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Substituted benzoquinazolinones. Part 2: Synthesis of amino-, and sulfanyl-derivatives of benzo[*f*]- and benzo[*h*]quinazolinones

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ABSTRACT

Amino- and sulfanyl-derivatives of benzoquinazolinones **16a**–**c**, **20a**–**c** and **21a**–**c** were prepared under palladium-catalyzed Buchwald–Hartwig coupling reaction using bromobenzoquinazolinones **15**, **19a**, **19b** and 1-substituted piperazines or mercaptans. The combination of $Pd(OAc)_2$ with XantPhos proved to be the best for these conversions in the presence of KO*t*-Bu, in 1,4-dioxane as a solvent, at 90–100 °C. The 8-bromobenzo[*f*]quinazolin-1(2*H*)-one **15** was synthesized via condensation of the ethyl or *tert*-butyl 2-amino-8-bromonaphthalene-1-carboxylate **6**, **10** with formamide, followed by reaction with 3,4-dimethoxybenzyl bromide. However, the 6-bromobenzo[*h*]quinazolin-4(3*H*)-ones **19a**, **19b** were prepared from ethyl 4-bromo-1-[(*tert*-butoxycarbonyl)amino]naphthalene-2-carboxylate (**17**).
Biological screening of the potential cytotoxicity of compounds **16a**, **20a**, **20c** on HT29 and HCT116 cell lines, has shown that compound **20a** has a significant anticancer activity.

1. Introduction

Heterocyclic systems containing a quinazolinone skeleton are commonly known to have anticonvulsant, antimicrobial or anticancer properties.[1] For example, 2-amino-6-methyl-5-(pyridine-4-ylsulfanyl)quinazolin-4(3*H*)-one (AG337, Thymitaq), was studied in clinical trials (I and II Phase), and shown significant evidence of anticancer activity.[2] There are some alkyl-/arylthio analogues of quinazoline, known to have cytotoxic activity against MCF-7 cell line and Hela cervix cell line and also the pharmacological activity as anti-tuberculosis agent.[3] The considerable interest because of the diverse range of biological properties involves also the benzo[*h*]- and benzo[*f*]- analogues of quinazolinones, although these constitute less explored derivatives. The potential use of amino-benzo[*h*]quinazolinones, and benzo[*h*]quinazolines in the treatment of cardiovascular, nervous system disease or in cancer therapy and also the antiviral activity of their analogs, are just a few examples out of many, which may be mentioned.[4] Additionally, it is suggested that they can act, as inhibitors of thymidylate synthase, thus may be the evidence of the utility of this group of compounds in the treatment of cancer.[5]

Initially, the main area of our interest was the study on the synthesis and the cytotoxic activities of 6-substituted benzo[*h*]quinazolinones. In the previous work, we noticed that 3-(4-methoxybenzyl)-6-(morpholin-4-yl)benzo[*h*]quinazolin-4(3*H*)-one exhibits high cytotoxicity to human colorectal adenocarcinoma cell line—HT29, IC_{50}=4.12 μM and its activity was higher than of cisplatin, IC_{50}=8.47 μM. Simultaneously, 6-morpholine derivative shows much lower cytotoxicity to normal human lymphocytes (IC_{50}=178.11 μM).[6] The achieved results became an obvious contribution to the further research on the benzoquinazolinones and their amino derivatives. Moreover, in view of the significant and important biological properties of sulfanyl derivatives of quinazolinone, mentioned above, our interest focused also on the area of sulfanyl analogues of benzoquinazolinones.

In continuation with this study, we want to show the route for the synthesis of 8-bromobenzo[*f*]quinazolinones and then their transformation into new amino- and sulfanyl-derivatives **C** or **D**, using palladium catalyzed cross-coupling reactions (Scheme 1).

Furthermore, we would like to widen the scope of the application of the Buchwald–Hartwig coupling reaction, and synthesize

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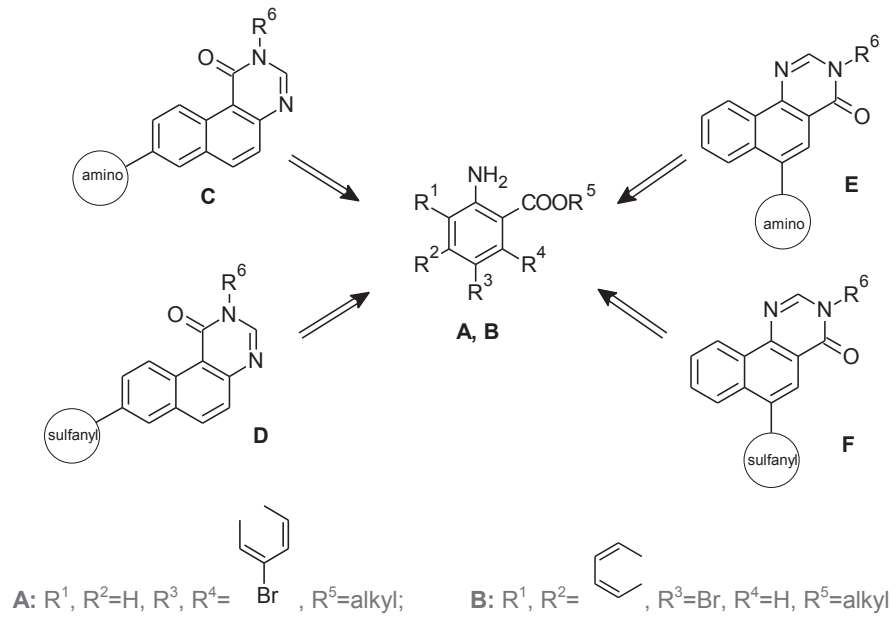


Scheme 1. Synthetic routes for the preparation of benzo[*f*]quinazolin-1(2*H*)-one and benzo[*h*]quinazolin-4(3*H*)-one derivatives.

the new 6-amino- and 6-sulfanyl derivatives of benzo[*h*]quinazolin-4(3*H*)-ones **E**, **F**. Selected newly obtained benzo[*h*]quinazolin-4(3*H*)-one and benzo[*f*]quinazolin-1(2*H*)-one derivatives were evaluated against two human cancer cell lines: HT29 and HCT116.

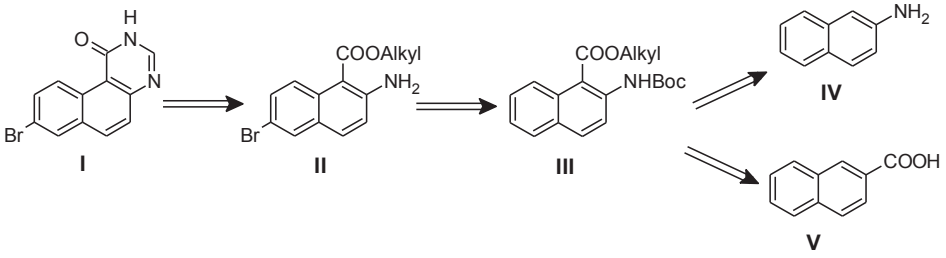
2. Results and discussion

The key compound in the synthetic route for the preparation of the target amino- and sulfanyl-derivatives of benzo[*f*]quinazolin-1(2*H*)-one **C**, **D** was 8-bromobenzo[*f*]quinazolin-1(2*H*)-one (**I**) (Scheme 2). The proposed retrosynthetic analysis led, via the bromoamino ester **II** to the 2-[(*tert*-butoxycarbonyl)amino]naphthalene-1-carboxylate **III** as a key substrate, which could be prepared from the 2-naphthylamine[7a] (**IV**) or naphthalene-2-carboxylic acid[7b] (**V**) (Scheme 2).

An alternative path for synthesizing 1-substituted *N*-Boc-2-aminonaphthalenes, is the procedure consisting of bromine-lithium exchange reaction between 1-bromo- derivative of *N*-Boc-2-naphthylamine with *n*-BuLi and then reaction of the generated aryllithium species with an electrophile.

At first our interest was focused on the application of the aza-Fries rearrangement of the Boc group. This type of rearrangement is often used as an useful method in the synthesis of *tert*-butyl esters, from di-Boc-substituted *ortho*-bromoanilines.[9] On the other hand, methodology of the aza-Fries rearrangement is slightly similar to commonly known *O*-aryl-carbamate or trialkylsilyl ethers and esters rearrangements.[10]

The synthetic way for preparation of bromobenzo[*f*]quinazolinone **I** through the aza-Fries rearrangement was showed in Scheme 3.

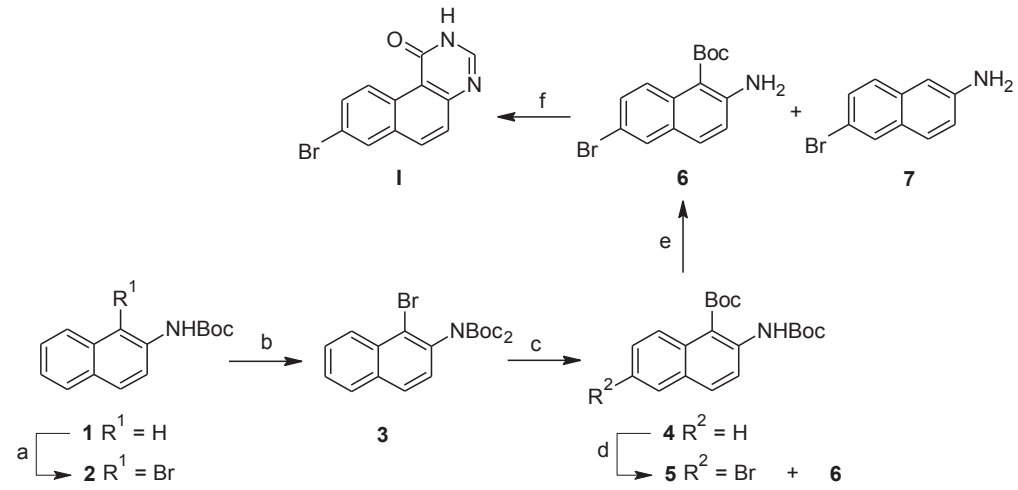


Scheme 2. Retrosynthetic analysis of 8-bromobenzo[*f*]quinazolin-1(2*H*)-one (**I**).

Continuing our interest in the area of application of organometallic compounds to the functionalization of aromatic systems, we considered to apply the directed metalation reaction as a key step in the preparation of the appropriate carbamate **III** from *N*-Boc-2-naphthylamine. However, the treatment of *N*-Boc-2-naphthylamine with *t*-BuLi, followed by electrophile quench gives as a result a mixture of two regioisomers: 1- and 3-substituted *N*-Boc-2-aminonaphthalene, with a predominance of 3-substituted derivative.[8]

Di-*tert*-butyl (1-bromonaphthalen-2-yl)imidodicarbonate (**3**) was synthesized from *N*-Boc-2-naphthylamine (**1**) in two steps. The regioselective bromination of **1** with *N*-bromosuccinimide gave 1-bromo carbamate **2** (Scheme 3) in 95% yield and the further acylation of **2** with Boc_2O in the presence of DMAP led to *N*,*N*-diBoc derivative **3**, in 89% yield.

