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Novel synthesis of angular thiazolo[5,4-*f*] and [4,5-*h*]quinazolines, preparation of their linear thiazolo[4,5-*g*] and [5,4-*g*]quinazoline analogs

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ABSTRACT

Synthesis of 9-oxo-8,9-dihydrothiazolo[5,4-*f*]quinazoline-2-carbonitrile (**1**) or 6-oxo-6,7-dihydrothiazolo [4,5-*h*]quinazoline-2-carbonitrile (**2**) was reinvestigated with the ambition of varying the position of the thiazole ring linked to the quinazolin-4-one moiety, in order to synthesize two novel linear tricyclic 8-oxo-7,8-dihydrothiazolo[4,5-*g*]quinazoline-2-carbonitrile (**3**) and 8-oxo-7,8-dihydrothiazolo[5,4-*g*]quinazoline-2-carbonitrile (**4**). The routes described in this paper open the door to various substitutions and transformations for an access to libraries of potent biologically active heterocyclic compounds.

1. Introduction

Our research groups are mainly invested in the synthesis of C,N,S- or C,N,O-containing heterocyclic precursors of bioactive molecules able to modulate the activity of kinases in signal transduction.[1–5] In the course of our work, the multi-step synthesis of the 8*H*-thiazolo [5,4-*f*]quinazolin-9-one (**A**) and its regio-isomer 7*H*-thiazolo[4,5-*h*] quinazolin-6-one (**B**) was described for the first time 10 years ago under microwave heating.[6,7] The chemical highlight of this work was the use of 4,5-dichloro-1,2,3-dithiazolium chloride (Appel salt[8]), a versatile reagent, which can be used in the design of novel heterocyclic skeletons and especially for the conception of nitrile-bearing heteroarenes with broad applications in biological sciences.[8] Apart from this work, chemistry of both heterocyclic ring systems (**A** and **B** in Fig.1) was explored and reactivity of the carbonitrile function present in position 2 of the thiazole ring was studied, allowing easy synthesis of various amidine, imidazoline, and imidate derivatives.[2,3] Brief studies of their structure–activity relationships as dual CDK1/GSK-3 kinases inhibitors were described.[2] The major drawback observed during this work was linked to the instability of the carbonitrile group generated by the transformation of imino-1,2,3-dithiazoles intermediates. At that time, it was not possible to isolate 9-oxo-8,9-dihydrothiazolo[5,4-*f*]quinazoline-2-carbonitrile (**1**) or 6-oxo-6,7-dihydrothiazolo[4,5-*h*]quinazoline-2-carbonitrile (**2**) (Fig. 1) with both an unsubstituted pyrimidin-4-one moiety and a thiazole ring itself substituted in position 2 by the versatile carbonitrile group.

Because we thought that the synthesis of such intermediates would grant access to many derivatives and thus the preparation of a library of interesting molecules, we decided to reinvestigate the synthesis of these thiazolo[5,4-*f*]quinazolin-4-one (**1**) and thiazolo [4,5-*h*]quinazolin-4-one (**2**) and to explore the possibility of varying the position of the thiazole ring linked to the quinazolin-4-one moiety in order to synthesize two novel linear tricyclic 8-oxo-7,8-dihydrothiazolo[4,5-*g*]quinazoline-2-carbonitrile (**3**) and 8-oxo-7,8-dihydrothiazolo[5,4-*g*]quinazoline-2-carbonitrile (**4**) (Fig. 1). Here again we decided to examine the possibilities offered by the thermal transformation of intermediate *N*-arylimino-1,2,3-dithiazoles themselves obtained by condensation of Appel salt with aromatic amines. This paper describes the results of our

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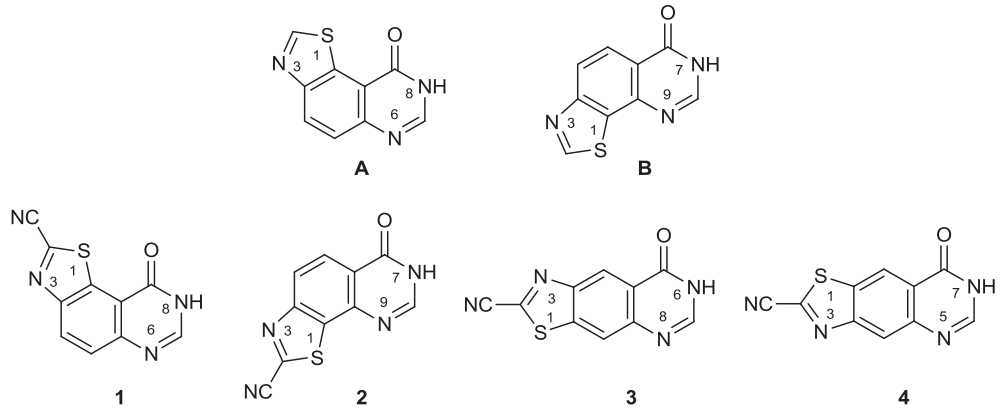


Fig. 1. Target molecules of this study.

investigations. In an overall aspect, this work also aims at showing the crucial utility of microwaves in organic reactions, especially in heterocyclic syntheses where harsh thermal conditions are sometimes required.[9]

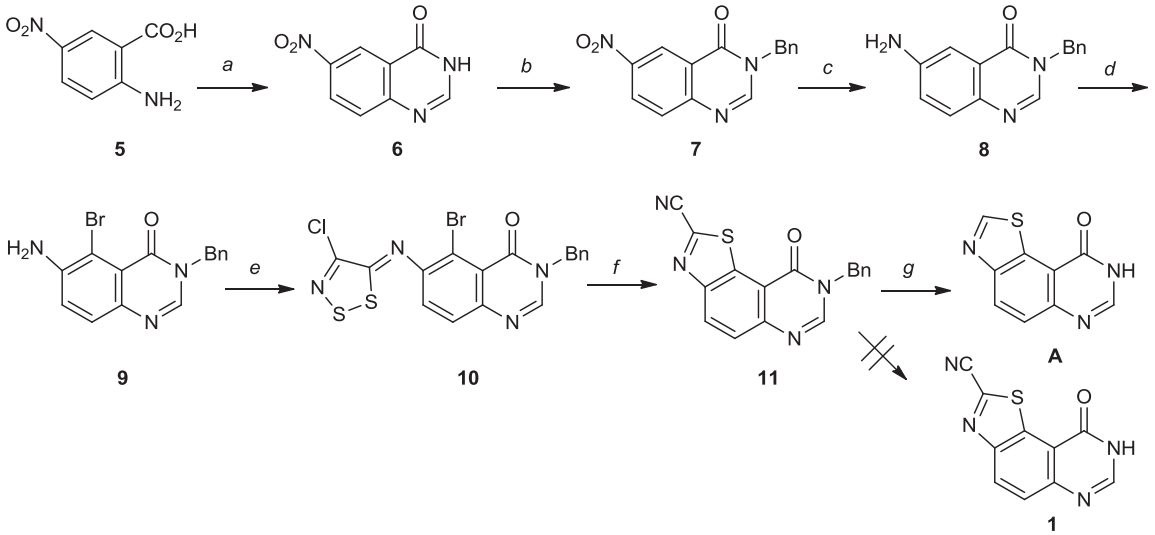
2. Results and discussion

2.1. Synthesis of the angular 9-oxo-8,9-dihydrothiazolo[5,4-*f*] quinazoline-2-carbonitrile (1) or 6-oxo-6,7-dihydrothiazolo [4,5-*h*]quinazoline-2-carbonitrile (2)

The synthetic route previously described for rings **A** and **B** is depicted in Scheme 1.[6] The expected 9-oxo-thiazoloquinazoline-2-carbonitrile derivatives (**A** or **B** in Fig. 1) were obtained in six steps from commercially available 5-nitro- or 4-nitroanthranilic acid. For example, in the case of **A**, 6-nitro-3*H*-quinazolin-4-one (**6**) was synthesized by atmospheric microwave heating of 5-nitroanthranilic acid (**5**) with 5 equiv of formamide (150 °C).[10] Selective N-alkylation in position 3 of the quinazolin-4-one ring was performed at atmospheric pressure by treatment of **6** with sodium hydride and benzyl bromide as alkylating agent. Reduction of the 3-substituted-6-nitroquinazolin-4-one (**7**) led to the 6-amino derivative **8** by using ammonium formate for catalytic transfer hydrogenation in ethanol. Compound **8** was brominated in the presence of bromine in acetic acid, to give the *ortho* brominated imine **9**. The latter was condensed with 4,5-dichloro-1,2,3-dithiazolium chloride (Appel salt) in dichloromethane at room temperature. Addition of pyridine led to the desired imino-1,2,3-dithiazoloquinazolinone **10**. Product **11** was obtained by microwave-assisted thermolysis consisting into a rapid heating of the starting imine **10** (1 min at 160 °C in a sealed tube) in the presence of copper(I) iodide in pyridine. Access to ring **A** was performed by heating the protected compound **11** in sulfuric acid, involving deprotection of the nitrogen group and decyanation (hydrolysis+decarboxylation) of the thiazole moiety. Technology used for heating, reaction times, and yields are given in Scheme 1.

This route (Scheme 1) was the result of various trials and experiments,[1–7] which demonstrated that: (a) in step *b*, protection of the nitrogen atom in position 3 of the pyrimidine part was absolutely necessary for a good access to the expected ring. The method afforded a small amount of an *O*-benzylated derivative, usually eliminated by chromatography; (b) no matter the method, final deprotection of this nitrogen atom involved loss of the carbonitrile function in position 2 of the thiazole moiety, leading to the unsubstituted 8*H*-thiazolo[5,4-*f*]quinazolin-9-one (**A**); (c) step *g*, prior transformation of the cyano group into amidines, amides, or imidates never allowed the successive debenzylation of the pyrimidine ring.

