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Regioselective Synthesis and Biological Evaluation of *N*-Substituted 2-Aminoquinazolin-4-ones

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The reaction of methyl anthranilates with *N*-arylcyanamides in the presence of *p*-TsOH in *t*-BuOH under reflux afforded predominantly 3-arylquinazolin-4-ones. In contrast, the reaction of same reactants with TMSCl in *t*-BuOH at 60 °C followed by Dimroth rearrangement in aqueous ethanolic sodium hydroxide gave exclusive the regioisomers, 2-(*N*-arylamino)quinazolin-4-ones. The regioselective synthesis of *N*-aryl-substituted 2-aminoquinazolin-4-ones can be further applied to the synthesis of benzimidazo[2,1-*b*]quinazolin-12-ones.

Introduction

Quinazoline is a benzene-fused pyrimidine derivative frequently appeared in a wide variety of natural products and artificial substances.[1, 2] Owing to its structural resemblance to pteridine, purine and pyrimidine, quinazoline has often been employed as bioisosteric replacement for these biologically essential heterocycles in molecular design and become an attractive target for synthetic chemists.[3-5] Amino-substituted quinazolinone derivatives are among the most common quinazoline derivatives. Their structures feature similar hydrogen-bond donor/acceptor properties as folic acid, guanine and cytosine, and could well mimic the interaction of these biomolecules with their molecular targets (**Figure 1**).[6, 7] As a result, amino-substituted quinazolinones are privileged scaffolds commonly integrated into the design of biologically interested compounds.[8-10] Our studies on aminoquinazolinones emerged out of long-standing interests in the synthesis and biological activities of pyrimidine derivatives. Since we have previously reported the synthesis and biological evaluation of some 4-aminoquinazolin-2-one derivatives,[11] we devoted our continuous efforts to the studies of *N*-substituted 2-aminoquinazolin-4-ones.

A perusal of literature reveals that several 2-aminoquinazolin-4-one derivatives have been shown to display a range of diverse biological activities (**Figure 2**).[10, 12-14] Although the synthesis and biological evaluation of 2-aminoquinazolin-4-ones with substituents on the 2-amino group have been extensively studied,[15-18] we found that the regio-structural isomers, 3-substituted 2-aminoquinazolin-4-ones, have much less been explored, mainly due to the lack of a general synthetic method.[19, 20] Naturally occurring quinazoline alkaloids are primarily biogenetically derived from anthranilates originated from the shikimate pathway.[21, 22] Albeit a number of synthetic strategies started from benzoic acid or aniline derivatives have been developed, chemical preparation of aminoquinazoline derivatives also often utilize anthranilic acid derivatives as synthetic precursors.[2, 23-25] Therefore, the reaction of anthranilic acid derivatives with monosubstituted urea, thiourea, cyanamide and their equivalent reagents becomes the most straightforward approach toward *N*-substituted 2-aminoquinazolin-4-one derivatives.

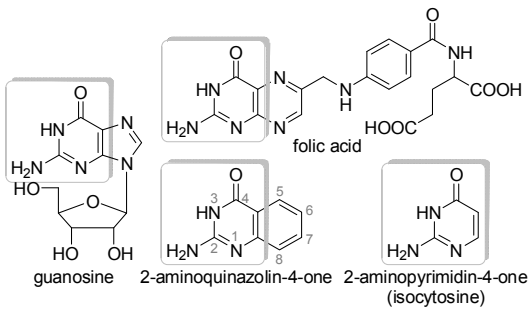

Figure 1. Structures of 2-aminoquinazolin-4-one, guanosine, folic acid, and isocytosine

In the course of our studies on the synthetic application of *N*-substituted cyanamides,[26] the formation of 2-aminoquinazolin-4-ones from the reaction of anthranilate derivatives and cyanamides attracted our attention. Our retrosynthetic analysis of 3-subtituted and N^2-substituted 2-aminoquinazolin-4-ones both led to anthranilates and *N*-substituted cyanamides as common precursors. Thus, we

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Electronic Supplementary Information (ESI) available: [copies of ^{1}H and ^{13}C NMR spectra and X-ray structural data (cif)]. See DOI: 10.1039/x0xx00000x

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speculated that the reaction of anthranilates and *N*-substituted cyanamides would result in a regioisomeric mixture containing both 3-subtituted and N^2-substituted 2-aminoquinazolin-4-ones (**Scheme 1**). However, literature survey revealed that the reaction of anthranilates with *N*-substituted cyanamides mostly afforded only 2-(*N*-substituted-amino)quinazolin-4-ones and the 3-substituted congener was nearly absent from the reactions.[27, 28] In an effort to explore the chemical synthesis and biological profiles of 2-aminoquinazolin-4-one derivatives, we embarked on the investigation to alter the regioselectivity of the above-mentioned reaction for the synthesis of 3-substituted 2-aminoquinazolin-4-ones.

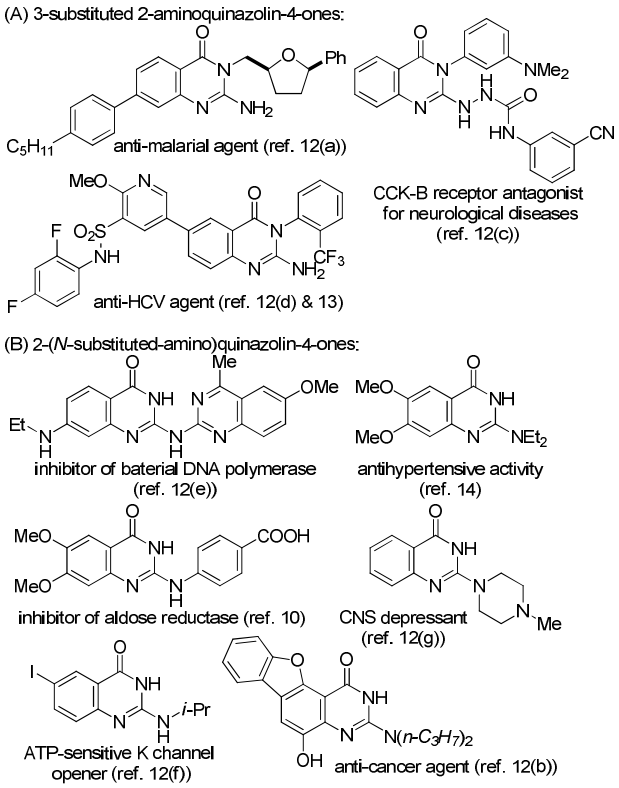
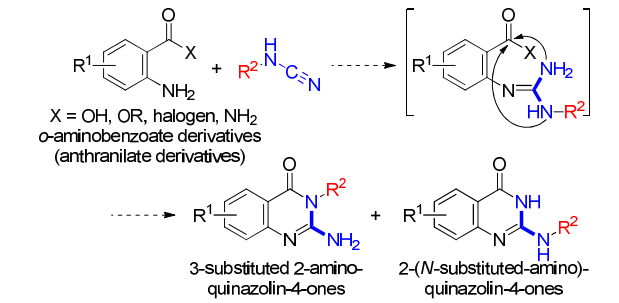


Figure 2. Biologically active 2-aminoquinazolin-4-one derivatives

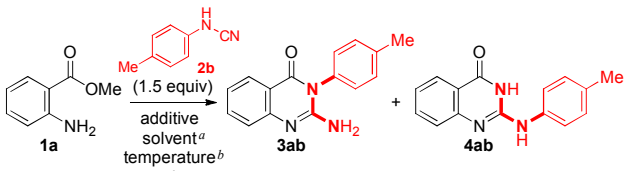


Scheme 1. Retrosynthetic analysis of *N*-substituted 2-aminoquinazolin-4-ones

Results and discussion

In 2008, K. S. Shikhaliev *et al.* reported that 2-(*N*-substituted-amino)quinazolin-4-ones were obtained from the reaction of methyl anthranilates with *N*-substituted cyanamides in the presence of concentrated hydrochloric acid.[27] Hence, Shikhaliev's condition was adopted in our initial attempts in order to explore the reaction outcome. Our reaction of methyl anthranilate (**1a**) with *N*-(*p*-tolyl)cyanamide (**2b**) in the presence of concentrated hydrochloric acid in isopropyl alcohol under reflux afforded a mixture of two products, which were identified as 2-amino-3-(*p*-tolyl)quinazolin-4-one (**3ab**, 44%) and the regioisomer, 2-(*p*-tolylamino)quinazolin-4-one (**4ab**, 14%) (entry 1 in **Table 1**). The major byproduct from the reaction is *N*-(*p*-tolyl)urea from acidic hydrolysis of the cyanamide **2b**.[29] It is notable that the 3-aryl-2-aminoquinazolin-4-one was the major product from our reaction and the result was contradictive to Shikhaliev's observation that they only obtained the 2-(*N*-substituted-amino)quinazolin-4-ones from the reaction.[30]

Table 1. Optimization of the reaction condition



entry	additive (1.2 equiv)[a]	solvent[b] (0.5 M)	yield[c] 3ab	yield[c] 4ab	overall yield
1	*aq. conc.* HCl	*i*-PrOH	44%	14%	58%
2	AcCl	*i*-PrOH	24%	2%	26%
3	AcCl	MeOH	10%	0%	10%
4	AcCl	EtOH	24%	3%	27%
5	AcCl	*t*-BuOH	67%	6%	73%
6	AcCl	*t*-amyl-OH	65%	18%	83%
7	pyridinium chloride	*t*-BuOH	13%	42%	55%
8	TMSCl	*t*-BuOH (60 °C)	56%	41%	97%
9	TMSCl	*t*-BuOH	50%	36%	86%
10	AcOH	*t*-BuOH	4%	trace	4%
11	TFA	*t*-BuOH	1%	2%	3%
12	MsOH	*t*-BuOH	72%	3%	75%
13	TfOH	*t*-BuOH	73%	5%	78%
14	CSA	*t*-BuOH	76%	6%	82%
15	$TsOH\cdot H_2O$	*t*-BuOH	76%	2%	78%
16	$TsOH\cdot H_2O$ (0.5 equiv)	*t*-BuOH	33%	30%	63%
17	$TsOH\cdot H_2O$ (2.0 equiv)	*t*-BuOH	57%	3%	60%
18	PPTS	*t*-BuOH	16%	32%	48%
19	$CuCl_2$ (0.4 equiv)	*t*-BuOH	19%	26%	45%
20	$FeCl_3$ (0.4 equiv)	*t*-BuOH	8%	15%	23%
21	$TsOH\cdot H_2O$	*t*-amyl-OH	72%	3%	75%
22	$TsOH\cdot H_2O$	1,4-dioxane	45%	trace	45%
23	$TsOH\cdot H_2O$	MeCN	66%	4%	70%
24	$TsOH\cdot H_2O$	toluene	47%	4%	51%

[a] additive = 1.2 equiv, unless specified elsewhere ; [b] reaction temperature = reflux, unless specified elsewhere; [c] isolated yields

The preliminary result suggested that the direct condensation reaction of anthranilates with cyanamides would potentially provide a feasible route for the synthesis of 3-substituted 2-aminoquinazolin-4-one derivatives. Thus, this reaction was chosen as a model reaction to investigate whether the formation of 3-substituted 2-aminoquinazolin-4-ones can be optimized to reach a synthetically meaningful

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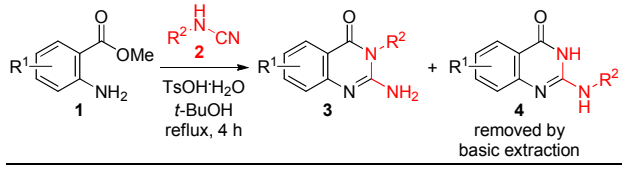
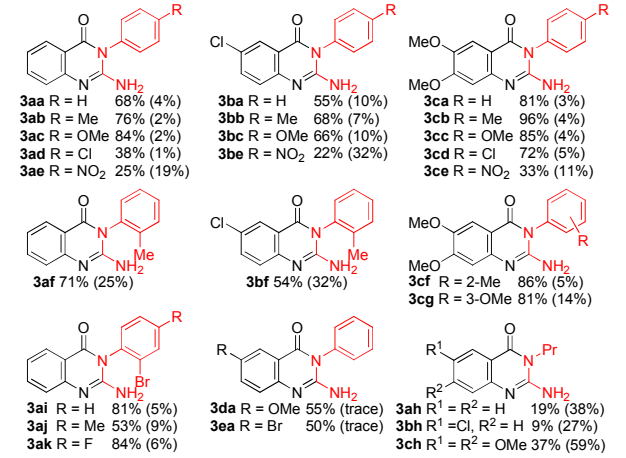
yield. The screening of the reaction conditions started with various Brønsted and Lewis acids in different solvents (part of the results is summarized in **Table 1**). The survey of reaction conditions showed that the maximal yield for the formation of 3-(*p*-tolyl)-2-aminoquinazoline (**3ab**) was obtained when the reaction was carried out at reflux temperature in *t*-butyl alcohol in the presence of stoichiometric *p*-toluenesulfonic acid.[31] Meanwhile, 2-(*p*-tolylamino)quinazolin-4-one (**4ab**) was obtained nearly in a minimal yield from this reaction (entry 15 in **Table 1**).

