4.45 (d, J = 5.6 Hz, 2H), 6.57–6.62 (m, 1H), 6.63 (d, J = 8.6 Hz, 1H), 7.23–7.38 (m, 6H), 7.92 (dd, J = 8.1, 1.8 Hz, 1H), 8.16 (br. s., 1H).

5.10.40. 2-(Benzylamino)benzoic acid (21)

The general basic ester hydrolysis conditions were followed utilizing ester **20** (7.9 g, 100%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4.46 (s, 2H), 6.53–6.59 (m, 1H), 6.67 (d, J = 7.8 Hz, 1H), 7.23–7.37 (m, 6H), 7.81 (dd, J = 8.0, 1.6 Hz, 1H).

5.10.41. Methyl 4-[2-({[2-(benzylamino)phenyl]carbonyl}amino)ethoxy]benzoate (22)

The general amide coupling procedure was followed utilizing acid **21** (0.88 g, 66%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.85 (q, J = 5.6 Hz, 2H), 3.89 (s, 3H), 4.19 (t, J = 5.2 Hz, 2H), 4.41 (d, J = 5.6 Hz, 2H), 6.53 (br t, J = 5.4 Hz, 1H), 6.56–6.65 (m, 2H), 6.91–6.95 (m, 2H), 7.21–7.25 (m, 2H), 7.29–7.39 (m, 5H), 7.98–8.01 (m, 2H), 8.02–8.06 (m, J = 4.8 Hz, 1H).

5.10.42. Methyl 4-[2-(1-benzyl-2,4-dioxo-1,4-dihydroquinazolin-3(2*H*)-yl)ethoxy]benzoate (23)

The general quinazolinedione cyclization procedure was followed utilizing aminoamide **22** (0.23 g, 67%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.87 (s, 3H), 4.38 (t, J = 6.2 Hz, 2H), 4.63 (t, J = 6.2 Hz, 2H), 5.39 (s, 2H), 6.91–6.96 (m, 2H), 7.12 (d, J = 8.3 Hz, 1H), 7.20–7.36 (m, 6H), 7.52–7.58 (m, 1H), 7.94–7.98 (m, 2H), 8.24 (dd, J = 7.8, 1.3 Hz, 1H).

5.10.43. 4-[2-(1-Benzyl-2,4-dioxo-1,4-dihydroquinazolin-3(2*H*)-yl)ethoxy]benzoic acid (24)

The general basic ester hydrolysis conditions were followed utilizing ester **23** (0.2 g, 95%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4.33–4.39 (m, 2H), 4.44 (t, J = 5.9 Hz, 2H), 5.40 (s, 2H), 6.99–7.05 (m, 2H), 7.23–7.37 (m, 7H), 7.64–7.71 (m, 1H), 7.85–7.90 (m, 2H), 8.10 (dd, J = 8.2, 1.6 Hz, 1H), 12.61 (s, 1H). HRMS: $C_{24}H_{20}N_2O_5$ requires $(M+1)^+$ at m/z 417.1445; found, 417.1449.

5.10.44. 3-(2-Chloroethyl)-1-(diphenylmethyl)quinazoline-2,4(1*H*,3*H*)-dione (25)

The general N-1 quinazolinedione alkylation conditions were followed utilizing 3-(2-chloroethyl)quinazoline-2,4(1*H*,3*H*)-dione and 1,1′-(bromomethanediyl)dibenzene (61%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.65 (t, J = 6.8 Hz, 2H), 3.81 (t, J = 6.8 Hz, 2H), 4.45–4.58 (m, 2H), 7.05–7.18 (m, 2H), 7.20–7.43 (m, 11H), 7.66 (s, 1H), 8.22 (d, J = 8.0 Hz, 1H).

5.10.45. Methyl 4-{2-[1-(diphenylmethyl)-2,4-dioxo-1,4-dihydroquinazolin-3(2*H*)-yl]ethoxy}benzoate (26)

The general phenol alkylation conditions were followed utilizing chloride **25** and methyl 4-hydroxybenzoate (27%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.87 (s, 3H), 4.34 (t, J = 6.0 Hz, 2H), 4.60 (t, J = 6.0 Hz, 2H), 6.88 (d, J = 8.7 Hz, 2H), 7.05–7.18 (m, 2H), 7.20–7.38 (m, 11H), 7.67 (s, 1H), 7.94 (d, J = 8.7 Hz, 2H), 8.21 (d, J = 7.9 Hz, 1H).

5.10.46. 4-{2-[1-(Diphenylmethyl)-2,4-dioxo-1,4-dihydroquinazolin-3(2*H*)-yl]ethoxy}benzoic acid (27)

The general basic ester hydrolysis conditions were followed utilizing ester **26** (47%, chromatography followed by hexanes trituration). ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.21 (t, J = 6.2 Hz, 2H), 4.37 (t, J = 6.2 Hz, 2H), 6.73 (d, J = 8.6 Hz, 2H), 7.16–7.27 (m, 2H), 7.27–7.40 (m, 10H), 7.45–7.54 (m, 1H), 7.57 (s, 1H), 7.74 (d, J = 8.8 Hz, 2H), 7.74 (d, 3H), 8.11 (dd, J = 7.8, 1.5 Hz, 1H); HRMS: $C_{30}H_{24}N_2O_5$ requires $(M+1)^+$ at m/z 493.1763; found, 493.1757.

5.10.47. 2-Amino-4-chlorobenzoic acid (29)

The general nitro reduction conditions were followed utilizing nitro compound **28** (3.25 g, 55%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.37 (d, J = 8.79 Hz, 1H), 6.56 (dd, J = 8.52, 2.20 Hz, 1H), 6.64 (s, 2H), 6.77 (d, J = 1.92 Hz, 1H), 7.20–7.40 (m, 10H), 7.70 (d, J = 8.52 Hz, 1H), 9.11 (d, J = 8.79 Hz, 1H).

5.10.48. 7-Chloro-3-(diphenylmethyl)quinazoline-2,4(1*H*,3*H*)-dione (30)

The general quinazolinedione cyclization procedure was followed utilizing aminoamide **29** (64%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.71 (d, J = 1.8 Hz, 1H), 7.16 (dd, J = 8.5, 1.8 Hz, 1H), 7.27–7.47 (m, 10H), 7.51 (s, 1H), 8.03 (d, J = 8.5 Hz, 1H), 10.80 (s, 1H).

5.10.49. Ethyl [2-(4-{[7-chloro-3-(diphenylmethyl)-2,4-dioxo-3,4-dihydroquinazolin-1(2*H*)-yl]methyl}phenyl)-1,3-oxazol-4-yl]acetate (31a)

The general N-1 quinazolinedione alkylation conditions were followed utilizing **30** and ethyl [2-(4-bromomethylphenyl) oxazol-4-yl] acetate (82%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21 (t, J = 7.2 Hz, 3H), 3.68 (s, 2H), 4.10 (d, J = 7.2 Hz, 2H), 5.42 (s, 2H), 7.25–7.48 (m, 15H), 7.91 (d, J = 8.1 Hz, 2H), 8.06 (d, J = 8.1 Hz, 2H).

5.10.50. Ethyl [2-(4-{[7-chloro-3-(diphenylmethyl)-2,4-dioxo-3,4-dihydroquinazolin-1(2*H*)-yl]methyl}phenyl)-1,3-oxazol-4-yl]acetate (32a)

The general basic ester hydrolysis conditions were followed utilizing ester **31a** (96%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.11 (s, 2H), 5.41 (s, 2H), 7.26–7.50 (m, 16H), 7.82 (s, 1H), 7.88 (d, J = 8.1 Hz, 2H), 8.07 (d, J = 8.3 Hz, 1H); ^{13}C NMR (DMSO-d_6) 172.18, 160.62, 158.83, 150.37, 140.94, 140.28, 140.01, 138.14, 137.88, 135.92, 130.36, 129.56, 128.39, 128.08, 127.18, 126.99, 126.54, 125.98, 123.35, 114.66, 114.20, 59.57, 46.25, 36.69; HRMS: $C_{33}H_{24}ClN_3O_5$ requires $(M+1)^+$ at m/z 578.1477; found, 578.1474.

5.10.51. Methyl 4-{2-[7-chloro-3-(diphenylmethyl)-2,4-dioxo-3,4-dihydroquinazolin-1(2*H*)-yl]ethoxy}benzoate (31b)

The general N-1 quinazolinedione alkylation conditions were followed utilizing **30** and methyl 4-(2-bromoethoxy) benzoate (96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.88 (s, 3H), 4.33 (t, J = 5.1 Hz, 2H), 4.48 (t, J = 5.1 Hz, 2H), 6.77–6.84 (m, 2H), 7.19–7.45 (m, 11H), 7.49 (s, 1H), 7.53 (d, J = 1.8 Hz, 1H), 7.92–7.98 (m, 2H), 8.12 (d, J = 8.5 Hz, 1H).

5.10.52. 4-{2-[7-Chloro-3-(diphenylmethyl)-2,4-dioxo-3,4-dihydroquinazolin-1(2*H*)-yl]ethoxy}benzoic acid (32b)

The general basic ester hydrolysis conditions were followed utilizing ester **31b** (82%). ^{1}H NMR (400 MHz, acetone-d_6) δ 4.40–4.50 (m, 2H), 4.60–4.72 (m, 2H), 6.88–6.94 (m, 2H), 7.24–7.36 (m, 7H), 7.37–7.44 (m, 4H), 7.49 (s, 1H), 7.81 (d, J = 1.8 Hz, 1H), 7.90–7.96 (m, 2H), 8.07 (d, J = 8.5 Hz, 1H); HRMS: $C_{30}H_{23}ClN_2O_5$ requires $(M+1)^+$ at m/z 527.1368; found, 527.1368.

5.10.53. 2-Amino-*N*-(diphenylmethyl)-4-fluorobenzamide (33a)

The general amide coupling procedure was followed utilizing 2-amino-4-fluorobenzoic acid (2.3 g, >100%). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 5.80 (s, 1H), 6.32–6.38 (m, 1H), 6.39 (s, 1H), 6.51–6.58 (m, 1H), 7.15–7.47 (m, 13H).

5.10.54. 3-(Diphenylmethyl)-7-fluoroquinazoline-2,4(1*H*,3*H*)-dione (34a)

The general quinazolinedione cyclization procedure was followed utilizing aminoamide **33a** ((1.1 g, 50%, two steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.38 (dd, J = 8.93, 2.33 Hz, 1H), 6.99–6.99 (m, 1H), 7.28–7.50 (m, 10H), 7.55 (s, 1H), 8.15 (dd, J = 8.93, 5.91 Hz, 1H), 10.98 (s, 1H).

5.10.55. *tert*-Butyl 4-({(2*E*)-4-[3-(diphenylmethyl)-7-fluoro-2,4-dioxo-3,4-dihydroquinazolin-1(2*H*)-yl]but-2-en-1-yl}oxy)benzoate (35a)

The general N-1 quinazolinedione alkylation conditions were followed utilizing **34a** (246 mg, 72%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.62 (s, 9H), 4.76 (br s, 2H), 4.60 (br s, 1H), 5.82–6.00 (m, 2H), 6.82–7.00 (m, 3H), 7.29–7.55 (m, 11H), 7.56 (s, 1H), 7.95 (d, J = 8.8 Hz, 2H), 8.26 (dd, J = 8.8, 6.3 Hz, 1H).