In a recent exploration of the possibilities offered by such synthesis to access to novel antifungal agents,[11] it was discovered that



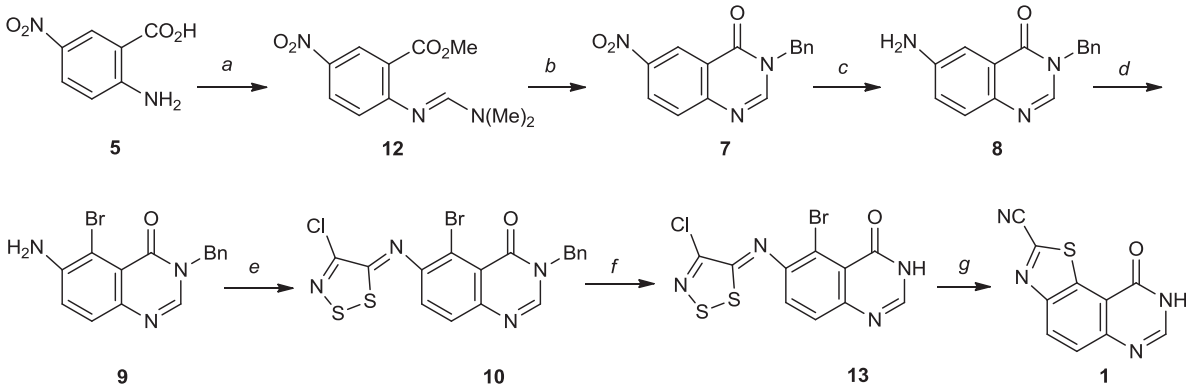
Scheme 1. Reagents and conditions: (a) formamide (5 equiv), 150 °C (μW), 40 min, 87%; (b) benzyl bromide, NaH, DMF, 140 °C (μW), 30 min, 95%; (c) HCO_2NH_4, Pd/C, EtOH, 85 °C (μW), 10 min, 92%; (d) Br_2, AcOH, rt, 2 h; (e) Appel's salt, pyridine, DCM, rt, 3 h, 82%; (f) CuI, pyridine, 115 °C (μW), 15 min, 83%; (g) concd H_2SO_4, 130 °C (μW), 15 min, 40%.

deprotection of the benzylated nitrogen by treatment of intermediate **10**, with aluminum chloride ($AlCl_3$) in toluene, was possible without decomposition of the reactive and sometimes instable imino-1,2,3-dithiazole ring present on the starting molecule. Taking into account these results, we decided to reinvestigate the synthesis of thiazolo[5,4-*f*]- (**1**) or thiazolo[4,5-*h*]quinazolinone (**2**), associated to a recent work on the synthesis of 4-substituted quinazolines[12] via a microwave-assisted Dimroth rearrangement.[13]

The route described in Scheme 2 started from 5-nitroanthranilic acid (**5**), which was treated with *N*,*N*-dimethylformamidedimethylacetal (DMFDMA) under microwave heating at 105 °C for 15 min. The resulting *N*,*N*-dimethylformamidine **12** was in fact a methyl ester due to the capacity of DMFDMA to alkylate nitrogen or oxygen atoms as described in various papers.[14] The methyl ester **12** was heated with benzylamine in the presence of acetic acid at 118 °C for 20 min (time measured when the mixture has reached the programmed temperature after a ramp period of 3 min under a power at 400 W). Compound **7** was then obtained in two steps in a good average yield of 92%. This result is comparable to the yield obtained in the previous process (Scheme 1) but this novel access to **7** can be considered more efficient and easier in practice. The other part of this synthesis was the same as described above until compound **10** was obtained. The latter was heated at 85 °C for 30 min under microwaves with excess of $AlCl_3$ (5.5 equiv) in toluene and afforded deprotected quinazolinone **13** in a quantitative yield. Cyclization of **13** into the tricyclic thiazolo[5,4-*f*]quinazoline **1** was accomplished in an excellent yield (97%), with microwave heating (atmospheric pressure) in the presence of CuI in pyridine at 115 °C for 15 min. The resulting 9-oxo-8,9-dihydrothiazolo[5,4-*f*]quinazoline-2-carbonitrile (**1**) was obtained in seven steps in an overall yield of 42%.

via the key N^3-benzylated and brominated aminoquinazolin-4-one intermediates (framed compounds in Scheme 4) themselves obtained from the two anthranilic acid isomers.

2.2.1. Synthesis of key N^3-benzylated and brominated aminoquinazolin-4-ones. The synthesis of 6-amino-3-benzyl-7-bromoquinazolin-4(3*H*)-one is depicted in Scheme 5; it was firstly studied from 5-nitroanthranilic acid. Unfortunately, various conditions of bromination of the intermediates stayed infructuous or gave inseparable mixtures containing the desired product. Failure to obtain the proper precursors led us to investigate a new synthetic route from methyl 4-bromoanthranilate (**21**), which was treated by DMFDMA in the usual conditions. The resulting *N*,*N*-dimethylformamidine **22** was then heated in acetic acid in the presence of benzylamine to afford the 3-benzyl-7-bromoquinazolin-4(3*H*)-one (**23**) in an excellent yield (99%). Unfortunately its nitration yielded polynitrated derivatives as we presumed, especially on the benzyl group. Taking into account these results, it was decided to cyclize the starting anthranilic methyl ester **21** or the formamidine **22** into the unsubstituted 7-bromoquinazolin-4-one (**24**) before performing nitration. The reaction of **21** or **22** with formamide at 200 °C gave the brominated product **24** in quantitative yield. Nitration with a mixture of nitric and sulfuric acid gave the 7-bromo-6-nitroquinazolin-4(3*H*)-one (**25**) in a good yield (79%). N^3-Benzylation of the pyrimidin-4-one part of the molecule was realized as described in the preceding studies, by treatment of the starting material with benzyl bromide in the presence of sodium hydride. Reduction of the resulting 3-benzyl-7-bromo-6-nitroquinazolin-4(3*H*)-one (**26**) was successfully performed by treatment with iron in the presence of acetic acid and ethanol. The key 6-amino-3-benzyl-7-bromoquinazolin-4(3*H*)-one (**27**) was obtained in four steps in average yield of 49%. It can be



Scheme 2. Reagents and conditions: (a) DMF/DMA, DMF, 105 °C (μW), 15 min, 93%; (b) benzylamine, AcOH, 118 °C (μW), 20 min, 99%; (c) HCO_2NH_4, Pd/C, EtOH, 85 °C (μW), 20 min, quant.; (d) Br_2, AcOH, rt, 2 h, quant.; (e) Appel salt, pyridine, DCM, rt, 3 h, 51%; (f) $AlCl_3$, toluene, 85 °C (μW), 30 min, 90%; (g) CuI, pyridine, 115 °C (μW), 15 min, 97%.

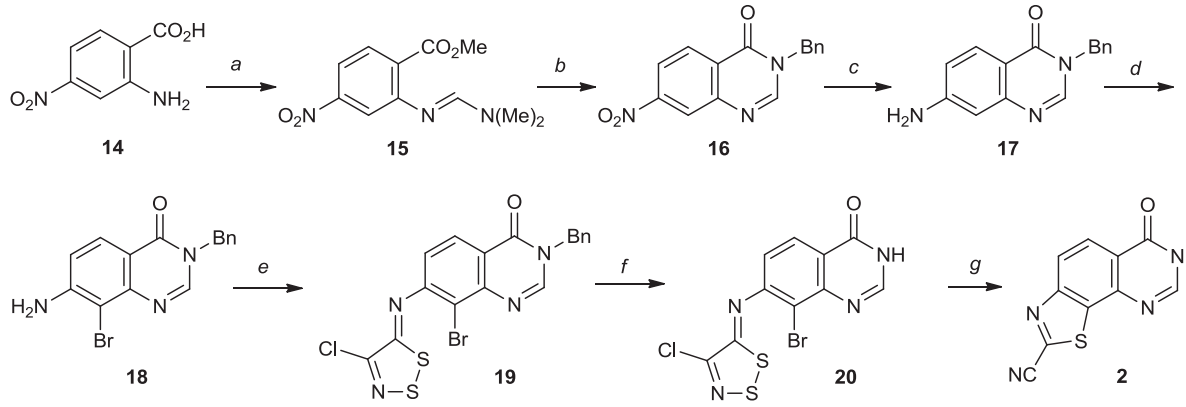
Starting from 4-nitroanthranilic acid (**14**), the same route was experimented for the synthesis of 6-oxo-6,7-dihydrothiazolo[4,5-*h*]quinazoline-2-carbonitrile (**2**) in a good overall yield (20%). Details of products obtained (**15**–**20**), experimental conditions, heating method, times, and yields are given in Scheme 3.

