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Oxidative Rearrangement of Isatins with Arylamines Using H_2O_2 as Oxidant: A Facile Synthesis of Quinazoline-2,4-diones and Evaluation of Their Antibacterial Activity

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A green and highly efficient synthetic method for the synthesis of quinazoline-2,4-diones with hydrogen peroxide as the terminal oxidant has been developed. The reaction features the mild reaction conditions, broad substrate scope, metal-free catalysts, and sole byproduct water. A plausible mechanism for this process was proposed. Moreover, an antibacterial activity study was performed to evaluate the antimicrobial activities towards two Gram-negative bacterial strains (*Escherichia coli*, and *Klebsiella pneumonia*) and two Gram-positive bacterial strains (*Staphylococcus epidermidis*, and *Staphylococcus aureus*) using the Broth microdilution method.

Keywords antibacterial activity, hydrogen peroxide, isatins, quinazoline-2,4-diones, rearrangement

Introduction

As an important class of nitrogen-containing heterocycles, quinazolinone is one of the ubiquitous structural motifs that occur in natural products and pharmaceutically active molecules.[1] Among them, quinazoline-2,4-dione and its derivatives are important compounds for their wide range of biological activities, such as anti-inflammatory,[2] antihypertensive,[3] anticancer,[4] antitumor,[5] and antibacterial activity.[6] During recent decades, conventional synthetic routes, including the reactions of acyl azides or amines with triphosgene, *o*-aminobenzamides with phosgene, isatoic anhydride with amines, anthranilic acids with ureas, and the reactions of potassium cyanates, isocyanates, and anthranilates with *N*-aryldithio carbamates, have been developed for constructing the quinazoline-2,4-dione framwork.[7] In view of the great value of quinazoline-2,4-diones and their analogs, various new methodologies for their synthesis have been developed. For example, Azizian *et al*. reported rearrangement of 4-imino-(1*H*,4*H*)-3,1-benzoxazine-2-ones with *m*-chloroperbenzoic acid as oxidant,[8] Alper *et al*. utilized *o*-iodoanilines with heterocumulenes (*e.g.* isocyanates, carbodiimides, and ketenimines) to obtain various quinazoline-2,4-diones by using a catalyst system comprising palladium acetate-bidentate phosphine under carbon monoxide pressure.[9] Recently, some new, efficient and practical methods have been reported. Yu reported selenium-catalyzed carbonylation of *o*-nitrobenzamides with carbon monoxide as a source of carbonyl,[10] Wang *et al*. developed a green method of iodine-catalyzed reaction of 2-aminobenzamides and triethyl orthoformate or triphosgene in ionic liquid,[11] Willis *et al*. reported tandem palladium-catalyzed urea arylation-intramolecular ester amidation sequence to a diverse range of functionalized quinazolinedione products.[12] Bergman *et al*. and Finlay *et al*. utilized hydrogen peroxide as oxidant for the preparation of quinazolino[4,5-*b*] quinazoline-6,8-dione and quinazolin-4-amine in the presence of NaOH.[13] Therefore, the development of a simple, effective, mild and economic method for the preparation of quinazolinones is still highly desirable.

Aqueous 30% hydrogen peroxide has recently been utilized as an attractive and environmentally benign oxidant in organic synthesis,[14] because 30% hydrogen peroxide is inexpensive, easy to handle, safely stored and low toxicity considerations.[15] Furthermore, aqueous 30% hydrogen peroxide was also considered to be one of the most straightforward, clean, and versatile oxidant[16] from both an environmental and economic perspective because H_2O_2 has a high content of active oxygen and generates water as the sole byproduct.[17] As a part of our ongoing efforts to determine the synthesis of heterocyclic compounds and evaluation of their antibacterial activity,[18] herein, we report a green one-pot pathway for synthesis of quinazoline-2,4-dione derivatives with isatins and arylamines by using aqueous 30% hydrogen peroxide as oxidant in good to excellent yields (Scheme 1). In addition, assessment results against two

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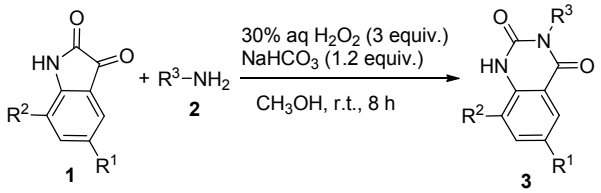
Gram-negative bacterial strains (*E. coli*, and *K. pneumonia*) and two Gram-positive bacterial strains (*S. epidermidis*, and *S. aureus*) indicated that several compounds exhibit moderate antibacterial activity specifically for the multi-drug resistant strain, *S. aureus*, which provided unusual leads for further optimization during the drug discovery process.