Subsequently, a series of *N*-substituted cyanamdes (**2**), prepared from corresponding nitriles *via* Tiemann rearrangement,[26] were subjected to the condensation reactions with various methyl anthranilates (**1**) under the optimized *p*-TsOH condition (entry 15 in **Table 1**) in order to establish the scope and generality of the reaction. Our investigation showed that this reaction protocol is highly regioselective for the formation of 3-substituted 2-aminoquinazolin-4-ones (**3**), except *N*-(*p*-nitrophenyl)cycnamide (**2e**) and *N*-propylcyanamide (**2h**) gave moderate yields with poor regioselectivity. Nevertheless, 2-(*N*-substituted-amino)quinazolin-4-ones (**4**) can be easily separated from the product mixtures by alkaline extraction attributed to its fairly acidic *N*-3 proton. Therefore, this serendipitous discovery provided an effective approach for the synthesis of 3-substituted 2-aminoquinazolin-4-ones (**3**) (**Scheme 2**).

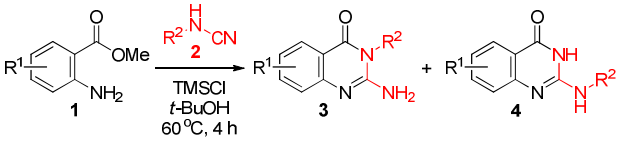




Percent yields in parentheses are the isolated yields for the corresponding compound **4** from the reactions.

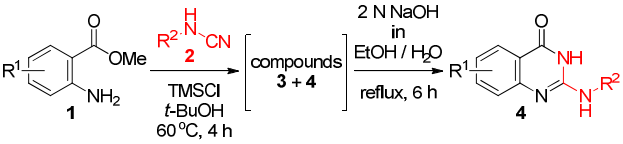
Scheme 2. Reactions of anthranilates (**1**) with *N*-substituted cyanamdes (**2**) under *p*-TsOH condition

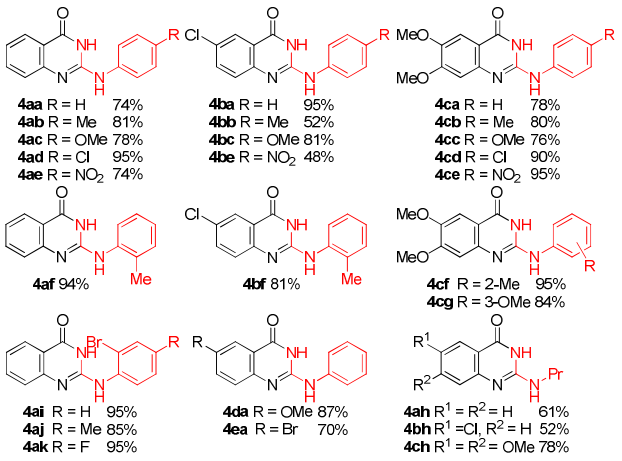
During the survey of conditions, we observed that the model reaction can reach the maximum overall yield when trimethylsilyl chloride was used as the acid (entry 8 in **Table 1**), regardless both regioisomers were obtained in comparable amounts. Since 2-(*N*-substituted-amino)quinazolin-4-ones (**4**) can be readily separated from the product mixture by alkaline extraction, the direct condensations of anthranilates with *N*-substituted cyanamdes at 60 °C in the presence of TMSCl in *t*-BuOH became an handy procedure to produce two separable regioisomers in one pot. A set of selected examples was demonstrated in **Scheme 3**.



3aa : **4aa**	=	76 : 14	**3bc** : **4bc**	=	57 : 20
3ab : **4ab**	=	75 : 25	**3be** : **4be**	=	35 : 44
3ac : **4ac**	=	75 : 6	**3ca** : **4ca**	=	65 : 19
3ad : **4ad**	=	74 : 10	**3cb** : **4cb**	=	56 : 37
3ae : **4ae**	=	0 : 79	**3cc** : **4cc**	=	55 : 24
3af : **4af**	=	70 : 30	**3cd** : **4cd**	=	44 : 33
3ah : **4ah**	=	19 : 44	**3ce** : **4ce**	=	20 : 80
3ba : **4ba**	=	68 : 14	**3cg** : **4cg**	=	28 : 65
3bb : **4bb**	=	65 : 26			

Scheme 3. Reactions of anthranilates (**1**) with *N*-substituted cyanamdes (**2**) under TMSCl condition





Scheme 4. Reactions of anthranilates (**1**) with *N*-substituted cyanamdes (**2**) under TMSCl condition followed by Dimroth rearrangement

Through a thorough literature review of 2-aminoquinazolin-4-ones, we found that R. J. Grout and M. W. Partridge reported that 3-substituted 2-aminoquinazolin-4-ones can be converted into the corresponding 2-(*N*-substituted-amino)quinazolin-4-ones in 10 N sodium hydroxide solution under reflux for 8 hours.[32] We interpreted that the alkaline-promoted translocation of the *exo*- and *endo*-cyclic guanidino nitrogens (3-N and N^2-amino nitrogens) on 2-aminoquinazolin-4-ones is an example of Dimroth rearrangement.[33-35] We pondered that a combination of the

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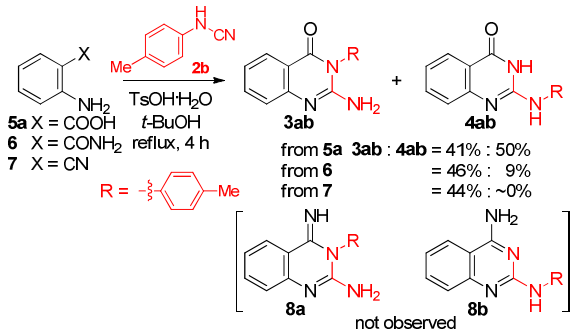
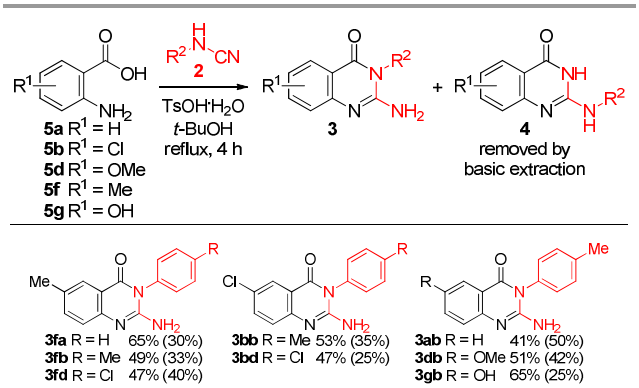
high-yielded but poor regioselective condensation reaction (**Scheme 3**) followed by Dimroth rearrangement to convert 3-substituted 2-aminoquinazolin-4-ones into 2-(*N*-substituted-amino)quinazolin-4-ones *in situ* would allow the preparation of 2-(*N*-substituted-amino)quinazolin-4-ones to be more effective. To validate our hypothesis, *N*-substituted cyanamides (**2**) were reacted with anthranilates (**1**) in the presence of TMSCl in *t*-BuOH at 60 °C for 4 hours. The reaction mixtures were then subjected to Dimroth rearrangement in 2 N aqueous ethanolic sodium hydroxide solution under reflux for 6 hours. Our investigation demonstrated that the two-step sequential reactions in one pot can afford exclusively 2-(*N*-substituted-amino)quinazolin-4-ones (**4**) in very good yields (**Scheme 4**).



Scheme 5. Reactions of anthranilate derivatives **5a**, **6** and **7** with *N*-(*p*-tolyl)cyanamide (**2b**) under *p*-TsOH condition

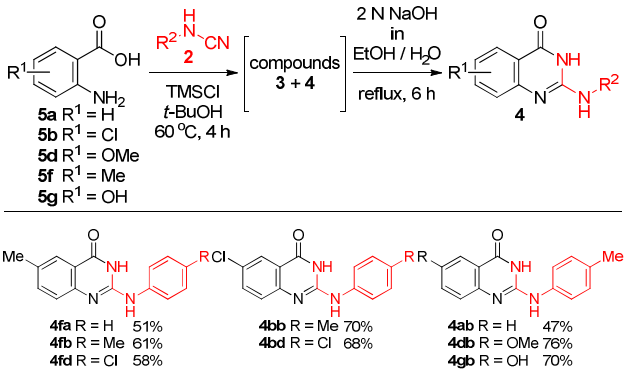
The success in the regioselective synthesis of 2-aminoquinazolin-4-one derivatives from methyl anthranilates prompted us to examine the reaction of *N*-substituted cyanamides (**2**) with other anthranilate derivatives. Anthranilic acid (**5a**), anthranilamide (**6**) and anthranilonitrile (**7**) are abundant and commercially available derivatives in anthranilate family. These anthranilate derivatives were subjected to the reactions with *N*-(*p*-tolyl)cyanamide (**2b**) and *p*-TsOH in *t*-BuOH at reflux temperature. Our results showed that the reaction of anthranilic acid (**5a**) gave a mixture of both 3-(*p*-tolyl) and N^2-(*p*-tolyl) 2-aminoquinazolin-4-ones (**3ab** and **4ab**, respectively) in a very good overall yield with poor regioselectivity. Meanwhile, the reactions of anthranilamide (**6**) and anthranilonitrile (**7**) both resulted in the formation of 3-(*p*-tolyl)-2-aminoquinazolin-4-one (**3ab**) as the major product but only in moderate yields. It is noticeable that either 2-amino-4-imino-3-(*p*-tolyl)-3,4-dihydroquinazoline (**8a**) or 4-amino-2-(*N*-(*p*-tolyl)amino)quinazoline (**8b**) was not obtained from the reaction of anthranilonitrile (**7**). We rationalized that the trace amount of water in the reaction participated the cyclization process and introduced the 4-oxo substituent *via* acidic hydrolysis (**Scheme 5**).

Since anthranilic acid (**5a**) is the upstream precursor for methyl anthranilate (**2a**), we herein also demonstrated that 2-aminoquinazolin-4-ones can be prepared directly from the condensation reactions of anthranilic acids (**5**) with *N*-substituted cyanamides (**2**). A series of anthranilic acids (**5**) were reacted with *N*-substituted cyanamides (**2**) under our *p*-TsOH condition (entry 15 in **Table 1**) to give the corresponding regioisomeric mixtures of 2-aminoquinazolin-4-ones (**3** and **4**) in very good yields with inferior regioselectivities (**Scheme 6**). For comparison purpose, the same set of examples was subjected to our TMSCl condition (entry 8 in **Table 1**) followed by Dimroth rearrangement. The reactions formed the desired 2-(*N*-substituted-amino)quinazolin-4-ones (**4**) but the overall yields are lower than the reactions under *p*-TsOH (**Scheme 7**).



Percent yields in parentheses are the isolated yields for the corresponding compound **4** from the reactions.