2.2. Synthesis of 8-oxo-7,8-dihydrothiazolo[4,5-*g*]quinazoline-2-carbonitrile (3) and 8-oxo-7,8-dihydrothiazolo[5,4-*g*] quinazoline-2-carbonitrile (4)

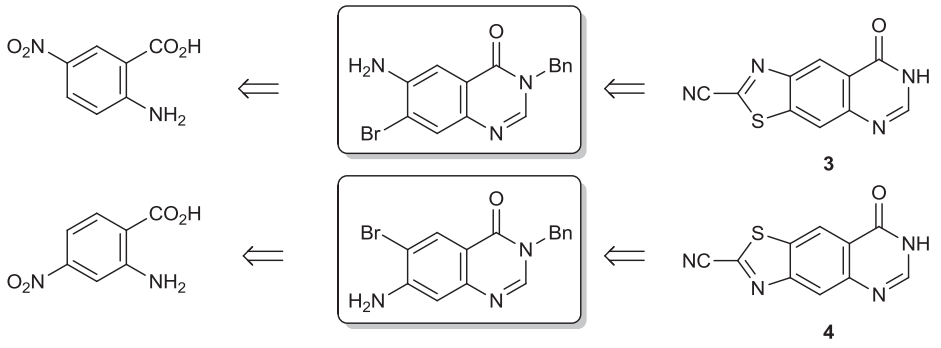
At this point of our work, we decided to investigate the possibility to obtain two novel linear tricyclic 8-oxo-7,8-dihydrothiazolo[4,5-*g*] quinazoline-2-carbonitrile (**3**) and 8-oxo-7,8-dihydrothiazolo[5,4-*g*] quinazoline-2-carbonitrile (**4**) by using a similar route. The retrosynthetic pathways depicted in Scheme 4 were inspired from the work described above. It suggested to prepare the target molecules

noticed that the first step of this synthesis can be performed from methyl 4-bromo-2-nitrobenzoate (**28**) as depicted in Scheme 5 via a one-pot reductive N-heterocyclization of various 2-nitrobenzoic acid or ester derivatives with formamide, in the presence of a molar equivalent amount of indium(III) chloride ($InCl_3$).[11,15]

In contrast with 6-amino-3-benzyl-7-bromoquinazolin-4(3*H*)-one (**27**), its 7-amino-3-benzyl-6-bromo isomer (**33**) was prepared from 4-nitroanthranilic acid (**14**) as suggested in the retrosynthetic Scheme 4. The simultaneous formations of the imino group and esterification of the acid function were easily realized by with DMFDMA. Regardless of the method used to selectively brominate the intermediate methyl 2-([(dimethylamino)methylene]amino)-4-nitrobenzoate (**15**), compound **31** was never isolated but rather led to various unidentified compounds. Instead, partial hydrolysis of **15** with aqueous hydrochloric acid (8%) gave the methyl 2-amino-4-nitrobenzoate (**29**) in quantitative yield. It can be

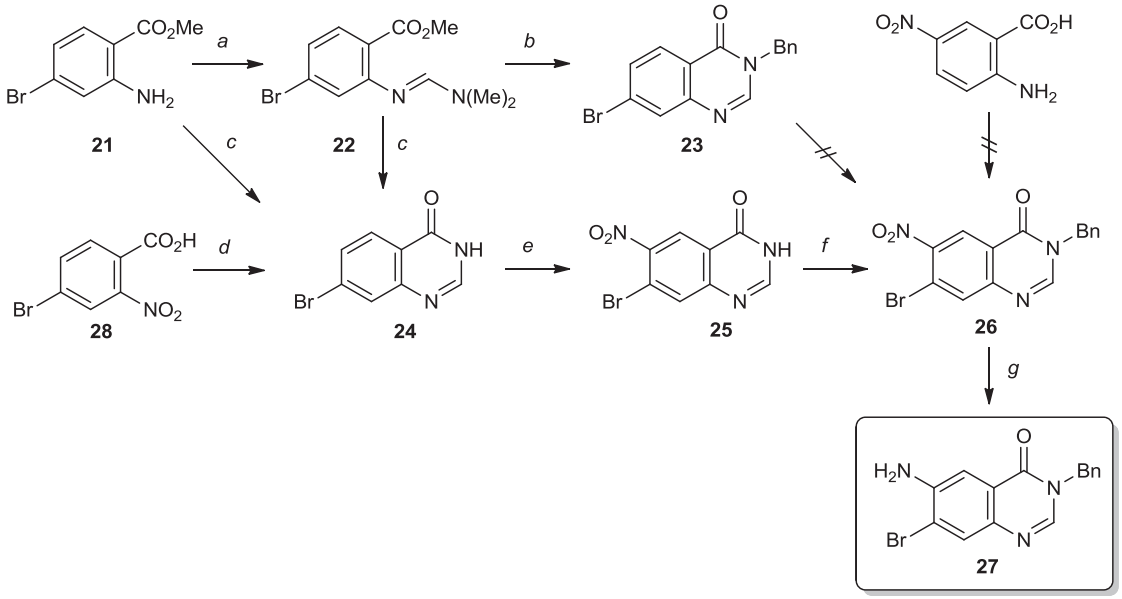


Scheme 3. Reagents and conditions: (a) DMFDMA, DMF, 105 °C (μW), 15 min, 92%; (b) $BnNH_2$, AcOH, 118 °C (μW), 20 min, 90%; (c) HCO_2NH_4, Pd/C, EtOH, 85 °C (μW), 20 min, 75%; (d) NBS, DMF, rt, 2 h, 84%; (e) Appel salt, pyridine, DCM, rt, 3 h, 70%; (f) $AlCl_3$, toluene, 85 °C (μW), 30 min, 73%; (g) CuI, pyridine, 115 °C (μW), 15 min, 75%.

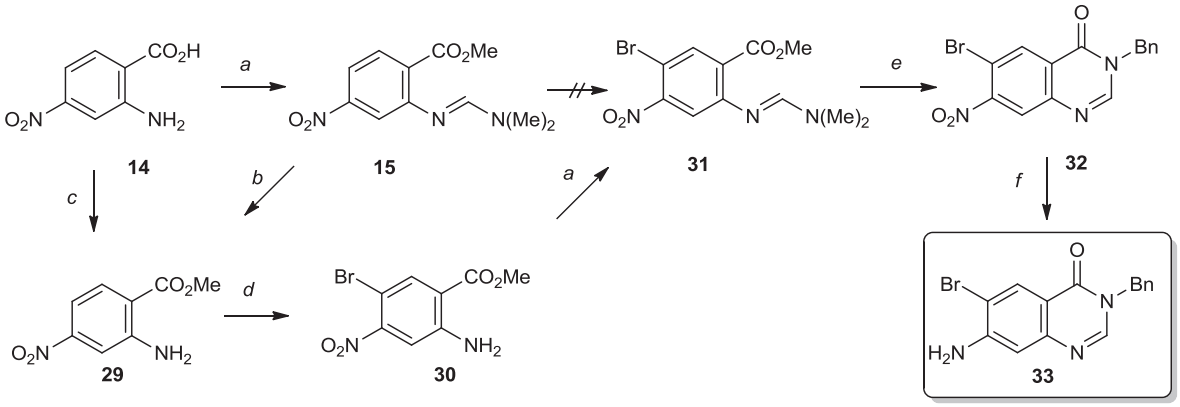


Scheme 4. Proposed retrosynthetic pathway for the synthesis of **3** and **4**.

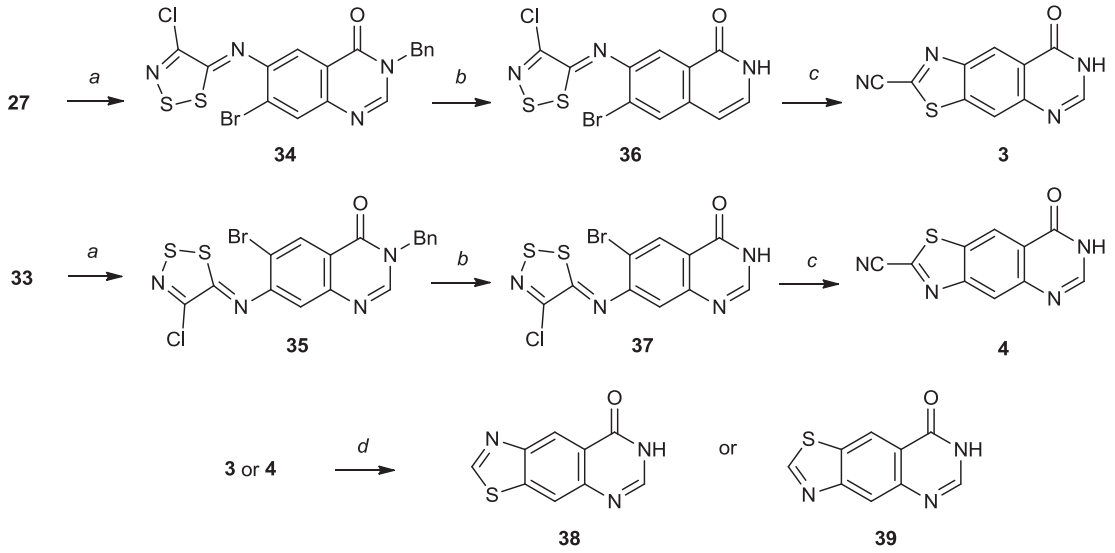
noticed that the two steps described for the synthesis of **29** can be realized from **14** in an efficient one pot procedure (93% yield). The following step consisted in a regioselective introduction of the bromide atom on the desired position of the methyl anthranilate **30**. The brominated derivative **30** was treated with DMFDMA and the intermediate formamidine **31** was cyclized into the 3-benzyl-6-bromo-7-nitroquinazolin-4(3*H*)-one (**32**). The fifth step involved reduction of the nitro group in order to furnish the expected 7-amino-3-benzyl-6-bromoquinazolin-4(3*H*)-one (**33**) in an overall yield of 70% (Scheme 6).