In the next step 1-bromo-*N*,*N*-diBoc-2-naphthylamine **3** was treated with 1.1 equiv of *n*-BuLi, at −78 °C in Et_2O, as solvent.[9] The bromine-lithium exchange, followed by N→C migration of the Boc



Scheme 3. Synthesis of benzoquinazolinone **I**. Reagents and conditions: (a) NBS, acetonitrile, 0 °C; (b) Boc_2O, DMAP, Et_3N, DCM, 50–60 °C; (c) *n*-BuLi, THF, −78 °C; (d) NBS, acetonitrile, 50 °C; (e) HCl*aq* in 1,4-dioxane, 60 °C; (f) formamide, 180–190 °C.

group, produced smoothly the required ester **4**, in a good yield (65%).

The next stage of the synthetic route shown in Scheme 3, includes the preparation of bromo derivative **5**. The bromination of ester **4** using NBS, as a mild brominating agent[11] in acetonitrile at room temperature (5 h), unfortunately ended in failure. However, when the reaction temperature was increased up to 50 °C and except that the reaction time was extended to 12 h (the reaction progress was monitored by TLC), *tert*-[butyl 6-bromo-2-(*tert*-butoxycarbonyl)amino]naphthalene-1-carboxylate (**5**) was formed, in a moderate yield (48%). Additionally, a small amount of aminoester **6** (20%) was produced too. In our view, the preparation of **6** is a process involving in the first step bromination of **4** and next slowly cleavage of the Boc group in **5**. It cannot be ruled that the formation of **6**, may be caused by several factors such as excess of NBS,[12] formation of side products, influence of temperature and effect of solvent. We observed that the extension of the reaction time led to the increase in a yield of amine **6**.

Furthermore, the formation of aminoester **6** and carbamate **5** side by side, may suggest that the deprotection of the amine group in **5** proceeds under milder reaction conditions, different from typical ones described in literature.[6,13] The best effect of cleavage of the Boc group in **5** was observed with using a mixture of 0.5 M HCl*aq* and 1,4-dioxane in the ratio 1:1.5 (v/v). The TLC analyses showed that the formation of product **6** from *N*-Boc derivative **5** proceeded slowly and the reaction was being carried out for 15 h. Additionally, besides **6**, 6-bromonaphthalen-2-amine (**7**) was isolated from the reaction mixture too. Compound **7** was identified by NMR and HRMS spectroscopy. This fact implied that aminoester **6** is probably unstable in the solution and it easily converts into **7**. Thus, the deprotection of **5** gave **6** and amine **7**, in a 40% and 39% yield, respectively.

In the final step, 8-bromobenzo[*f*]quinazolin-1(2*H*)-one (**I**), was synthesized through the cyclization of *tert*-butyl 2-amino-6-bromonaphthalene-1-carboxylate (**6**) with formamide. However, product **I** was only formed in a low yield (20%). Due to this fact, and the synthetic problems with the selective deprotection of the amine group in the presence of the *tert*-butyl ester one, we decided to use the ethyl ester **8** as a more stable substrate for the synthesis of bromobenzo[*f*]quinazolinone (**I**) (Scheme 4).

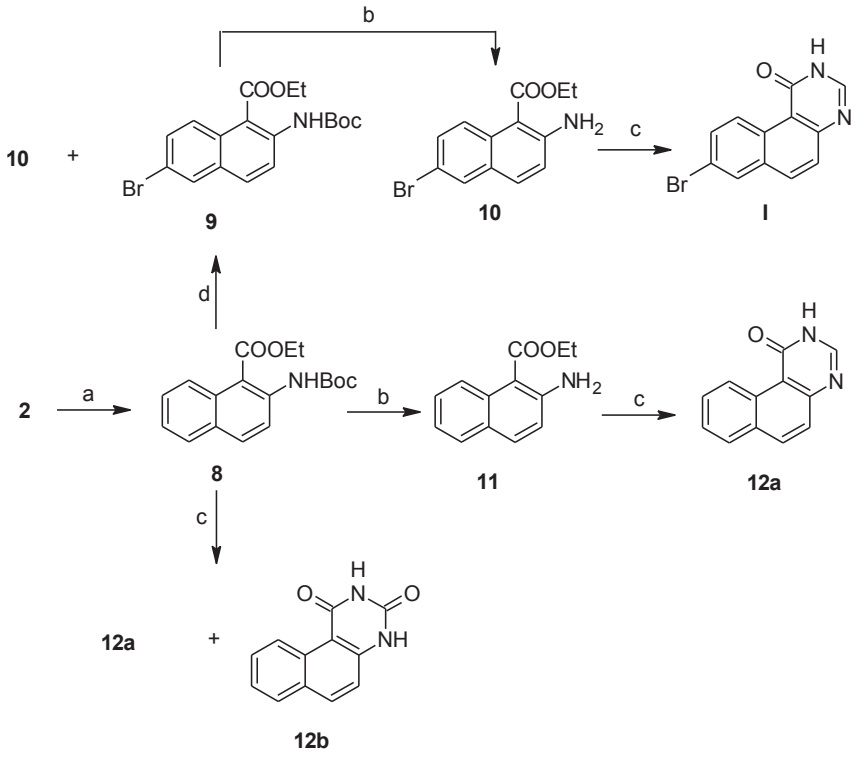
The treatment of bromo derivative **2** (Scheme 4) with 2.2 equiv of *n*-BuLi,[14] in Et_2O (−20 °C, 2 h) and then with 1 equiv ClCOOEt at −20 °C efficiently generated the ethyl carbamate **8** (68%). Lowering the temperature of reaction from −20 °C to −78 °C, or/and the shortening time of reaction, led to a lower yield of ester **8** (5–10%).

The bromination of ethyl ester **8** with NBS, in acetonitrile, was slightly effective than *tert*-butyl ester **4** and the product **9** was obtained in 50% yield (Scheme 4). Also in this case, derivative **9** was able to transform spontaneously under the reaction conditions to the corresponding amine **10**, which was separated in ca. 20% yield. The cleavage of Boc group in **9** using the mixture of 0.5 M HCl*aq* and 1,4-dioxane in the ratio 1:5 (v/v), at room temperature, led to **10** in 56% yield In the same reaction conditions carbamate **8** gave an appropriate amine **11** in 77% yield. Thereby, the synthesis of corresponding amino esters **10**, **11** was less complicated than **6**. The treatment of ethyl 2-amino-1-carboxylates **10** or **11** (Scheme 4) with formamide afforded the corresponding benzo[*f*]quinazolin-1(2*H*)-ones **I** or **12a** without any problems, in excellent yields, 94% and 92%, respectively.

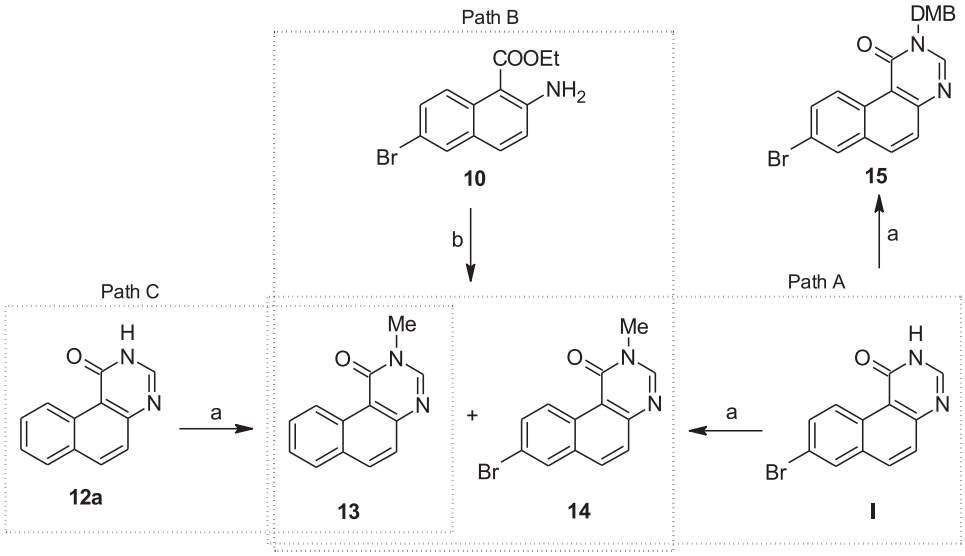
On the other hand, we observed that the result of treatment of ester **8** with formamide under temperature conditions (180–190 °C) was the formation of a mixture of **12a** and **12b**. The mechanism of transformations of **8** into **12a** and **12b**[15] is not completely clear. However, it seems that formamide and its thermal stability play important role in the preparation of **12a** and **12b**. It is known that formamide partially decomposes into CO and NH_3, at a high temperature (>180 °C).[16] Therefore, formamide can probably act as a source of ammonia and in the reaction with **8** forms benzo[*f*]quinazolin-1,3(2*H*,4*H*)-dione **12b**. On the other hand, as it was shown earlier *tert*-butoxycarbonylamine moiety in **8** or **9** is very prone to cleavage. Thus, it is likely that Boc-protected derivative **8** under basic conditions,[17] can convert to the amine **11**, which after reaction with formamide afforded finally benzo[*f*]quinazolin-1(2*H*)-one **12a**.

In our previous works we observed that Buchwald–Hartwig amination reactions proceed only for *N*-protected quinazolinone derivatives.[6,19] Hence, the one of the essential steps, before palladium catalyzed coupling reaction between amines and bromobenzoquinazolinones, was the synthesis of *N*-alkylated derivatives **14**, **15** (Scheme 5). The typical procedure of their preparation involves the use of appropriate halides (e.g., benzyl or methyl halides) in the presence of a base (K_2CO_3, Cs_2CO_3).[6,19] At first, in our research we decided to try to synthesize 8-bromo-2-methylbenzo[*f*]-quinazolin-1(2*H*)-one (**14**).

The bromoquinazolinone **I** was treated with MeI/K_2CO_3 in acetone (Scheme 5, path A) afforded a mixture of **14** and a product of dehalogenation **13**, in 65% (^{1}H NMR) and 35% (^{1}H NMR) yields, respectively. Alternatively, we used the *N*-methylformamide to the cyclization reaction with **10** (Scheme 5, path B). Unfortunately, amine **10** was found to be not reactive to MeNHCHO at 150 °C



Scheme 4. Synthesis of benzoquinazolinones **I**, **12a** and benzoquinazolindione **12b**. Reagents and conditions: (a) *n*-BuLi, ClCOOEt, Et_2O, −20 °C; (b) HCl*aq* in 1,4-dioxane, 70 °C; (c) formamide, 180–190 °C; (d) NBS, acetonitrile, 50 °C.