5.10.56. 4-({(2*E*)-4-[3-(Diphenylmethyl)-7-fluoro-2,4-dioxo-3,4-dihydroquinazolin-1(2*H*)-yl]but-2-en-1-yl}oxy)benzoic acid (36a)

The general acidic ester hydrolysis conditions were followed utilizing ester **35a** (175 mg, 77%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.26 (dd, J = 8.9, 6.3 Hz, 1H), 8.06 (d, J = 8.9 Hz, 2H), 7.54 (s, 1H), 7.38–7.50 (m, 8H), 6.80–7.05 (m, 6H), 5.85–6.00 (m, 2H), 4.75–4.80 (m, 2H), 4.60–4.65 (m, 2H); HRMS: calcd for $C_{32}H_{25}FN_2O_5-H+$, 535.16747; found, 535.1693.

5.10.57. 2-Amino-*N*-(diphenylmethyl)-4-nitrobenzamide (33b)

The general amide coupling procedure was followed utilizing 2-amino-4-nitrobenzoic acid (3.3 g, 58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.84 (br s, 2H), 6.37 (d, J = 7.33 Hz, 1H), 6.61 (d, J = 6.57 Hz, 1H), 7.24–7.54 (m, 13H).

5.10.58. 3-(Diphenylmethyl)-7-nitroquinazoline-2,4(1*H*,3*H*)-dione (34b)

The general quinazolinedione cyclization procedure was followed utilizing aminoamide **33b** (2.48 g, 70%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.25–7.38 (m, 11H), 7.92–7.98 (m, 2H), 8.13 (d, J = 8.6 Hz, 1H).

5.10.59. *tert*-Butyl 4-({(2*E*)-4-[3-(diphenylmethyl)-7-nitro-2,4-dioxo-3,4-dihydroquinazolin-1(2*H*)-yl]but-2-en-1-yl}oxy)benzoate (35b)

The general N-1 quinazolinedione alkylation conditions were followed utilizing **34b** (0.60 g, 75%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.46 (s, 9H), 1.46 (s, 9H), 4.46 (s, 2H), 4.72 (s, 2H), 5.83 (s, 2H), 6.71 (d, J = 9.0 Hz, 2H), 7.12–7.32 (m, 10H), 7.38 (s, 1H), 7.76 (d, J = 8.9 Hz, 2H), 7.84–7.92 (m, 2H), 8.26 (d, J = 8.8 Hz, 1H).

5.10.60. 4-({(2*E*)-4-[3-(Diphenylmethyl)-7-nitro-2,4-dioxo-3,4-dihydroquinazolin-1(2*H*)-yl]but-2-en-1-yl}oxy)benzoic acid (36b)

The general acidic ester hydrolysis conditions were followed utilizing ester **35b** (0.02 g, 65%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.27 (d, J = 9.3 Hz, 1H), 7.85–7.93 (m, 4H), 7.38 (s, 1H), 7.14–7.30 (m, 10H), 6.77 (d, J = 8.9 Hz, 2H), 5.84 (br s, 2H), 4.74 (br s, 2H), 4.49 (br s, 2H); ^{13}C NMR (DMSO-d_6) 169.46, 160.16, 158.84, 151.48, 149.87, 140.50, 137.97, 130.52, 130.29, 128.42, 128.05, 127.19, 126.19, 119.75, 116.90, 112.97, 110.26, 67.03, 59.88, 44.93; HRMS: $C_{32}H_{25}N_3O_7$ requires $(M+1)^+$ at m/z 564.1765; found, 564.1764.

5.10.61. *tert*-Butyl 4-({(2*E*)-4-[7-amino-3-(diphenylmethyl)-2,4-dioxo-3,4-dihydroquinazolin-1(2*H*)-yl]but-2-en-1-yl}oxy)benzoate (35c)

The general nitro reduction conditions were followed utilizing nitro compound **35b** (0.11 g, 58%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.46 (s, 9H), 4.41 (d, J = 4.4 Hz, 2H), 4.53 (br s, 2H), 5.60–5.84 (m, 2H), 6.07 (s, 1H), 6.33 (dd, J = 8.7, 1.6 Hz, 1H), 6.72 (d, J = 8.9 Hz, 2H), 7.10–7.26 (m, 10H), 7.40 (s, 1H), 7.77–7.85 (m, 3H).

5.10.62. 4-({(2*E*)-4-[7-Amino-3-(diphenylmethyl)-2,4-dioxo-3,4-dihydroquinazolin-1(2*H*)-yl]but-2-en-1-yl}oxy)benzoic acid (36c)

The general acidic ester hydrolysis conditions were followed utilizing ester **36c** (0.08 g, 74%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.73 (d, J = 8.5 Hz, 2H), 7.54 (d, J = 8.7 Hz, 1H), 7.10–7.25 (m, 10H), 6.85 (d, J = 8.8 Hz, 2H), 6.32 (d, J = 8.8 Hz, 1H), 6.18–6.23 (m, 2H), 5.60–5.85 (m, 2H), 4.47 (br s, 4H), 3.12 (s, 2H); ^{13}C NMR (DMSO-d_6) 160.56, 158.74, 155.59, 150.40, 141.49, 138.90, 130.54, 129.97, 128.26, 127.96, 127.59, 126.85, 126.75, 112.85, 110.11, 102.93, 95.83, 67.10, 58.39, 44.17, 30.39; HRMS: $C_{32}H_{27}N_3O_5$ requires $(M+1)^+$ at m/z 534.2023; found, 534.2023.

5.10.63. 2-Amino-*N*-(diphenylmethyl)-4-methylbenzamide (33c)

The general amide coupling procedure was followed utilizing 2-amino-4-methylbenzoic acid (1.4 g, 67%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.25 (s, 3H), 6.36 (d, J = 7.1 Hz, 1H), 6.46 (d, J = 8.1 Hz, 1H), 6.49 (s, 1H), 6.53 (d, J = 7.1 Hz, 1H), 7.24–7.39 (m, 12H).

5.10.64. 3-(Diphenylmethyl)-7-methylquinazoline-2,4(1*H*,3*H*)-dione (34c)

The general quinazolinedione cyclization procedure was followed utilizing aminoamide **33c** (1.46 g, 97%, crude). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.50 (s, 3H), 7.08–7.7.20 (m, 2H), 7.30–7.65 (m, 11H), 7.92 (d, J = 8.0 Hz, 1H).

5.10.65. *tert*-Butyl 4-({(2*E*)-4-[3-(diphenylmethyl)-7-methyl-2,4-dioxo-3,4-dihydroquinazolin-1(2*H*)-yl]but-2-en-1-yl}oxy) benzoate (35d)

The general N-1 quinazolinedione alkylation conditions were followed utilizing **34c** (0.23 g, 67%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.29 (s, 3H), 4.43 (d, J = 4.7 Hz, 2H), 4.62 (d, J = 3.5 Hz, 2H), 5.65–5.88 (m, 2H), 6.70–6.79 (m, 3H), 6.92 (d, J = 8.1 Hz, 1H), 7.10–7.32 (m, 10H), 7.41 (s, 1H), 7.78 (d, J = 8.9 Hz, 2H), 7.97 (d, J = 8.0 Hz, 1H).

5.10.66. 4-({(2*E*)-4-[3-(Diphenylmethyl)-7-methyl-2,4-dioxo-3,4-dihydroquinazolin-1(2*H*)-yl]but-2-en-1-yl}oxy)benzoic acid (36d)

The general acidic ester hydrolysis conditions were followed utilizing ester **35d** (0.12 g, 54%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (d, J = 8.0 Hz, 1H), 8.03 (d, J = 8.9 Hz, 2H), 7.54 (s, 1H), 7.26–7.43 (m, 10H), 7.05 (d, J = 8.1 Hz, 1H), 6.88–6.92 (m, 3H), 5.78–6.02 (m, 2H), 4.75–4.77 (m, 2H), 4.57–4.59 (m, 2H), 2.42 (s, 3H), ^{13}C

NMR (DMSO-d_6) 169.60, 161.00, 158.56, 150.12, 146.47, 139.69, 138.44, 133.44, 130.46, 128.32, 128.19, 128.04, 127.78, 127.04, 126.93, 124.17, 114.92, 112.86, 112.71, 67.04, 59.16, 44.26, 21.71; HRMS: $C_{33}H_{28}N_2O_5$ requires $(M+1)^+$ at *m/z* 533.2071; found, 533.2071.

5.10.67. 2-Amino-*N*-(diphenylmethyl)-5-fluorobenzamide (33d)

The general amide coupling procedure was followed utilizing 2-amino-5-fluorobenzoic acid (0.78 g, 38%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.80 (br s, 1H), 6.45 (m, 2H), 7.25–7.66 (m, 14H).

5.10.68. 3-(Diphenylmethyl)-6-fluoroquinazoline-2,4(1*H*,3*H*)-dione (34d)

The general quinazolinedione cyclization procedure was followed utilizing aminoamide **33d** (1.1 g, 52%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.69 (dd, *J* = 8.93, 4.26 Hz, 1H), 7.24–7.51 (m, 11H), 7.55 (s, 1H), 7.80 (dd, *J* = 8.38, 2.88 Hz, 1H), 10.91 (s, 1H).

5.10.69. Methyl 4-({(2*Z*)-4-[3-(diphenylmethyl)-6-fluoro-2,4-dioxo-3,4-dihydroquinazolin-1(2*H*)-yl]but-2-en-1-yl}oxy)benzoate (35e)

The general N-1 quinazolinedione alkylation conditions were followed utilizing **34d** (0.28 g, 87%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.93 (s, 3H), 4.80 (d, *J* = 5.77 Hz, 2H), 4.92 (d, *J* = 6.04 Hz, 2H), 5.64–5.77 (m, 1H), 5.91–6.04 (m, 1H), 6.96 (d, *J* = 8.79 Hz, 2H), 7.19 (dd, *J* = 9.20, 3.98 Hz, 1H), 7.26–7.48 (m, 11H), 7.54 (s, 1H), 7.92 (dd, *J* = 8.24, 3.02 Hz, 1H), 8.03 (d, *J* = 8.79 Hz, 2H).

5.10.70. 4-({(2*Z*)-4-[3-(Diphenylmethyl)-6-fluoro-2,4-dioxo-3,4-dihydroquinazolin-1(2*H*)-yl]but-2-en-1-yl}oxy)benzoic acid (36e)

The general basic ester hydrolysis conditions were followed utilizing ester **35e** (90 mg, 31%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.80 (d, *J* = 5.77 Hz, 2H), 4.92 (d, *J* = 6.04 Hz, 2H), 5.64–5.78 (m, 1H), 5.91–6.05 (m, 1H), 6.96 (d, *J* = 8.79 Hz, 2H), 7.19 (dd, *J* = 9.20, 3.98 Hz, 1H), 7.26–7.50 (m, 11H), 7.54 (s, 1H), 7.92 (dd, *J* = 8.24, 3.02 Hz, 1H), 8.03 (d, *J* = 8.79 Hz, 2H); ^{13}C NMR (DMSO-d_6) 169.57, 158.79, 158.57, 156.39, 149.89, 138.15, 136.41, 133.49, 130.52, 128.95, 128.40, 128.03, 127.68, 127.61, 127.12, 123.19, 122.95, 117.28, 117.21, 116.59, 116.52, 113.53, 113.29, 112.98, 63.72, 59.63, 41.76; HRMS: $C_{32}H_{25}FN_2O_5$ requires $(M+1)^+$ at *m/z* 537.1820; found, 537.1819.