Scheme 5. Reagents and conditions: (a) DMFDMA, DMF, 105 °C (μW), 15 min, 96%; (b) benzylamine, AcOH, 118 °C (μW), 25 min, 99%; (c) formamide (40 equiv), 200 °C (μW), 40 min, quant.; (d) formamide, $InCl_3$, 150 °C (μW), 40 min, 81%; (e) HNO_3, H_2SO_4, 100 °C (μW), 1 h, 79%; (f) benzyl bromide, NaH, DMF, (μW) 30 min, 84%; (g) Fe, AcOH/EtOH, reflux, 1 h, 96%.



Scheme 6. Reagents and conditions: (a) DMFDMA, DMF, 105 °C (μW), 15 min, 92% (**15**), 96% (**31**); (b) HCl (8%), MeOH, 100 °C (μW), 15 min, quant.; (c) DMFDMA, DMF, 105 °C (μW), 15 min, then HCl (8%), 100 °C (μW), 15 min, 93%; (d) NBS, DMF, rt, 6 h, 92%; (e) benzylamine, AcOH, 118 °C (μW), 25 min, 92%; (f) Fe, AcOH/EtOH, reflux, 1 h, 92%.



Scheme 7. Reagents and conditions: (a) Appel salt, pyridine, DCM, rt, 2 h, 58% (**34**), 72% (**35**); (b) $AlCl_3$, toluene, 75 °C (μW), 30 min, 90% (**36**), 72% (**37**); (c) CuI, pyridine, 115 °C (μW), 15 min, 86% (**3**), 80% (**4**); (d) HBr (48%), 115 °C (μW), 30 min, 93% (**38**), 92% (**39**).

*2.2.2. 8-Oxo-7,8-dihydrothiazolo[4,5-g]quinazoline-2-carbonitrile (**3**) and 8-oxo-7,8-dihydrothiazolo[5,4-g]quinazoline-2-carbonitrile (**4**) (Scheme 7).* With the 6-(or 7-)amino-3-benzyl-7-(or 6-)bromoquinazolin-4(3*H*)-ones (**27** and **33**) in hands, the second part of the synthetic route was realized according to our previous results. The next step was the condensation of the starting amines with Appel salt in usual conditions of temperature (rt) and time (2 h). The two imino-1,2,3-dithiazoles **34** and **35** were treated with $AlCl_3$ in toluene for 30 min to afford to the N^3-free quinazolin-4-ones **36** and **37** in good yields (90% and 72%, respectively). Thermal cyclization in the presence of copper(I) iodide in pyridine as solvent gave the target 8-oxo-7,8-dihydrothiazolo[4,5-*g*]quinazoline-2-carbonitrile (**3**) and 8-oxo-7,8-dihydrothiazolo[5,4-*g*]quinazoline-2-carbonitrile (**4**) in good yields (86% and 80%, respectively). Hydrolysis and decarboxylation of the carbonitrile function led to the unsubstituted rings **38**[16a] and **39**[16b] (93% and 92%, respectively).

3. Conclusion

We performed the synthesis of various tricyclic heterocyclic skeletons, varying the position of the thiazole ring linked to the quinazolin-4-one moiety. The simultaneous presence of the reactive cyano group and the pyrimidin-4-one part on the same molecules (**1**–**4**) open the door to various substitutions and transformations for an access to libraries of potent biologically active heterocyclic compounds. The interest of the multi-step routes described in this paper is also to allow further modulations of the final compounds (**1**–**4**). The use of formamidine intermediates (e.g., **12**, **15**, **22**, and **31**) offered some advantages although it may be observed that each modification of the substituent in N^3 of the pyrimidine ring will generate three or four intermediates for which synthetic and biological interests are not really established yet. Despite this drawback, this work constitutes the only route to novel tricyclic systems with potential pharmaceutical interest.

4. Experimental section

4.1. General

All reactions were monitored by thin-layer chromatography with silica gel 60 F_{254} pre-coated aluminum plates (0.25 mm). Visualization was performed with a UV light.

Melting points of solid compounds were measured on a WME Köfler hot-stage with a precision of ±2 °C and are uncorrected. IR spectra were recorded on a Perkin–Elmer Spectrum 100 Series FT-IR spectrometer. Liquids and solids were applied on the Single Reflection Attenuated Total Reflectance (ATR) Accessories. Absorption bands are given in cm^{-1}.

^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on a Brucker DXP 300 spectrometer at 300, 75, and 282 MHz, respectively. Abbreviations used for peak multiplicities are s: singlet, d: doublet, t: triplet, q: quadruplet, and m: multiplet. Coupling constants *J* are in hertz and chemical shifts are given in parts per million and calibrated with DMSO-d_6 or D_2O (residual solvent signals). Mass spectra analysis was performed by the Mass Spectrometry Laboratory of the University of Rouen. Mass spectra (EI) were recorded with a Waters LCP 1er XR spectrometer.

Microwave experiments were conducted in a commercial microwave reactor especially designed for synthetic chemistry. RotoSYNTH™ (Milestone S.r.l. Italy) is a multi-mode cavity with a microwave power delivery system ranging from 0 to 1200 W. The temperatures of the reactions were mainly monitored via contactless infrared pyrometer, which was calibrated in control experiments with a fibre-optic contact thermometer protected in Teflon™ coated ceramic well inserted directly in the reaction mixture. Reaction time described correspond to the time measured when the mixture has reached the programmed temperature, after a ramp period of 3 min. Open vessel experiments were carried out in a 100–250 mL round bottom flask fitted with a reflux condenser. The vessel contents were stirred by means of an adjustable rotating magnetic plate located below the floor of the microwave cavity and a Teflon-coated magnetic stir bar inside the vessel. Temperature and power profiles were monitored in both cases through the EASY-Control software provided by the manufacturer.

Dichloromethane was distilled from CaH_2 under argon. NBS was recrystallized in water. Other reagents and solvents were used as provided by chemical companies.

Appel salt was prepared according to literature procedure,[8a] by addition of chloroacetonitrile (1 equiv) to a solution of sulfur dichloride (5 equiv) in dichloromethane (50 mL). Adogen™ (3–4 drops) was then added and the reaction was placed in a bowl of cold water.[17] The mixture was left for 18 h without stirring under $CaCl_2$ tube protection: the dark olive green solid was removed from the wall of the flask, filtered off under a blanket of argon, washed abundantly with dichloromethane, and dried under vacuum for 2–3 h (average yield: 85%): mp 172–174 °C (dec) [172 °C (dec)[16]]; IR (Nujol) cm^{-1} 1707, 1358s, 1280s, 1253, 1083, 917, 828s, and 605.

4.2. Synthesis of 9-oxo-8,9-dihydrothiazolo[5,4-*f*]quinazoline-2-carbonitrile (1)

*4.2.1. (E)-Methyl 2-((dimethylamino)methyleneamino)-5-nitrobenzoate (**12**).* A stirred mixture of **5** (20.0 g, 110 mmol) and DMFDMA (36.5 mL, 275 equiv) in DMF (110 mL) was heated at 105 °C for 15 min (350 W). After cooling until room temperature, the crude mixture was diluted with water and the aqueous layer was extracted with ethyl acetate. The organic layers were combined and washed with water and brine. After drying over $MgSO_4$, evaporation of solvent gave the expected product **12** (25.7 g, yield 93%) as a yellow powder: mp 82 °C; IR ν_{max} (cm^{-1}): 3098, 3076, 2949, 2905, 1706, 1623, 1568, 1497, 1321, 1106, 974, 837, 744, 699; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.31 (d, J=2.7 Hz, 1H, H_{Ar}), 8.18 (dd, J=9.0, 2.7 Hz, 1H, H_{Ar}), 7.94 (s, 1H, NCH), 7.18 (d, J=9.0 Hz, 1H, H_{Ar}), 3.79 (s, 3H, OCH_3), 3.10 (s, 3H, NCH_3), 2.97 (s, 3H, NCH_3); ^{13}C NMR (75 MHz, DMSO-d_6) δ 166.6, 157.4, 155.0, 140.0, 126.8, 125.5, 125.1, 120.7, 52.0, 34.1 (2C); HRMS calcd for $C_{11}H_{13}N_3O_4$ $[M+H]^+$ 252.0984 found 252.0974.

*4.2.2. 3-Benzyl-6-nitroquinazolin-4-one (**7**).* Benzylamine (3.26 mL, 1.5 equiv) was added dropwise to a solution of **12** (5.0 g, 19.9 mmol) in acetic acid (40 mL). After 20 min of heating at 118 °C (400 W), the reaction mixture was diluted with water and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with a saturated solution of $NaHCO_3$, water, and brine, successively. After drying over $MgSO_4$, evaporation of the solvent gave a crude residue, which was purified by column chromatography on silica gel using ethyl acetate/dichloromethane (5:5, v/v) as eluent to furnish **7** (5.54 g, yield 99%) as a white powder: mp 166 °C (lit.[5] 164 °C); spectra data for compounds **7** are consistent with assigned structure, as previously described in Ref. 5.

*4.2.3. 6-Amino-3-benzylquinazolin-4(3H)-one (**8**).* A stirred mixture of **7** (5.50 g, 19.6 mmol), ammonium formate (6.17 g, 97.9 mmol), and a catalytic amount of 10% palladium charcoal in ethanol (120 mL) was heated at 85 °C (300 W) for 20 min. The reaction mixture was filtered through Celite and washed with hot ethanol. The solvent was removed in vacuo to give the crude product, which was dissolved in ethyl acetate, washed with water, dried over $MgSO_4$, and concentrated under reduced pressure to provide the reduced compound **8** (4.92 g, quantitative yield) as a brown powder: mp 168 °C (lit.[5] 174 °C); spectra data for compound **8** are consistent with assigned structures, as previously described in Ref. 5.