Scheme 5. Synthesis of *N*-protected derivatives **13** and **14** and **15**. Reagents and conditions: (a) MeI or DMBBr, K_2CO_3, acetone, 55 °C; (b) MeNHCHO, 170 °C, K_2CO_3.

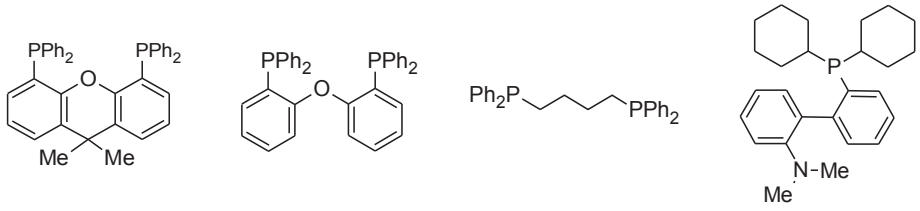
(18 h). However, an increase in the temperature up to 170 °C simultaneously with the addition of K_2CO_3 (1 equiv) afforded also a mixture of **14** (21%, ^{1}H NMR) and **13** (11%, ^{1}H NMR) (Scheme 5, path B). The formation of compounds **14** and **13** was observed by NMR spectroscopy but they were not isolated in individual forms because of difficulty in their separation. The formation of compound **13**, next to the desired product **14** was confirmed by comparing NMR data with those obtained for *N*-Me-benzoquinazolinone **13** (92%) synthesized from benzo[*f*]quinazolinon-1(2*H*)-one (**12a**) (Scheme 5, path C). Until now, in the cyclization reactions of the halogen derivatives of aromatic amino acids with *N*-methylformamide, the dehalogenation product has not been observed, but in contrast to our work, those reactions were performed without K_2CO_3.[7] In the literature, we can found some reports about the dehalogenation processes of haloarenes which are possible in the presence of inorganic bases like as Cs_2CO_3, K_2CO_3 or NaOH.[18]

Finally, due to the problem with synthesis of methyl derivative **14**, described above, we decided to use in the coupling reaction with amines and mercaptans the 8-bromo-2-(3,4-dimethoxybenzyl)benzo[*f*]quinazolin-1(2*H*)-one (**15**), which was obtained by reaction of **I** with DMBBr in 54% yield.

Before starting the synthesis of target amino- and sulfanyl-*N*-(3,4-dimethoxybenzyl)benzo[*f*]quinazolinone derivatives **16a**–**c** (Scheme 5), three ligands: dppb, DPEPhos, DavePhos, and also $Pd(OAc)_2$, $(NH_4)_2PdCl_4$ as palladium sources were tested as alternative catalytic systems in the Buchwald–Hartwig amination reaction, relative to XantPhos/$Pd(OAc)_2$ system, demonstrated in previous works.[6,19]

The tests were performed with 1-(4-fluorophenyl)piperazine, in 1,4-dioxane as solvent, at 90–100 °C. The obtained results were shown in Table 1.

Table 1
The efficiency of catalytic systems for the Buchwald–Hartwig coupling reactions



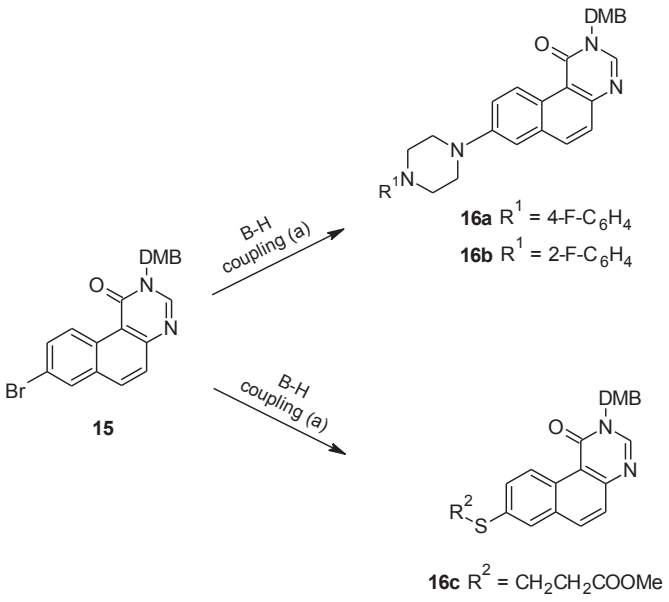
XantPhos DPEPhos dppb DavePhos

Entry	[Pd] (15 mol %)	Ligand (15 mol %)	Base (1.5 equiv)	Yield of 16a (%)[a]
1	$Pd(OAc)_2$	DPEPhos	KO*t*-Bu	23
2	$Pd(OAc)_2$	DavePhos	KO*t*-Bu	80
3	$Pd(OAc)_2$	dppb	KO*t*-Bu	0
4	$(NH_4)_2PdCl_4$	XantPhos	KO*t*-Bu	Trace
5	$Pd(OAc)_2$	XantPhos	KO*t*-Bu	86

Reaction conditions: 1-(4-fluorophenyl)piperazine (3 equiv), solvent: 1,4-dioxane, reaction time: 20 h, temperature: 90–100 °C.
[a] Yield of isolated and purified product.

As depicted in Table 1, the combination of $Pd(OAc)_2$, with DPEPhos (entry 1), or DavePhos (entry 2) in the presence of KO*t*-Bu as base led to the formation of coupling product **16a** (Scheme 6) from moderate to good yields. Although, both of these catalytic systems worked, $Pd(OAc)_2$/DavePhos system proved to be more productive and afforded aminated product **16a** in 80% yield. On the other hand, when dppb was used as a ligand (entry 3), compound **16a** was not formed. The future investigations showed that the combination of $Pd(OAc)_2$ with XantPhos (entry 5) resulted in an excellent yield of **16a**. However, replacement of the $Pd(OAc)_2$ by the ammonium tetrachloropalladate(II) contributed to an enormous yield decrease (entry 4).

Based on the results presented in Table 1, the corresponding amino and sulfanyl derivatives **16b** and **16c** were then synthesized from bromolactam **15** using the $Pd(OAc)_2$/XantPhos system, in 35% and 75% yields, respectively. The proposed structures of the new compounds were confirmed with the aid of spectroscopic analyses (NMR, FTIR and HRMS).



Scheme 6. Preparation of amino- and sulfanyl-derivatives **16a**–**c**. Reagents and conditions: (a) $Pd(OAc)_2$, XantPhos, KO*t*-Bu, amine 1,4-dioxane, 100 °C.

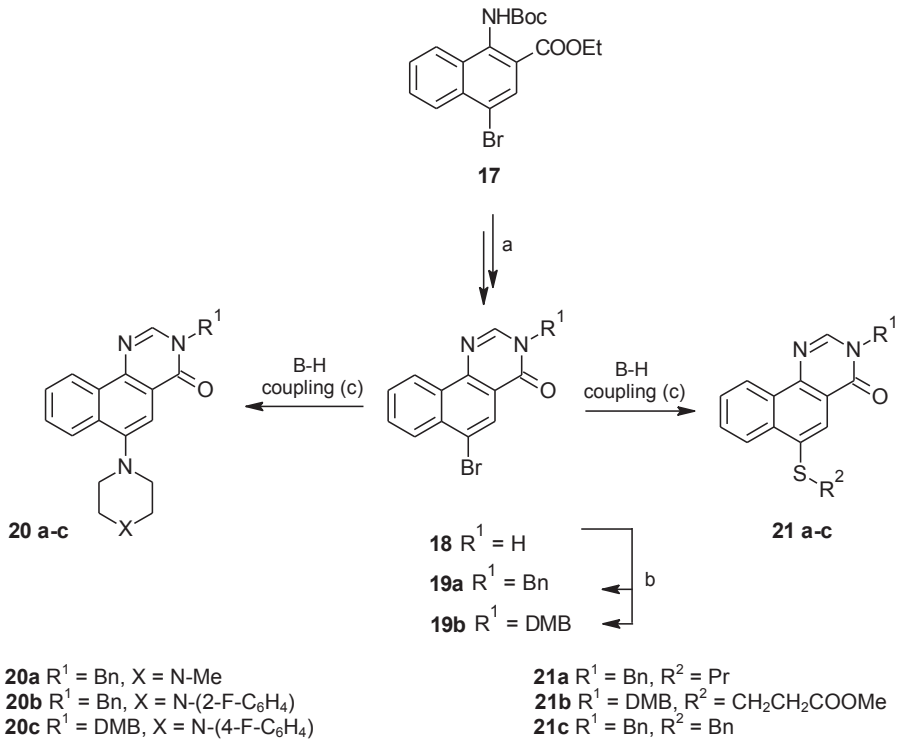
In the last part of our research, we wanted to synthesize a few more examples of amino- and sulfanyl-derivatives of benzo[*h*]quinazolinone. For this purpose, we focused on the arylation reactions of the selected piperazine and piperidine derivatives with 6-bromobenzo[*h*]quinazolinones **19a**, **19b** (Scheme 7). The 6-bromobenzo[*h*]quinazolin-4(3*H*)-one **18** was prepared using our previously described procedure[6] involving a) synthesis of the ethyl 1-[(*tert*-butoxycarbonyl)amino]naphthalene-2-carboxylate via directed *ortho*-metalation methodology b) bromination of the naphthalene ring using NBS c) deprotection of the amine group from **17**, and next ring closure with formamide, which led to the bromobenzoquinazolinone **18**.

The coupling of **19a**, **19b** with 4-(4-fluorophenyl)-, 4-(2-fluorophenyl)- and 4-methyl-piperazines was allowed to generate new benzo[*h*]quinazolinone derivatives **20a**–**c**, substituted at the 6 position by a piperazin-1-yl moiety, in good yields (41–67%). Unfortunately, to our surprise when the piperidine derivatives, like as 2-ethyl- or 4-(2-hydroxyethyl)-, were used in the coupling, the formation of appropriate products were not observed.

Additionally, the investigation of the possibility of synthesis of novel sulfanyl benzoquinazolinone derivatives, containing a new C–S bond via palladium-catalyzed cross-coupling reactions of lactams **19a**, **19b** with mercaptans ended successfully. The coupling reactions of bromide **19a**, **19b** with alkyl mercaptans, using 30 mol %/30 mol % $Pd(OAc)_2$/XantPhos,[19] gave the desired sulfanyl derivatives **21a**–**c** in very good yields (62–81%, Scheme 6). However, when electron-donating substituent, such as OMe, was present in *N*-benzyl group (here DMB group), the arylation of benzyl mercaptan did not take place.