Scheme 6. Reactions of anthranilic acids (**5**) with *N*-substituted cyanamdes (**2**) under *p*-TsOH condition



Scheme 7. Reactions of anthranilic acids (**5**) with *N*-substituted cyanamdes (**2**) under TMSCl condition followed by Dimroth rearrangement

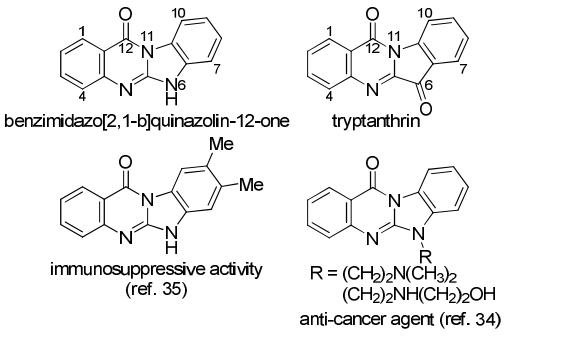


Figure 3. Benzimidazo[2,1-*b*]quinazolin-12-ones and tryptanthrin

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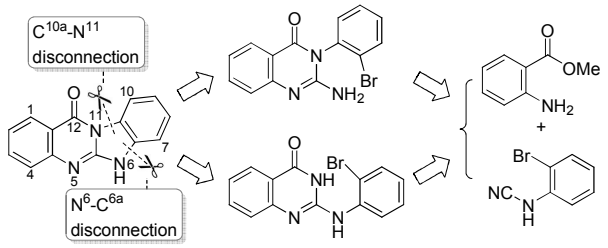
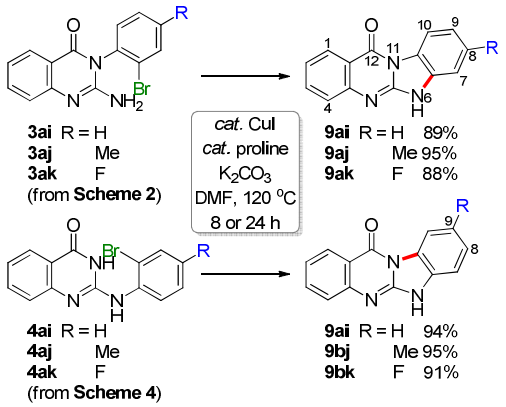
Benzimidazo[2,1-*b*]quinazolin-12-one (**9ai**), a tetracyclic heterocycle constituted by benzimidazole-fused quinazolin-4-one, is a 6-deoxo-6-aza analog of natural occurring quinazoline alkaloid, tryptanthrin (**Figure 3**). Benzimidazo[2,1-*b*]quinazolin-12-one (**9ai**) inherits most of structural features and similar biological profiles from tryptanthrin derivatives. In particular, a series of benzimidazo[2,1-*b*]quinazolin-12-one derivatives were demonstrated to possess significant immunosuppressive and antiproliferative activities.[36, 37] The unique structural motif with interesting biological activities has stimulated interests from synthetic chemists to develop practical synthesis toward benzimidazo[2,1-*b*]quinazolin-12-ones.

Our retrosynthetic analysis by disconnection of C^{10a}-N^{11} or N^{6}-C^{6a} bond of benzimidazo[2,1-*b*]quinazolin-12-one (**9ai**) leads to either 3-aryl-2-aminoquinazolin-4-one or 2-(*N*-arylamino)quinazolin-4-one derivatives, respectively. We anticipated that the tetracyclic heterocycle could be constructed from either 3-(2-bromophenyl)-2-aminoquinazolin-4-one or 2-(*N*-(2-bromophenyl)amino)quinazolin-4-one derivatives *via* metal-catalyzed C-N bond formation (**Scheme 8**). Thus, the synthesis of benzimidazo[2,1-*b*]quinazolin-12-ones was undertaken to demonstrate the synthetic application of our regioselective synthesis of *N*-subtituted 2-aminoquinazolin-4-ones.



Scheme 8. Retrosynthetic analysis of benzimidazo[2,1-*b*]quinazolin-12-ones

Acid-catalyzed condensation reaction of methyl anthranilate (**1a**) with a series of *N*-(2-bromophenyl)cyanamides (**2i**-**k**) afforded pairs of regioisomers, 3-(2-bromophenyl)-2-aminoquinazolin-4-ones (**3ai**-**ak**) and 2-(*N*-(2-bromophenyl)amino)quinazolin-4-ones (**4ai**-**ak**), individually under our regioselective conditions. Subsequently, both *N*-(2-bromophenyl)-substituted 2-aminoquinazolin-4-ones (**3ai**-**ak** and **4ai**-**ak**) were subjected to the intramolecular C-N bond formation reaction in the presence of copper(I) iodide as the catalyst, L-proline as the ligand, potassium carbonate as the base in DMF at 120 °C.[38] The intramolecular C-N bond formation reactions furnished the corresponding tetracyclic heterocycles **9** in very good yields. It is worth to mentioned that the Cu(I) catalyzed reaction of 3-(4-substituted-2-bromophenyl)-2-aminoquinazolin-4-ones (**3aj** and **3ak**) resulted in the formation of 8-substituted benzimidazo[2,1-*b*]quinazolin-12-ones (**9aj** and **9ak**, respectively), while 2-(*N*-(4-substituted-2-bromophenyl)amino)quinazolin-4-ones (**4aj** and **4ak**) afforded 9-substituted adducts (**9bj** and **9bk**, respectively). Our synthetic approach demonstrated that the same anthranilate and *N*-(2-bromophenyl)cyanamides could give two regioisomeric 2-aminoquinazolin-4-ones under two different reaction conditions and, after the C-N bond formation, two different regioisomeric benzimidazo[2,1-*b*]quinazolin-12-ones could be obtained if *N*-(2-bromophenyl)cyanamides possess additional substituents.



Scheme 9. Synthesis of benzimidazo[2,1-*b*]quinazolin-12-ones from methyl anthranilate (**1a**) and *N*-(2-bromophenyl)cyanamides (**2i**-**k**)

Preliminary anti-cancer activity of synthesized 2-aminoquinazolin-4-one derivatives has also been evaluated. All the synthesized compounds were subjected to cytotoxicity assay against human leukemia cell line HL-60[39] and the results are summarized in **Table 2**. The results indicated that several compounds showed the IC_{50} of anti-leukemia activity in the single-digit micromolar range. Notably, both **4ae** and **4cb** show the same magnitude order in the sub-μM range as clinically used etoposide (VP-16).

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Table 2. Cytotoxicity against human leukemia cell line HL-60[39]

compound	R^1	R^3	IC_{50} (μM)
3aa	H	Ph	40
3ab	H	4-Me-C_6H_4	20
3ac	H	4-MeO-C_6H_4	35
3ad	H	4-Cl-C_6H_4	40
3ae	H	4-NO_2-C_6H_4	> 200
3af	H	2-Me-C_6H_4	40
3ah	H	Pr	134
3ai	H	2-Br-C_6H_4	> 200
3aj	H	2-Br-4-Me-C_6H_3	14
3ak	H	2-Br-4-F-C_6H_3	16
3ba	6-Cl	Ph	17
3bb	6-Cl	4-Me-C_6H_4	55
3bc	6-Cl	4-MeO-C_6H_4	80
3bd	6-Cl	4-Cl-C_6H_4	80
3be	6-Cl	4-NO_2-C_6H_4	2.26
3bf	6-Cl	2-Me-C_6H_4	50
3bh	6-Cl	Pr	79
3ca	6,7-di-MeO	Ph	40
3cb	6,7-di-MeO	4-Me-C_6H_4	45
3cc	6,7-di-MeO	4-MeO-C_6H_4	35
3cd	6,7-di-MeO	4-Cl-C_6H_4	15
3ce	6,7-di-MeO	4-NO_2-C_6H_4	38
3cf	6,7-di-MeO	2-Me-C_6H_4	152
3cg	6,7-di-MeO	3-MeO-C_6H_4	50
3ch	6,7-di-MeO	Pr	> 200
3da	6-MeO	Ph	> 200
3db	6-MeO	4-Me-C_6H_4	76
3ea	6-Br	Ph	84
3fa	6-Me	Ph	90
3fb	6-Me	4-Me-C_6H_4	50
3fd	6-Me	4-Cl-C_6H_4	68
3gb	6-HO	4-Me-C_6H_4	5.98

compound	R^1	R^2	IC_{50} (μM)
4aa	H	Ph	60
4ab	H	4-Me-C_6H_4	35
4ac	H	4-MeO-C_6H_4	100
4ad	H	4-Cl-C_6H_4	1.97
4ae	H	4-NO_2-C_6H_4	0.67
4af	H	2-Me-C_6H_4	50
4ah	H	Pr	30
4ai	H	2-Br-C_6H_4	> 200
4aj	H	2-Br-4-Me-C_6H_3	1.49
4ak	H	2-Br-4-F-C_6H_3	4.79
4ba	6-Cl	Ph	10
4bb	6-Cl	4-Me-C_6H_4	7.38
4bc	6-Cl	4-MeO-C_6H_4	18
4bd	6-Cl	4-Cl-C_6H_4	1.01
4be	6-Cl	4-NO_2-C_6H_4	0.99
4bf	6-Cl	2-Me-C_6H_4	30
4bh	6-Cl	Pr	135
4ca	6,7-di-MeO	Ph	20
4cb	6,7-di-MeO	4-Me-C_6H_4	0.11
4cc	6,7-di-MeO	4-MeO-C_6H_4	25
4cd	6,7-di-MeO	4-Cl-C_6H_4	6.28
4ce	6,7-di-MeO	4-NO_2-C_6H_4	20
4cf	6,7-di-MeO	2-Me-C_6H_4	16
4cg	6,7-di-MeO	3-MeO-C_6H_4	13
4ch	6,7-di-MeO	Pr	87
4da	6-MeO	Ph	48
4db	6-MeO	4-Me-C_6H_4	7.81
4ea	6-Br	Ph	8.8
4fa	6-Me	Ph	> 200
4fb	6-Me	4-Me-C_6H_4	5.18
4fd	6-Me	4-Cl-C_6H_4	> 200
4gb	6-HO	4-Me-C_6H_4	24

compound	R^8	R^9	IC_{50} (μM)
9ai	H	H	11
9aj	Me	H	> 200
9ak	F	H	> 200
9bj	H	Me	39
9bk	H	F	76

compound		IC_{50} (μM)
Dox	(doxorubicin)	0.03
VP-16	(etoposide)	0.12

Conclusions

In summary, we disclosed the regioselective synthesis of *N*-substituted 2-aminoquinazolin-4-ones from methyl anthranilates and *N*-substituted cyanamdes *via* acid-prompted condensation reactions. By choosing different reaction conditions, the same set of reactants can undergo two different reaction pathways to afford two different regioisomeric products, 3-substituted or N^2-substituted 2-aminoquinazolin-4-one derivatives, which allowed the preparation of a wider variety of *N*-substituted 2-aminoquinazolin-4-ones from readily available precursors. Further applications of these approaches would be amenable to the synthesis of more complicated quinazoline-containing heterocycles.

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Experimental section

General information

The chemical shift values are reported in δ values (parts per million, ppm) relative to the standard chemical shift for the hydrogen residue peak and carbon-13 peak in the deuterated solvent, $CDCl_3$, or DMSO-d_6.[40] The coupling constant (*J*) values are expressed in hertz (Hz). The numbers of protons directly attached to the individual carbons were determined by ^{13}C NMR DEPT experiments. Thin-layer chromatography (TLC) was performed on silica gel plates. Compounds on TLC were visualized by illumination under UV light (254 nm), or dipped into 10% phosphomolybdic acid in ethanol followed by charring on a hot plate. Solvent systems are expressed as a volumetric ratio (*v/v*) of the less polar component to the more polar component. Silica gel (230-400 mesh) was used for flash column chromatography and this technique has been described by W. C. Still *et al.*[41] Evaporations were carried out under reduced pressure (water aspirator or vacuum pump) with the bath temperature below 50 °C unless specified otherwise. Materials obtained from commercial suppliers were used without further purification.