*4.2.4. 6-Amino-3-benzyl-5-bromoquinazolin-4(3H)-one (**9**).* A solution of bromine (920 μL, 17.9 mmol) in dichloromethane (20 mL) was added dropwise, under an inert atmosphere, to a solution of **8** (5.0 g, 19.9 mmol) in acetic acid (200 mL). After stirring for 2 h at room temperature, the reaction mixture was diluted with water and the product was extracted with ethyl acetate. The combined organic layers were washed with a saturated solution of $NaHCO_3$, water, and brine, successively. Evaporation of solvent gave the expected product **9** (6.57 g, quantitative yield) as brown powder: mp 190 °C (lit.[5] 184 °C); spectra data for compound **9** are consistent with assigned structure, as previously described in Ref. 5.

*4.2.5. 3-Benzyl-5-bromo-6-(4-chloro-5H-1,2,3-dithiazol-5-ylideneamino)quinazolin-4(3H)-one (**10**).* A suspension of **9** (4.0 g, 12.1 mmol) and 4,5-dichloro-1,2,3-dithiazolium chloride (Appel salt) (3.78 g, 18.5 mmol) in dichloromethane (120 mL) was stirred at room temperature under an argon atmosphere. After 1 h of stirring at room temperature, pyridine (2 equiv) was added and the mixture was stirred again 2 h at room temperature. The resulting solution was concentrated under reduced pressure. The crude residue was purified by chromatography on silica gel with ethyl acetate/dichloromethane (5:95 then 10:90, v/v) to give the expected compound **10** (2.90 g, yield 51%) as a yellow powder: mp 210 °C (lit.[5] 198 °C); spectra data for compound **10** are consistent with assigned structure, as previously described in Ref. 5.

*4.2.6. 5-Bromo-6-(4-chloro-5H-1,2,3-dithiazol-5-ylideneamino)quinazolin-4(3H)-one (**13**).* A mixture of **10** (2.27 g, 4.87 mmol) and $AlCl_3$ (3.57 g, 26.8 mmol) in toluene (50 mL) was heated at 85 °C (300 W) for 30 min. The resulting mixture was neutralized to pH 7 with a saturated solution of $NaHCO_3$ and the product was extracted with ethyl acetate. The organic layers were washed with water, brine and dried over $MgSO_4$. Evaporation of the solvent provided a crude product, which was purified by column chromatography on silica gel with ethanol/dichloromethane (2:98 then 5:95, v/v) as eluent to furnish the expected compound **13** (1.65 g, yield 90%) as an orange powder: mp 258 °C; IR ν_{max} (cm^{-1}) 3457, 3063, 2909, 1666, 1621, 1590, 1568, 1492, 1442, 1377, 1377, 1294, 1239, 1171, 1109, 948, 863, 807; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.40 (br s, 1H, NH), 8.18 (s, 1H, H_{Ar}), 7.77 (d, 1H, J=8.7 Hz, H_{Ar}), 7.60 (d, 1H, J=8.7 Hz, H_{Ar}); ^{13}C NMR (75 MHz, DMSO-d_6) δ 163.2, 159.2, 150.3, 147.8, 145.9, 145.5, 128.9, 124.8, 121.6, 111.4; HRMS calcd for $C_{10}H_5{}^{79}Br^{35}ClN_4OS_2$ $[M+H]^+$ 374.8777 found 374.8761.

*4.2.7. 9-Oxo-8,9-dihydrothiazolo[5,4-f]quinazoline-2-carbonitrile (**1**).* A suspension of **13** (1.46 g, 3.9 mmol) and copper(I) iodide (CuI, 1.49 g, 7.8 mmol) in pyridine (40 mL) was irradiated under

microwaves at 115 °C (300 W) for 15 min. After cooling, the mixture was diluted in ethyl acetate, washed with sodium thiosulfate solution. The organic layer was dried over $MgSO_4$, and the solvent was removed in vacuo. The crude residue was purified by column chromatography on silica gel with ethyl acetate/dichloromethane (5:5, v/v) as eluent to furnish the thiazoloquinazolinone **1** (0.860 g, yield 97%) as an orange powder: mp >265 °C; IR ν_{max} (cm^{-1}) 3160, 3048, 2855, 2232 (CN), 1659, 1608, 1590, 1460, 1382, 1354, 1303, 1274, 1225, 1164, 1110, 1013, 973, 897, 859, 832; ^1H NMR (300 MHz, DMSO-d_6) δ 8.22 (d, J=9.0 Hz, 1H, H_{Ar}), 7.41 (s, 1H, H_{Ar}), 7.95 (d, J=9.0 Hz, 1H, H_{Ar}); ^{13}C NMR (75 MHz, DMSO-d_6) δ 159.3, 149.9, 149.1, 146.9, 138.8, 131.1, 129.7, 127.6, 116.0, 113.4 (CN); HRMS calcd for $C_{10}H_5N_4OS$ $[M+H]^+$ 229.0184 found 229.0170.

4.3. Synthesis of 6-oxo-6,7-dihydrothiazolo[4,5-*h*]quinazoline-2-carbonitrile (2)

*4.3.1. (E)-Methyl 2-[(dimethylamino)methyleneamino]-4-nitrobenzoate (**15**).* According to the procedure described for **12** in Section (4.2.1.), reaction of 4-nitroanthranilic acid **14** (10.0 g, 55 mmol) and DMFDMA (19 mL, 138 mmol) in DMF (60 mL), at 105 °C (350 W) for 15 min, gave compound **15** (12.70 g, yield 92%) as an orange solid: mp 75 °C; IR ν_{max} (cm^{-1}) 3103, 2955, 2911, 1706, 1634, 1513, 1343, 1282, 1101, 897, 826, 738; ^1H NMR (300 MHz, DMSO-d_6) δ 7.93 (s, 1H, NCH), 7.82 (d, J=2.4 Hz, 1H, H_{Ar}), 7.75 (dd, J=8.1, 2.4 Hz, 1H, H_{Ar}), 7.63 (d, J=8.1 Hz, 1H, H_{Ar}), 3.79 (s, 3H, OCH_3), 3.07 (s, 3H, NCH_3), 2.92 (s, 3H, NCH_3); ^{13}C NMR (75 MHz, DMSO-d_6) δ 167.6, 154.8, 151.8, 149.3, 132.4, 129.4, 115.1, 113.8, 52.0 (OCH_3), 34.1 (2C); HRMS calcd for $C_{11}H_{13}N_3O_4$ $[M+H]^+$ 252.0984 found 252.0974.

*4.3.2. 3-Benzyl-7-nitroquinazolin-4-one (**16**).* According to the procedure described for compound **7** in Section (4.2.2.), reaction of **15** (4.0 g, 15.9 mmol) and benzylamine (2.61 mL, 23.9 mmol) in acetic acid (30 mL), at 118 °C (400°W) for 20 min, gave product **16** (4.02 g, yield 90%) as a pale yellow powder: mp 160 °C (lit.[5] 160 °C); spectra data for **16** are consistent with assigned structure, as previously described in Ref. 5.

*4.3.3. 7-Amino-3-benzylquinazolin-4(3H)-one (**17**).* According to the procedure described for **8** in Section (4.2.3.), reaction of compound **16** (3 g, 10.7 mmol), ammonium formate (3.48 g, 53.5 mmol), and a catalytic amount of 10% palladium charcoal in ethanol (60 mL), at 85 °C (300 W) for 20 min, gave product **17** (2.02 g, yield 75%) as a pale brown powder: mp 172 °C (lit.[5] 175 °C); spectra data for **17** are consistent with assigned structure, as previously described in Ref. 5.

*4.3.4. 7-Amino-3-benzyl-8-bromoquinazolin-4(3H)-one (**18**).* *N*-Bromosuccinimide (NBS, 1.56 g, 8.8 mmol) was added portion-wise to a solution of **17** (2.20 g, 8.8 mmol) in DMF (80 mL). After 2 h of stirring at room temperature, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layers were combined and washed with water and brine. Evaporation of the solvent provided product **18** (2.40 g, yield 84%) as a white solid: mp 228 °C (lit.[5] 224 °C); spectra data for **18** are consistent with assigned structure, as previously described in Ref. 5.

*4.3.5. 3-Benzyl-8-bromo-7-(4-chloro-5H-1,2,3-dithiazol-5-ylideneamino)quinazolin-4(3H)-one (**19**).* According to the procedure described for **10** in Section (4.2.5.), reaction of compound **18** (1.50 g, 4.54 mmol) and 4,5-dichloro-1,2,3-dithiazolium chloride (Appel salt) (1.42 g, 6.81 mmol) in dichloromethane (45 mL), at room temperature for 3 h, gave product **19** (1.48 g, yield 70%) as an orange powder: mp 200 °C (lit.[5] 202 °C); spectra data for **19** are consistent with assigned structure, as previously described in Ref. 5.

*4.3.6. 8-Bromo-7-(4-chloro-5H-1,2,3-dithiazol-5-ylideneamino)quinazolin-4(3H)-one (**20**).* According to the procedure described for **13** in Section (4.2.6.), reaction of **19** (1.45 g, 3.11 mmol) and $AlCl_3$ (3.57 g, 26.8 mmol) in toluene (50 mL), at 85 °C (300 W) for 30 min, gave product **20** (0.853 g, yield 73%) as an orange powder: mp >265 °C; IR ν_{max} (cm^{-1}) 3072 (N–H), 2906, 1688, 1588, 1418, 1380, 1241, 1155, 989, 916, 871; ^1H NMR (300 MHz, DMSO-d_6) δ 12.53 (br s, 1H, NH), 8.25 (d, J=3.6 Hz, 1H, H_{Ar}), 8.19 (d, ^3J=8.4 Hz, 1H, H_{Ar}), 7.30 (d, ^3J=8.4 Hz, 1H, H_{Ar}); ^1H NMR (DMSO-d_6+D_2O, 300 MHz) δ 8.19 (d, J=8.4 Hz, 1H, H_{Ar}), 8.16 (s, 1H, $H_{Ar}2$), 7.27 (d, J=8.4 Hz, 1H, H_{Ar}); ^{13}C NMR (75 MHz, DMSO-d_6) δ 163.4, 160.2, 156.0, 147.8, 146.7, 145.8, 127.7, 120.3, 118.1, 111.8; HRMS calcd for $C_{10}H_5{}^{79}Br^{35}ClN_4OS_2$ $[M+H]^+$ 374.8777 found 374.8786.