Scheme 1 Synthesis of quinazoline-2,4-dione derivatives via the rearrangement oxidation of isatins and arylamines using aqueous 30% hydrogen peroxide as oxidant

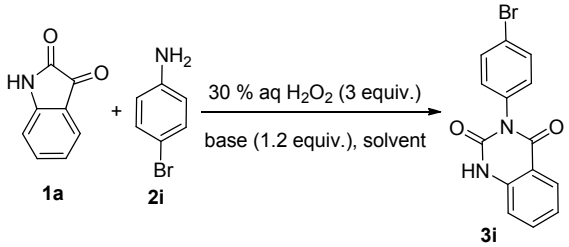


Results and Discussion

We started by studying the tandem reaction of isatin (**1a**), 4-bromoaniline (**2i**), KF and 30% aqueous H_2O_2 in MeOH at room temperature for 8 h (Table 1, entry 13). To our delight, the reaction afforded 3-phenylquinazoline-2,4(1*H*,3*H*)-dione (**3i**) in 50% yield. The reaction was further carried out in various bases, solvents and temperatures to improve the yield, the results were summaried in Table 1. The yield of **3i** could be increased to 92% when $NaHCO_3$ was used as base (Table 1, entry 6). When using other inorganic bases, such as NaOH, Na_2CO_3, a lower yield was obtained (Table 1, entries 14, 15). In comparison to inorganic base, a trace product was detected by LC-MS when organic bases were used, such as pyridine, Et_3N, and DMAP (Table 1 entries 10—12). It was found that base was found to be critical for the reaction, a trace yield of the product was observed by LC-MS in the absence of base (Table 1, entry 9). To determine the ideal solvent for the transformation, we investigated the model reaction in dichlormethane (DCM, 75%), tetrahydrofuran (THF, 56%), Et_2O (47%), dimethylformamide (DMF, 80%), acetonitrile (75%), MeOH (92%), EtOH (69%), and H_2O (28%) (Table 1, entries 1—8). The desired product **3i** was obtained in all the tested solvents, and the polar solvent MeOH gave the best isolated yield (Table 1, entry 6). The influences of reaction time and temperature were also investigated, but the results were negative (Table 1, entries 16—20). Thus, $NaHCO_3$ was considered to be the best base, MeOH was the best solvent and the reaction time was 8 h at room temperature (Table 1, entry 6).

With the optimized conditions in hand, we investigated the substrate scope of isatins and arylamines to test the generality of this reaction, the results are summarized in Table 2. It was found that a variety of arylamines reacted smoothly with isatin **2a** to give the desired products in moderate to excellent yields. It was

Table 1 Optimization of reaction conditions[a]



Entry	Base	Solvent	*T*/℃	Time/h	Yield[b]/%
1	$NaHCO_3$	DCM	r.t.	8	75
2	$NaHCO_3$	THF	r.t.	8	56
3	$NaHCO_3$	Et_2O	r.t.	8	47
4	$NaHCO_3$	DMF	r.t.	8	80
5	$NaHCO_3$	Acetonitrile	r.t.	8	75
6	$NaHCO_3$	MeOH	r.t.	8	92
7	$NaHCO_3$	EtOH	r.t.	8	69
8	$NaHCO_3$	H_2O	r.t.	8	28
9	—	MeOH	r.t.	8	trace
10	Pyridine	MeOH	r.t.	8	trace
11	DMAP	MeOH	r.t.	8	trace
12	Et_3N	MeOH	r.t.	8	trace
13	KF	MeOH	r.t.	8	50
14	NaOH	MeOH	r.t.	8	23
15	Na_2CO_3	MeOH	r.t.	8	45
16	$NaHCO_3$	MeOH	r.t.	4	62
17	$NaHCO_3$	MeOH	r.t.	12	92
18	$NaHCO_3$	MeOH	0	8	79
19	$NaHCO_3$	MeOH	60	8	82
20	$NaHCO_3$	MeOH	reflux	8	80