5.10.71. Methyl 4-({(2*E*)-4-[3-(diphenylmethyl)-6-fluoro-2,4-dioxo-3,4-dihydroquinazolin-1(2*H*)-yl]but-2-en-1-yl}oxy)benzoate (35f)

The general N-1 quinazolinedione alkylation conditions were followed utilizing **34d** (267 mg, 81%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.92 (s, 3H), 4.59 (d, *J* = 4.40 Hz, 2H), 4.80 (d, *J* = 3.85 Hz, 2H), 5.80–6.03 (m, 2H), 6.86–6.92 (m, 2H), 7.14 (dd, *J* = 9.07, 3.85 Hz, 1H), 7.27–7.48 (m, 11H), 7.54 (s, 1H), 7.91 (dd, *J* = 8.24, 3.02 Hz, 1H), 7.97–8.02 (m, 2H).

5.10.72. 4-({(2*E*)-4-[3-(Diphenylmethyl)-6-fluoro-2,4-dioxo-3,4-dihydroquinazolin-1(2*H*)-yl]but-2-en-1-yl}oxy)benzoic acid (36f)

The general basic ester hydrolysis conditions were followed utilizing ester **35f** (98 mg. 39%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.61 (d, *J* = 4.12 Hz, 2H), 4.80 (d, *J* = 3.85 Hz, 2H), 5.93 (m, 2H), 6.93 (d, *J* = 9.07 Hz, 2H), 7.15 (dd, *J* = 9.34, 3.85 Hz, 1H), 7.27–7.49 (m, 11H), 7.55 (s, 1H), 7.92 (dd, *J* = 8.24, 3.02 Hz, 1H), 8.07 (d, *J* = 9.07 Hz, 2H); ^{13}C NMR (DMSO-d_6) 169.62, 160.35, 158.78, 158.58, 156.38, 149.80, 138.19, 136.45, 133.42, 130.48, 128.36, 128.05, 127.92, 127.12, 126.71, 123.18, 122.95, 117.67, 117.59, 116.48, 116.41, 113.41, 113.17, 112.88, 67.07, 59.61, 44.77; HRMS: $C_{32}H_{25}FN_2O_5$ requires $(M+1)^+$ at *m/z* 537.1820; found, 537.1819.

5.10.73. 2-Amino-5-chloro-*N*-(diphenylmethyl)benzamide (33e)

The general amide coupling procedure was followed utilizing 2-amino-5-chlorobenzoic acid (2.9 g, 60%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.55 (br s, 2H), 6.35 (d, *J* = 7.33 Hz, 1H), 6.50 (d, *J* = 6.82 Hz, 1H), 6.62 (d, *J* = 8.84 Hz, 1H), 7.16 (dd, *J* = 8.72, 2.40 Hz, 1H), 7.27–7.40 (m, 11H).

5.10.74. 6-Chloro-3-(diphenylmethyl)quinazoline-2,4(1*H*,3*H*)-dione (34e)

The general quinazolinedione cyclization procedure was followed utilizing aminoamide **33e** (1.2 g, 65%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.66 (d, *J* = 8.52 Hz, 1H), 7.24–7.61 (m, 12H), 8.10 (d, *J* = 2.47 Hz, 1H), 10.91 (s, 1H).

5.10.75. Methyl 4-({(2*Z*)-4-[6-chloro-3-(diphenylmethyl)-2,4-dioxo-3,4-dihydroquinazolin-1(2*H*)-yl]but-2-en-1-yl}oxy)benzoate (35g)

The general N-1 quinazolinedione alkylation conditions were followed utilizing **34e** (270 mg, 62%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.93 (s, 3H), 4.80 (d, *J* = 5.77 Hz, 2H), 4.90 (d, *J* = 6.04 Hz, 2H), 5.64–5.75 (m, 1H), 5.91–6.03 (m, 1H), 6.91–6.99 (m, 2H), 7.16 (d, *J* = 8.79 Hz, 1H), 7.27–7.47 (m, 11H), 7.53 (s, 1H), 7.59 (dd, *J* = 9.07, 2.47 Hz, 1H), 7.99–8.05 (m, 2H), 8.21 (d, *J* = 2.75 Hz, 1H).

5.10.76. 4-({(2*Z*)-4-[6-chloro-3-(diphenylmethyl)-2,4-dioxo-3,4-dihydroquinazolin-1(2*H*)-yl]but-2-en-1-yl}oxy)benzoic acid (36g)

The general basic ester hydrolysis conditions were followed utilizing ester **35g** ((200 mg, 41%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.82 (d, *J* = 5.77 Hz, 2H), 4.91 (d, *J* = 6.04 Hz, 2H), 5.65–5.77 (m, 1H), 5.91–6.04 (m, 1H), 6.98 (d, *J* = 8.79 Hz, 2H), 7.17 (d, *J* = 8.79 Hz, 1H), 7.26–7.48 (m, 10H), 7.54 (s, 1H), 7.60 (dd, *J* = 8.79, 2.47 Hz, 1H), 8.09 (d, *J* = 8.79 Hz, 2H), 8.21 (d, *J* = 2.47 Hz, 1H); ^{13}C NMR (DMSO-d_6) 169.46, 160.04, 158.46, 149.80, 138.51, 138.02, 135.01. 133.47, 130.43, 128.90, 128.34, 127.96, 127.45, 127.12, 127.05, 116.97, 116.69, 112.86, 63.63, 59.58, 41.62; HRMS: $C_{32}H_{25}ClN_2O_5$ requires $(M+1)^+$ at *m/z* 553.1525; found, 553.1525.

5.10.77. Methyl 4-({(2*E*)-4-[6-chloro-3-(diphenylmethyl)-2,4-dioxo-3,4-dihydroquinazolin-1(2*H*)-yl]but-2-en-1-yl}oxy)benzoate (35h)

The general N-1 quinazolinedione alkylation conditions were followed utilizing **34e** (280 mg, 90%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.91 (s, 3H), 4.58 (d, *J* = 4.40 Hz, 2H), 4.78 (d, *J* = 4.12 Hz, 2H), 5.78–6.03 (m, 2H), 6.85–6.92 (m, 2H), 7.10 (d, *J* = 8.79 Hz, 1H), 7.27–7.47 (m, 10H), 7.54 (s, 1H), 7.57 (dd, *J* = 8.93, 2.61 Hz, 1H), 7.95–8.02 (m, 2H), 8.20 (d, *J* = 2.47 Hz, 1H).

5.10.78. 4-({(2*E*)-4-[6-Chloro-3-(diphenylmethyl)-2,4-dioxo-3,4-dihydroquinazolin-1(2*H*)-yl]but-2-en-1-yl}oxy)benzoic acid (36h)

The general basic ester hydrolysis conditions were followed utilizing ester **35h** (119 mg, 44%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.60 (d, *J* = 4.40 Hz, 2H), 4.79 (d, *J* = 3.85 Hz, 2H), 5.78–6.05 (m, 2H), 6.93 (d, *J* = 8.79 Hz, 2H), 7.11 (d, *J* = 8.79 Hz, 1H), 7.26–7.50 (m, 10H), 7.52–7.64 (m, 2H), 8.07 (d, *J* = 8.79 Hz, 2H), 8.21 (d, *J* = 2.47 Hz, 1H); ^{13}C NMR (DMSO-d_6) 169.57, 160.09. 158.53, 149.69, 138.54, 138.05, 134.99, 133.21, 130.41, 128.28, 127.96, 127.77, 127.09, 127.05, 126.96, 126.45, 117.33, 116.58, 112.78, 66.96, 59.54, 44.60; HRMS: $C_{32}H_{25}ClN_2O_5$ requires $(M+1)^+$ at *m/z* 553.1525; found, 553.1527.

5.10.79. 3-(Diphenylmethyl)quinazoline-2,4(1*H*,3*H*)-dione (38a)

The general isatoic anhydride aminolysis conditions were followed utilizing 2-amino-*N*-(diphenylmethyl)benzamide **37a** (1.18 g, 68%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.17–7.24 (m, 2H), 7.25–7.38 (m, 12H), 7.90 (dd, J = 8.1, 1.5 Hz, 1H), 11.51 (s, 1H).

5.10.80. *tert*-Butyl (4-{[3-(diphenylmethyl)-2,4-dioxo-3,4-dihydroquinazolin-1(2*H*)-yl]methyl}phenyl)acetate (39a)

The general N-1 quinazolinedione alkylation conditions were followed utilizing **38a** (83 mg, 51%). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.50 (s, 9H), 3.69 (s, 2H), 5.41 (s, 2H), 6.81 (d, J = 7.7 Hz, 1H), 7.08 (d, J = 8.5 Hz, 1H), 7.13–7.42 (m, 10H), 7.45–7.52 (m, 4H), 7.52–7.60 (m, 1H), 7.63 (s, 1H), 8.28 (dd, J = 7.8, 1.2 Hz, 1H).

5.10.81. (4-{[3-(Diphenylmethyl)-2,4-dioxo-3,4-dihydroquinazolin-1(2*H*)-yl]methyl}phenyl)acetic acid (40a)

The general acidic ester hydrolysis conditions were followed utilizing ester **39a** (34 mg, 50%). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 3.81 (s, 2H), 5.40 (s, 2H), 6.84 (d, J = 7.4 Hz, 1H), 7.00 (d, J = 8.5 Hz, 1H), 7.13–7.41 (m, 10H), 7.47 (d, J = 6.9 Hz, 5H), 7.62 (s, 1H), 8.25 (dd, J = 8.0, 1.4 Hz, 1H); HRMS: $C_{30}H_{24}N_2O_4$ requires $(M+1)^+$ at m/z 477.1814; found, 477.1808.

5.10.82. Methyl (4-{[3-(diphenylmethyl)-2,4-dioxo-3,4-dihydroquinazolin-1(2*H*)-yl]methyl}phenoxy)acetate (39b)

The general N-1 quinazolinedione alkylation conditions were followed utilizing **38a** and methyl (4-bromomethylphenoxy) acetate (89%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.68 (s, 3H), 4.76 (s, 2H), 5.28 (s, 2H), 6.87 (d, J = 8.7 Hz, 2H), 7.18 (d, J = 8.7 Hz, 2H), 7.24–7.36 (m, 11H), 7.38 (s, 1H), 7.44 (s, 1H), 7.67–7.72 (m, 1H), 8.05 (dd, J = 7.8, 1.5 Hz, 1H).

5.10.83. (4-{[3-(Diphenylmethyl)-2,4-dioxo-3,4-dihydroquinazolin-1(2*H*)-yl]methyl}phenoxy)acetic acid (40b)

The general basic ester hydrolysis conditions were followed utilizing ester **39b** (98%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.63 (s, 2H), 5.27 (s, 2H), 6.84 (d, J = 9.0 Hz, 2H), 7.17 (d, J = 9.0 Hz, 2H), 7.23–7.47 (m, 12H), 7.67–7.72 (m, 1H), 8.04 (dd, J = 7.8, 1.4 Hz, 1H); ^{13}C NMR (DMSO-d_6) 170.42, 161.15, 158.31, 150.55, 139.67, 138.34, 135.49, 128.33, 128.07, 127.43, 127.10, 126.84, 123.01, 115.14, 115.09, 114.66, 67.85, 59.35, 45.78, 42.31; HRMS: $C_{30}H_{24}N_2O_5$ requires $(M+1)^+$ at m/z 493.1758; found, 493.1757.