General procedure for cytotoxicity assay (Table 2)

Leukemia cell line HL-60 was obtained from ATCC. HL-60 was cultivated in RPMI 1640 media (Mediatech, Inc. Manassas, VA, USA) containing 10% fetal calf serum, 100 unit/mL penicillin, 100 mg/mL streptomycin, and 2 mM glutamine in a 5% CO_2 incubator at 37 °C. Cytotoxicity was measured by MTT assay after continuous treatment with the tested compounds for 4 days as described. The quantitative results of IC_{50} were estimated with the 3 replicates data.[39]

[General procedure 1] Preparation of 3-substituted 2-aminoquinazolin-4-one (3) under the optimized *p*-TsOH condition (Scheme 2)

To a mixture of *N*-substituted cyanamide[26] (**2**, 1.5 equiv) and methyl anthranilate (**1**, 1.0 equiv) in *tert*-butanol (0.5 M) was added *p*-toluenesulfonic acid monohydrate (1.2 equiv). The mixture was heated at reflux temperature for 4 hours. After cooling to room temperature, the solvent was removed under reduced pressure, and the residue was partitioned between $CHCl_3$ and 2 N NaOH aqueous solution. The organic layer was washed with saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$, and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography to give 3-substituted 2-aminoquinazolin-4-one (**3**). An analytical sample of 3-substituted 2-aminoquinazolin-4-one (**3**) was obtained by recrystallization from $CHCl_3$ / MeOH or $CHCl_3$ / EtOH (approximately 1 : 5 (*v/v*)). The regioisomer, 2-(*N*-substituted-amino)quinazolin-4-one (**4**), was retrieved by acidifying the aqueous layer with 2 N aqueous acetic acid solution (0.8 equiv to the 2 N NaOH aqueous solution) followed by $CHCl_3$ extraction. The $CHCl_3$ layer was washed with saturated aqueous Na_2CO_3 solution, saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$, and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography to give 2-(*N*-substituted-amino)quinazolin-4-one (**4**).

2-Amino-3-phenylquinazolin-4-one[19, 42] (3aa)

Compound **3aa** was prepared by *general procedure 1*. The product (**3aa**, solid, 0.6201 g, 2.614 mmol, 64%, R_f = 0.20 ($CHCl_3$ / MeOH = 98 : 2)) was purified by flash column chromatography ($CHCl_3$ / MeOH = 99 : 1). m.p. 245–250 °C ($CHCl_3$ / MeOH); ^1H NMR (DMSO-d_6, 500 MHz) δ 7.89 (d, 1H, *J* = 8.0 Hz), 7.62–7.50 (m, 4H), 7.35 (d, 2H, *J* = 7.5 Hz), 7.25 (d, 1H, *J* = 8.0 Hz), 7.12 (t, 1H, *J* = 7.5 Hz), 6.27 (br, 2H, NH_2); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 162.3, 152.1, 150.6, 135.9, 134.9 (CH), 130.4 (CH), 129.6 (CH), 129.3 (CH), 127.0 (CH), 124.4 (CH), 122.0 (CH), 117.3; MS (EI, 70 eV) *m/z* 77 (22), 237 (100) (M^+); HRMS (APCI, TOF) calcd for $C_{14}H_{12}N_3O$: 238.0980 (M+H). Found: 238.0986.

2-Amino-3-(4-tolyl)quinazolin-4-one[38] (3ab)

Compound **3ab** was prepared by *general procedure 1* or *general procedure 3*. The product (**3ab**, solid, 0.1471 g, 0.586 mmol, 76%, R_f = 0.35 ($CHCl_3$ / MeOH = 98 : 2)) was purified by flash column chromatography ($CHCl_3$ / MeOH = 99 : 1). m.p. 266 °C ($CHCl_3$ / MeOH); ^1H NMR (DMSO-d_6, 400 MHz) δ 7.88 (dd, 1H, *J* = 8.0, 1.2 Hz), 7.60 (dt, 1H, *J* = 7.2, 1.6 Hz), 7.36 (d, 2H, *J* = 8.0 Hz), 7.25–7.21 (m, 3H), 7.10 (dt, 1H, *J* = 8.0, 0.8 Hz), 6.23 (br, 2H, NH_2), 2.40 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 161.9, 151.8, 150.1, 138.5, 134.3 (CH), 132.8, 130.5 (CH), 128.5 (CH), 126.5 (CH), 123.9 (CH), 121.4 (CH), 116.8, 20.8 (CH_3); MS (EI, 70 eV) *m/z* 90 (19), 251 (100) (M^+); HRMS (APCI, TOF) calcd for $C_{15}H_{14}N_3O$: 252.1137 (M+H). Found: 252.1132.

2-Amino-3-propylquinazolin-4-one[42] (3ah)

Compound **3ah** was prepared by *general procedure 1*. The product (**3ah**, solid, 0.2586 g, 1.273 mmol, 19%, R_f = 0.15 ($CHCl_3$ / MeOH = 98 : 2)) was purified by flash column chromatography ($CHCl_3$ / MeOH = 99 : 1). m.p. 182–184 °C; ^1H NMR (DMSO-d_6, 500 MHz) δ 7.87 (d, 1H, *J* = 8.0 Hz), 7.53 (dt, 1H, *J* = 7.5, 1.5 Hz), 7.16 (d, 1H, *J* = 8.0 Hz), 7.06 (t, 1H, *J* = 7.0 Hz), 6.97 (br, 2H, NH_2), 3.92 (t, 2H, *J* = 7.5 Hz, CH_2), 1.62-1.55 (m, 2H, CH_2), 0.87 (t, 3H, *J* = 7.5 Hz, CH_3); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 162.3, 152.2, 149.8, 134.5 (CH), 126.8 (CH), 123.9 (CH), 121.9 (CH), 116.4, 42.9 (CH_2), 20.7 (CH_2), 11.2 (CH_3); MS (ESI^+) *m/z* 204 (100) (M+H); HRMS (ESI^+, TOF) calcd for $C_{11}H_{14}N_3O$: 204.1137 (M+H). Found: 204.1115.

2-Amino-3-(2-bromophenyl)quinazolin-4-one (3ai)

Compound **3ai** was prepared by *general procedure 1*. The product (**3ai**, solid, 0.9679 g, 3.06 mmol, 87%, R_f = 0.30 (CH_2Cl_2 / MeOH = 98 : 2)) was purified by flash column chromatography (CH_2Cl_2 / MeOH = 99 : 1). m.p. 237–238 °C; ^1H NMR (DMSO-d_6, 400 MHz) δ 7.89 (dd, 1H, *J* = 7.9, 1.4 Hz), 7.85 (dd, 1H, *J* = 8.0, 1.2 Hz), 7.62 (dt, 1H, *J* = 7.8, 1.6 Hz), 7.60–7.51 (m, 2H), 7.46 (dt, 1H, *J* = 7.8, 2.0 Hz), 7.25 (d, 1H, *J* = 8.0 Hz), 7.12 (t, 1H, *J* = 8.0 Hz), 6.44 (br, 2H, NH_2); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 161.6, 151.4, 150.8, 135.08 (CH), 135.06, 134.1

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(CH), 131.7 (CH), 131.6 (CH), 130.0 (CH), 127.0 (CH), 124.4 (CH), 123.2, 122.0 (CH), 116.9; MS (EI, 20 eV) *m/z* 236 (100), 315 (22) (M^+), 317 (20) (M+2); HRMS (EI, sector) calcd for $C_{14}H_{10}BrN_3O$: 315.0007. Found: 315.0000.

2-Amino-3-(2-bromo-4-methylphenyl)quinazolin-4-one (3aj)

Compound **3aj** was prepared by *general procedure 1*. The product (**3aj**, solid, 0.3509 g, 1.06 mmol, 53%, R_f = 0.25 (CH_2Cl_2 / MeOH = 98 : 2)) was purified by flash column chromatography (CH_2Cl_2 / MeOH = 99 : 1). m.p. 293–294 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.88 (dd, 1H, *J* = 8.0, 1.2 Hz), 7.68 (s, 1H), 7.61 (t, 1H, *J* = 8.4 Hz), 7.38 (s, 2H), 7.24 (d, 1H, *J* = 8.0 Hz), 7.11 (t, 1H, *J* = 7.6 Hz), 6.42 (br, 2H, NH_2), 2.40 (s, 3H, Me); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 161.7, 151.6, 150.8, 141.7, 135.0 (CH), 134.3 (CH), 132.4, 131.0 (CH), 130.6 (CH), 127.0 (CH), 124.4 (CH), 122.8, 121.9 (CH), 116.9, 20.9 (CH_3); MS (EI, 20 eV) *m/z* 250 (100), 329 (17) (M^+), 331 (16) (M+2); HRMS (EI, sector) calcd for $C_{15}H_{12}BrN_3O$: 329.0164. Found: 329.0165.

2-Amino-6-chloro-3-(4-tolyl)quinazolin-4-one (3bb)

Compound **3bb** was prepared by *general procedure 1* or *general procedure 3*. The product (**3bb**, solid, 0.6341 g, 2.219 mmol, 68%, R_f = 0.33 ($CHCl_3$ / MeOH = 98 : 2)) was purified by flash column chromatography ($CHCl_3$ / MeOH = 99 : 1). m.p. 315 °C ($CHCl_3$ / MeOH); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.80 (d, 1H, *J* = 2.5 Hz), 7.61 (dd, 1H, *J* = 8.8, 2.5 Hz), 7.37 (d, 2H, *J* = 8.1 Hz), 7.25 (d, 1H, *J* = 8.8 Hz), 7.23 (d, 2H, *J* = 8.1 Hz), 6.42 (br, 2H, NH_2), 2.40 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 161.5, 152.7, 149.5, 139.2, 134.8 (CH), 133.0, 131.0 (CH), 128.9 (CH), 126.6 (CH), 125.7 (CH), 125.6, 118.2, 21.3 (CH_3); MS (EI, 70 eV) *m/z* 123 (18), 285 (100) (M^+), 287 (23) (M+2); HRMS (APCI, TOF) calcd for $C_{15}H_{13}ClN_3O$: 286.0747 (M+H). Found: 286.0742.

2-Amino-6,7-dimethoxy-3-phenylqinazolin-4-one (3ca)

Compound **3ca** was prepared by *general procedure 1*. The product (**3ca**, solid, 1.3160 g, 4.426 mmol, 81%, R_f = 0.23 ($CHCl_3$ / MeOH = 98 : 2)) was purified by flash column chromatography ($CHCl_3$ / MeOH = 99 : 1). m.p. 253–256 °C ($CHCl_3$ / MeOH); ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.57 (t, 2H, *J* = 7.0 Hz), 7.51 (t, 1H, *J* = 7.5 Hz), 7.32 (d, 2H, *J* = 7.5 Hz), 7.23 (s, 1H), 6.71 (s, 1H), 5.98 (br, 2H, NH_2), 3.85 (s, 3H, Me), 3.77 (s, 3H, Me); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 161.6, 155.6, 151.3, 146.8, 145.7, 136.2, 130.4 (CH), 129.5 (CH), 129.3 (CH), 109.5, 106.7 (CH), 105.7 (CH), 56.14 (CH_3), 56.09 (CH_3); MS (EI, 70 eV) *m/z* 280 (28), 282 (57), 297 (100) (M^+); HRMS (ESI^+, TOF) calcd for $C_{16}H_{16}N_3O_3$: 298.1192 (M+H). Found: 298.1198.