3. Cytotoxic activity

The cytotoxic activities of three new *N*-(3,4-dimethoxybenzyl) benzo[*f*]quinazolin-1(2*H*)-one **16a** and *N*-benzyl-, and *N*-(3, 4-



Scheme 7. Synthesis of amino- and sulfanyl-derivatives of benzo[*h*]quinazolinone. Reagents and conditions: (a) i. TFA, DCM, 0 °C; ii. formamide, 190–200 °C; (b) BnBr or DMBBr, K_2CO_3, acetone, 55 °C; (c) $Pd(AcO)_2$, XantPhos, KO*t*-Bu or DIPEA, amine or mercaptan, 1,4-dioxane, 90–100 °C.

dimethoxybenzyl)-benzo[*h*]quinazolin-4(3*H*)-ones **20a**, **20c** were evaluated against two selected cancer cell lines: HT29—a human colorectal adenocarcinoma cell line and HCT116—a human colorectal carcinoma cell line, using the MTT test. Furthermore, the cytotoxicity of compounds **16a**, **20a**, **20c** was determined towards the normal human lymphocytes. The obtained IC_{50} values (i.e., the concentration of the compound that inhibits 50% growth) were collected in Table 2. In addition, the cytotoxicity (IC_{50} values) of three known compounds, 3-benzyl-6-[4-(2-fluorophenyl)piperazin-1-yl]quinazolin-4(3*H*)-one, 3-(4-Methoxybenzyl)-6-(morpholin-4-yl)benzo[*h*]quinazolin-4(3*H*)-one and benzo[*h*]quinazolin-4(3*H*)-one, which were evaluated in our recent papers,[6,19] and of cisplatin were included in Table 2, in order to interpret the obtained results.

lower cytotoxic in comparison to **20a** against both HCT116 and HT29 cell lines. It can suggest that the insertion of 4-fluorophenyl group to the piperazinyl substituent contributes significantly to the reduction cytotoxic properties. A similar effect showed compound **20c**. Additionally, it exhibited a reversal of activity towards tested cancer cell lines and demonstrated a higher cytotoxicity against HT29 than derivative **16a**. Generally, the introduction of the 4-(4-fluorophenyl)piperazin-1-yl group into the aryl ring causes a reduction of activity the compounds **16a** and **20c**, which showed a significant cytotoxicity only at higher concentrations.

The reduced cytotoxicity of the compounds **16a** and **20c** towards the cancer cells had also an impact on their toxicity against normal lymphocytes. Benzoquinazolinones **16a**, **20c** were practically non-toxic (IC_{50}>500 μM, Table 2). On the other hand, lactam **20a** in-

Table 2
The IC_{50} values obtained for HT29 and HCT116 cell lines and normal human lymphocytes

Compound	IC_{50} values (μM)		
	HT29	HCT116	Lymphocytes
16a	201.00	135.00	532.50
20a	30.00	17.00	49.00
20c	169.00	237.00	501.67
3-Benzyl-6-[4-(2-fluorophenyl)piperazin-1-yl]quinazolin-4(3*H*)-one[19]	50.90	46.00	196.67
3-(4-Methoxybenzyl)-6-(morpholin-4-yl)benzo[*h*]quinazolin-4(3*H*)-one[6]	4.12	—	178.11
Benzo[*h*]quinazolin-4(3*H*)-one[6]	154.95	—	>250
Cisplatin[20]	8.47	3.78(72 h)	6.83

The tested benzoquinazolinones **16a**, **20a**, **20c** showed a differential activity. The most interesting results were obtained for compound **20a**, which exhibited the highest and a carcinoma-specific cytotoxicity against both tested cancer cell lines. However, HT29 cells were more resistant to **20a** (IC_{50}=30 μM) than HCT116 ones (IC_{50}=17 μM).

A similar correlation was observed for the compound **16a**. It showed a stronger toxicity to HTC116 cells, but it was much less toxic than compounds **20a**. Compound **16a** was more than 6-fold

dicated considerably higher cytotoxicity against lymphocytes (IC_{50}=49 μM) than compounds **16a** and **20c**, but it was still almost a twofold less toxic to ones than to cancer cells.

4. Conclusion

In the present research was developed an alternative method for the synthesis of the benzo[*f*]quinazolinone-1(2*H*)-ones **I**, **12a**, using ethyl ester **8** or *tert*-butoxyl ester **4** as precursors. The application of

bromine-lithium exchange reaction and the aza-Fries rearrangement to obtain the benzoquinazolinone skeleton was shown. Also, were presented the synthetic problems associated with the modification of 2-naphthylamine derivatives. Ultimately, following the Buchwald–Hartwig type reaction, a series of novel amine or sulfanyl derivatives of benzo[*f*]quinazolinone-1(2*H*)-one **16a**–**c** and benzo[*h*]quinazolinone-1(2*H*)-one **20a**–**c**, **21a**–**c** was created. The received results of biological screening tests showed that some explored compounds could have potential applications in pharmacology, but they require further investigations in this direction.

5. Experimental section

5.1. Chemistry

5.1.1. General. Melting points were determined on a Boetius hot stage apparatus and were uncorrected. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a Bruker Advance III spectrometer at 600 MHz, 150 MHz and 565 MHz, respectively. The residual $CDCl_3$ or DMSO-d_6 signal was used for reference ($CDCl_3$ at 7.26 ppm or DMSO-d_6 at 2.54 ppm for ^{1}H NMR and $CDCl_3$ at 77.0 ppm or DMSO-d_6 at 39.0 ppm for ^{13}C NMR). ^{19}F NMR spectra were obtained without ^{1}H-decoupling. Coupling constants (*J*) are given in Hertz (Hz). IR spectra were recorded on a Nexus FT-IR spectrometer. LC-HRMS analyses were carried out using a liquid chromatograph (Agilent Technologies series 1200) coupled to a tandem mass spectrometer (Agilent Technologies 6538 UHD Accurate Mass Q-TOF LC/MS) equipped with a HPLC-chip-cube allowing nanoelectrospray ionization of analytes. The instrument is housed in the Laboratory of Separation and Spectroscopic Method Applications, Center for Interdisciplinary Research, KUL, Lublin, Poland. Instrument control and data acquisition were performed using an Agilent Technologies Mass Hunter Acquisition module (version B.04). High resolution mass spectra were acquired in the positive ion scan mode at 100–1000 *m*/*z*. The capillary potential was set at −1750 V and the fragmentor was set at 100 V. Mobile phase consisted of water-acetonitrile-0.1% formic acid. A large capacity chip (160 nL) 150 mm C18, 5 μm was used. Internal mass calibration was enabled, using two reference mass ions (121.0509 and 922.0098). The mass accuracy for MS scans was<1 ppm. The analytical thin layer chromatography tests (TLC) were carried out on Sigma Aldrich (Supelco) silica gel plates (Kiselgel 60 F_{254}, layer thickness 0.2 mm) and the spots were visualized using UV lamp. The flash column chromatography purifications were performed on Fluka silica gel (Silica gel 60, 0.040–0.063 mm). *n*-Butyllithium solution in hexane (Aldrich) was each time titrated before use.[21] All reactions with organolithium and organopalladium compounds were performed under an argon atmosphere using standard Schlenk technique.

Tetrahydrofuran, diethyl ether and 1,4-dioxane were distilled from sodium benzophenone ketyl prior to use. Commercially available solvents and reagents: Boc_2O, 1-naphthylamine, 2-naphthylamine, ethyl chloroformate, *N*-bromosuccinimide (NBS), formamide, *N*-methylformamide (MeNHCHO), 3,4-dimethoxybenzyl bromide (DMBBr), methyl iodide (MeI), benzyl bromide (BnBr), potassium *tert*-butoxide (KO*t*-Bu), *N*,*N*-diisopropylethylamine (DIPEA), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (XantPhos), 2-dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl (DavePhos), 1,4-bis(diphenylphosphino)butane (dppb), (oxydi-2,1-phenylene)bis(diphenylphosphine) (DPEPhos), ammonium tetrachloropalladate(II) ($(NH_4)_2PdCl_4$), palladium(II)acetate ($Pd(OAc)_2$), 1-methylpiperazine, 1-(2-fluorophenyl)-piperazine, 1-(4-fluorophenyl) piperazine, benzyl mercaptan, 1-propanethiol, methyl-3-mercaptopropionate were purchased from Sigma–Aldrich and were used without further purification. Compounds **17**, **18** and **19a** were prepared by the procedure presented in our previous work.[6]

5.2. Biology

5.2.1. Cells cultures. The experiments were performed with the use of HCT116 (colorectal carcinoma) and HT29 (colorectal adenocarcinoma) cancer cell lines (human colon cancer cells) derived from the American Type Culture Collection (ATCC; CCL-247, HTB-38) and human lymphocytes obtained from the Blood Donation Centre (Lodz, Poland). HCT116 cells were cultured in RPMI 1640 medium (CytoGen) supplemented with 10% FBS (Foetal Bovine Serum, CytoGen) and penicillin/streptomycin solution (1%). RPMI 1640 medium (CytoGen) was used for HT29 cells contained FBS (10%), penicillin/streptomycin solution (1%) and MEM non-essential amino acids solution (1%). Human lymphocytes were cultured in RPMI 1640 medium complemented with inactivated FBS (15%), penicillin/streptomycin (1%) and mitogen PHA (1%, phytohemagglutinin; CytoGen). Cells were cultured at 37 °C in a 5% CO_2 humidified atmosphere.

5.2.2. Inhibition growth assay. Cancer cells and human lymphocytes were grown for 24 h on 96-well plates at a density of $6–8\times10^3$ cells/well and 8×10^5 cells/well, respectively. Then the cells were treated with the tested compounds for 72 h. After the treatment MTT dye dissolved in PBS was added to each plate well (20 μL, 5 mg/mL) for 4 h. Purple crystals formed in cancer cells after reduction of MTT were dissolved by DMSO (100 μL/well) after removing of the medium. In the case of lymphocytes it was done by adding 100 μL of 20% DMF and 50% SDS mixture to each well for 24 h. Absorbance at 595 nm was measured with a spectrophotometer PowerWave XS (BioTek Instruments, Inc.). The cell survival effect was expressed as the IC_{50}value which is the concentration of the compound required to reduce cell survival to 50% as compared to the negative control. The experiments were done in triplicate. All the results were presented as the means±SD.

5.2.3. MTT assay. MTT assay is a quantitative colorimetric method to determine cell proliferation after treatment with the tested compounds. It is widely used to estimate the cytotoxic effect of chemicals on different types of cells. The assay is based on the reduction of the yellow water soluble tetrazolium MTT (3-(4,5-dimethylthiazolyl-2)-2,5-diphenyltetrazolium bromide) by mitochondrial enzymes of living (not dead) cells which results in formation of an insoluble purple formazan product. Formazan crystals are solubilized with organic solvent. The amount of formazan is measured spectrophotometrically and it is directly proportional to the number of living cells.