5.10.84. Methyl 4-(4-{[3-(diphenylmethyl)-2,4-dioxo-3,4-dihydroquinazolin-1(2*H*)-yl]methyl}phenoxy)butanoate (39c)

The general N-1 quinazolinedione alkylation conditions were followed utilizing **38a** and methyl 4-(4-bromomethylphenoxy) butyrate (87%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.91–1.98 (m, 2H), 2.44 (t, J = 7.4 Hz, 2H), 3.59 (s, 3H), 3.93 (t, J = 6.3 Hz, 2H), 5.27 (s, 2H), 6.85 (d, J = 8.4 Hz, 2H), 7.17 (d, J = 8.4 Hz, 2H), 7.24–7.40 (m, 12H), 7.44 (s, 1H), 7.66–7.72 (m, 1H), 8.05 (dd, J = 7.8, 1.6 Hz, 1H).

5.10.85. 4-(4-{[3-(Diphenylmethyl)-2,4-dioxo-3,4-dihydroquinazolin-1(2*H*)-yl]methyl}phenoxy)butanoic acid (40c)

The general basic ester hydrolysis conditions were followed utilizing ester **39c** (99%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.85–1.95 (m, 2H,), 2.35 (t, J = 7.4 Hz, 2H), 3.93 (t, J = 6.3 Hz, 2H), 5.27 (s, 2H), 6.86 (d, J = 8.5 Hz, 2H), 7.17 (d, J = 8.5 Hz, 2H), 7.24–7.40 (m, 12H), 7.44 (s, 1H), 7.66–7.74 (m, 1H), 8.05 (dd, J = 7.8, 1.4 Hz, 1H); ^{13}C NMR (DMSO-d_6) 175.89, 161.07, 157.95, 150.47, 139.59, 138.25, 135.41, 128.25, 127.99, 127.75, 127.47, 127.03, 122.95, 115.03, 114.49, 67.69, 59.29, 45.68, 33.73, 25.88; HRMS: $C_{32}H_{28}N_2O_5$ requires $(M+1)^+$ at m/z 521.2071; found, 502.2071.

5.10.86. Ethyl [2-(4-{[3-(diphenylmethyl)-2,4-dioxo-3,4-dihydroquinazolin-1(2*H*)-yl]methyl}phenyl)-1,3-oxazol-4-yl]acetate (39d)

The general N-1 quinazolinedione alkylation conditions were followed utilizing **38a** and ethyl [2-(4-bromomethylphenyl) oxazol-4-yl] acetate (98%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.23 (t, J = 7.2 Hz, 3H), 3.68 (s, 2H), 4.10 (q, J = 7.2 Hz, 2H), 5.42 (s, 2H), 7.25–7.50 (m, 15H), 7.65–7.73 (m, 1H), 7.90 (d, J = 8.1 Hz, 2H), 8.07 (d, J = 8.1 Hz, 1H).

5.10.87. [2-(4-{[3-(Diphenylmethyl)-2,4-dioxo-3,4-dihydroquinazolin-1(2*H*)-yl]methyl}phenyl)-1,3-oxazol-4-yl]acetic acid (40d)

The general basic ester hydrolysis conditions were followed utilizing ester **39d** (83%, chromatography and trituration with hexane/$CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.59 (s, 2H), 5.42 (s, 2H), 7.26–7.45 (m, 15H), 7.71 (m, 1H), 7.90 (d, J = 8.5 Hz, 2H), 8.04 (br s, 1H), 8.07 (d, J = 8.0 Hz, 1H); ^{13}C NMR (DMSO-d_6) 161.13, 158.82, 150.43, 139.65, 138.22, 138.16, 135.88, 135.53, 128.28, 127.99, 127.04, 126.95, 126.37, 125.90, 123.10, 115.11, 114.86, 59.34, 46.12, 36.33; HRMS: $C_{33}H_{25}N_3O_5$ requires $(M+1)^+$ at m/z 544.1867; found, 544.1866.

5.10.88. Methyl 4-({5-[3-(diphenylmethyl)-2,4-dioxo-3,4-dihydroquinazolin-1(2*H*)-yl]pentyl}oxy)benzoate (39e)

The general N-1 quinazolinedione alkylation conditions were followed utilizing **38a** and methyl 4-(5-bromo-1-pentoxy) benzoate (74%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.48–1.60 (m, 3H), 1.73–1.81 (m, 3H), 3.81 (s, 3H), 3.95 (t, J = 6.0 Hz 2H), 4.14 (t, J = 5 Hz, 2H), 6.87 (d, J = 9.0 Hz, 2H), 7.17–7.37 (m, 12H), 7.42 (d, J = 8.7 Hz, 1H), 7.63–7.70 (m, 1H), 7.98 (d, J = 9.0 Hz, 2H), 8.35 (dd, J = 7.8, 1.2 Hz, 1H).

5.10.89. 4-({5-[3-(Diphenylmethyl)-2,4-dioxo-3,4-dihydroquinazolin-1(2*H*)-yl]pentyl}oxy)benzoic acid (40e)

The general basic ester hydrolysis conditions were followed utilizing ester **39e** (25%, chromatography and trituration with hexane/EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.50–1.63 (m, 2H), 1.72–1.90 (m, 4H), 3.99 (t, J = 6.3 Hz, 2H), 4.14 (t, J = 6.5 Hz, 2H), 6.90 (d, J = 9.0 Hz, 2H), 7.15–7.38 (m, 7H), 7.39–7.45 (m, 4H), 7.55 (s, 1H), 7.66 (t, J = 6.0 Hz, 1H), 8.04 (d, J = 9.0 Hz, 2H), 8.23 (d, J = 8.9 Hz, 2H); ^{13}C NMR (DMSO-d_6) 169.68, 161.13, 159.29, 149.94, 139.61, 138.36, 135.66, 132.54, 130.54, 128.36, 128.30, 128.01, 127.02, 122.82, 114.99, 114.67, 112.69, 67.19, 59.09, 42.96, 28.38, 26.56, 22.67; HRMS: $C_{33}H_{30}N_2O_5$ requires $(M+1)^+$ at m/z 535.2227; found, 535.2228.

5.10.90. Methyl 4-{3-[3-(diphenylmethyl)-2,4-dioxo-3,4-dihydroquinazolin-1(2*H*)-yl]propoxy}benzoate (39h)

The general N-1 quinazolinedione alkylation conditions were followed utilizing **38a** and methyl 4-(3-bromo-1-propoxy) benzoate (85%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.08–2.13 (m, 2H), 3.81 (s, 3H), 4.12 (d, J = 6.0 Hz, 2H), 4.28 (d, J = 6.7 Hz, 2H), 6.93 (d, J = 8.7 Hz, 2H), 7.23–7.35 (m, 11H), 7.37 (s, 1H), 7.56 (d, J = 8.7 Hz, 1H), 7.73–7.79 (m, 1H), 7.87 (d, J = 9.0 Hz, 2H), 8.05 (dd, J = 7.8, 1.2 Hz, 1H).

5.10.91. 4-{3-[3-(Diphenylmethyl)-2,4-dioxo-3,4-dihydroquinazolin-1(2*H*)-yl]propoxy}benzoic acid (40h)

The general basic ester hydrolysis conditions were followed utilizing ester **39h** (97%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.07–2.15 (m, 2H), 4.11 (t, J = 5.5 Hz, 2H), 4.28 (t, J = 5.5 Hz, 2H), 6.91 (d, J = 9.0 Hz, 2H), 7.25–7.36 (m, 11H), 7.38 (s, 1H), 7.56 (d, J = 8.3 Hz, 1H), 7.73–7.81 (m, 1H), 7.86 (d, J = 9.0 Hz, 2H), 8.04 (d, J = 7.8 Hz, 1H); ^{13}C NMR (DMSO-d_6) 169.34, 161.10, 158.94, 149.98, 139.67, 138.31, 135.49, 130.44, 128.26, 127.92, 126.93,

122.74, 115.05, 114.44, 112.64, 64.91, 59.05, 40.61, 26.67; HRMS: $C_{31}H_{26}N_2O_5$ requires $(M+1)^+$ at *m/z* 507.1914; found, 507.1914.

5.10.92. Methyl 4-({(2*E*)-4-[3-(diphenylmethyl)-2,4-dioxo-3,4-dihydroquinazolin-1(2*H*)-yl]but-2-en-1-yl}oxy)benzoate (39i)

The general N-1 quinazolinedione alkylation conditions were followed utilizing **38a** (270 mg, 83%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.58 (d, *J* = 4.67 Hz, 2H), 4.81 (d, *J* = 3.85 Hz, 2H), 5.93 (m, 2H), 6.89 (d, *J* = 9.07 Hz, 2H), 7.16 (d, *J* = 8.24 Hz, 1H), 7.23–7.40 (m, 7H), 7.41–7.49 (m, 4H), 7.57 (s, 1H), 7.60–7.69 (m, 1H), 7.99 (d, *J* = 8.79 Hz, 2H), 8.25 (dd, *J* = 7.97, 1.37 Hz, 1H).

5.10.93. 4-({(2*E*)-4-[3-(Diphenylmethyl)-2,4-dioxo-3,4-dihydroquinazolin-1(2*H*)-yl]but-2-en-1-yl}oxy)benzoic acid (40i)

The general basic ester hydrolysis conditions were followed utilizing ester **39i** (248 mg, 96%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.60 (d, *J* = 4.40 Hz, 2H), 4.81 (d, *J* = 3.85 Hz, 2H), 5.82–6.07 (m, 2H), 6.93 (d, *J* = 9.07 Hz, 2H), 7.17 (d, *J* = 8.52 Hz, 1H), 7.23–7.42 (m, 7H), 7.43–7.51 (m, 4H), 7.59 (s, 1H), 7.61–7.70 (m, 1H), 8.07 (d, *J* = 8.79 Hz, 2H), 8.26 (d, *J* = 7.97 Hz, 1H); ^{13}C NMR (DMSO-d_6) 169.63, 161.02, 158.52, 149.93, 139.57, 138.27, 135.43, 133.21, 130.40, 128.25, 128.14, 127.96, 127.74, 126.98, 126.80, 122.90, 114.99, 114.92, 112.80, 66.98, 59.23, 44.32; HRMS: $C_{32}H_{26}N_2O_5$ requires $(M+1)^+$ at *m/z* 519.1914; found, 519.1913.

5.10.94. Methyl (4-{2-[3-(diphenylmethyl)-2,4-dioxo-3,4-dihydroquinazolin-1(2*H*)-yl]ethoxy}phenyl)acetate (39j)

The general N-1 quinazolinedione alkylation conditions were followed utilizing **38a** and methyl [4-(2-bromoethoxy)phenyl] acetate (96%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.57 (s, 2H), 3.58 (s, 3H), 4.25 (t, *J* = 5.7 Hz, 2H), 4.52 (t, *J* = 5.5 Hz, 2H), 6.73 (d, *J* = 8.5 Hz, 2H), 7.11 (d, *J* = 8.5 Hz, 2H), 7.25–7.36 (m, 11H), 7.39 (s, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.76–7.82 (m, 1H), 8.03 (dd, *J* = 7.6, 1.8 Hz, 1H).