[General procedure 2] Preparation of 2-(*N*-substituted-amino)quinazolin-4-one (4) under the optimized TMSCl condition followed by Dimroth rearrangement (Scheme 4)

To a mixture of *N*-substituted cyanamide[26] (**2**, 1.5 equiv) and methyl anthranilate (**1**, 1.0 equiv) in *tert*-butanol (0.5 M) was added trimethylsilyl chloride (1.2 equiv). The mixture was heated at 60 °C for 4 hours. After cooling to room temperature, the mixture was added aqueous ethanolic NaOH solution (4 N NaOH aqueous solution / EtOH = 1 : 1 (*v*/*v*), 4 times of volume of *t*-BuOH to bring the final reaction concentration to 0.1 M) and the reaction mixture was heated at reflux temperature for 6 hours. The volatile solvents were removed under reduced pressure, and the resulting solution was partitioned between $CHCl_3$ and water. The aqueous layer was acidified with 2 N aqueous acetic acid solution (0.8 equiv to the 4 N NaOH aqueous solution), and then extracted with $CHCl_3$. The $CHCl_3$ layer was washed with saturated aqueous Na_2CO_3 solution, saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$, and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography to give 2-(*N*-substituted-amino)quinazolin-4-one (**4**). An analytical sample of 2-(*N*-substituted-amino)quinazolin-4-one (**4**) was obtained by recrystallization from $CHCl_3$ / MeOH or $CHCl_3$ / EtOH (approximately 1 : 5 (*v*/*v*)).

2-(*N*-Phenylamino)quinazolin-4-one[16, 43-45] (4aa)

Compound **4aa** was prepared by *general procedure 2*. The product (**4aa**, solid, 0.6351 g, 2.677 mmol, 74%, R_f = 0.16 (Hex / EtOAc = 7 : 3)) was purified by flash column chromatography ($CHCl_3$ / MeOH = 99 : 1). m.p. 264–265 °C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 10.81 (br, 1H, NH), 8.66 (br, 1H, NH), 7.97 (d, 1H, *J* = 7.0 Hz), 7.74 (d, 2H, *J* = 8.0 Hz), 7.65 (t, 1H, *J* = 7.0 Hz), 7.40 (d, 1H, *J* = 8.5 Hz), 7.35 (t, 1H, *J* = 8.0 Hz), 7.23 (t, 1H, *J* = 7.5 Hz), 7.04 (t, 1H, *J* = 7.5 Hz); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 161.6, 150.0, 147.4, 139.0, 134.4 (CH), 128.8 (CH), 125.9 (CH), 125.3 (CH), 123.0 (CH), 122.5 (CH), 119.3 (CH), 118.4; MS (ESI^-) *m/z* 236 (100) (M-H); HRMS (ESI^-, TOF) calcd for $C_{14}H_{11}N_3O$: 236.0829 (M-H). Found: 236.0831.

2-(*N*-(4-Tolyl)amino)quinazolin-4-one[16, 43, 44] (4ab)

Compound **4ab** was prepared by *general procedure 2*. The product (**4ab**, solid, 0.500 g, 1.989 mmol, 81%, R_f = 0.28 ($CHCl_3$ / MeOH = 98 : 2)) was purified by flash column chromatography ($CHCl_3$ / MeOH = 99 : 1). m.p. 275 °C ($CHCl_3$ / MeOH); ^{1}H NMR (DMSO-d_6, 500 MHz) δ 10.8 (br, 1H, NH), 8.54 (br, 1H, NH), 7.96 (dd, 1H, *J* = 7.5, 1.0 Hz), 7.63 (t, 1H, *J* = 7.5 Hz), 7.61 (d, 2H, *J* = 8.5 Hz), 7.37 (d, 1H, *J* = 8.5 Hz), 7.21 (t, 1H, *J* = 7.5 Hz), 7.15 (d, 2H, *J* = 8.5 Hz), 2.27 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 161.6, 150.1, 147.5, 136.4, 134.4 (CH), 131.5, 129.2 (CH), 125.9 (CH), 125.3 (CH), 122.8 (CH), 119.5 (CH), 118.3, 20.4 (CH_3); MS (EI, 70 eV) *m/z* 251 (100) (M^+); HRMS (ESI^+, TOF) calcd for $C_{15}H_{14}N_3O$: 252.1137 (M+H). Found: 252.1134.

2-(*N*-Propylamino)quinazolin-4-one (4ah)

Compound **4ah** was prepared by *general procedure 2*. The product (**4ah**, solid, 0.2489 g, 1.22 mmol, 61%, R_f = 0.12 ($CHCl_3$ / MeOH = 98 : 2)) was purified by flash column chromatography ($CHCl_3$ / MeOH = 99 : 1). m.p. 189–190 °C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 10.79 (br, 1H, NH), 7.87 (dd, 1H, *J* = 8.0, 1.5 Hz), 7.55 (dt, 1H, *J* = 7.8, 2.0 Hz), 7.24 (d, 1H, *J* = 8.0 Hz), 7.09 (t, 1H, *J* = 7.5 Hz), 6.29 (br, 1H, NH), 3.28 (m, 2H, propyl), 1.59-1.52 (m, 2H, propyl), 0.92 (t, 3H, *J* = 7.5 Hz, propyl); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 162.7, 151.3, 134.5 (CH), 126.4 (CH), 124.8, 122.0 (CH), 117.8, 42.4 (CH_2), 22.6

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(CH_2), 11.8 (CH_3); ^{13}C NMR (added a drop of TFA, DMSO-d_6, 125 MHz) δ 160.4, 150.8, 139.6, 136.7 (CH), 127.8 (CH), 125.9 (CH), 118.1 (CH), 116.4, 44.1 (CH_2), 22.3 (CH_2), 11.5 (CH_3); MS (ESI$^+$) *m/z* 204 (100) (M+H); HRMS (ESI$^+$, TOF) calcd for $C_{11}H_{14}N_3O$: 204.1137 (M+H). Found: 204.1138.

2-(*N*-(2-Bromophenyl)amino)quinazolin-4-one (4ai)

Compound **4ai** was prepared by *general procedure 2*. The product (**4ai**, light red solid, 0.9385 g, 2.99 mmol, 95%, R_f = 0.21 ($CHCl_3$ / MeOH = 98 : 2)) was purified by flash column chromatography ($CHCl_3$ / MeOH = 99 : 1). m.p. 275–276 °C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 11.46 (br, 1H, NH), 8.33 (br, 1H), 8.17 (br, 1H, NH), 7.96 (dd, 1H, *J* = 8.0, 1.0 Hz), 7.67–7.62 (m, 2H), 7.41 (t, 1H, *J* = 8.5 Hz), 7.34 (d, 1H, *J* = 8.0 Hz), 7.24 (t, 1H, *J* = 7.8 Hz), 7.06 (t, 1H, *J* = 8.3 Hz); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 163.0, 148.6, 137.1, 135.2 (CH), 133.3 (CH), 128.8 (CH), 126.6 (CH), 125.8 (CH), 125.6, 124.9 (CH), 124.0 (CH), 119.1, 115.7; MS (EI, 20 eV) *m/z* 236 (100), 315 (13) (M$^+$), 317 (12) (M+2); HRMS (EI, sector) calcd for $C_{14}H_{10}BrN_3O$: 315.0007. Found: 315.0003.

2-(*N*-(2-Bromo-4-methylphenyl)amino)quinazolin-4-one (4aj)

Compound **4aj** was prepared by *general procedure 2*. The product (**4aj**, white solid, 0.5613 g, 1.70 mmol, 85%, R_f = 0.13 ($CHCl_3$ / MeOH = 98 : 2)) was purified by flash column chromatography ($CHCl_3$ / MeOH = 99 : 1). m.p. 260–261 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.52 (br, 1H, NH), 8.17 (br, 1H), 8.06 (br, 1H, NH), 7.96 (d, 1H, *J* = 6.8 Hz), 7.62 (t, 1H, *J* = 8.2 Hz), 7.49 (d, 1H, *J* = 1.2 Hz), 7.32 (d, 1H, *J* = 8.4 Hz), 7.22 (t, 2H, *J* = 7.4 Hz), 2.29 (s, 3H, Me); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 162.3, 150.3, 148.3, 135.3, 134.8 (CH), 134.3, 133.1 (CH), 129.2 (CH), 126.4 (CH), 125.7 (CH), 124.8 (CH), 123.6 (CH), 118.9, 115.5, 20.4 (CH_3); MS (EI, 20 eV) *m/z* 250 (100), 329 (13) (M$^+$), 331 (13) (M+2); HRMS (EI, sector) calcd for $C_{15}H_{12}BrN_3O$: 329.0164. Found: 329.0168.

6-Chloro-2-(*N*-(4-tolyl)amino)quinazolin-4-one (4bb)

Compound **4bb** was prepared by *general procedure 2*. The product (**4bb**, solid, 0.4920 g, 1.721 mmol, 52%, R_f = 0.30 ($CHCl_3$ / MeOH = 98 : 2)) was purified by flash column chromatography ($CHCl_3$ / MeOH = 99 : 1). m.p. 300 °C (decomp.); ^{1}H NMR (DMSO-d_6, 500 MHz) δ 10.94 (br, 1H, NH), 8.60 (br, 1H, NH), 7.86 (d, 1H, *J* = 2.5 Hz), 7.63 (dd, 1H, *J* = 9.0, 2.5 Hz),7.58 (d, 2H, *J* = 8.0 Hz), 7.37 (d, 1H, *J* = 9.0 Hz), 7.14 (d, 2H, *J* = 8.0 Hz), 2.27 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 160.7, 149.0, 147.9, 136.1, 134.3 (CH), 131.8, 129.2 (CH), 127.4 (CH), 126.7, 124.8 (CH), 119.7 (CH), 119.4, 20.4 (CH_3); MS (EI, 70 eV) *m/z* 124 (26), 285 (100) (M$^+$), 287 (32) (M+2); HRMS (ESI$^+$, TOF) calcd for $C_{15}H_{13}ClN_3O$: 286.0747 (M+H). Found: 286.0748.

6,7-Dimethoxy-2-(*N*-phenylamino)quinazolin-4-one[46] (4ca)

Compound **4ca** was prepared by *general procedure 2*. The product (**4ca**, solid, 0.6957 g, 2.34 mmol, 78%, R_f = 0.10 ($CHCl_3$ / MeOH = 98 : 2)) was purified by flash column chromatography ($CHCl_3$ / MeOH = 99 : 1). m.p. 256–257 °C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 10.64 (br, 1H, NH), 8.54 (br, 1H, NH), 7.73 (d, 2H, *J* = 7.5 Hz), 7.35 (dd, 2H, *J* = 7.5, 1.0 Hz), 7.32 (s, 1H), 7.02 (t, 1H, *J* = 7.5 Hz), 6.90 (s, 1H), 3.88 (s, 3H, Me), 3.81 (s, 3H, Me); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 161.4, 155.4, 147.2, 146.6, 146.5, 139.7, 129.3 (CH), 122.6 (CH), 119.5 (CH), 111.1, 107.2 (CH), 106.0 (CH), 56.3 (CH_3), 56.1 (CH_3); MS (ESI$^-$) *m/z* 296 (100) (M-H); HRMS (ESI$^-$, TOF) calcd for $C_{16}H_{14}N_3O_3$: 296.1041 (M-H). Found: 296.1055.

[General procedure 3] Preparation of 3-substituted 2-aminoquinazolin-4-one (3) and 2-(*N*-substituted-amino)quinazolin-4-one (4) from corresponding anthranilic acids (5) under the optimized *p*-TsOH condition (Scheme 6)

To a mixture of *N*-substituted cyanamide[26] (**2**, 1.5 equiv) and anthranilic acid (**5**, 1.0 equiv) in *tert*-butanol (0.5 M) was added *p*-toluenesulfonic acid monohydrate (1.2 equiv). The mixture was heated at reflux temperature for 4 hours. After cooling to room temperature, the solvent was removed under reduced pressure, and the residue was partitioned between $CHCl_3$ and 2 N NaOH aqueous solution. The organic layer was washed with saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$, and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography to give 3-substituted 2-aminoquinazolin-4-one (**3**). An analytical sample of 3-substituted 2-aminoquinazolin-4-one (**3**) was obtained by recrystallization from $CHCl_3$ / MeOH or $CHCl_3$ / EtOH (approximately 1 : 5 (*v*/*v*)). The regioisomer, 2-(*N*-substituted-amino)quinazolin-4-one (**4**), was retrieved by acidifying the aqueous layer with 2 N aqueous acetic acid solution (0.8 equiv to the 2 N NaOH aqueous solution) followed by $CHCl_3$ extraction. The $CHCl_3$ layer was washed with saturated aqueous Na_2CO_3 solution, saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$, and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography to give 2-(*N*-substituted-amino)quinazolin-4-one (**4**).