*4.3.7. 6-Oxo-6,7-dihydro[1,3]thiazolo[4,5-h]quinazoline-2-carbonitrile (**2**).* According to the procedure described for compound **1** in Section (4.2.7.), reaction of **20** (0.50 g, 1.33 mmol) and copper(I) iodide (CuI, 0.507 g, 2.7 mmol) in pyridine (20 mL), at 115 °C (300 W) for 15 min, gave product **2** (0.224 g, yield 75%) as a beige powder: mp >265 °C; IR ν_{max} (cm^{-1}) 3176, 3062, 2868, 2238 (CN), 1679, 1618, 1442, 1346, 1238, 923, 798; ^1H NMR (300 MHz, DMSO-d_6) δ 12.83 (br s, 1H, NH), 8.40 (s, 1H, H_{Ar}), 8.32 (d, J=9.0 Hz, 1H, H_{Ar}), 8.29 (d, J=9.0 Hz, 1H, H_{Ar}); ^{13}C NMR (75 MHz, DMSO-d_6) δ 160.0, 155.0, 148.3, 144.8, 140.2, 133.2, 125.5, 122.3, 120.7, 113.0; HRMS calcd for $C_{10}H_3N_4OS$ $[M-H]^-$ 227.0028 found 227.0023.

4.4. Synthesis of 8-oxo-7,8-dihydrothiazolo[4,5-g]quinazoline-2-carbonitrile (3)

*4.4.1. (E)-Methyl 4-bromo-2-((dimethylamino)methyleneamino)-benzoate (**22**).* According to the procedure described for **12** in Section (4.2.1.), reaction of methyl 4-bromoanthranilate **21** (4.0 g, 17.4 mmol) and DMFDMA (3.8 mL, 43.5 mmol) in DMF (40 mL), at 105 °C (350 W) for 15 min, gave product **22** (4.76 g, yield 96%) as a dark purple oil: IR ν_{max} (cm^{-1}) 3098, 3076, 2944, 1721, 1629, 1574, 1379, 1231, 1086, 911, 871, 772; ^1H NMR (300 MHz, DMSO-d_6) δ 7.71 (s, 1H, NCH), 7.41 (d, J=8.1 Hz, 1H, H_{Ar}), 7.17 (d, J=2.0 Hz, 1H, H_{Ar}), 7.13 (dd, J=8.1, 2.0 Hz, 1H, H_{Ar}), 3.73 (s, 3H, OCH_3), 3.02 (s, 3H, NCH_3), 2.89 (s, 3H, NCH_3); ^{13}C NMR (75 MHz, DMSO-d_6) δ 167.6, 154.0, 152.9, 130.8, 125.0, 124.7, 123.5, 123.0, 51.6, 33.8 (2C); HRMS calcd for $C_{11}H_{14}{}^{79}BrN_2O_2$ $[M+H]^+$ 285.0239 found 285.0236, for $C_{11}H_{14}{}^{81}BrN_2O_2$ $[M+H]^+$ 287.0218 found 287.0220.

*4.4.2. 3-Benzyl-7-bromoquinazolin-4-one (**23**).* According to the procedure described for compound **7** in Section (4.2.2.), reaction of **22** (3.80 g, 13.3 mmol) and benzylamine (2.18 mL, 20 mmol) in acetic acid (60 mL), at 118 °C (400 W) for 25 min, gave product **23** (4.15 g, yield 99%) as a white solid: mp 122 °C; IR ν_{max} (cm^{-1}) 3030, 2948, 1666, 1594, 1362, 1312, 1274, 811, 777, 694; ^1H NMR (300 MHz, DMSO-d_6) δ 8.62 (s, 1H, H_{Ar}), 8.03 (d, J=8.4 Hz, 1H, H_{Ar}), 7.85 (d, J=2.4 Hz, 1H, H_{Ar}), 7.64 (dd, J=8.4, 2.4 Hz, 1H, H_{Ar}), 7.39–7.25 (m, 5H, Ph), 5.19 (s, 2H, CH_2Ph); ^{13}C NMR (75 MHz, DMSO-d_6) δ 159.6, 149.3, 149.0, 136.5, 130.1, 129.5, 128.6 (2C), 128.1, 127.9, 127.7 (2C), 120.7, 49.0; HRMS calcd for $C_{15}H_{12}{}^{79}BrN_2O_2$ $[M+H]^+$ 315.0133 found 315.0133, for $C_{15}H_{12}{}^{81}BrN_2O_2$ $[M+H]^+$ 317.0113 found 315.0107.

*4.4.3. 7-Bromoquinozolin-4-one (**24**).* A mixture of 4-bromoanthranilate (**21**, 1.25 g, 5.4 mmol) and formamide (8.60 mL, 40 equiv) was heated at 200 °C (350 W) for 35 min. After cooling, the reaction mixture was diluted with water and the product was extracted with ethyl acetate. The combined organic layers were washed with water and brine. After drying over $MgSO_4$, evaporation of the solvent gave

product **24** (1.21 g, quantitative yield) as a white powder: mp 260–258 °C (lit.[9] 259–258 °C); IR ν_{max} (cm^{-1}) 3466 (N–H), 3050, 1668 (C=O), 1609, 1239, 858; ^1H NMR (300 MHz, DMSO-d_6) δ 12.41 (br s, 1H, NH), 8.14 (s, 1H, H_{Ar}), 8.03 (d, J=8.7 Hz, 1H, H_{Ar}), 7.89 (d, J=1.8 Hz, 1H, H_{Ar}), 7.69 (dd, J=8.7, 1.8 Hz, 1H, H_{Ar}); ^{13}C NMR (75 MHz, DMSO-d_6) δ 160.3, 149.8, 156.8, 129.8, 129.3, 128.0 (2C), 121.6; HRMS calcd for $C_8H_6{}^{79}BrN_2O$ $[M+H]^+$ 224.9663 found 224.9665, for $C_8H_6{}^{81}BrN_2O$ 226.9643 found 226.9651.

*4.4.4. 7-Bromo-6-nitroquinozolin-4-one (**25**).* HNO_3 (550 μL, 2 equiv) was added dropwise to a solution of **24** (1.47 g, 6.53 mmol) in H_2SO_4 (23 mL) maintained at 0 °C. The reaction was heated at 100 °C (400 W) for 1 h. After cooling, the resulting mixture was quenched in ice water and pH was adjusted to 7 with NaOH (20%). The product was extracted with ethyl acetate. The organic layers were washed with water and brine, and then dried over $MgSO_4$. Evaporation of the solvent provided a crude residue, which was purified by column chromatography on silica gel with ethanol/dichloromethane (1:99, v/v) as eluent to furnish the expected compound **25** (1.34 g, yield 79%) as a white powder: mp >265 °C; IR ν_{max} (cm^{-1}) 3504 (N–H), 3082, 1695 (C=O), 1656, 1605, 1518, 1332, 1249, 810; ^1H NMR (300 MHz, DMSO-d_6) δ 12.82 (br s, 1H, NH), 8.65 (s, 1H, H_{Ar}), 8.32 (s, 1H, H_{Ar}), 8.20 (s, 1H, H_{Ar}); ^{13}C NMR (75 MHz, DMSO-d_6) δ 159.5, 151.3, 149.5, 146.6, 133.2, 123.8, 122.1, 118.9; HRMS calcd for $C_8H_3{}^{79}BrN_3O_3$ $[M-H]^-$ 267.9358 found 267.9355, for $C_8H_3{}^{81}BrN_3O_3$ $[M-H]^-$ 269.9337 found 269.9327.

*4.4.5. 3-Benzyl-7-bromo-6-nitroquinazolin-4-one (**26**).* NaH (60% dispersion) (0.40 g, 10.18 mmol) was added portion-wise to a stirred solution of **25** (2.50 g, 9.25 mmol) in DMF (25 mL). Then, benzyl bromide (1.2 mL, 10.18 mmol) was added dropwise. The solution was heated at 80 °C (400 W) for 10 min. After cooling, the reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with water and brine. The solvent was evaporated and the product purified by column chromatography on silica gel with ethyl acetate/dichloromethane (5:5, v/v) as eluent to provide **26** (2.80 g, 84%) as a white powder: mp 170–168 °C; IR ν_{max} (cm^{-1}) 3082, 1679, 1602, 1532, 1350, 1216, 813; ^1H NMR (300 MHz, DMSO-d_6) δ 8.80 (s, 1H, H_{Ar}), 8.67 (s, 1H, H_{Ar}), 8.22 (s, 1H, H_{Ar}), 7.41–7.30 (m, 5H, Ph), 5.22 (s, 2H, CH_2Ph); ^{13}C NMR (75 MHz, DMSO-d_6) δ 159.0, 151.9, 150.5, 147.2, 136.1, 133.3, 128.6 (2C), 127.8, 127.7 (2C), 124.1, 121.2, 119.0, 49.4; HRMS calcd for $C_{15}H_{11}{}^{79}BrN_3O_3$ $[M+H]^+$ 359.9984 found 359.9983.