5.10.95. (4-{2-[3-(Diphenylmethyl)-2,4-dioxo-3,4-dihydroquinazolin-1(2*H*)-yl]ethoxy}phenyl)acetic acid (40j)

The general basic ester hydrolysis conditions were followed utilizing ester **39j** (88%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.46 (s, 2H), 4.19–4.25 (m, 2H), 4.48–4.55 (m, 2H), 6.73 (d, *J* = 8.5 Hz, 2H), 7.11 (d, *J* = 8.5 Hz, 2H), 7.25–7.37 (m, 11H), 7.40 (s, 1H), 7.66 (d, *J* = 7.8 Hz, 1H), 7.75–7.83 (m, 1H), 8.03 (dd, *J* = 7.8, 1.5 Hz, 1H); ^{13}C NMR (DMSO-d_6) 174.40, 160.99, 155.63, 150.19, 139.94, 138.25, 135.38, 132.55, 129.87, 128.28, 128.11, 127.93, 126.98, 122.87, 115.03, 114.89, 113.35, 64.52, 59.13, 45.10, 42.64; HRMS: $C_{31}H_{26}N_2O_5$ requires $(M+1)^+$ at *m/z* 507.1913; found, 507.1914.

5.10.96. 2-Amino-5-bromo-*N*-(diphenylmethyl)benzamide (37c)

The general isatoic anhydride aminolysis conditions were followed utilizing 6-bromo-2*H*-3,1-benzoxazine-2,4(1*H*)-dione (1.14 g, 32%, yellow solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 5.58 (s, 2H), 6.34 (d, *J* = 7.3 Hz, 1H), 6.51 (d, *J* = 7.1 Hz, 1H), 6.57 (d, *J* = 8.6 Hz, 1H), 7.26–7.33 (m, 7H), 7.34–7.40 (m, 4H), 7.47 (d, *J* = 2.3 Hz, 1H).

5.10.97. 6-Bromo-3-(diphenylmethyl)quinazoline-2,4(1*H*,3*H*)-dione (38c)

The general quinazolinedione cyclization procedure was followed utilizing aminoamide **37c** (92%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.62 (d, *J* = 8.7 Hz, 1H), 7.25–7.50 (m, 10H), 7.60 (d, *J* = 8.7 Hz, 1H), 8.23 (*J* = 2.1 Hz, 1H).

5.10.98. Methyl 4-({(2*Z*)-4-[6-bromo-3-(diphenylmethyl)-2,4-dioxo-3,4-dihydroquinazolin-1(2*H*)-yl]but-2-en-1-yl}oxy) benzoate (39k)

The general N-1 quinazolinedione alkylation conditions were followed utilizing **38c** and methyl *cis*-4-(4-chlorobut-2-enyloxy) benzoate (75%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.90 (s, 3H), 4.77 (d, *J* = 6.3 Hz, 2H), 4.87 (d, *J* = 6.3 Hz, 2H), 5.60–5.71 (m, 1H), 5.89–6.00 (m, 1H), 6.92 (d, *J* = 8.8 Hz, 2H), 7.08 (d, *J* = 8.8 Hz, 1H), 7.24–7.43 (m, 10H), 7.50 (s, 1H), 7.70 (d, 8.8 Hz, 1H), 7.99 (d, *J* = 9.0 Hz, 2H), 8.33 (s, 1H).

5.10.99. 4-({(2*Z*)-4-[6-Bromo-3-(diphenylmethyl)-2,4-dioxo-3,4-dihydroquinazolin-1(2*H*)-yl]but-2-en-1-yl}oxy)benzoic acid (40k)

The general basic ester hydrolysis conditions were followed utilizing ester **39k** (35%, chromatography and trituration with hexane/EtOAc). ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.77 (d, *J* = 5.6 Hz, 2H), 4.87 (d, *J* = 5.3 Hz, 2H), 5.57–5.67 (m, 1H), 5.80–5.92 (m, 1H), 6.85 (d, *J* = 8.8 Hz, 2H), 7.24–7.38 (m, 12H), 7.79 (d, *J* = 8.8 Hz, 2H), 7.92 (dd, *J* = 8.8, 2.3 Hz, 1H), 8.09 (d, *J* = 2.3 Hz, 1H); ^{13}C NMR (DMSO-d_6) 169.35, 160.04, 158.84, 149.88, 138.95, 138.10. 137.83, 130.58, 130.11, 128.91, 128.41, 128.03, 127.55, 127.13, 117.26, 117.13, 114.78, 113.08, 63.73, 61.62, 59.66, 41.66, 28.65; HRMS: $C_{32}H_{25}BrN_2O_5$ requires $(M+1)^+$ at *m/z* 597.1019; found, 597.1021.

5.10.100. Methyl 4-({(2*E*)-4-[6-bromo-3-(diphenylmethyl)-2,4-dioxo-3,4-dihydroquinazolin-1(2*H*)-yl]but-2-en-1-yl}oxy) benzoate (39l)

The general N-1 quinazolinedione alkylation conditions were followed utilizing **38c** and methyl *trans*-4-(4-bromobut-2-enyloxy) benzoate (89%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.89 (s, 3H), 4.52–4.60 (m, 2H), 4.70–4.80 (m, 2H), 5.78–5.98 (m, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 7.03 (d, *J* = 8.5 Hz, 1H), 7.25–7.45 (m, 10H), 7.50 (s, 1H), 7.68 (d, *J* = 8.5 Hz, 1H), 7.98 (d, *J* = 8.7 Hz, 2H), 8.32 (d, *J* = 2.7 HZ, 1H).

5.10.101. 4-{[(E)-4-(3-Benzhydryl-6-bromo-2,4-dioxo-3,4-dihydro-1(2H)-quinazolinyl)-2-butenyl]oxy}benzoic acid (40l)

The general basic ester hydrolysis conditions were followed utilizing ester **39l** (84%, trituration with pentane/EtOAc). ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.51 (d, *J* = 4.29 Hz, 2H), 4.76 (s, 2H), 5.83–5.95 (m, 2H), 6.77 (d, *J* = 8.84 Hz, 2H), 7.25–7.36 (m, 11H), 7.40 (d, *J* = 8.84 Hz, 1H), 7.74–7.80 (m, 2H), 7.91 (dd, *J* = 8.97, 2.40 Hz, 1H), 8.09 (d, *J* = 2.27 Hz, 1H); ^{13}C NMR (DMSO-d_6) 169.40, 160.10, 158.88, 149.78, 139.00, 138.14, 137.81, 130.56, 130.04, 128.37, 128.05, 127.80, 127.13, 126.56, 117.63, 117.03, 114.77, 113.01, 67.09, 59.64, 44.65, 28.69; HRMS: $C_{32}H_{25}BrN_2O_5$ requires $(M+1)^+$ at *m/z* 597.1019; found, 597.1021.

5.10.102. Methyl 3-({(2*E*)-4-[7-chloro-3-(diphenylmethyl)-2,4-dioxo-3,4-dihydroquinazolin-1(2*H*)-yl]but-2-en-1-yl}oxy) benzoate (39m)

The general N-1 quinazolinedione alkylation conditions were followed utilizing **30** (223 mg, 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.88 (s, 3H), 4.57 (dd, *J* = 4.5, 1.0 Hz, 2H), 4.73 (d, *J* = 3.8 Hz, 2H), 5.80–6.01 (m, 2H), 7.04–7.08 (m, 1H), 7.12 (d, *J* = 1.8 Hz, 1H), 7.19 (dd, *J* = 8.5, 1.6 Hz, 1H), 7.27–7.36 (m, 7H), 7.38–7.43 (m, 4H), 7.50 (s, 1H), 7.52 (dd, *J* = 2.8, 1.5 Hz, 1H), 7.61–7.64 (m, 1H), 8.13 (d, *J* = 8.3 Hz, 1H).

5.10.103. 3-({(2*E*)-4-[7-Chloro-3-(diphenylmethyl)-2,4-dioxo-3,4-dihydroquinazolin-1(2*H*)-yl]but-2-en-1-yl}oxy)benzoic acid (40m)

The general basic ester hydrolysis conditions were followed utilizing ester **39m** (90 mg, 91%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4.60 (d, *J* = 4.5 Hz, 2H), 4.78 (d, *J* = 3.3 Hz, 2H), 5.84–5.98 (m, 2H),

7.12–7.18 (m, 1H), 7.24–7.43 (m, 14H), 7.49–7.54 (m, 2H), 8.03 (d, J = 8.3 Hz, 1H); ^{13}C NMR (DMSO-d_6) 167.03, 160.50, 158.00, 149.93, 140.77, 140.29, 138.19, 132.17, 130.14, 129.63, 128.36, 128.28, 128.04, 127.61, 127.44, 127.11, 127.07, 126.98, 126.87, 123.15, 121.66, 119.36, 114.93, 114.74, 114.04, 67.27, 59.48, 44.46; HRMS: $C_{32}H_{25}ClN_2O_5$ requires $(M+1)^+$ at m/z 553.1525; found, 553.1524.

5.10.104. 1-[(2*E*)-4-Bromobut-2-en-1-yl]-7-chloro-3-(diphenylmethyl)quinazoline-2,4(1*H*,3*H*)-dione (42a)

The general N-1 quinazolinedione alkylation conditions were followed utilizing **30** and *trans*-1,4-dibromo-2-butene (84%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.91 (d, J = 6.3 Hz, 2H), 4.68–4.73 (m, 2H), 5.75–5.94 (m, 2H), 7.12 (d, J = 2.0 Hz, 1H), 7.20 (dd, J = 8.5, 2.0 Hz, 1H), 7.24–7.43 (m, 10H), 7.50 (s, 1H), 8.14 (d, J = 8.5 Hz, 1H).

5.10.105. Methyl 4-({(2*E*)-4-[7-chloro-3-(diphenylmethyl)-2,4-dioxo-3,4-dihydroquinazolin-1(2*H*)-yl]but-2-en-1-yl}oxy)benzoate (43a)

The general phenol alkylation conditions were followed utilizing **42a** and methyl 4-hydroxybenzoate (1.23 g, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.88 (s, 3H), 4.57 (dd, J = 4.55, 1.26 Hz, 2H), 4.73 (d, J = 3.79 Hz, 2H), 5.79–5.99 (m, 2H), 6.87 (d, J = 8.84 Hz, 2H), 7.12 (d, J = 1.77 Hz, 1H), 7.20 (dd, J = 8.34, 1.77 Hz, 1H), 7.27–7.36 (m, 6H), 7.37–7.43 (m, 4H), 7.50 (s, 1H), 7.96 (d, J = 8.84 Hz, 2H), 8.14 (d, J = 8.34 Hz, 1H).

5.10.106. 4-({(2*E*)-4-[7-Chloro-3-(diphenylmethyl)-2,4-dioxo-3,4-dihydroquinazolin-1(2*H*)-yl]but-2-en-1-yl}oxy)benzoic acid (44a)

The general basic ester hydrolysis conditions were followed utilizing ester **43a** (1.15 g, 91%, chromatography and trituration with hexane/EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.58–4.60 (m, 2H), 4.70–4.73 (m, 2H), 5.80–6.00 (m, 2H), 6.90 (d, J = 9.1 Hz, 2H), 7.10–7.50 (m, 13H), 8.03 (d, J = 8.8 Hz, 2H), 8.14 (d, J = 8.4 Hz, 1H); HRMS: calcd for $C_{32}H_{25}ClN_2O_5$ + Na, 575.13497; found, 575.1338; Anal. Calcd for $C_{32}H_{25}ClN_2O_5$: C, 69.50; H, 4.56; N, 5.07. Found: C, 69.71; H, 4.50; N, 4.96.