5.3. Synthesis of 2-naphthylamine derivatives 1, 2 and 3

N-Boc-2-naphthylamine (**1**),[22a] *tert*-butyl (1-bromonaphthalen-2-yl)carbamate (**2**),[23a,b] di-*tert*-butyl(1-bromonaphthalen-2-yl) imidodicarbonate (**3**),[23b] were prepared by a procedure similar to that in the literature.

*5.3.1. N-Boc-2-naphthylamine (**1**).*[22] White needles, yield: 83%, mp 92–93 °C (Hex) (lit. only ESI-TOF HRMS[22b,c]); IR (KBr cm^{-1}) 1694; ^{1}H NMR ($CDCl_3$): δ 7.99 (s, 1H, 1Ar–H), 7.76–7.75 (m, 3H, 6,7,8Ar–H), 7.45–7.42 (m, 1H, 3Ar–H), 7.38–7.34 (m, 2H, 4,5Ar–H), 6.62 (br s, 1H, NH), 1.56 (s, 9H, Boc-Me); ^{13}C NMR ($CDCl_3$): δ 152.8, 135.9, 134.2, 130.2, 128.9, 127.7, 127.5, 126.6, 124.6, 119.3, 114.7, 80.8, 28.5.

*5.3.2. tert-Butyl (1-bromonaphthalen-2-yl)carbamate (**2**).*[22,23] White crystal solid, yield: 95%, R_f (DCM:PE 1:1)=0.56; mp

88–89 °C (lit. 90–91 °C,[23a] 85.8–87 °C[23b] or ESI-TOF HRMS[22b,c]); IR (KBr cm^{-1}) 1733; ^1H NMR ($CDCl_3$): δ 8.37 (d, 1H, J=9.0, 8Ar–H), 8.15 (d, 1H, J=8.5, 5Ar–H), 7.80–7.78 (m, 2H, 7,6Ar–H), 7.57–7.55 (m, 1H, 3 or 4Ar–H), 7.44–7.41 (m, 1H, 3 or 4Ar–H), 7.32 (br s, 1H, NH), 1.57 (s, 9H, Boc-Me); ^{13}C NMR ($CDCl_3$): δ 152.8, 135.0, 132.3, 131.1, 128.4, 128.3, 127.8, 126.5, 125.2, 119.8, 110.2, 81.4, 28.5.

*5.3.3. Di-tert-butyl (1-bromonaphthalen-2-yl)imidodicarbonate (**3**).*[22,23] White crystal solid, yield: 89%, R_f (DCM:PE 3:1)=0.26; mp 151–154 °C (lit. 109.5–111.5 °C[23b] or ESI-TOF HRMS[22b,c]); IR (KBr cm^{-1}) 1755, 1798; ^1H NMR ($CDCl_3$): δ 8.31 (d, 1H, J=8.4, 3Ar–H), 7.85 (d, 1H, J=8.0, 8Ar–H), 7.80 (d, 1H, J=8.6, 5Ar–H), 7.62–7.60 (m, 1H, 4Ar–H), 7.56–7.54 (m, 1H, 7Ar–H), 7.32 (d, 1H, J=8.6, 6Ar–H), 1.38 (s, 18H, 2×Boc-Me); ^{13}C NMR ($CDCl_3$): δ (150.8)×2, 136.8, 133.6, 132.6, (128.2)×2, 127.9, 127.6, 127.1, 127.0, 123.5, (83.0)×2, (28.0)×2.

5.4. Synthesis of *tert*-butyl 2-[(*tert*-butoxycarbonyl)amino] naphthalene-1-carboxylate (4), by the aza-Fries rearrangement

Under argon, to a solution of di-*tert*-butyl (1-bromonaphthalen-2-yl)imidodicarbonate (**3**) (2.4 mmol) in dry Et_2O (15 mL) at −78 °C, *n*-BuLi in hexanes (2.65 mmol) was added dropwise. The reaction mixture was stirred at this temperature for 15 min. After this time, to the reaction mixture, a saturated solution of NH_4Cl (20 mL) was added. The water layer was separated and extracted subsequently with Et_2O (3×20 mL). The organic phase was dried over $MgSO_4$ and concentrated till dryness. The crude material was separated by flash chromatography.

*5.4.1. tert-Butyl 2-[(tert-butoxycarbonyl)amino]naphthalene-1-carboxylate (**4**).* Pale yellow oil, yield: 65%, R_f (DCM/PE 2:1)=0.5; IR (film cm^{-1}) 1731, 1681; ^1H NMR ($CDCl_3$): δ 8.72 (br s, 1H, NH), 8.34 (d, 1H, J=9.1, 3Ar–H), 8.22 (d, 1H, J=8.6, 8Ar–H), 7.87 (d, 1H, J=9.1, 4Ar–H), 7.77 (d, 1H, J=8.1, 5Ar–H), 7.51–7.48 (m, 1H, 7Ar–H), 7.40–7.38 (m, 1H, 6Ar–H), 1.71 (s, 9H, Boc-Me), 1.55 (s, 9H, Boc-Me); ^{13}C NMR ($CDCl_3$): δ 167.6, 153.1, 137.5, 132.2, 131.2, 130.1, 128.4, 127.4, 125.3, 124.7, 119.9, 116.4, 83.4, 80.8, 28.6, 28.5; HRMS (ESI-LC/MS) m/z calcd for $C_{20}H_{25}NO_4$: 343.1784; found $[M]^+$: 343.1781.

5.5. Synthesis of ethyl 2-[(*tert*-butoxycarbonyl)amino]naphthalene-1-carboxylate (8), by the bromine-lithium exchange reaction

Under argon, to a solution of *tert*-butyl (1-bromonaphthalen-2-yl)carbamate (**2**) (1.55 mmol) in dry Et_2O (15 mL), at −20 °C, *n*-BuLi in hexanes (3.41 mmol) was added dropwise. The reaction mixture was stirred at this temperature for 2 h. Next, to the reaction mixture was added dropwise at −20 °C, a solution of ethyl chloroformate (1.55 mmol) and whole was further stirred at −20 °C for 2 h. After this time, to the reaction mixture, a saturated solution of NH_4Cl (20 mL) was added. The water layer was separated and extracted subsequently with Et_2O (3×20 mL). The organic phase was dried over $MgSO_4$ and concentrated till dryness. The crude material was separated by flash chromatography.

*5.5.1. Ethyl 2-[(tert-butoxycarbonyl)amino]naphthalene-1-carboxylate (**8**).* Colorless oil, yield: 68%, R_f (PE/AcOEt 10:1)=0.46; IR (film cm^{-1}) 1734, 1685; ^1H NMR ($CDCl_3$): δ 9.02 (br s, 1H, NH), 8.42 (d, 1H, J=9.1, 3Ar–H), 8.26 (d, 1H, J=8.6, 8Ar–H), 7.90 (d, 1H, J=9.1, 4Ar–H), 7.78 (d, 1H, J=7.9, 5Ar–H), 7.52–7.49 (m, 1H, 7Ar–H), 7.41–7.39 (m, 1H, 6Ar–H), 4.57 (q, 2H, J=7.1, CH_2), 1.55 (s, 9H, Boc-Me), 1.50 (t, 3H, J=7.1, Me); ^{13}C NMR ($CDCl_3$): δ 168.8, 153.0, 138.9, 133.0, 131.4, 130.0, 128.5, 127.7, 125.5, 124.8, 119.7, 114.0, 81.0, 61.8, 28.5, 14.5; HRMS (ESI-LC/MS) m/z calcd for $C_{18}H_{21}NO_4$: 315.1471; found $[M]^+$: 315.1470.

5.6. General procedure for the preparation of bromo derivatives 5 and 9

To a solution of the appropriate ester **4** or **8** (0.63 mmol) in acetonitrile (20 mL) at room temperature a solution of NBS (0.7 mmol) in acetonitrile (5 mL) was added dropwise. The resulting mixture was heated to 60 °C in about 15 h. The reaction was continued under these conditions until TLC analysis of the reaction mixture indicated the absence of starting material **4** or **8**. After the reaction acetonitrile was removed under reduced pressure and the bromo derivative was separated by flash chromatography.

*5.6.1. tert-Butyl 6-bromo-2-[(tert-butoxycarbonyl)amino]naphthalene-1-carboxylate (**5**).* Orange solid, yield: 48%, R_f (DCM/PE 1:1)= 0.4; mp 105–107 °C; IR (KBr cm^{-1}) 1726, 1682; ^1H NMR ($CDCl_3$): δ 8.82 (br s, 1H, NH), 8.39 (d, 1H, J=9.2, 3Ar–H), 8.12 (d, 1H, J=9.2, 8Ar–H), 7.92 (d, 1H, J=2.0, 5Ar–H), 7.77 (d, 1H, J=9.2, 4Ar–H), 7.55 (dd, 1H, J=2.0, 9.2, 7Ar–H), 1.70 (s, 9H, Boc-Me), 1.54 (s, 9H, Boc-Me); ^{13}C NMR ($CDCl_3$): δ 167.2, 153.0, 138.2, 131.3, 131.2, 130.7, 130.3, 129.9, 127.3, 120.9, 118.5, 116.1, 83.3, 81.1, 28.6, 28.5; HRMS (ESI-LC/MS) m/z calcd for $C_{20}H_{24}BrNO_4$: 421.0889; found $[M]^+$: 421.0887.

*5.6.2. Ethyl 6-bromo-2-[(tert-butoxycarbonyl)amino]naphthalene-1-carboxylate (**9**).* Pale orange solid, yield: 50%, R_f (PE/AcOEt 10:1)= 0.44; mp 105–107 °C; IR (KBr cm^{-1}) 1718, 1672; ^1H NMR ($CDCl_3$): δ 9.10 (br s, 1H, NH), 8.47 (d, 1H, J=9.2, 3Ar–H), 8.16 (d, 1H, J=9.2, 8Ar–H), 7.93 (d, 1H, J=1.5, 5Ar–H), 7.80 (d, 1H, J=9.2, 4Ar–H), 7.57–7.55 (m, 1H, 7Ar–H), 4.56 (q, 2H, J=7.1, CH_2), 1.54 (s, 9H, Boc-Me), 1.49 (t, 3H, J=7.1, Me); ^{13}C NMR ($CDCl_3$): δ 168.4, 152.9, 139.5, 132.1, 131.1, 130.9, 130.4, 130.0, 127.4, 120.7, 118.6, 81.2, 62.0, 29.9, 28.5, 14.4; HRMS (ESI-LC/MS) m/z calcd for $C_{18}H_{20}BrNO_4$: 393.0576; found $[M]^+$: 393.0575.