2-Amino-6-chloro-3-(4-chlorophenyl)quinazolin-4-one (3bd)

Compound **3bd** was prepared by *general procedure 3*. The product (**3bd**, solid, 0.6227 g, 2.034 mmol, 47%, R_f = 0.30 ($CHCl_3$ / MeOH = 98 : 2) was purified by flash column chromatography (CH_2Cl_2 / MeOH = 99 : 1). m.p. 315–317 °C ($CHCl_3$ / MeOH); ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.79 (d, 1H, *J* = 2.5 Hz), 7.62 (d, 2H, *J* = 8.5 Hz), 7.61 (dd, 1H, *J* = 8.5, 3.0 Hz), 7.41 (d, 2H, *J* = 8.0 Hz), 7.24 (d, 2H, *J* = 8.5 Hz), 6.59 (br, 2H, NH_2); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 161.4, 152.4, 149.5, 134.9 (CH), 134.6, 134.4, 131.3 (CH), 130.5 (CH), 126.6 (CH), 125.7 (CH), 125.6, 118.1; MS (EI, 70 eV) *m/z* 305 (100) (M$^+$), 307 (62) (M+2), 309 (17) (M+4); HRMS (ESI$^+$, TOF) calcd for $C_{14}H_{10}Cl_2N_3O$: 306.0201 (M+H). Found: 306.0193.

2-Amino-6-methoxy-3-(4-tolyl)quinazolin-4-one (3db)

Compound **3db** was prepared by *general procedure 3*. The product (**3db**, solid, 0.2457 g, 0.873 mmol, 44%, R_f = 0.3 (CH_2Cl_2 / MeOH = 99 : 1) was purified by flash column chromatography (CH_2Cl_2 / MeOH = 99 : 1). m.p. 259-260 °C; ^{1}H

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NMR (DMSO-d_6, 400 MHz) δ 7.37 (d, 2H, *J* = 8.0 Hz), 7.30 (d, 1H, *J* = 2.8 Hz), 7.26 (dd, 1H, *J* = 8.8, 2.8 Hz), 7.21 (d+d, 2H+1H, *J* = 8.4 Hz), 6.06 (br, 2H, NH_2), 3.78 (s, 3H, Me), 2.40 (s, 3H, Me); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 161.6, 154.2, 150.4, 144.5, 138.5, 133.0, 130.4 (CH), 128.5 (CH), 125.6 (CH), 124.2 (CH), 116.9, 106.4 (CH), 55.4 (CH_3), 20.8 (CH_3); MS (ESI$^+$) *m/z* 282 (100) (M+H); HRMS (ESI$^+$, TOF) calcd for $C_{16}H_{15}N_3O_2$: 282.1243 (M+H). Found: 282.1245.

2-Amino-6-hydroxy-3-(4-tolyl)quinazolin-4-one (3gb)

Compound **3gb** was prepared by *general procedure 3*. The product (**3gb**, soild, 0.1523 g, 0.296 mmol, 57%, R_f = 0.11 (CH_2Cl_2 / MeOH = 98 : 2) was purified by flash column chromatography (CH_2Cl_2 / MeOH = 98 : 2); m.p. 287 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.51 (br, 1H, OH), 7.36 (d, 2H, *J* = 8.1 Hz), 7.23 (d, 1H, *J* = 2.1 Hz), 7.18 (d, 2H, *J* = 8.2 Hz), 7.14–7.08 (m, 2H, Ar), 5.85 (br, 2H, NH_2), 2.39 (s, 3H, Me); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 161.8, 152.4, 149.9, 143.1, 138.7, 133.1, 130.6 (CH), 128.6 (CH), 125.5 (CH), 124.4 (CH), 117.4, 109.5 (CH), 21.0 (CH_3); MS (EI, 70 eV) *m/z* 266 (90), 267 (100) (M$^+$); HRMS (EI, sector) calcd for $C_{15}H_{13}N_3O_2$: 267.1008. Found: 267.1010.

[General procedure 4] Preparation of 2-(*N*-substituted-amino)quinazolin-4-one (4) from corresponding anthranilic acids (5) under the optimized TMSCl condition followed by Dimroth rearrangement (Scheme 7)

To a mixture of *N*-substituted cyanamide[26] (**2**, 1.5 equiv) and anthranilic acid (**1**, 1.0 equiv) in *tert*-butanol (0.5 M) was added trimethylsilyl chloride (1.2 equiv). The mixture was heated at 60 °C for 4 hours. After cooling to room temperature, the mixture was added aqueous ethanolic NaOH solution (4 N NaOH aqueous solution / EtOH = 1 : 1 (*v*/*v*), 4 times of volume of *t*-BuOH to bring the final reaction concentration to 0.1 M) and the reaction mixture was heated at reflux temperature for 6 hours. The volatile solvents were removed under reduced pressure, and the resulting solution was partitioned between $CHCl_3$ and water. The aqueous layer was acidified with 2 N aqueous acetic acid solution (0.8 equiv to the 4 N NaOH aqueous solution), and then extracted with $CHCl_3$. The $CHCl_3$ layer was washed with saturated aqueous Na_2CO_3 solution, saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$, and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography to give 2-(*N*-substituted-amino)quinazolin-4-one (**4**). An analytical sample of 2-(*N*-substituted-amino)quinazolin-4-one (**4**) was obtained by recrystallization from $CHCl_3$ / MeOH or $CHCl_3$ / EtOH (approximately 1 : 5 (*v*/*v*)).

6-Chloro-2-(*N*-(4-chlorophenyl)amino)quinazolinone (4bd)

Compound **4bd** was prepared by *general procedure 4*. The product (**4bd**, solid, 0.8437 g, 2.755 mmol, 68%, R_f = 0.25 ($CHCl_3$ / MeOH = 98 : 2) was purified by flash column chromatography ($CHCl_3$ / MeOH = 99 : 1). m.p. >320 °C (IPA / DMF); ^{1}H NMR (DMSO-d_6, 500 MHz) δ 11.04 (br, 1H, NH), 8.85 (br, 1H, NH), 7.89 (d, 1H, *J* = 2.5 Hz), 7.75 (d, 2H, *J* = 8.5 Hz), 7.67 (dd, 1H, *J* = 8.5, 2.5 Hz), 7.42 (d, 1H, *J* = 8.5 Hz), 7.39 (d, 2H, *J* = 9.0 Hz); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 161.1, 149.1, 148.1, 138.2, 134.9 (CH), 129.1 (CH), 128.0 (CH), 127.6, 126.8, 125.3 (CH), 121.6 (CH), 120.1; MS (ESI$^+$) *m/z* 306 (100) (M+H), 308 (55) (M+H+2), 310 (9) (M+H+4); HRMS (ESI$^+$, TOF) calcd for $C_{14}H_{10}Cl_2N_3O$: 306.0201 (M+H). Found: 306.0200.

6-Methoxy-2-(*N*-(4-tolyl)amino)quinazolinone (4db)

Compound **4db** was prepared by *general procedure 4*. The product (**4db**, solid, 0.2134 g, 0.759 mmol, 76%, R_f = 0.1 (CH_2Cl_2 / MeOH = 99 : 1) was purified by flash column chromatography (CH_2Cl_2 / MeOH = 98 : 2). m.p. 277–278 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.81 (br, 1H, NH), 8.46 (br, 1H, NH), 7.59 (d, 2H, *J* = 8.0 Hz), 7.37 (d, 1H, *J* = 2.8 Hz), 7.35 (d, 1H, *J* = 8.8 Hz), 7.27 (dd, 1H, *J* = 8.8, 2.8 Hz), 7.14 (d, 2H, *J* = 8.4 Hz), 3.81 (s, 3H, Me), 2.27 (s, 3H, Me); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 161.5, 155.2, 146.2, 144.4, 136.6, 131.1 129.2 (CH), 126.8 (CH), 123.8 (CH), 119.1 (CH), 118.5, 106.2 (CH), 55.4 (CH_3), 20.4 (CH_3); MS (ESI$^+$) *m/z* 282 (100) (M+H); HRMS (ESI$^+$, TOF) calcd for $C_{16}H_{15}N_3O_2$: 282.1243 (M+H). Found: 282.1242.

6-Hydroxy-2-(*N*-(4-tolyl)amino)quinazolin-4-one (4gb)

Compound **4gb** was prepared by *general procedure 4*. The product (**4gb**, soild, 0.3255 g, 1.21 mmol, 70%, R_f = 0.05 (CH_2Cl_2 / MeOH = 98 : 2) was purified by flash column chromatography (CH_2Cl_2 / MeOH = 96 : 4); m.p. 180 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.02 (br, 1H, NH), 9.48 (br, 1H, OH), 7.83 (d, 2H, *J* = 8.0 Hz), 7.33 (d, 1H, *J* = 2.6 Hz), 7.21 (d, 1H, *J* = 8.7 Hz), 7.08 (d, 2H, *J* = 8.7 Hz), 7.06 (dd, 1H, *J* = 8.2, 2.9 Hz), 2.26 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 161.7, 153.4, 145.6, 143.1, 136.9, 131.0 (CH), 129.3 (CH), 126.7 (CH), 123.9 (CH), 119.0, 118.9, 109.2 (CH), 20.4 (CH_3); MS (EI, 70 eV) *m/z* 266 (95), 267 (100) (M$^+$); HRMS (EI, sector) calcd for $C_{15}H_{13}N_3O_2$: 267.1008. Found: 267.1007.

[General procedure 5] Preparation of benzimidazo[2,1-*b*]quinazolin-12-one derivatives (9) from 3-(2-bromophenyl)-2-aminoquinazolin-4-ones (3ai-3ak) or 2-(*N*-(2-bromophenyl)amino)quinazolin-4-ones (4ai-4ak) (Scheme 9)

To a mixture of *N*-(2-bromophenyl)-substituted 2-aminoquinazolin-4-one (**3ai**-**ak** or **4ai**-**ak**) (1.0 equiv), L-proline (0.2 equiv), and potassium carbonate (4.0 equiv) in DMF (0.2 M) was added copper(I) iodide (0.1 equiv) at room temperature. The flask was capped with septum, and then evacuated and backfilled with argon gas for three times. The reaction mixture was stirred at 120 °C for 8 hours (for **3ai**-**ak**) or 24 hours (for **4ai**-**ak**). The solvent was removed by reduced pressure, and the residue was partitioned between $CHCl_3$ and saturated aqueous NH_4OAc solution. The organic layer was concentrated under reduced pressure. The residue was dissolved in a mixture of $CHCl_3$ and *conc.* aqueous NH_4OH solution (1 : 1 (*v*/*v*), 0.1 M) and the mixture was stirred at room temperature for 1.5 hours (The purpose was to separate the trace amount of copper residue from the product.). The resulting undissolved solid was collected. The organic layer was dried over anhydrous $MgSO_4$ and concentrated under

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reduced pressure. The residue was combined with the undissolved solid and purified with flash column chromatography to give benzimidazo[2,1-*b*]quinazolin-12-one (**9**). An analytical sample of benzimidazo[2,1-*b*]quinazolin-12-one (**9**) was obtained by recrystallization from $CHCl_3$ / MeOH or $CHCl_3$ / EtOH (approximately 1 : 1 (*v*/*v*)).

During structural characterization of benzimidazo[2,1-*b*]quinazolin-12-ones (**9**) with NMR spectroscopy, we observed obscure ^{13}C NMR spectra with indistinct and broad peaks as well as obvious missing peaks, particularly for the quaternary carbons. We rationalized that the nitrogen-bonded protons of benzimidazo[2,1-*b*]quinazolin-12-ones (**9**) can rapidly hopping among the basic nitrogens inter- and intra-molecularly in solution. The dynamic process involves at least the equilibrium between two non-equivalent structures and the transient states in between, which caused significant peak broadening due to non-equivalent environments for the carbons nearby the basic nitrogens. Therefore, for NMR spectroscopic characterization purpose, an additional set of ^1H & ^{13}C NMR spectra for benzimidazo[2,1-*b*]quinazolin-12-ones (**9**) were acquired with the addition of one drop of TFA, which was intended to saturate the basic nitrogen sites with additional proton source to prevent the proton transfer. As a result, the carbon skeletons of benzimidazo[2,1-*b*]quinazolin-12-ones (**9**) were confirmed unambiguously by both unprotonated and protonated ^{13}C NMR spectra.