5.10.107. 7-Chloro-1-[(2*Z*)-4-chlorobut-2-en-1-yl]-3-(diphenylmethyl)quinazoline-2,4(1*H*,3*H*)-dione (42b)

The general N-1 quinazolinedione alkylation conditions were followed utilizing **30** and *cis*-1,4-dichloro-2-butene (70%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.21 (d, J = 8.0 Hz, 2H), 4.81 (dd, J = 11.0, 1.2 Hz, 2H), 5.58–5.69 (m, 1H), 5.88–6.00 (m, 1H), 7.17–7.46 (m, 12H), 7.50 (s, 1H), 8.14 (d, J = 8.7 Hz, 1H).

5.10.108. Methyl 4-({(2*Z*)-4-[7-chloro-3-(diphenylmethyl)-2,4-dioxo-3,4-dihydroquinazolin-1(2*H*)-yl]but-2-en-1-yl}oxy)benzoate (43b)

The general phenol alkylation conditions were followed utilizing **42b** and methyl 4-hydroxybenzoate (78%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.89 (s, 3H), 4.77 (d, J = 5.4 Hz, 2H), 4.85 (d, J = 6.0 Hz, 2H), 5.62–5.73 (m, 1H), 5.90–6.05 (m, 1H), 6.94 (d, J = 9.0 Hz, 2H), 7.18–7.23 (m, 2H), 7.24–7.45 (m, 11H), 7.50 (s, 1H), 7.98 (d, J = 7.5 Hz, 2H), 8.13 (d, J = 9.0 Hz, 1H).

5.10.109. 4-({(2*Z*)-4-[7-Chloro-3-(Diphenylmethyl)-2,4-dioxo-3,4-dihydroquinazolin-1(2*H*)-yl]but-2-en-1-yl}oxy)benzoic acid (44b)

The general basic ester hydrolysis conditions were followed utilizing ester **43b** (93%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.77 (d, J = 5.31 Hz, 2H), 4.90 (d, J = 6.06 Hz, 2H), 5.57–5.69 (m, 1H), 5.81–5.94 (m, 1H), 6.80–6.86 (m, 2H), 7.23–7.39 (m, 12H), 7.50 (d, J = 1.77 Hz, 1H), 7.77–7.82 (m, 2H), 8.03 (d, J = 8.34 Hz, 1H). HRMS: $C_{32}H_{25}ClN_2O_5$ requires $(M+1)^+$ at m/z 553.1525; found, 553.1530.

5.10.110. 1-[(2*Z*)-4-Chlorobut-2-en-1-yl]-3-(diphenylmethyl) quinazoline-2,4(1*H*,3*H*)-dione (42c)

The general N-1 quinazolinedione alkylation conditions were followed utilizing **38a** (80 mg, 30%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.26 (d, J = 7.97 Hz, 2H), 4.89 (d, J = 6.04 Hz, 2H), 5.61–5.73 (m, 1H), 5.84–5.99 (m, 1H), 7.18–7.41 (m, 7H), 7.41–7.50 (m, 4H), 7.57 (s, 1H), 7.64–7.74 (m, 1H), 8.26 (dd, J = 7.97, 1.37 Hz, 1H).

5.10.111. Methyl 4-({(2*Z*)-4-[3-(diphenylmethyl)-2,4-dioxo-3,4-dihydroquinazolin-1(2*H*)-yl]but-2-en-1-yl}oxy)benzoate (43c)

The general phenol alkylation conditions were followed utilizing **42c** and methyl 4-hydroxybenzoate (80 mg, 78%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.93 (s, 3H), 4.81 (d, J = 5.77 Hz, 2H), 4.92 (d, J = 6.04 Hz, 2H), 5.64–5.80 (m, 1H), 5.90–6.03 (m, 1H), 6.96 (d, J = 9.06 Hz, 2H), 7.18–7.39 (m, 8H), 7.41–7.49 (m, 4H), 7.58 (s, 1H), 7.62–7.71 (m, 1H), 8.02 (d, J = 9.07 Hz, 2H), 8.25 (dd, J = 7.97, 1.37 Hz, 1H).

5.10.112. 4-({(2*Z*)-4-[3-(Diphenylmethyl)-2,4-dioxo-3,4-dihydroquinazolin-1(2*H*)-yl]but-2-en-1-yl}oxy)benzoic acid (44c)

The general basic ester hydrolysis conditions were followed utilizing ester **43c** (20 mg, 19%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.78–4.87 (d, J = 5.77 Hz, 2H), 4.93 (d, J = 6.04 Hz, 2H), 5.68–5.81 (m, 1H), 5.90–6.03 (m, 1H), 6.95–7.03 (d, J = 9.07 Hz, 2H), 7.42–7.51 (m, 4H), 7.59 (s, 1H), 7.63–7.71 (m, 1H), 8.09 (d, J = 9.07 Hz, 2H), 8.26 (dd, J = 7.97, 1.37 Hz, 1H); HRMS: $C_{32}H_{26}N_2O_5$ requires $(M+1)^+$ at m/z 519.1914; found, 519.1913.

5.10.113. 7-Chloro-1-(4-bromobutyl)-3-(diphenylmethyl) quinazoline-2,4(1*H*,3*H*)-dione (42d)

The general N-1 quinazolinedione alkylation conditions were followed utilizing **30** and 1,4-dibromobutane (82%, 4 equiv, 4 h at room temperature, then 40 min at 50–70 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.80–1.98 (m, 4H), 3.43 (t, J = 6.3 Hz, 2H), 4.04–4.14 (m, 2H), 6.90–7.42 (m, 12H), 7.50 (s, 1H), 8.15 (d, J = 9.0 Hz, 1H).

5.10.114. Methyl 4-{4-[7-chloro-3-(diphenylmethyl)-2,4-dioxo-3,4-dihydroquinazolin-1(2*H*)-yl]butoxy}benzoate (43d)

The general phenol alkylation conditions were followed utilizing **42d** and methyl 4-hydroxybenzoate (56%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.80–1.97 (m, 4H), 3.88 (s, 3H), 4.02–4.06 (m, 2H), 4.10–4.17 (m, 2H), 6.88 (d, J = 8.5 Hz, 2H), 7.18 (s, 2H), 7.24–7.42 (m, 10H), 7.50 (s, 1H), 7.97 (d, J = 8.7 Hz, 2H), 8.14 (d, J = 8.7 Hz, 1H).

5.10.115. 4-{4-[7-Chloro-3-(diphenylmethyl)-2,4-dioxo-3,4-dihydroquinazolin-1(2*H*)-yl]butoxy}benzoic acid (44d)

The general basic ester hydrolysis conditions were followed utilizing ester **43d** (98%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.75 (s, 4H), 3.96 (s, 2H), 4.14 (s, 2H), 6.71–6.78 (m, 2H), 7.24–7.37 (m, 12H), 7.66 (d, J = 1.77 Hz, 1H), 7.72–7.78 (m, 2H), 8.03 (d, J = 8.34 Hz, 1H); ^{13}C NMR (DMSO-d_6) 169.67, 160.43, 158.96, 149.85, 140.75, 140.40, 138.13, 133.07, 130.42, 130.18, 128.26, 127.95, 127.02, 122.95, 114.29, 113.92, 112.60, 66.79, 59.23, 43.02, 25.64, 23.37; HRMS: $C_{32}H_{27}ClN_2O_5$ requires $(M+1)^+$ at m/z 555.1681; found, 555.1687.

5.10.116. 1-(6-Bromohexyl)-3-(diphenylmethyl)quinazoline-2,4(1*H*,3*H*)-dione (42e)

The general N-1 quinazolinedione alkylation conditions were followed utilizing **38a** and 1,6-dibromohexane (57%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35–1.50 (m, 4H), 1.66–1.78 (m, 2H), 1.79–1.90 (m, 2H), 3.38 (t, J = 6.6 Hz, 2H), 4.09 (t, J = 7.5 Hz, 2H), 7.12–7.37 (m, 8H), 7.38–7.45 (m, 4H), 7.55 (s, 2H), 7.65 (t, J = 6.3 Hz, 1H), 8.22 (d, J = 9.0 Hz, 1H).

5.10.117. Methyl 4-({6-[3-(diphenylmethyl)-2,4-dioxo-3,4-dihydroquinazolin-1(2*H*)-yl]hexyl}oxy)benzoate (43e)

The general phenol alkylation conditions were followed utilizing **42e** and methyl 4-hydroxybenzoate (100% crude yield, used in the next step without further purification). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35–1.63 (m, 4H), 1.73–1.85 (m, 4H), 3.88 (s, 3H), 3.98 (t, J = 6.6 Hz, 2H), 4.14 (t, J = 6.5 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 7.15–7.35 (m, 7H), 7.39–7.45 (m, 4H), 7.65 (t, J = 6.0 Hz, 1H), 7.96 (d, J = 9.0 Hz, 2H), 8.22 (d, J = 8.8 Hz, 1H).

5.10.118. 4-({6-[3-(Diphenylmethyl)-2,4-dioxo-3,4-dihydroquinazolin-1(2*H*)-yl]hexyl}oxy)benzoic acid (44e)

The general basic ester hydrolysis conditions were followed utilizing ester **43e** (75%, hexane/EtOAc trituration). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35–1.60 (m, 4H), 1.70–1.83 (m, 4H), 4.02 (t, J = 6.6 Hz, 2H), 4.11 (t, J = 6.5 Hz, 2H), 6.90 (d, J = 8.8 Hz, 2H), 7.15–7.35 (m, 7H), 7.39–7.45 (m, 4H), 7.68 (t, J = 6.0 Hz, 1H), 8.03 (d, J = 9.0 Hz, 2H), 8.21 (d, J = 8.8 Hz, 1H); mp 142–143 °C; HRMS: $C_{34}H_{32}N_2O_5$ requires $(M+1)^+$ at m/z 549.2384; found, 549.2390.

5.10.119. 1-(7-Bromoheptyl)-3-(diphenylmethyl)quinazoline-2,4(1*H*,3*H*)-dione (42f)

The general N-1 quinazolinedione alkylation conditions were followed utilizing **38a** and 1,7-dibromoheptane (79%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28–1.45 (m, 6H), 1.63–1.77 (m, 4H), 1.83 (t, J = 9.0 Hz, 2H), 3.39 (t, J = 9.0 Hz, 2H), 4.08 (t, J = 9.0 Hz, 2H), 7.10–7.38 (m, 7H), 7.41 (m, 4H), 7.55 (s, 1H), 7.66 (t, 6.0 Hz, 1H), 8.22 (d, J = 6.0 Hz, 2H).