5.7. Synthesis of amino esters 6, 10, 11

a) Procedure for synthesis of ester **6**

To a solution of bromo ester **5** (0.37 mmol) in 1,4-dioxane (4.8 mL) at room temperature, 3.3 mL HCl (0.5M, 1.66 mmol) was added. The resulting mixture was then heated at 70 °C for 15 h until TLC analysis of the reaction mixture indicated the absence of starting material **5**. After the reaction was completed, all the volatile materials were removed under reduced pressure and water (5 mL) was added to residue. The mixture was adjusted with saturated $NaHCO_3$ and then extracted with DCM (3×20 mL). The combined extracts were dried over $MgSO_4$, concentrated under reduced pressure. A crude mixture was subjected to column chromatography to give amines **6** and **7**.

*5.7.1. tert-Butyl 2-amino-6-bromonaphthalene-1-carboxylate (**6**).* Red-orange oil, yield: 30%, R_f (PE/AcOEt 5:1)=0.56; IR (film cm^{-1}) 3486, 3369, 1676; ^1H NMR ($CDCl_3$): δ 8.35 (d, 1H, J=9.3, 8Ar–H), 7.77 (d, 1H, J=2.2, 5Ar–H), 7.53 (d, 1H, J=8.9, 3Ar–H), 7.49 (dd, 1H, J=2.2, 9.3, 7Ar–H), 6.83 (d, 1H, J=8.9, 4Ar–H), 5.46 (br s, 2H, NH_2), 1.68 (s, 9H, Boc-Me); ^{13}C NMR ($CDCl_3$): δ 168.4, 148.9, 132.6, 131.8, 130.6, 130.3, 129.1, 126.9, 120.4, 115.7, 106.2, 82.2, 28.8; HRMS (ESI-LC/MS) m/z calcd for $C_{15}H_{16}BrNO_2$: 321.0364; found $[M]^+$: 321.0362.

*5.7.2. 6-Bromonaphthalen-2-amine (**7**).*[24] Pale red solid, yield: 39%, R_f (DCM/Hex 2:1)=0.28; mp 118–120 °C (lit. 127–128 °C[24a]); IR

(KBr cm^{-1}) 3412, 3323; ^1H NMR ($CDCl_3$): δ 7.83 (s, 1H, 1Ar–H), 7.56 (d, 1H, J=8.6, 5Ar–H), 7.45–7.41 (m, 2H, 7,8Ar–H), 6.96–6.94 (m, 2H, 3,4Ar–H), 3.86 (br s, 2H, NH_2); ^{13}C NMR ($CDCl_3$): δ 144.7, 133.6, 129.8, 129.7, 129.2, 128.5, 127.6, 119.2, 115.8, 108.5.

b) Procedure for synthesis of ester **10** and **11**

To a solution of bromo ester **8** or **9** (1.37 mmol) in 1,4-dioxane (27.4 mL) at room temperature, 5.5 mL HCl (0.5M, 2.74 mmol) was added. The resulting mixture was then heated at 70 °C for 18 h until TLC analysis of the reaction mixture indicated the absence of starting material **8** or **9**. After the reaction was completed, all the volatile materials were removed under reduced pressure and water (5 mL) was added to residue. The mixture was adjusted with saturated $NaHCO_3$ and then extracted with DCM (3×20 mL). The combined extracts were dried over $MgSO_4$, concentrated under reduced pressure. The appropriate amines **10**, **11** were separated from the residue by flash chromatography.

*5.7.3. Ethyl 2-amino-6-bromonaphthalene-1-carboxylate (**10**).* Orange solid, yield: 56%, R_f (PE/AcOEt 10:1)=0.14; mp 64–67 °C; IR (KBr cm^{-1}) 3426, 3316, 1659; ^1H NMR ($CDCl_3$): δ 8.41 (d, 1H, J=9.3, 8Ar–H), 7.77 (s, 1H, 5Ar–H), 7.57 (d, 1H, J=8.9, 3Ar–H), 7.51 (d, 1H, J=9.3, 7Ar–H), 6.85 (d, 1H, J=8.9, 4Ar–H), 5.86 (br s, 2H, NH_2), 4.49 (q, 2H, J=7.1, CH_2), 1.48 (t, 3H, J=7.1, Me); ^{13}C NMR ($CDCl_3$): δ 169.2, 149.9, 133.2, 131.9, 131.0, 130.5, 129.2, 127.0, 120.4, 115.9, 104.1, 60.9, 14.6; HRMS (ESI-LC/MS) m/z calcd for $C_{13}H_{12}BrNO_2$: 293.0051; found $[M]^+$: 293.0052.

*5.7.4. Ethyl 2-aminonaphthalene-1-carboxylate (**11**).* Pale orange solid, yield: 77%, R_f (PE/AcOEt 10:1)=0.1; mp 64–66 °C; IR (KBr cm^{-1}) 3419, 3316, 1656; ^1H NMR ($CDCl_3$): δ 8.53 (d, 1H, J=8.7, 8Ar–H), 7.69 (d, 1H, J=8.8, 4Ar–H), 7.66 (d, 1H, J=7.9, 5Ar–H), 7.49–7.45 (m, 1H, 7Ar–H), 7.28–7.25 (m, 1H, 6Ar–H), 6.85 (d, 1H, J=8.8, 3Ar–H), 5.80 (br s, 2H, NH_2), 4.53 (q, 2H, J=7.1, CH_2), 1.51 (t, 3H, J=7.1, Me); ^{13}C NMR ($CDCl_3$): δ 169.6, 149.6, 134.3, 133.2, 128.7, 128.0, 127.9, 125.1, 122.5, 119.2, 104.4, 60.8, 14.7; HRMS (ESI-LC/MS) m/z calcd for $C_{13}H_{13}NO_2$: 215.0946; found $[M]^+$: 215.0946.

5.8. Preparation of benzo[*f*]quinazolinone I, 12a,b

A mixture of ester **6** or **8** or **10** (0.24 g, 0.82 mmol) in formamide (20 mL) was stirred and heated to 180–190 °C and held at this temperature for 10 h. After this time reaction mixture was cooled and water was added (80 mL). The precipitated solid was filtered from the solution and then was purified by flash chromatography.

*5.8.1. 8-Bromobenzo[f]quinazolin-1(2H)-one (**I**).* White solid, yield: 20% (from **6**), 94% (from **10**) R_f (acetonitrile/Hex 10:1)=0.5; mp 320–323 °C; IR (KBr cm^{-1}) 1667; ^1H NMR (DMSO-d_6): δ 12.69 (br s, 1H, NH), 9.79 (d, 1H, J=9.2, 10Ar–H), 8.35 (d, 1H, J=2.2, 7Ar–H), 8.30 (s, 1H, 3Ar–H), 8.27 (d, 1H, J=8.9, 6Ar–H), 7.88 (dd, 1H, J=2.2, 9.2, 9Ar–H), 7.76 (d, 1H, J=8.9, 5Ar–H); ^{13}C NMR (DMSO-d_6): δ 161.2, 151.1, 146.6, 134.3, 132.9, 131.1, 130.3, 129.0, 128.5, 127.5, 119.8, 115.7; HRMS (ESI-LC/MS) m/z calcd for $C_{12}H_7BrN_2O$: 273.9742; found $[M]^+$: 273.9742.

*5.8.2. Benzo[f]quinazolin-1(2H)-one (**12a**).*[4a,b] White solid, yield: 92%, R_f (acetonitrile/AcOEt 1:1)=0.34; mp 259–262 °C (lit. 260 °C[4b]); IR (KBr cm^{-1}) 1676; ^1H NMR (DMSO-d_6): δ 12.59 (br s, 1H, NH), 9.86 (d, 1H, J=8.6, 10Ar–H), 8.30–8.27 (m, 2H, 3,7Ar–H), 8.07 (d, 1H, J=7.8, 5Ar–H), 7.77–7.74 (m, 1H, 9Ar–H), 7.71 (d, 1H, J=8.8, 8Ar–H), 7.68–7.66 (m, 1H, 6Ar–H); ^{13}C NMR (DMSO-d_6): δ 161.5, 150.9, 146.2, 135.4, 131.3, 130.4, (128.4)×2, 126.5, 126.3, 126.1, 115.7; HRMS (ESI-LC/MS) m/z calcd for $C_{12}H_8N_2O$: 196.0637; found $[M]^+$: 196.0637.

*5.8.3. Benzo[f]quinazolin-1,3(2H,4H)-dione (**12b**).*[15] Beige solid, yield: 28%, R_f (AcOEt)=0.34; mp 358–360 °C (lit. 342 °C[15]); IR (KBr cm^{-1}) 1706, 1659; ^1H NMR (DMSO-d_6): δ 11.45 (br s, 1H, NH), 11.34 (br s, 1H, NH), 9.57 (d, 1H, J=8.7, 10Ar–H), 8.18 (d, 1H, J=8.8, 5Ar–H), 7.94 (d, 1H, J=7.8, 7Ar–H), 7.68–7.66 (m, 1H, 9Ar–H), 7.53–7.50 (m, 1H, 8Ar–H), 7.35 (d, 1H, J=8.8, 6Ar–H); ^{13}C NMR (DMSO-d_6): δ 163.9, 150.0, 142.8, 136.3, 130.7, 129.2, 129.0, 128.7, 125.0, 124.5, 116.0, 105.3; HRMS (ESI-LC/MS) m/z calcd for $C_{12}H_8N_2O_2$: 212.0586; found $[M]^+$: 212.0586.

5.9. Synthesis of mixture of 13 and 14

5.9.1. Method A. A mixture of ester **10** (0.13 g, 0.44 mmol) and K_2CO_3 (0.44 mmol) in *N*-methylformamide (10 mL) was stirred and heated to 180 °C and held at this temperature for 15 h. After this time, the solvent was removed under reduced pressure and the residue was purified by flash chromatography.

5.9.2. Method B. A mixture of benzo[*f*]quinazolinone **12a** (0.18 g, 0.65 mmol) and K_2CO_3 (0.65 mmol) in dry acetone (20 mL) was heated to 55 °C, held for 30 min at 55 °C and then the methyl iodide (0.72 mmol) was added. The reaction was continued at 55 °C for 10 h. After cooling to room temperature mixture was concentrated under reduce pressure and then the residue was purified by flash chromatography.