*4.4.6. 6-Amino-3-benzyl-7-bromoquinazolin-4(3H)-one (**27**).* A stirred mixture of **26** (1.0 g, 2.8 mmol) and iron powder (0.775 g, 13.9 mmol) in ethanol (7.5 mL) and acetic acid (7.5 mL) was refluxed for 30 min. The reaction mixture was diluted with water, neutralized with a saturated solution of $NaHCO_3$ and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with a saturated solution of $NaHCO_3$ followed with water and brine. Evaporation of solvent gave the crude residue, which was purified by column chromatography on silica gel with ethyl acetate/dichloromethane (0%–100%) as eluent to furnish **27** (0.892 g, yield 96%) as a white powder: mp 168–166 °C; IR ν_{max} (cm^{-1}) 3453 (NH_2), 3332, 3020, 1669, 1621, 1595, 1483, 1213, 836; ^1H NMR (300 MHz, DMSO-d_6) δ 8.28 (s, 1H, H_{Ar}), 7.78 (s, 1H, H_{Ar}), 7.47 (s, 1H, H_{Ar}), 7.33–7.30 (m, 5H, Ph), 5.89 (br s, 2H, NH_2), 5.15 (s, 2H, CH_2Ph); ^{13}C NMR (75 MHz, DMSO-d_6) δ 156.7, 145.4, 144.4, 139.0, 137.0, 130.6, 128.6 (2C), 127.6, 127.5 (2C), 122.3, 116.0, 108.1, 48.6; HRMS calcd for $C_{15}H_{13}{}^{79}BrN_3O$ $[M+H]^+$ 330.0242 found 330.0239, for $C_{15}H_{13}{}^{81}BrN_3O$ $[M+H]^+$ 332.0222 found 332.0222.

*4.4.7. 3-Benzyl-7-bromo-6-(4-chloro-5H-1,2,3-dithiazol-5-ylideneamino)quinazolin-4(3H)-one (**34**).* According to the procedure described for **10** in Section (4.2.5.), reaction of compound **27** (1.20 g, 3.63 mmol) and 4,5-dichloro-1,2,3-dithiazolium chloride (Appel salt) (1.14 g, 5.45 mmol) in dichloromethane (35 mL), at room temperature for 2 h, gave product **34** (0.980 g, yield 58%) as an orange powder: mp 214–216 °C; IR ν_{max} (cm^{-1}) 1677 (C=O), 1586, 1451, 1366, 868; ^1H NMR (300 MHz, DMSO-d_6) δ 8.62 (s, 1H, H_{Ar}), 8.16 (s, 1H, H_{Ar}), 8.00 (s, 1H, H_{Ar}), 7.41–7.29 (m, 5H, Ph), 5.21 (s, 2H, CH_2Ph); ^{13}C NMR (75 MHz, DMSO-d_6) δ 162.6, 159.5, 148.7, 148.2, 146.5, 146.2, 136.5, 132.1, 128.7 (2C), 127.2 (2C), 123.5, 122.2, 114.3, 49.1; HRMS calcd for $C_{17}H_{10}{}^{79}Br^{35}ClN_4OS_2$ $[M+H]^+$ 464.9246 found 464.9254.

*4.4.8. 7-Bromo-6-(4-chloro-5H-1,2,3-dithiazol-5-ylideneamino)quinazolin-4(3H)-one (**36**).* According to the procedure described for **13** in Section (4.2.6.), reaction of **34** (1.50 g, 3.22 mmol) and $AlCl_3$ (2.36 g, 17.7 mmol) in toluene (30 mL), at 85 °C (300 W) for 30 min, gave product **36** (1.35 g, yield 90%) as an orange powder: mp >265 °C; IR ν_{max} (cm^{-1}) 3451 (N–H), 3030, 1671 (C=O), 1596, 1447, 1273, 861.4; ^1H NMR (300 MHz, DMSO-d_6) δ 12.51 (br s, 1H, NH), 8.14 (s, 1H, H_{Ar}), 8.12 (s, 1H, H_{Ar}), 7.98 (s, 1H, H_{Ar}); ^{13}C NMR (75 MHz, DMSO-d_6) δ 162.4, 160.1, 147.7, 147.1, 146.6, 146.2, 132.0, 123.5, 123.1, 114.0; HRMS calcd for $C_{10}H_5{}^{79}Br^{35}ClN_4OS_2$ $[M+H]^+$ 374.8777 found 374.8786.

*4.4.9. 8-Oxo-7,8-dihydrothiazolo[4,5-g]quinazoline-2-carbonitrile (**3**).* According to the procedure described for compound **1** in Section (4.2.7.), reaction of **36** (1.20 g, 3.30 mmol) and copper(I) iodide (CuI, 1.26 g, 6.6 mmol) in pyridine (40 mL), at 115 °C (300 W) for 15 min, gave product **3** (0.670 g, yield 86%) as a beige powder: mp >265 °C; IR ν_{max} (cm^{-1}) 3468, 3054, 2227 (ν CN), 1676 (ν C=O), 1619, 1468, 1278; ^1H NMR (300 MHz, DMSO-d_6) δ 12.48 (br s, 1H, NH), 8.91 (s, 1H, H_{Ar}), 8.69 (s, 1H, H_{Ar}), 8.22 (s, 1H, H_{Ar}); ^{13}C NMR (75 MHz, DMSO-d_6) δ 160.7 (C=O), 149.4, 147.0, 146.3, 140.9, 139.4, 122.8, 122.0, 121.4, 113.1 (CN); HRMS calcd for $C_{10}H_3N_4OS$ $[M-H]^-$ 227.0028 found 227.0039.

*4.4.10. Thiazolo[4,5-g]quinazolin-8(7H)-one (**38**).* A mixture of **3** (0.250 g, 1.10 mmol) and HBr (48% in water, 5 mL) was heated at 115 °C (450 W) for 30 min. After cooling, the reaction mixture was diluted with water, neutralized with a saturated solution of $NaHCO_3$ and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with a saturated solution of $NaHCO_3$ followed with water and brine. Evaporation of solvent gave the expected product **38** (0.255 g, yield 93%) as a beige powder: mp >265 °C; IR ν_{max} (cm^{-1}) 3455, 3038, 1670, 1615, 1445, 1278, 845; ^1H NMR (300 MHz, DMSO-d_6) δ 12.34 (br s, 1H, NH), 9.55 (s, 1H, H_{Ar}), 8.74 (s, 1H, H_{Ar}), 8.54 (s, 1H, H_{Ar}), 8.14 (s, 1H, H_{Ar}); ^{13}C NMR (75 MHz, DMSO-d_6) δ 161.1, 158.8, 151.4, 145.2, 145.0, 130.5, 121.3, 120.8, 119.6, 108.0; HRMS calcd for $C_9H_6N_3OS$ $[M+H]^+$ 204.0232 found 204.0220.

4.5. Synthesis of 8-oxo-7,8-dihydrothiazolo[5,4-g]quinazoline-2-carbonitrile (4)

*4.5.1. Methyl 2-amino-4-nitrobenzoate (**29**).* A stirred mixture of 4-nitroanthranilic acid **14** (10.0 g, 54.9 mmol) and DMFDMA (19.1 mL, 143 mmol) in DMF (55 mL) was heated at 105 °C (350 W) for 15 min. The resulting mixture was acidified to pH 2 with HCl (8% in water) (80 mL) and heated at 100 °C (450 W) for 10 min. After cooling at room temperature, the crude mixture was neutralized with a saturated solution of $NaHCO_3$ and extracted with ethyl acetate. The organic layers were combined and washed with water and brine. After drying over $MgSO_4$, evaporation of solvent gave **29** (10.0 g, yield 93%) as an yellow powder: mp 158 °C; IR ν_{max} (cm^{-1}) 3493, 3377, 2957, 1699, 1583, 1344, 1245, 1082, 866, 819, 726; ^1H NMR (300 MHz, DMSO-d_6) δ 7.91 (dd, J=8.7, 1.2 Hz, 1H, H_{Ar}), 7.67 (dd, J=2.4, 1.2 Hz, 1H, H_{Ar}), 7.25 (ddd, J=8.7, 2.4, 1.2 Hz, 1H, H_{Ar}), 7.14

(br s, 2H, NH_2), 3.84 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6) δ 166.6, 151.5, 150.8, 132.6, 113.1, 110.8, 108.1, 52.0; HRMS calcd for $C_8H_8N_2O_4$ $[M+H]^+$ 197.0562 found 197.0561.

*4.5.2. Methyl 2-amino-5-bromo-4-nitrobenzoate (**30**).* NBS (3.81 g, 21.4 mmol) was added portion-wise to a solution of **29** (4.0 g, 20.4 mmol) in DMF (200 mL). After stirring for 6 h at room temperature, the reaction mixture was diluted with water and the product was extracted with ethyl acetate. The combined organic layers were washed with water and brine, and then dried over $MgSO_4$. Evaporation of the solvent provided a crude product, which was purified by column on silica, with dichloromethane/petroleum ether (gradient from 0:10 to 6:4, v/v) as solvent to give **30** (5.10 g, yield 92%) as an orange powder: mp 142 °C; IR ν_{max} (cm^{-1}) 3491, 3387, 2960, 1702, 1629, 1571, 1521, 1436, 1251, 1097, 835, 793; ^1H NMR (300 MHz, DMSO-d_6) δ 8.01 (s, 1H, H_{Ar}), 7.38 (s, 1H, H_{Ar}), 7.21 (br s, 2H, NH_2), 3.84 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6) δ 165.5, 152.5, 150.6, 136.2, 112.8, 112.5, 94.0, 52.2; HRMS calcd for $C_8H_7{}^{79}BrN_2O_4$ $[M-H]^-$ 272.9511 found 272.9500, for $C_8H_7{}^{81}BrN_2O_4$ $[M-H]^-$ 274.9490 found 274.9489.