5.10.120. Methyl 4-({7-[3-(diphenylmethyl)-2,4-dioxo-3,4-dihydroquinazolin-1(2*H*)-yl]heptyl}oxy)benzoate (43f)

The general phenol alkylation conditions were followed utilizing **42f** and methyl 4-hydroxybenzoate (100% crude yield, used in the next step without further purification). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32–1.51 (m, 6H), 1.63–1.83 (m, 4H), 3.89 (s, 3H), 3.99 (t, J = 6.6 Hz, 2H), 4.10 (t, J = 6.6 Hz, 2H), 6.88 (d, J = 6.8 Hz, 2H), 7.15–7.38 (m, 8H), 7.39–7.45 (m, 4H), 7.55 (s, 1H), 7.65 (t, J = 6.0 Hz, 1H), 7.97 (d, J = 9.0 Hz, 2H), 8.21 (d, J = 8.9 Hz, 1H).

5.10.121. 4-({7-[3-(Diphenylmethyl)-2,4-dioxo-3,4-dihydroquinazolin-1(2*H*)-yl]heptyl}oxy)benzoic acid (44f)

The general basic ester hydrolysis conditions were followed utilizing ester **43f** (89%, hexane/EtOAc trituration); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30–1.50 (m, 6H), 1.63–1.83 (m, 4H), 4.00 (t, J = 6.6 Hz, 2H), 4.09 (t, J = 6.6 Hz, 2H), 6.92 (d, J = 6.8 Hz, 2H), 7.15–7.38 (m, 7H), 7.39–7.45 (m, 4H), 7.55 (s, 1H), 7.65 (t, J = 6.0 Hz, 1H), 8.04 (d, J = 9.0 Hz, 2H), 8.22 (d, J = 8.9 Hz, 1H); mp 131–132 °C; HRMS: $C_{35}H_{34}N_2O_5$ requires $(M+1)^+$ at m/z 563.2541; found, 563.2537.

5.10.122. *tert*-Butyl 4-({(2*E*)-4-[3-(diphenylmethyl)-7-(methylthio)-2,4-dioxo-3,4-dihydroquinazolin-1(2*H*)-yl]but-2-en-1-yl}oxy)benzoate (45a)

The general nucleophilic substitution procedure was followed utilizing sodium thiomethoxide (122 mg, 58%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.58 (s, 9H), 2.48 (s, 3H), 4.55 (br s, 2H), 4.76 (br s, 2H), 5.80–5.98 (m, 2H), 6.78–6.90 (m, 3H), 7.05 (d, J = 8.5 Hz, 1H), 7.23–7.56 (m, 10H), 7.83–7.98 (m, 2H), 8.02–8.16 (m, 1H).

5.10.123. 4-({(2*E*)-4-[3-(Diphenylmethyl)-7-(methylthio)-2,4-dioxo-3,4-dihydroquinazolin-1(2*H*)-yl]but-2-en-1-yl}oxy)benzoic acid (46a)

The general acidic ester hydrolysis conditions were followed utilizing ester **45a** (70 mg, 88%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01–8.15 (m, 3H), 7.52 (s, 1H), 7.23–7.44 (m, 10H), 7.05 (d, J = 8.3 Hz, 1H), 6.80–6.95 (m, 3H), 5.80–6.00 (m, 2H), 4.77 (br s, 2H), 4.58 (br s, 2H), 2.50 (s, 3H); HRMS: $C_{33}H_{28}N_2O_5S$ requires $(M+1)^+$ at m/z 565.1792; found, 565.1793.

5.10.124. *tert*-Butyl 4-({(2*E*)-4-[3-(diphenylmethyl)-7-(methylsulfonyl)-2,4-dioxo-3,4-dihydroquinazolin-1(2*H*)-yl]but-2-en-1-yl}oxy)benzoate (45b)

A solution of sulfide **45a** (122 mg, 0.2 mmol), TPAP (12 mg, 10 mol %), NMO (119 mg, 3 equiv), and 4 Å molecular sieves (200 mg) in acetonitrile (4 mL) was stirred at room temperature for 16 h. The solution was evaporated and flash chromatographed (30–40% EtOAc–hexanes) to afford sulfone **45b** (63 mg, 28%) as a white foam. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.58 (s, 9H), 3.05 (s, 3H), 4.56 (s, 2H), 4.84 (s, 2H), 5.94 (s, 2H), 6.82 (d, J = 9.0 Hz, 2H), 7.25–7.42 (m, 10H), 7.51 (s, 1H), 7.70–7.75 (m, 2H), 7.89 (d, J = 8.9 Hz, 2H), 8.41 (d, J = 8.2 Hz, 1H).

5.10.125. 4-({(2*E*)-4-[3-(Diphenylmethyl)-7-(methylsulfonyl)-2,4-dioxo-3,4-dihydroquinazolin-1(2*H*)-yl]but-2-en-1-yl}oxy) benzoic acid (46b)

The general acidic ester hydrolysis conditions were followed utilizing ester **45b** (50 mg, 84%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.41 (d, J = 8.1 Hz, 1H), 8.02 (d, J = 8.8 Hz, 2H), 7.70–7.76 (m, 2H), 7.51 (s, 1H), 7.16–7.42 (m, 10H), 6.87 (d, J = 8.9 Hz, 2H), 5.94 (s, 2H), 4.85 (s, 2H), 4.58 (s, 2H), 3.06 (s, 3H); HRMS: $C_{33}H_{28}N_2O_7S$ requires $(M+1)^+$ at m/z 597.1690; found, 597.1690.

5.10.126. *tert*-Butyl 4-({(2*E*)-4-[3-(diphenylmethyl)-2,4-dioxo-7-(phenylthio)-3,4-dihydroquinazolin-1(2*H*)-yl]but-2-en-1-yl} oxy)benzoate (45c)

To a solution of thiophenol (139 μL, 4 equiv) in DMF (1 mL) was added neat 60% NaH (54 mg, 4 equiv). After stirring room temperature for 30 min, fluoride **35a** (200 mg, 0.34 mmol) was added as a DMF (2 mL) solution. After 4.5 h, the solution was quenched with water, diluted with ethyl acetate, washed with water and brine, dried, filtered, evaporated, and flash chromatographed (20–30% EtOAc–hexanes) to afford sulfide **45c** (200 mg, 86%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.58 (s, 9H), 4.45 (d, J = 5.0 Hz, 2H), 4.53 (d, J = 5.0 Hz, 2H), 5.44–5.55 (m, 2H), 5.68–5.79 (m, 2H), 6.70 (s, 1H), 6.86 (d, J = 9.0 Hz, 2H), 6.99 (d, J = 8.4 Hz, 1H), 7.23–7.58 (m, 16H), 7.94 (d, J = 8.9 Hz, 2H), 8.04 (d, J = 8.5 Hz, 1H).

5.10.127. 4-({(2*E*)-4-[3-(Diphenylmethyl)-2,4-dioxo-7-(phenylthio)-3,4-dihydroquinazolin-1(2*H*)-yl]but-2-en-1-yl} oxy)benzoic acid (46c)

The general acidic ester hydrolysis conditions were followed utilizing ester **45c** (54 mg, 78%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (m, 3H), 7.16–7.55 (m, 11H), 6.99 (d, J = 8.5 Hz, 1H), 6.91 (d, J = 8.8 Hz, 2H), 6.71 (s, 1H), 5.50–5.82 (m, 2H), 4.45–4.60 (m, 4H); HRMS: $C_{38}H_{30}N_2O_5S$ requires $(M+1)^+$ at m/z 627.1948; found, 627.1952.

5.10.128. *tert*-Butyl 4-({(2*E*)-4-[3-(diphenylmethyl)-7-methoxy-2,4-dioxo-3,4-dihydroquinazolin-1(2*H*)-yl]but-2-en-1-yl}oxy) benzoate (45d)

A solution of fluoride **35a** (200 mg, 0.34 mmol) and potassium hydroxide (112 mg, 5 equiv) in methanol (2 mL) and THF (2 mL) was heated at 50 °C for 16 h. The cooled solution was neutralized with 10% aq HCl, diluted with ethyl acetate, washed with water and brine, dried, filtered, evaporated, and flash chromatographed (30% EtOAc–hexanes) to afford methyl ether **45d** (106 mg, 53%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.58 (s, 9H), 3.84 (s, 3H), 4.55 (br s, 2H), 4.73 (br s, 2H), 5.79–5.97 (m, 2H), 6.55 (s, 1H), 6.76 (d, J = 9.1 Hz, 1H), 6.84 (d, J = 8.5 Hz, 2H), 7.24–7.48 (m, 10H), 7.53 (s, 1H), 7.90 (d, J = 8.4 Hz, 2H), 8.14 (d, J = 8.8 Hz, 1H).

5.10.129. 4-({(2*E*)-4-[3-(Diphenylmethyl)-7-methoxy-2,4-dioxo-3,4-dihydroquinazolin-1(2*H*)-yl]but-2-en-1-yl}oxy) benzoic acid (46d)

The general acidic ester hydrolysis conditions were followed utilizing ester **45d** (80 mg, 88%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.81 (d, J = 8.9 Hz, 1H), 7.69 (d, J = 8.7 Hz, 2H), 7.00–7.25 (m, 11H), 6.82 (d, J = 8.7 Hz, 2H), 6.75 (dd, J = 8.9, 2.0 Hz, 1H), 6.67 (s, 1H), 5.75–5.80 (m, 2H), 4.64 (br s, 2H), 4.48 (br s, 2H), 3.69 (s, 3H); ^{13}C NMR (DMSO-d_6) 169.53, 164.90, 160.62, 158.81, 150.26, 141.51, 138.49, 132.50, 130.53, 130.29, 128.30, 128.02, 127.13, 127.01, 112.94, 110.48, 108.22, 99.16, 67.03, 59.00, 55.87, 44.41; HRMS: $C_{33}H_{28}N_2O_6$ requires $(M+1)^+$ at m/z 549.2020; found, 549.2020.

5.10.130. *tert*-Butyl 4-({(2*E*)-4-[3-(diphenylmethyl)-2,4-dioxo-7-phenoxy-3,4-dihydroquinazolin-1(2*H*)-yl]but-2-en-1-yl}oxy) benzoate (45e)

To a solution of phenol (159 mg, 5 equiv) in DMF (1 mL) was added neat 60% NaH (68 mg, 5 equiv). After stirring room temperature for 30 min, fluoride **35a** (200 mg, 0.34 mmol) was added as a DMF (2 mL) solution and the reaction was heated at 60 °C for 16 h. The solution was quenched with water, diluted with ethyl acetate, washed with water and brine, dried, filtered, evaporated, and flash chromatographed (10% EtOAc–hexanes) to afford ether **45e** (150 mg, 66%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.58 (s, 9H), 4.49 (d, J = 4.6 Hz, 2H), 4.63 (d, J = 5.0 Hz, 2H), 5.63–5.90 (m, 2H), 6.64 (d, J = 2.0 Hz, 1H), 6.79 (dd, J = 8.9, 2.1 Hz, 1H), 6.85 (d, J = 9.0 Hz, 2H), 7.07 (d, J = 8.9 Hz, 2H), 7.23–7.46 (m, 10H), 7.52 (s, 1H), 7.92 (d, J = 8.8 Hz, 2H), 8.14 (d, J = 8.8 Hz, 1H).