*5.9.3. Mixture of 2-Methylbenzo[f]quinazolin-1(2H)-one (**13**) and 8-bromo-2-Methylbenzo[f]quinazolin-1(2H)-one (**14**).* Beige solid, yield (from ^1H NMR): **13** 11%, **14** 21% (Method A) or **13** 35%, **14** 65% (Method B), respectively; R_f (PE/AcOEt 4:1)=0.22; IR (KBr cm^{-1}) 1664, 1657; ^1H NMR ($CDCl_3$): δ 9.97 (d, 1H, J=8.6, Ar–H), 9.86 (d, 1H, J=9.2, Ar–H), 8.25–8.24 (m, 2H, Ar–H), 8.14 (d, 1H, J=8.8, Ar–H), 8.08 (d, 1H, J=2.1, Ar–H), 8.03 (d, 1H, J=8.8, Ar–H), 7.93 (d, 1H, J=8.0, Ar–H), 7.83–7.81 (m, 1H, Ar–H), 7.78–7.71 (m, 3H, Ar–H), 7.66–7.63 (m, 1H, Ar–H), 3.71 (s, 3H, Me), 3.70 (s, 3H, Me); ^{13}C NMR ($CDCl_3$): δ 161.9, 161.7, (150.8)×2, 147.6, 147.4, 135.8, 134.5, 133.6, 132.3, 131.9, 131.0, 130.4, 129.5, 129.3, 129.2, 128.9, 128.4, 127.5, 127.0, 126.1, 112.2, 115.9, 115.8, (34.8)×2.

5.10. Synthesis of compound 13, 15 and 19b

A mixture of benzoquinazolinone **I** or **12a** or **18** (0.72 mmol) and K_2CO_3 (0.72 mmol) in dry acetone (20 mL) was heated to 55 °C, held for 30 min at 55 °C and then the corresponding bromide or iodide (0.78 mmol DMBBr, BnBr or MeI) was added. The reaction was continued at 55 °C for 20 h. After cooling to room temperature mixture was concentrated under reduce pressure and then the crude product was purified by flash chromatography.

*5.10.1. 2-Methylbenzo[f]quinazolin-1(2H)-one (**13**).* Beige solid, yield: 90%, R_f (acetonitrile/AcOEt 1:1)=0.5; mp 130–132 °C; IR (KBr cm^{-1}) 1657; ^1H NMR ($CDCl_3$): δ 9.96 (d, 1H, J=8.6, 10Ar–H), 8.22 (s, 1H, 3Ar–H), 8.12 (d, 1H, J=8.8, 5Ar–H), 7.92 (d, 1H, J=8.0, 7Ar–H), 7.77–7.74 (m, 1H, 9Ar–H), 7.70 (d, 1H, J=8.8, 6Ar–H), 7.65–7.62 (m, 1H, 8Ar–H), 3.69 (s, 3H, Me); ^{13}C NMR ($CDCl_3$): δ 161.9, 150.8, 147.4, 135.8, 132.3, 131.0, 128.9, 128.4, 127.5, 127.0, 126.1, 115.8, 34.8; HRMS (ESI-LC/MS) m/z calcd for $C_{13}H_{10}N_2O$: 210.0793; found $[M]^+$: 210.0792.

*5.10.2. 8-Bromo-2-(3,4-dimethoxybenzyl)benzo[f]quinazolin-1(2H)-one (**15**).* White solid, yield: 54%, R_f (AcOEt/Hex 10:1)=0.42; mp 198–201 °C; IR (KBr cm^{-1}) 1667; ^1H NMR (DMSO-d_6): δ 9.79 (d, 1H, J=9.2, 10Ar–H), 8.82 (s, 1H, 3Ar–H), 8.37 (d, 1H, J=2.2, 7Ar–H), 8.29

(d, 1H, *J*=8.8, 5Ar–H), 7.89 (dd, 1H, *J*=2.5, 9.2, 9Ar–H), 7.77 (d, 1H, *J*=8.8, 6Ar–H), 7.13 (d, 1H, *J*=2.0, 5DMB-H), 6.96 (dd, 1H, *J*=2.0, 8.3, 1 or 2DMB-H), 6.91 (d, 1H, *J*=8.3, 1 or 2DMB-H), 5.23 (s, 2H, CH_2), 3.75 (s, 3H, Me), 3.71 (s, 3H, Me); ^{13}C NMR (DMSO-d_6): δ 160.2, 150.3, 149.0, 148.8, 148.5, 134.6, 133.1, 131.3, 130.4, 129.0, 128.9, 128.6, 127.4, 120.5, 119.9, 114.8, 112.3, 111.9, 55.6, 55.5, 49.1; HRMS (ESI-LC/MS) *m*/*z* calcd for $C_{21}H_{18}BrN_2O_3$: 425.0495; found $[M+H]^+$: 425.0495.

*5.10.3. 6-Bromo-3-(3,4-dimethoxybenzyl)benzo[h]quinazolin-4(3H)-one (**19b**).* Pale yellow solid, yield: 45%, R_f (PE/AcOEt 3:1)=0.7; mp 182–185 °C; IR (KBr cm^{-1}) 1670; ^{1}H NMR (DMSO-d_6): δ 8.98 (d, 1H, *J*=8.2, 10Ar–H), 8.86 (s, 1H, 3Ar–H), 8.36 (s, 1H, 5Ar–H), 8.26 (d, 1H, *J*=8.3, 7Ar–H), 7.97–7.94 (m, 1H, 8Ar–H), 7.88–7.85 (m, 1H, 9Ar–H), 7.12 (d, 1H, *J*=1.9, 5DMB-H), 6.96 (dd, 1H, *J*=1.9, 8.3, 1 or 2DMB-H), 6.91 (d, 1H, *J*=8.3, 1 or 2DMB-H), 5.20 (s, 2H, CH_2), 3.75 (s, 3H, Me), 3.72 (s, 3H, Me); ^{13}C NMR (DMSO-d_6): δ 159.0, 149.1, 148.8, 148.6, 146.0, 133.3, 131.0, 130.5, 128.8, 126.8, 125.1, 124.9, (120.5)×2, 118.6, 112.3, 112.0, (55.6)×2, 49.1; HRMS (ESI-LC/MS) *m*/*z* calcd for $C_{21}H_{18}BrN_2O_3$: 425.0495; found $[M+H]^+$: 425.0495.

5.11. General procedure for the palladium-catalyzed C–N and C–S bonds formations. Synthesis of compound 16a–c, 20a–c, 21a–c

The reaction was carried out under an argon atmosphere in an oven dried resealable Schlenk flask. A resealable Schlenk flask was charged with bromobenzoquinazolinone **15** or **19a**,**b** (0.12 mmol), freshly distilled 1,4-dioxane (3 mL) and $Pd(OAc)_2$ (15 mol%), XantPhos (15 mol%), KO*t*-Bu (0.18 mmol), and the appropriate amine (0.35 mmol) for synthesis of aminobenzoquinazolinones **16a**,**b** and **20a–c** or $Pd(OAc)_2$ (30 mol%), XantPhos (30 mol%), DIPEA (0.24 mmol), the appropriate mercaptan (0.24 mmol) for synthesis of sulfanylbenzoquinazolinones **16c** and **21a–c**. The whole mixture was stirred and heated at 90–100 °C for 20 h. After this time the reaction mixture was cooled and diluted with chloroform (5 mL). The solid was filtered off, washed with chloroform (2 mL) and the filtrate concentrated. The product was purified by flash chromatography.

*5.11.1. 2-(3,4-Dimethoxybenzyl)-8-[4-(4-fluorophenyl)piperazin-1-yl]benzo[f]quinazolin-1(2H)-one (**16a**).* Lemon solid, yield: 86%, R_f (AcOEt/Hex 3:1)=0.42; mp 210–213 °C; IR (KBr cm^{-1}) 1659; ^{1}H NMR ($CDCl_3$): δ 9.87 (d, 1H, *J*=9.4, 10Ar–H), 8.23 (s, 1H, 3Ar–H), 8.02 (d, 1H, *J*=8.8, 5 or 6Ar–H), 7.67 (d, 1H, *J*=8.8, 5 or 6Ar–H), 7.52 (dd, 1H, *J*=2.3, 9.4, 9Ar–H), 7.30–7.28 (m, 1H, 7Ar–H), 7.02–6.94 (m, 6H, 4-FPP-H, DMB), 6.84 (d, 1H, *J*=8.1, DMB), 5.25 (s, 2H, CH_2), 3.86 (s, 6H, (Me)×2), 3.59–3.53 (m, 4H, 4-FPP-H), 3.37–3.33 (m, 4H, 4-FPP-H); ^{13}C NMR ($CDCl_3$): δ 161.4, 149.7, 149.4, (148.7)×2, 145.9, 135.0, 134.0, (128.8)×2, 128.7, 128.6, 126.6, 120.8, 120.4, 118.8, 118.7, 116.3, 116.0, 115.8, 111.7, (56.2)×2, 50.8, 49.9, (49.1)×2; ^{19}F NMR (DMSO-d_6): δ −123.75 to −125.04 (m); HRMS (ESI-LC/MS) *m*/*z* calcd for $C_{31}H_{30}FN_4O_3$: 525.2296; found $[M+H]^+$: 525.2296.

*5.11.2. 2-(3,4-Dimethoxybenzyl)-8-[4-(2-fluorophenyl)piperazin-1-yl]benzo[f]quinazolin-1(2H)-one (**16b**).* Pale yellow solid, yield: 35%, R_f (AcOEt/Hex 3:1)=0.40; mp 211–214 °C; IR (KBr cm^{-1}) 1657; ^{1}H NMR (DMSO-d_6): δ 9.87 (d, 1H, *J*=8.4, 10Ar–H), 8.80 (s, 1H, 3Ar–H), 8.31 (d, 1H, *J*=8.8, 5Ar–H), 8.08 (d, 1H, *J*=7.9, 9Ar–H), 7.78–7.67 (m, 4H, 6Ar–H, 2-FPP-H), 7.59–7.54 (m, 1H, 2-FPP-H), 7.14 (d, 1H, *J*=1.8, 7Ar–H), 6.97–6.91 (m, 3H, DMB-H), 5.25 (s, 2H, CH_2), 3.76–3.74 (m, 4H, 2-FPP-H), 3.72–3.71 (m, 4H, 2-FPP-H), 3.29 (s, 6H, Me); ^{13}C NMR (DMSO-d_6): δ 160.4, 155.4, 154.1, 150.1, 149.3, 148.7, 148.6, 148.5, 135.6, 131.5, 130.2, 130.1, 129.1, 128.8, 128.5, 126.6, 126.4, 126.0, 125.3, 122.8, 120.4, 116.5, 116.4, 114.7, 112.2, 111.9, (55.5)×2, 48.9; ^{19}F NMR (DMSO-d_6): δ −124.11 to −125.06 (m); HRMS (ESI-LC/MS) *m*/*z* calcd for $C_{31}H_{30}FN_4O_3$: 525.2296; found $[M+H]^+$: 525.2296.