Benzimidazo[2,1-*b*]quinazolin-12-one[15, 38, 47-49] **(9ai)**
Compound **9ai** was prepared by the *general procedure 5* from **3ai** or **4ai**. The product (**9ai** from **3ai**, soild, 0.1042 g, 0.44 mmol, 89%, R_f = 0.21 ($CHCl_3$ / MeOH = 98 : 2)) was purified by flash column chromatography (CH_2Cl_2 / MeOH = 98 : 2) then recrystallized from $CHCl_3$ / EtOH (about 1 : 1 (*v*/*v*)) (white solid, 0.0760 g, 0.32 mmol, 65%). Alternatively, the product (**9ai** from **4ai**, solid, 0.2214 g, 0.94 mmol, 94%, R_f = 0.21 ($CHCl_3$ / MeOH = 98 : 2)) was purified by flash column chromatography (CH_2Cl_2 / MeOH = 98 : 2) then recrystallized from $CHCl_3$ / EtOH (about 1 : 1 (*v*/*v*)) (white solid, 0.0918 g, 0.39 mmol, 39%). m.p. 342–343 °C; ^1H NMR (DMSO-d_6, 600 MHz) δ 8.41 (d, 1H, *J* = 7.8 Hz), 8.23 (dd, 1H, *J* = 8.4, 1.8 Hz), 7.78 (td 1H, *J* = 7.8, 1.2 Hz), 7.52 (d, 1H, *J* = 7.8 Hz), 7.48 (d, 1H, *J* = 7.8 Hz), 7.43 (td, 1H, *J* = 7.5, 0.8 Hz), 7.33 (td, 1H, *J* = 8.1, 0.8 Hz), 7.29 (t, 1H, *J* = 7.8 Hz); ^{13}C NMR (DMSO-d_6, 150 MHz) δ 159.5, 147.5, 146.0, 135.1, 127.7, 127.2, 126.2, 122.6, 122.1, 121.5, 115.4, 115.1, 112.5; ^1H NMR (added a drop of TFA, DMSO-d_6, 600 MHz) δ 8.46 (d, 1H, *J* = 7.8 Hz), 8.29 (dd, 1H, *J* = 8.1, 1.5 Hz), 7.89–7.86 (m, 1H), 7.63 (dd, 2H, *J* = 8.4, 5.2 Hz), 7.53 (t, 1H, *J* = 8.4 Hz), 7.47–7.40 (m, 2H); ^{13}C NMR (added a drop of TFA, DMSO-d_6, 150 MHz) δ 158.9, 146.5, 142.1, 136.2, 133.3, 127.9, 127.3, 127.2, 124.6, 123.6, 120.2, 116.0, 115.6, 113.6; MS (EI, 20 eV) *m/z* 235 (100) (M^+); HRMS (EI, sector) calcd for $C_{14}H_9N_3O$: 235.0746. Found: 235.0747.

8-Methylbenzimidazo[2,1-*b*]quinazolin-12-one[38] **(9aj)**
Compound **9aj** was prepared by the *general procedure 5* from **3aj**. The product (**9aj**, soild, 0.0979 g, 0.39 mmol, 98%, R_f = 0.12 ($CHCl_3$ / MeOH = 98 / 2)) was purified by flash column chromatography (CH_2Cl_2 / MeOH = 98 : 2) then recrystallized from $CHCl_3$ / EtOH (about 1 : 1 (*v*/*v*)) (brown solid, 0.0746 g, 0.30 mmol, 75%). m.p. 285–286 °C; ^1H NMR (DMSO-d_6, 500 MHz) δ 12.44 (br, 1H), 8.26 (d, 1H, *J* = 8.0 Hz), 8.21 (d, 1H, *J* = 8.0 Hz), 7.76 (td, 1H, *J* = 7.8, 1.3 Hz), 7.51 (d, 1H, *J* = 8.0 Hz), 7.31 (t, 1H, *J* = 7.5 Hz), 7.26 (s, 1H), 7.09 (d, 1H, *J* = 8.0 Hz), 2.44 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 159.3, 147.7, 135.9, 134.9, 127.1, 125.3, 122.6, 122.4, 115.3, 115.0, 113.3, 21.8; ^1H NMR (added a drop of TFA, DMSO-d_6, 500 MHz) δ 8.27 (dd, 2H, *J* = 9.8, 3.8 Hz), 7.87 (t, 1H, *J* = 8.5 Hz), 7.65 (d, 1H, *J* = 8.0 Hz), 7.46 (t, 1H, *J* = 7.8 Hz), 7.40 (s, 1H), 7.22 (d, 1H, *J* = 8.5 Hz), 2.44 (s, 3H); ^{13}C NMR (added a drop of TFA, DMSO-d_6, 125 MHz) δ 158.5, 146.2, 141.4, 137.6, 136.4, 132.5, 128.0, 125.1, 125.02, 124.99, 120.0, 115.8, 115.7, 113.5, 21.9; MS (EI, 20 eV) *m/z* 249 (100) (M^+); HRMS (EI, sector) calcd for $C_{15}H_{11}N_3O$: 249.0902. Found: 249.0900.

9-Methylbenzimidazo[2,1-*b*]quinazolin-12-one (9bj)
Compound **9bj** was prepared by the *general procedure 5* from **4aj**. The product (**9bj**, soild, 0.0968 g, 0.39 mmol, 97%, R_f = 0.12 ($CHCl_3$ / MeOH = 98 : 2)) was purified by flash column chromatography (CH_2Cl_2 / MeOH = 98 : 2) then recrystallized from $CHCl_3$ / EtOH (about 1 : 1 (*v*/*v*)) (white solid, 0.0283 g, 0.11 mmol, 28%). m.p. 316–317 °C; ^1H NMR (DMSO-d_6, 500 MHz) δ 12.45 (br, 1H), 8.23 (s, 1H), 8.20 (d, 1H, *J* = 8.0 Hz), 7.75 (td, 1H, *J* = 7.8, 1.0 Hz), 7.49 (d, 1H, *J* = 8.0 Hz), 7.34 (d, 1H, *J* = 8.0 Hz), 7.30 (t, 1H, *J* = 7.5 Hz), 7.23 (d, 1, *J* = 8.0 Hz), 2.46 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 159.5, 147.5, 146.2, 135.0, 133.8, 130.8, 127.7, 127.2, 127.0, 122.5, 122.1, 115.6, 115.1, 112.9, 21.7; ^1H NMR (added a drop of TFA, DMSO-d_6, 500 MHz) δ 8.26 (dd, 2H, *J* = 6.3, 1.3 Hz), 7.86 (t, 1H, *J* = 8.3 Hz), 7.61 (d, 1H, *J* = 8.0 Hz), 7.48–7.42 (m, 2H), 7.31 (d, 1H, *J* = 8.0 Hz), 2.47 (s, 3H); ^{13}C NMR (added a drop of TFA, DMSO-d_6, 125 MHz) δ 158.8, 146.3, 142.2, 136.1, 133.1, 130.9, 128.0, 127.8, 127.3, 124.4, 120.2, 116.0, 115.4, 113.0, 21.7; MS (EI, 20 eV) *m/z* 249 (100) (M^+); HRMS (EI, sector) calcd for $C_{15}H_{11}N_3O$: 249.0902. Found: 249.0903.

Conflicts of interest

There are no conflicts to declare.

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References

1 T. Inokuma, M. Furukawa, T. Uno, Y. Suzuki, K. Yoshida, Y. Yano, K. Matsuzaki and Y. Takemoto, *Chem. Eur. J.*, 2011, **17**, 10470-10477.