*4.5.3. (E)-Methyl 5-bromo-2-((dimethylamino)methyleneamino)-4-nitrobenzoate (**31**).* According to the procedure described for **12** in Section (4.2.1.), reaction of **30** (1.50 g, 5.45 mmol) and DMFDMA (1.8 mL, 13.6 mmol) in DMF (12 mL), at 105 °C (350 W) for 15 min, gave product **31** (1.73 g, yield 96%) as an orange oil: IR ν_{max} (cm^{-1}) 3262, 3111, 1697, 1584, 1542, 1497, 1249, 1222, 1139, 1098, 913, 823, 781; ^1H NMR (300 MHz, DMSO-d_6) δ 7.91 (s, 1H, NCH), 7.85 (s, 1H, H_{Ar}), 7.68 (s, 1H, H_{Ar}), 3.78 (s, 3H, OCH_3), 3.05 (s, 3H, NCH_3), 2.91 (s, 3H, NCH_3); ^{13}C NMR (75 MHz, DMSO-d_6) δ 166.1, 155.1, 151.3, 151.2, 133.6, 130.8, 115.8, 102.0, 52.1, 33.9 (2C); HRMS calcd for $C_{11}H_{13}{}^{79}BrN_3O_4$ $[M+H]^+$ 330.0089 found 330.0075, for $C_{11}H_{13}{}^{81}BrN_3O_4$ $[M+H]^+$ 332.0069 found 332.0050.

*4.5.4. 3-Benzyl-6-bromo-7-nitroquinazolin-4-one (**32**).* According to the procedure described for compound **7** in Section (4.2.2.), reaction of **31** (1.25 g, 3.79 mmol) and benzylamine (6.20 mL, 5.69 mmol) in acetic acid (8 mL), at 118 °C (400 W) for 25 min, gave product **32** (1.26 g, yield 92%) as a white powder: mp 176–178 °C; IR ν_{max} (cm^{-1}) 3079, 3030, 3002, 1674, 1605, 1531, 1353, 1319, 1228, 949, 799; ^1H NMR (300 MHz, DMSO-d_6) δ 8.77 (s, 1H, H_{Ar}), 8.49 (s, 1H, H_{Ar}), 8.39 (s, 1H, H_{Ar}), 7.38–7.31 (m, 5H, Ph), 5.22 (s, 2H, CH_2Ph); ^{13}C NMR (75 MHz, DMSO-d_6) δ 158.3, 153.3, 150.6, 147.6, 136.1, 132.1, 128.6 (2C), 127.8, 127.7 (2C), 124.9, 123.8, 109.5, 49.4; HRMS calcd for $C_{15}H_{11}{}^{79}BrN_3O_3$ $[M+H]^+$ 359.9984 found 359.9997, for $C_{15}H_{11}{}^{81}BrN_3O_3$ $[M+H]^+$ 361.9963 found 361.9980.

*4.5.5. 7-Amino-3-benzyl-6-bromoquinazolin-4(3H)-one (**33**).* According to the procedure described for compound **27** in Section (4.4.6.), a stirred mixture of **32** (1.15 g, 3.20 mmol) and iron powder (0.894 g, 16.0 mmol) in ethanol (8.5 mL) and acetic acid (8.5 mL) was refluxed for 30 min. Product **33** (0.972 g, yield 92%) was obtained as a white powder: mp 210 °C; IR ν_{max} (cm^{-1}) 3460, 3321, 1657, 1601, 1581, 1480, 1272, 1234, 954, 864, 694; ^1H NMR (300 MHz, DMSO-d_6) δ 8.39 (s, 1H, H_{Ar}), 8.05 (s, 1H, H_{Ar}), 7.33–7.30 (m, 5H, Ph), 6.89 (s, 1H, H_{Ar}), 6.32 (br s, 2H, NH_2), 5.11 (s, 2H, CH_2Ph); ^{13}C NMR (75 MHz, DMSO-d_6) δ 158.7, 151.1, 148.8, 148.3, 137.1, 129.9, 128.6 (2C), 127.5 (2C), 111.7, 108.6, 108.1, 48.4; HRMS calcd for $C_{15}H_{13}{}^{79}BrN_3O$ $[M+H]^+$ 330.0242 found 330.0241, for $C_{15}H_{13}{}^{81}BrN_3O$ $[M+H]^+$ 332.0222 found 332.0225.

*4.5.6. 3-Benzyl-6-bromo-7-(4-chloro-5H-1,2,3-dithiazol-5-ylideneamino)quinazolin-4(3H)-one (**35**).* According to the procedure described for **10** in Section (4.2.5.), reaction of compound **33** (1.0 g, 3.03 mmol) and 4,5-dichloro-1,2,3-dithiazolium chloride (Appel salt) (0.948 g, 4.55 mmol) in dichloromethane (30 mL), at room temperature for 2 h, gave product **35** (1.02 g, yield 72%) as an orange powder: mp 176 °C; IR ν_{max} (cm^{-1}) 3027, 1650, 1576, 1442, 1396, 1354, 1249, 1157, 945, 896; ^1H NMR (300 MHz, DMSO-d_6) δ 8.64 (s, 1H, H_{Ar}), 8.42 (s, 1H, H_{Ar}), 7.51 (s, 1H, H_{Ar}), 7.40–7.30 (m, 5H, Ph), 5.20 (s, 2H, CH_2Ph); ^{13}C NMR (75 MHz, DMSO-d_6) δ 163.4, 158.6, 155.1, 149.2, 149.0, 146.1, 136.6, 131.0, 128.6 (2C), 127.7 (2C), 120.0, 115.8, 113.8, 49.0; HRMS calcd for $C_{17}H_{10}{}^{79}Br^{35}ClN_4OS_2$ $[M+H]^+$ 464.9246 found 464.9237.

*4.5.7. 6-Bromo-7-(4-chloro-5H-1,2,3-dithiazol-5-ylideneamino)quinazolin-4(3H)-one (**37**).* According to the procedure described for **13** in Section (4.2.6.), reaction of **35** (0.90 g, 1.93 mmol) and $AlCl_3$ (0.42 g, 10.6 mmol) in toluene (20 mL), at 85 °C (300 W) for 30 min, gave product **37** (0.660 g, yield 72%) as a yellow powder: mp 262 °C; IR ν_{max} (cm^{-1}) 3162, 2997, 1682, 1571, 1442, 1310, 1138, 909, 806, 758; ^1H NMR (300 MHz, DMSO-d_6) δ 12.43 (br s, 1H, NH), 8.38 (s, 1H, H_{Ar}), 8.15 (d, J=3.6 Hz, 1H, H_{Ar}), 7.48 (s, 1H, H_{Ar}); ^{13}C NMR (75 MHz, DMSO-d_6) δ 163.4, 159.2, 155.0, 149.7, 146.6, 146.1, 130.7, 121.0, 115.8, 113.2; HRMS calcd for $C_{10}H_5{}^{79}Br^{35}ClN_4OS_2$ $[M+H]^+$ 374.8777 found 374.8761.

*4.5.8. 8-Oxo-7,8-dihydro[1,3]thiazolo[5,4-g]quinazoline-2-carbonitrile (**4**).* According to the procedure described for compound **1** in Section (4.2.7.), reaction of **37** (0.60 g, 1.6 mmol) and copper(I) iodide (CuI, 0.609 g, 3.2 mmol) in pyridine (20 mL), at 115 °C (300 W) for 15 min, gave product **4** (0.292 g, yield 80%) as a beige powder: mp >265 °C; IR ν_{max} (cm^{-1}) 3147, 3049, 2922, 2245 (CN), 1671, 1608, 1439, 1400, 1319, 1263, 910, 896, 794; ^1H NMR (300 MHz, DMSO-d_6) δ 12.44 (br s, 1H, NH), 9.20 (s, 1H, H_{Ar}), 8.51 (s, 1H, H_{Ar}), 8.19 (s, 1H, H_{Ar}); ^{13}C NMR (75 MHz, DMSO-d_6) δ 160.3, 155.0, 147.2, 145.8, 142.4, 133.4, 122.8, 122.4, 121.9, 113.1; HRMS calcd for $C_{10}H_5N_4OS$ $[M+H]^+$ 229.0184 found 229.0184.

*4.5.9. Thiazolo[5,4-g]quinazolin-8(7H)-one (**39**).* According to the procedure described for **38** in Section (4.4.10.), heating of **4** (0.20 g, 0.87 mmol) and HBr (48% in water, 5 mL), at 115 °C (450 W) for 30 min, gave product **39** (0.162 g, yield 92%) as a white powder: mp >265 °C; IR ν_{max} (cm^{-1}) 3185, 3057, 2915, 2851, 1674, 1603, 1440, 1330, 1267, 919, 848, 791; ^1H NMR (300 MHz, DMSO-d_6) δ 12.30 (br s, 1H, NH), 9.68 (s, 1H, H_{Ar}), 9.01 (s, 1H, H_{Ar}), 8.32 (s, 1H, H_{Ar}), 8.14 (s, 1H, H_{Ar}); ^{13}C NMR (75 MHz, DMSO-d_6) δ 161.9, 160.6, 157.0, 146.4, 145.0, 132.5, 121.1, 120.5, 120.1; HRMS calcd for $C_9H_6N_3OS$ $[M+H]^+$ 204.0232 found 204.0231.

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