*5.11.3. Methyl {[2-(3,4-dimethoxybenzyl)-1-oxo-1,2dihydrobenzo[f]quinazolin-8-yl]-sulfanyl}propanoate (**16c**).* Pale yellow solid, yield: 75%, R_f (AcOEt/Hex 10:1)=0.68; mp 175–177 °C; IR (KBr cm^{-1}) 1735, 1656; ^{1}H NMR ($CDCl_3$): δ 9.88 (d, 1H, *J*=9.0, 10Ar–H), 8.33 (s, 1H, 3Ar–H), 8.05 (d, 1H, *J*=8.8, 5Ar–H), 7.84 (d, 1H, *J*=1.5, 7Ar–H), 7.75 (d, 1H, *J*=8.8, 6Ar–H), 7.70–7.68 (m, 1H, 9Ar–H), 6.97–6.95 (m, 2H, DMB-H), 6.85 (d, 1H, *J*=8.1, DMB-H), 5.25 (s, 2H, CH_2), 3.87 (s, 3H, Me), 3.86 (s, 3H, Me), 3.69 (s, 3H, CH_2CH_2COOMe), 3.32 (t, 2H, CH_2CH_2COOMe), 2.70 (t, 2H, CH_2CH_2COOMe); ^{13}C NMR ($CDCl_3$): δ 172.2, 161.1, 149.8, 149.6, 146.9, 135.2, 135.0, 132.9, (130.1)×2, (129.3)×2, (128.2)×2, 128.1, (127.8)×2, 126.6, 121.0, 116.1, (111.8)×2; HRMS (ESI-LC/MS) *m*/*z* calcd for $C_{25}H_{25}N_2O_5S$: 465.1479; found $[M+H]^+$: 465.1479.

*5.11.4. 3-Benzyl-6-(4-methylpiperazin-1-yl)benzo[h]quinazolin-4(3H)-one (**20a**).* White solid, yield: 62%, R_f (MeOH/PE 10:2)=0.34; mp 171–173 °C; IR (KBr cm^{-1}) 1660; ^{1}H NMR ($CDCl_3$): δ 8.98 (dd, 1H, *J*=1.1, 8.0, 10Ar–H), 8.24 (s, 1H, 2Ar–H), 8.20 (d, 1H, *J*=7.8, 7Ar–H), 7.82 (s, 1H, 5Ar–H), 7.73–7.67 (m, 2H, 8, 9Ar–H), 7.40–7.30 (m, 5H, Bn-H), 5.28 (s, 2H, CH_2), 3.34 (br s, 4H, Pip-H), 2.94 (br s, 4H, Pip-H), 2.57 (s, 3H, Me); ^{13}C NMR ($CDCl_3$): δ 161.1, 145.2, 143.8, 136.0, 132.0, 131.4, 129.2, 129.0, (128.5)×2, 128.3, 127.2, 125.7, 123.7, 119.2, 109.8, (55.2)×2, (52.0)×2, 50.1; HRMS (ESI-LC/MS) *m*/*z* calcd for $C_{24}H_{25}N_4O$: 385.2023; found $[M+H]^+$: 385.2023.

*5.11.5. 3-Benzyl-6-[4-(2-fluorophenyl)piperazin-1-yl)benzo[h]quinazolin-4(3H)-one (**20b**).* Yellow solid, yield: 67%, R_f (DCM/PE/AcOEt 6:1:0.5)=0.52; mp 205–208 °C; IR (KBr cm^{-1}) 1667; ^{1}H NMR ($CDCl_3$): δ 9.01 (dd, 1H, *J*=1.0, 8.2, 10Ar–H), 8.31 (d, 1H, *J*=7.7, 7Ar–H), 8.28 (s, 1H, 2Ar–H), 7.88 (s, 1H, 5Ar–H), 7.76–7.69 (m, 2H, 8, 9Ar–H), 7.41–7.31 (m, 6H, DMB-H or 2-FPP-H), 7.16–7.05 (m, 3H, DMB-H or 2-FPP-H), 5.30 (s, 2H, CH_2), 3.51–3.46 (m, 8H, 2-FPP-H); ^{13}C NMR ($CDCl_3$): δ 161.1, 157.0, 155.0, 150.0, 149.0, 145.3, 143.5, 135.9, 132.1, 131.3, 129.4, 129.2, 129.1, 128.5, 128.3, 127.3, 125.7, 124.9, 123.8, 122.1, 120.3, 119.2, 116.7, 116.6, 109.9, (52.8)×2, (51.5)×2, 50.1. ^{19}F NMR (DMSO-d_6): δ −122.55 to −122.62 (m); HRMS (ESI-LC/MS) *m*/*z* calcd for $C_{29}H_{26}FN_4O$: 465.2085; found $[M+H]^+$: 465.2085.

*5.11.6. 3-(3,4-Dimethoxybenzyl-6-[4-(4-fluorophenyl)piperazin-1-yl)benzo[h]quinazolin-4(3H)-one (**20c**).* Yellow solid, yield: 67%, R_f (AcOEt/DCM 2:1)=0.74; mp 165–168 °C; IR (KBr cm^{-1}) 1657; ^{1}H NMR ($CDCl_3$): δ 8.99 (d, 1H, *J*=7.9, 10Ar–H), 8.30 (d, 1H, *J*=8.2, 7Ar–H), 8.25 (s, 1H, 2Ar–H), 7.85 (s, 1H, 5Ar–H), 7.74–7.68 (m, 2H, 8, 9Ar–H), 7.02–6.96 (m, 6H, DMB-H, 4-FPP-H), 6.84 (d, 1H, *J*=8.0, DMB-H), 5.22 (s, 2H, CH_2), 3.87 (s, 3H, Me), 3.86 (s, 3H, Me), 3.42–3.37 (m, 8H, 4-FPP-H); ^{13}C NMR ($CDCl_3$): δ 161.2, 158.5, 149.7, 149.4, 149.2, 145.1, 143.7, 132.1, 131.5, 129.1, 128.5, 127.3, 125.7, 122.8, 121.0, 119.2, 118.3, 118.2, 115.9, 115.7, 111.8, 111.7, 109.6, 56.2, 56.1, 53.1, 53.0, (50.9)×2, 49.9; ^{19}F NMR ($CDCl_3$): δ −124.7 to −124.2 (m); HRMS (ESI-LC/MS) *m*/*z* calcd for $C_{31}H_{30}FN_4O_3$: 525.2296; found $[M+H]^+$: 525.2296.

*5.11.7. 3-Benzyl-6-(propylsulfanyl)benzo[h]quinazolin-4(3H)-one (**21a**).* Beige solid, yield: 62%, R_f (DCM/AcOEt/PE 1:1:1)=0.68; mp 164–167 °C; IR (KBr cm^{-1}) 1657; ^{1}H NMR ($CDCl_3$): δ 9.00 (d, 1H, *J*=8.1, 10Ar–H), 8.41 (d, 1H, *J*=8.2, 7Ar–H), 8.29 (s, 1H, 2 or 5Ar–H), 8.17 (s, 1H, 2 or 5Ar–H), 7.78–7.75 (m, 1H, 8Ar–H), 7.73–7.70 (m, 1H, 9Ar–H), 7.41–7.31 (m, 5H, Bn-H), 5.29 (s, 2H, CH_2), 3.12 (t, 2H, *J*=7.3, $CH_2CH_2CH_3$), 1.83–1.77 (m, 2H, $CH_2CH_2CH_3$), 1.10 (t, 3H, *J*=7.3, $CH_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$): δ 160.8, 151.4, 145.8, 145.0, 135.9, 135.8, 134.8, 130.1, 129.6, 129.2, 128.6, 128.3, 127.5, 125.6, 124.8,

119.7, 118.8, 50.2, 35.3, 22.3, 13.8; HRMS (ESI-LC/MS) *m*/*z* calcd for $C_{22}H_{21}N_2OS$: 361.1369; found $[M+H]^+$: 361.1369.

*5.11.8. Methyl 3-[(3,4-dimethoxybenzyl-4-oxo-3,4-dihydrobenzo[h]quinazolin-6-yl)sulfanyl]-propanoate (**21b**).* White solid, yield: 81%, R_f (DCM/AcOEt/PE 1:3:0.5)=0.66; mp 125–127 °C; IR (KBr cm^{-1}) 1727, 1678; ^1H NMR ($CDCl_3$): δ 9.00 (d, 1H, *J*=8.2, 10Ar–H), 8.42 (d, 1H, *J*=8.3, 7Ar–H), 8.28 ((s, 1H)×2, 2,5Ar–H), 7.79–7.76 (m, 1H, 8Ar–H), 7.73–7.71 (m, 1H, 9Ar–H), 6.97–6.95 (m, 2H, DMB-H), 6.85 (d, 1H, *J*=8.3, DMB-H), 5.21 (s, 2H, CH_2), 3.87 (s, 3H, Me), 3.86 (s, 3H, Me), 3.68 (s, 3H, CH_2CH_2COOMe), 3.36 (t, 2H, *J*=7.3, CH_2CH_2COOMe), 2.73 (t, 2H, *J*=7.3, CH_2CH_2COOMe); ^{13}C NMR ($CDCl_3$): δ 172.0, 160.7, 149.7, 149.5, 146.2, 145.9, 135.2, 133.7, 130.4, 129.8, 128.2, 127.6, 125.6, 125.1, 122.3, 121.1, 118.6, 111.8, 111.7, 56.2, 56.1, 52.0, 50.0, 34.1, 28.8; HRMS (ESI-LC/MS) *m*/*z* calcd for $C_{25}H_{25}N_2O_5S$: 465.1479; found $[M+H]^+$: 465.1479.

*5.11.9. 3-Benzyl-6-(benzylsulfanyl)benzo[h]quinazolin-4(3H)-one (**21c**).* Beige solid, yield: 77%, R_f (DCM/AcOEt/PE 1:1:3)=0.54; mp 155–158 °C; IR (KBr cm^{-1}); ^1H NMR ($CDCl_3$): δ 8.99 (dd, 1H, *J*=1.1, 8.1, 10Ar–H), 8.38 (m, 1H, 7Ar–H), 8.27 (s 1H, 2 or 5Ar–H), 8.25 (s, 1H, 2 or 5Ar–H), 7.75–7.69 (m, 2H, 8, 9Ar–H), 7.40–7.23 (m, 10H, Bn-H), 5.28 (s, 2H, CH_2), 4.33 (s, 2H, CH_2); ^{13}C NMR ($CDCl_3$): δ 160.7, 146.1, 145.5, 136.5, 135.8, 135.2, 134.8, 130.2, 129.6, 129.2, 128.8, 128.5, 128.3, 127.6, 127.5, 125.6, 124.9, 121.1, 118.7, 50.1, 38.6; HRMS (ESI-LC/MS) *m*/*z* calcd for $C_{26}H_{21}N_2OS$: 409.1369; found $[M+H]^+$: 409.1369.

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