View Article Online
DOI: 10.1039/C8OB00624E

2 (a) K. M. Shakhidoyatov and B. Z. Elmuradov, *Chem. Nat. Compd.*, 2014, **50**, 781-800; (b) L. Ji-Feng, *Curr. Org. Synth.*, 2007, **4**, 223-237.
3 (a) A. Sahu, D. Kumar and R. K. Agrawal, *Anti-inflamm. Antiallergy Agents Med. Chem.*, 2017, **16**, 3-32; (b) M. H. Bule, I. Ahmed, F. Maqbool and M. A. Zia, *Int. J. Pharmacol.*, 2017, **13**, 818-831.
4 S. Ravez, O. Castillo-Aguilera, P. Depreux and L. Goossens, *Expert Opin. Ther. Pat.*, 2015, **25**, 789-804.
5 (a) A. Vijaychand, S. N. Manjula, E. N. Bharath and B. Divya, *Int. J. Pharma Bio Sci.*, 2011, **2**, 780-809; (b) L. Örfi, F. Wáczek, J. Pató, I. Varga, B. Hegymegi-Barakonyi, R. A. Houghten and G. Kéri, *Curr. Med. Chem.*, 2004, **11**, 2549-2553.
6 E. A. Meyer, M. Furler, F. Diederich, R. Brenk and G. Klebe, *Helv. Chim. Acta*, 2004, **87**, 1333-1356.
7 (a) W. Pendergast, S. H. Dickerson, I. K. Dev, R. Ferone, D. S. Duch and G. K. Smith, *J. Med. Chem.*, 1994, **37**, 838-844; (b) W. Pendergast, S. H. Dickerson, J. V. Johnson, I. K. Dev, R. Ferone, D. S. Duch and G. K. Smith, *J. Med. Chem.*, 1993, **36**, 3464-3471; (c) W. Pendergast, J. V. Johnson, S. H. Dickerson, I. K. Dev, D. S. Duch, R. Ferone, W. R. Hall, J. Humphreys, J. M. Kelly and D. C. Wilson, *J. Med. Chem.*, 1993, **36**, 2279-2291.
8 K. S. Sanjay, K. Vivek, K. A. Shiv, M. Rama and C. B. Anand, *Anti-cancer Agents Med. Chem.*, 2009, **9**, 246-275.
9 (a) D. J. McNamara, E. M. Berman, D. W. Fry and L. M. Werbel, *J. Med. Chem.*, 1990, **33**, 2045-2051; (b) P. R. Marsham, P. Chambers, A. J. Hayter, L. R. Hughes, A. L. Jackman, B. M. O'Connor, J. A. M. Bishop and A. H. Calvert, *J. Med. Chem.*, 1989, **32**, 569-575; (c) T. R. Jones, A. H. Calvert, A. L. Jackman, M. A. Eakin, M. J. Smithers, R. F. Betteridge, D. R. Newell, A. J. Hayter and A. Stocker, *J. Med. Chem.*, 1985, **28**, 1468-1476; (d) A. K. Ghose and G. M. Crippen, *J. Med. Chem.*, 1983, **26**, 996-1010; (e) J. Y. Fukunaga, C. Hansch and E. E. Steller, *J. Med. Chem.*, 1976, **19**, 605-611; (f) J. B. Hynes, W. T. Ashton, D. Bryansmith and J. H. Freisheim, *J. Med. Chem.*, 1974, **17**, 1023-1025; (g) W. T. Ashton, F. C. Walker, III and J. B. Hynes, *J. Med. Chem.*, 1973, **16**, 694-697.
10 J. DeRuiter, A. N. Brubaker, J. Millen and T. N. Riley, *J. Med. Chem.*, 1986, **29**, 627-629.
11 (a) T.-C. Chien, C.-S. Chen and J.-W. Chern, *J. Chin. Chem. Soc. (Taipei)*, 2005, **52**, 1237-1244; (b) T.-C. Chien, C.-C. Kuo, C.-S. Chen and J.-W. Chern, *J. Chin. Chem. Soc. (Taipei)*, 2004, **51**, 1401-1406.
12 (a) D. Rasina, M. Otikovs, J. Leitans, R. Recacha, O. V. Borysov, I. Kanepe-Lapsa, I. Domraceva, T. Pantelejevs, K. Tars, M. J. Blackman, K. Jaudzems and A. Jirgensons, *J. Med. Chem.*, 2016, **59**, 374-387; (b) P. Rizza, M. Pellegrino, A. Caruso, D. Iacopetta, M. S. Sinicropi, S. Rault, J. C. Lancelot, H. El-Kashef, A. Lesnard, C. Rochais, P. Dallemagne, C. Saturnino, F. Giordano, S. Catalano and S. Andò, *Eur. J. Med. Chem.*, 2016, **107**, 275-287; (c) J. K. Padia, M. Field, J. Hinton, K. Meecham, J. Pablo, R. Pinnock, B. D. Roth, L. Singh, N. Suman-Chauhan, B. K. Trivedi and L. Webdale, *J. Med. Chem.*, 1998, **41**, 1042-1049; (d) N. Bojjireddy, J. Botyanszki, G. Hammond, D. Creech, R. Peterson, D. C. Kemp, M. Snead, R. Brown, A. Morrison, S. Wilson, S. Harrison, C. Moore and T. Balla, *J. Biol. Chem.*, 2014, **289**, 6120-6132; (e) J. Guiles, X. Sun, I. A. Critchley, U. Ochsner, M. Tregay, K. Stone, J. Bertino, L. Green, R. Sabin, F. Dean, H. Garry Dallmann, C. S. McHenry and N. Janjic, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 800-802; (f) F. Somers, R. Ouedraogo, M.-H. Antoine, P. de Tullio, B. Becker, J. Fontaine, J. Damas, L. Dupont, B. Rigo, J. Delarge, P. Lebrun and B. Pirotte, *J. Med. Chem.*, 2001, **44**, 2575-2585; (g) C. M. Gupta, A. P. Bhaduri and N. M. Khanna, *J. Med. Chem.*, 1968, **11**, 392-395; (h) J. Hou, S. Wan, G. Wang, T. Zhang, Z. Li, Y. Tian, Y. Yu, X. Wu and J. Zhang, *Eur. J. Med. Chem.*, 2016, **118**, 276-289.
13 A. L. Leivers, M. Tallant, J. B. Shotwell, S. Dickerson, M. R. Leivers, O. B. McDonald, J. Gobel, K. L. Creech, S. L. Strum, A. Mathis, S. Rogers, C. B. Moore and J. Botyanszki, *J. Med. Chem.*, 2014, **57**, 2091-2106.
14 H. J. Hess, T. H. Cronin and A. Scriabine, *J. Med. Chem.*, 1968, **11**, 130-136.
15 T.-Q. Wei, P. Xu, S.-Y. Wang and S.-J. Ji, *Eur. J. Org. Chem.*, 2016, 5393-5398.
16 S. Sharma and A. Jain, *Tetrahedron Lett.*, 2014, **55**, 6051-6054.
17 (a) A. Caruso, J.-C. Lancelot, H. El-Kashef, A. Panno, M. S. Sinicropi, R. Legay, A. Lesnard, A. Lepailleur and S. Rault, *J. Heterocycl. Chem.*, 2014, **51**, E282-E293; (b) J. Debray, S. Bonte, O. Lozach, L. Meijer and M. Demeunynck, *Mol. Diversity*, 2012, **16**, 659-667; (c) W. Zeghida, J. Debray, S. Chierici, P. Dumy and M. Demeunynck, *J. Org. Chem.*, 2008, **73**, 2473-2475; (d) C. Wéber, Á. Demeter, G. I. Szendrei and I. Greiner, *Tetrahedron Lett.*, 2003, **44**, 7533-7536; (e) C. Wéber, A. Bielik, G. I. Szendrei and I. Greiner, *Tetrahedron Lett.*, 2002, **43**, 2971-2974; (f) A. Gopalsamy and H. Yang, *J. Comb. Chem.*, 2000, **2**, 378-381; (g) R.-Y. Yang and A. Kaplan, *Tetrahedron Lett.*, 2000, **41**, 7005-7008; (h) S. Buscemi and N. Vivona, *J. Chem. Soc., Perkin Trans. 2*, 1991, 187-189; (i) P. J. Garratt, C. J. Hobbs and R. Wrigglesworth, *J. Org. Chem.*, 1989, **54**, 1062-1069.
18 B. Erb, R. Akue, B. Rigo, B. Pirotte and D. Couturier, *J. Heterocycl. Chem.*, 2000, **37**, 253-260.
19 V. N. Murthy, S. P. Nikumbh, S. P. Kumar, L. V. Rao and A. Raghunadh, *Tetrahedron Lett.*, 2015, **56**, 5767-5770.
20 C. Lecoutey, C. Fossey, S. Rault and F. Fabis, *Eur. J. Org. Chem.*, 2011, 2785-2788.
21 (a) A. A. Morollo, M. G. Finn and R. Bauerle, *J. Am. Chem. Soc.*, 1993, **115**, 816-817; (b) P. P. Policastro, K. G. Au, C. T. Walsh and G. A. Berchtold, *J. Am. Chem. Soc.*, 1984, **106**, 2443-2444; (c) C. Y. P. Teng and B. Ganem, *J. Am. Chem. Soc.*, 1984, **106**, 2463-2464.
22 (a) D. R. Liljegren, *Phytochemistry*, 1971, **10**, 2661-2669; (b) D. R. Liljegren, *Phytochemistry*, 1968, **7**, 1299-1306.
23 D. Kikelj, *Sci. Synth.*, 2004, **16**, 573-749.
24 (a) T. M. M. Maiden and J. P. A. Harrity, *Org. Biomol. Chem.*, 2016, **14**, 8014-8025; (b) S. Y. Abbas, K. A. M. El-Bayouki and W. M. Basyouni, *Synth. Commun.*, 2016, **46**, 993-1035; (c) I. M. Abdou and S. S. Al-Neyadi, *Heterocycl. Commun.*, 2015, **21**, 115-132; (d) D. J. Connolly, D. Cusack, T. P. O'Sullivan and P. J. Guiry, *Tetrahedron*, 2005, **61**, 10153-10202; (e) G. A. El-Hiti, *Heterocycles*, 2000, **53**, 1839-1868.
25 (a) F. Dumitrascu and M. M. Popa, *Arkivoc*, 2014, 428-452; (b) D. Wang and F. Gao, *Chem. Cent. J.*, 2013, **7**, 95; (c) Y. Gao, Q. Xiong, R. An and X. Bao, *Chin. J. Org. Chem.*, 2011, **31**, 1529-1537.
26 C.-C. Lin, T.-H. Hsieh, P.-Y. Liao, Z.-Y. Liao, C.-W. Chang, Y.-C. Shih, W.-H. Yeh and T.-C. Chien, *Org. Lett.*, 2014, **16**, 892-895.
27 K. S. Shikhaliev, A. S. Shestakov, S. M. Medvedeva and N. V. Gusakova, *Russ. Chem. Bull.*, 2008, **57**, 170-176.
28 (a) A. Erdmann, L. Halby, F. Cantagrel, F. Sautel, G. Massiot and P. B. Arimondo, *Tetrahedron Lett.*, 2014, **55**, 3901-3904; (b) S. K. Mohamed, A. M. Soliman, M. A. A. El Remaily and H. Abdel-Ghany, *J. Heterocycl. Chem.*, 2013, **50**, 1425-1430; (c) A. S. Shestakov, I. S. Bushmarinov, O. E. Sidorenko, A. Y. Potapov, K. S. Shikhaliev and M. Y. Antipin, *Chem. Heterocycl. Compd.*, 2011, **47**, 316-320; (d) A. V. Dolzhenko, A. V. Dolzhenko and W.-K. Chui, *J. Heterocycl. Chem.*, 2008, **45**, 173-176; (e) W.-M. Chen and S.-H. Wan, *Synth. Commun.*, 2007, **37**, 53-61; (f) A. Kreutzberger and S. Balbach, *Pharmazie*, 1993, **48**, 17-20.

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DOI: 10.1039/C8OB00624E

29 C.-H. Wang, T.-H. Hsieh, C.-C. Lin, W.-H. Yeh, C.-A. Lin and T.-C. Chien, *Synlett*, 2015, **26**, 1823-1826.
30 Shikhaliev's experimental procedure[27] was carefully examined in order to account for the difference in regioselectivity. We found that, although the reaction conditions are presumably identical, the work-up and purification procedures are different. Shikhaliev *et al.* directly collected and purified the precipitate by recrystallization and the products were identified as the HCl salt of 2-arylaminoquinazolin-4-ones (**4**) in moderate to low yields. Whether there were other products in the filtrates was not mentioned. In contrast, we evaporated the solvent to dryness and purified all the separable compounds from the reaction. Therefore, both regioisomers were characterized as free base forms.
31 C.-J. Zeng, C.-J. Chen, C.-W. Chang, H.-T. Chen and T.-C. Chien, *Aust. J. Chem.*, 2014, **67**, 1134-1137.
32 R. J. Grout and M. W. Partridge, *J. Chem. Soc.*, 1960, 3540-3545.
33 Z. Wang, in *Comprehensive Organic Name Reactions and Reagents*, John Wiley & Sons, Inc., 2010, pp. 905-909.
34 O. Dimroth, *Liebigs Ann. Chem.*, 1909, **364**, 183-226.
35 (a) P. H. Boyle and M. F. Kelly, *Tetrahedron*, 1988, **44**, 5179-5188; (b) P. H. Boyle and R. J. Lockhart, *J. Org. Chem.*, 1985, **50**, 5127-5132; (c) W. V. Curran and R. B. Angier, *J. Am. Chem. Soc.*, 1958, **80**, 6095-6097.
36 L. D. Via, O. Gia, S. M. Magno, A. Da Settimo, A. M. Marini, G. Primofiore, F. Da Settimo and S. Salerno, *Farmaco*, 2001, **56**, 159-167.
37 W. H. W. Lunn, R. W. Harper and R. L. Stone, *J. Med. Chem.*, 1971, **14**, 1069-1071.
38 D. Yang, Y. Wang, H. Yang, T. Liu and H. Fu, *Adv. Synth. Catal.*, 2012, **354**, 477-482.
39 C.-H. Lee, M.-Y. Hsieh, L.-W. Hsin, H.-C. Chen, S.-C. Lo, J.-R. Fan, W.-R. Chen, H.-W. Chen, N.-L. Chan and T.-K. Li, *Biochem. Pharmacol.*, 2012, **83**, 1208-1216.
40 H. E. Gottlieb, V. Kotlyar and A. Nudelman, *J. Org. Chem.*, 1997, **62**, 7512-7515.
41 W. C. Still, M. Kahn and A. Mitra, *J. Org. Chem.*, 1978, **43**, 2923-2925.
42 J. Li, Y. Mi, J. He, X. Luo and E. Fan, *J. Heterocycl. Chem.*, 2013, **50**, 304-308.
43 S. Sharma, K. C. Basavaraju, A. K. Singh and D.-P. Kim, *Org. Lett.*, 2014, **16**, 3974-3977.
44 L. H. Gu, Z. Guo, L. He and Q. R. Qi, *Synthesis*, 2013, **45**, 2533-2544.
45 B. Roberts, D. Liptrot, T. Luker, M. J. Stocks, C. Barber, N. Webb, R. Dods and B. Martin, *Tetrahedron Lett.*, 2011, **52**, 3793-3796.
46 Q. Chao, L. Deng, H. Shih, L. M. Leoni, D. Genini, D. A. Carson and H. B. Cottam, *J. Med. Chem.*, 1999, **42**, 3860-3873.
47 A. A. Harutyunyan, *Russ. J. Org. Chem.*, 2016, **52**, 1012-1017.
48 K. K. Gnanasekaran, N. P. Muddala and R. A. Bunce, *Tetrahedron Lett.*, 2015, **56**, 7180-7183.
49 J. A. Bleda, P. M. Fresneda, R. Orenes and P. Molina, *Eur. J. Org. Chem.*, 2009, 2490-2504.

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DOI: 10.1039/C8OB00624E