5.10.131. 4-({(2*E*)-4-[3-(Diphenylmethyl)-2,4-dioxo-7-phenoxy-3,4-dihydroquinazolin-1(2*H*)-yl]but-2-en-1-yl}oxy) benzoic acid (46e)

The general acidic ester hydrolysis conditions were followed utilizing ester **45e** (90 mg, 95%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (d, J = 8.8 Hz, 1H), 8.04 (d, J = 8.9 Hz, 2H), 7.52 (s, 1H), 7.20–7.50 (m, 13H), 7.07 (dd, J = 8.7, 1.2 Hz, 2H), 6.90 (d, J = 8.9 Hz, 2H), 6.79 (dd, J = 8.8, 2.0 Hz, 1H), 6.65 (d, J = 2.1 Hz, 1H), 5.62–5.90 (m, 2H), 4.64 (d, J = 4.8 Hz, 2H), 4.53 (d, J = 4.7 Hz, 2H); HRMS: $C_{38}H_{30}N_2O_6$ requires $(M+1)^+$ at m/z 611.2177; found, 611.2175.

5.10.132. *tert*-Butyl 4-({(2*E*)-4-[3-(diphenylmethyl)-7-morpholin-4-yl-2,4-dioxo-3,4-dihydroquinazolin-1(2*H*)-yl]but-2-en-1-yl}oxy)benzoate (45f)

The general nucleophilic substitution procedure was followed utilizing morpholine (160 mg, 71%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.58 (s, 9H), 3.22–3.26 (m, 4H), 3.80–3.84 (m, 4H), 4.56 (s, 2H), 4.75 (br s, 2H), 5.80–6.00 (m, 2H), 6.39 (d, J = 1.9 Hz, 1H), 6.74 (dd, J = 9.0, 2.0 Hz, 1H), 6.83 (d, J = 9.1 Hz, 2H), 7.24–7.47 (m, 11H), 7.53 (s, 1H), 7.89 (d, J = 8.9 Hz, 2H), 8.05 (d, J = 8.9 Hz, 1H).

5.10.133. 4-({(2*E*)-4-[3-(Diphenylmethyl)-7-morpholin-4-yl-2,4-dioxo-3,4-dihydroquinazolin-1(2*H*)-yl]but-2-en-1-yl}oxy) benzoic acid (46f)

The general acidic ester hydrolysis conditions were followed utilizing ester **45f** (115 mg, 79%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (d, J = 8.9 Hz, 1H), 8.01 (d, J = 8.8 Hz, 2H), 7.53 (s, 1H), 7.26–7.42 (m, 8H), 6.87 (d, J = 8.8 Hz, 2H), 6.74 (dd, J = 9.0, 1.6 Hz, 1H), 6.36 (s, 1H), 5.80–6.00 (m, 2H), 4.76 (br s, 2H), 4.57–4.58 (m, 2H), 4.08–4.14 (m, 4H), 3.81–3.84 (m, 4H); ^{13}C NMR (DMSO-d_6) 160.54, 158.77, 155.70, 150.43, 141.14, 138.70, 130.54, 129.51, 128.28, 128.08, 128.00, 127.53, 126.93, 112.82, 109.81, 105.24, 97.53, 67.07, 65.70, 58.70, 46.82, 44.13; HRMS: $C_{36}H_{33}N_3O_6$ requires $(M+1)^+$ at m/z 604.2442; found, 604.2441.

5.10.134. *tert*-Butyl 4-({(2*E*)-4-[3-(diphenylmethyl)-2,4-dioxo-7-thiomorpholin-4-yl-3,4-dihydroquinazolin-1(2*H*)-yl]but-2-en-1-yl}oxy)benzoate (45g)

The general nucleophilic substitution procedure was followed utilizing thiomorpholine (90 mg, 39%).^{1}H NMR (300 MHz, $CDCl_3$) δ 1.58 (s, 9H), 2.62–2.67 (m, 4H), 3.71–3.78 (m, 4H), 4.52–4.55 (m, 2H), 4.70–4.75 (m, 2H), 5.80–5.95 (m, 2H), 6.31 (s, 1H), 6.65–6.70 (m, 1H), 6.84 (d, J = 8.9 Hz, 2H), 7.23–7.48 (m, 10H), 7.53 (s, 1H), 7.90 (d, J = 8.7 Hz, 2H), 8.02 (d, J = 9.0 Hz, 1H).

5.10.135. 4-({(2*E*)-4-[3-(Diphenylmethyl)-2,4-dioxo-7-thiomorpholin-4-yl-3,4-dihydroquinazolin-1(2*H*)-yl]but-2-en-1-yl}oxy)benzoic acid (46g)

The general acidic ester hydrolysis conditions were followed utilizing ester **45g** (24 mg, 29%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (dd, J = 8.9, 2.7 Hz, 3H), 7.52 (s, 1H), 7.23–7.42 (m, 8H), 6.88 (d, J = 8.9 Hz, 2H), 6.68 (dd, J = 9.0, 2.0 Hz, 1H), 6.32 (d, J = 2.0 Hz, 1H), 5.87–5.93 (m, 2H), 4.75–4.78 (m, 2H), 4.56–4.57 (m, 2H), 3.74–3.78 (m, 4H), 2.64–2.67 (m, 4H); HRMS: $C_{36}H_{33}N_3O_5S$ requires $(M+1)^+$ at m/z 620.2214; found, 660.2213.

5.10.136. Methyl 1-[1-{(2*E*)-4-[4-(*tert*-butoxycarbonyl) phenoxy]but-2-en-1-yl}-3-(diphenylmethyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl]piperidine-4-carboxylate (45h)

The general nucleophilic substitution procedure was followed utilizing methyl piperidine-4-carboxylate (165 mg, 68%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.58 (s 9H), 1.70–1.88 (m, 2H), 1.93–2.02 (m, 2H), 2.48–2.60 (m, 1H), 2.89–3.00 (m, 2H), 3.69 (s, 3H), 3.72–3.82 (m, 2H), 4.54–4.56 (m, 2H), 4.75 (s, 2H), 5.82–5.98 (m, 2H), 6.37 (s, 1H), 6.73 (d, J = 8.9 Hz, 1H), 6.84 (d, J = 8.9 Hz, 2H), 7.23–7.37 (m, 6H), 7.38 (m, 4H), 7.53 (s, 1H), 7.90 (d, J = 8.8 Hz, 2H), 8.01 (d, J = 9.0 Hz, 1H).

5.10.137. 4-({(2*E*)-4-[3-(Diphenylmethyl)-7-[4-(methoxycarbonyl)piperidin-1-yl]-2,4-dioxo-3,4-dihydroquinazolin-1(2*H*)-yl]but-2-en-1-yl}oxy)benzoic acid (46h)

The general acidic ester hydrolysis conditions were followed utilizing ester **45h** (140 mg, 92%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (d, J = 8.9 Hz, 1H), 8.00 (d, J = 8.9 Hz, 2H), 7.52 (s, 1H), 7.16–7.41 (m, 10H), 6.87–6.89 (m, 3H), 6.67 (s, 1H), 5.89–5.92 (m, 2H), 4.76 (br s, 2H), 4.56–4.57 (m, 2H), 3.73–3.80 (m, 2H), 3.71 (s, 3H), 3.05–3.13 (m, 2H), 2.55–2.65 (m, 1H), 1.82–2.15 (m, 4H); ^{13}C NMR (DMSO-d_6) 174.40, 169.89, 160.47, 158.73, 154.83, 141.31, 138.75, 132.93, 130.51, 129.65, 128.28, 128.11, 127.98, 127.63, 126.90, 112.79, 110.04, 104.34, 97.42, 67.06, 58.63, 51.48, 46.34, 44.07, 30.39, 26.80; HRMS: $C_3H_{37}N_3O_7$ requires $(M+1)^+$ at m/z 660.2704; found, 660.2701.

5.10.138. *tert*-Butyl 4-({(2*E*)-4-[3-(diphenylmethyl)-2,4-dioxo-7-(1*H*-1,2,4-triazol-1-yl)-3,4-dihydroquinazolin-1(2*H*)-yl]but-2-en-1-yl}oxy)benzoate (45i)

The general nucleophilic substitution procedure was followed utilizing 1,2,4-triazole, sodium derivative (160 mg, 73%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.58 (s, 9H), 4.57 (s, 2H), 4.84 (s, 2H), 5.96 (br s, 2H), 6.82 (d, J = 9.0 Hz, 2H), 7.25–7.55 (m, 12H), 7.65 (s, 1H), 7.85 (d, J = 9.1 Hz, 2H), 8.14 (s, 1H), 8.33 (d, J = 8.7 Hz, 1H), 8.68 (s, 1H).

5.10.139. 4-({(2*E*)-4-[3-(Diphenylmethyl)-2,4-dioxo-7-(1*H*-1,2,4-triazol-1-yl)-3,4-dihydroquinazolin-1(2*H*)-yl]but-2-en-1-yl} oxy)benzoic acid (46i)

The general acidic ester hydrolysis conditions were followed utilizing ester **45i** (112 mg, 77%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.51 (s, 2H), 4.86 (s, 2H), 5.93–5.99 (m, 2H), 6.75 (d, J = 8.84 Hz, 2H), 7.25–7.41 (m, 11H), 7.75 (d, J = 8.84 Hz, 2H), 7.80–7.87 (m, 2H), 8.20 (d, J = 8.59 Hz, 1H), 8.35 (s, 1H), 9.53 (s, 1H); ^{13}C NMR

(DMSO-d_6) 160.46, 158.87, 153.04, 150.04, 143.39, 141.63, 141.01, 138.24, 130.59, 128.38, 128.11, 128.06, 127.13, 126.62, 113.99, 113.69, 112.92, 104.83, 67.09, 59.47, 44.70; HRMS: $C_{34}H_{27}N_5O_5$ requires $(M+1)^+$ at *m/z* 586.2085; found, 586.2085.

5.11. Solubility determination procedure

Solubility was determined at pH 7.4 using a pION PSR4s instrument and software. Compounds were initially dissolved in DMSO at 8 mg/mL. Thirteen microliters of this stock solution was added to 1.0 mL of pH 7.4 pION buffer. The solution is mixed and allowed to settle for 18 h at room temperature, then filtered through a 0.2 μm filter plate (Corning, Acton, MA). The concentration of the filtrate was quantitated using a UV plate reader (Molecular Devices, Sunnyvale, CA). The solubility was derived using a single point standard.

5.12. Permeability (PAMPA) assay

Test compounds were dissolved in DMSO at 5 mg/mL. Ten microliters of this compound stock solution were diluted 200-fold in universal buffer at pH 7.4 and mixed by the robot to make a secondary stock solution (final concentration 25 μg/mL). Two hundred microliters of the secondary stock solution were added to the donor wells. The filter membrane was coated with 4 mL of phosphatidylcholine in dodecane (20 mg/mL) and the acceptor well was filled with 200 mL of pH 7.4 buffer. The acceptor filter plate was carefully put on the donor plate to form a 'sandwich' (consisting of the aqueous donor with test compound on the bottom, artificial lipid membrane in the middle, and aqueous acceptor on the top). The test compound diffused from the donor well through the lipid membrane and into the acceptor well. The 'sandwich' was left undisturbed at rt for 18 h while the permeation occurred. The concentration of drug in the acceptor, the donor, and the reference wells was determined using the UV plate reader. Effective permeability (P_e) of the compounds was calculated by using the pION PSR4p software. Samples were analyzed in triplicate and the average of the three runs was reported. Quality control standards (verapamil and theophylline) were run with each sample set to monitor the consistency of the analysis set.

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