[a] Reaction conditions: isatin **1a** (0.1 mmol), 4-bromine aniline **2i** (0.1 mmol) and hydrogen peroxide (0.03 mL, 30%), base (0.12 mmol) and solvent (1.5 mL). [b] Isolated yield.

observed that the electric nature of the substituent on the benzene ring of arylamines affected the yields of the products. As illustrated in Table 2, arylamines with electorn-withdrawing groups (*e.g.* —F, —Cl, —Br) (Table 2, entries 6—9) resulted in higher yields than those with electron-donating groups (*e.g.* —CH_3, —CH_2CH_3, —$CH(CH_3)_2$) (Table 2, entries 2, 3, 11—14). When arylamines with a strong electron-donating group (—OCH_3) or an iodine group were subjected to this reaction, the yields of the desired products decreased to 29% and 32% (Table 2, entries 4, 10). For arylamines with a strong electron-withdrawing group (—NO_2), the reaction hardly took place (Table 2, entry 15). Similarly, when other amines, such as aliphatic amines, heteroarylamines (Table 2, entries 31—33), and disubstituted arylamines, such as 2,6-dimethylaniline, 2-bromo-6-methylaniline (Table 2, entries 34, 35), were used as substrates under standard reaction conditions, no desired product was obtained. The structure of the

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product **3i** was conformed by X-ray crystallographic analysis as shown in Figure 1.

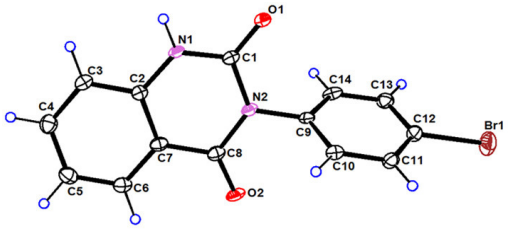
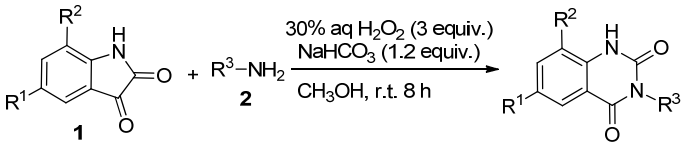


Figure 1 X-ray crystal structure of product **3i**.[19]

After the examination of arylamines, isatins were also investigated. Isatins with electron-withdrawing groups (*e.g.* —F, —Cl, —Br) resulted in higher yields than those with electron-donating groups (*e.g.* —CH_3, —CH_2CH_3) (Table 2, entries 16—18, 20, 21). When isatins with a strong electron-donating group (—OCH_3) or an iodine group were subjected to this reaction, the yield of the desired products decreased to 35% and 43%, respectively (Table 2, entries 19, 22, 26, 30).

On the basis of the results described above and previous studies,[20] we propose a possible mechanism for the rearrangement oxidation of isatin **1a** and arylamine

Table 2 Synthesis of quinazoline-2,4-diones via rearrangement oxidation of isatins and arylamines using hydrogen peroxide as an oxidant[a]



Entry	R^1, R^2	R^3	Product	Yield[b]/%
1	**1a** (H, H)	C_6H_5 (**2a**)	**3a**	71
2	**1a** (H, H)	4-$CH_3C_6H_4$ (**2b**)	**3b**	72
3	**1a** (H, H)	4-$CH_3CH_2C_6H_4$ (**2c**)	**3c**	71
4	**1a** (H, H)	4-$CH_3OC_6H_4$ (**2d**)	**3d**	29
5	**1a** (H, H)	3-$CH_3OC_6H_4$ (**2e**)	**3e**	27
6	**1a** (H, H)	4-FC_6H_4 (**2f**)	**3f**	90
7	**1a** (H, H)	4-ClC_6H_4 (**2g**)	**3g**	90
8	**1a** (H, H)	3-ClC_6H_4 (**2h**)	**3h**	89
9	**1a** (H, H)	4-BrC_6H_4 (**2i**)	**3i**	89
10	**1a** (H, H)	4-IC_6H_4 (**2j**)	**3j**	32
11	**1a** (H, H)	2-$CH_3C_6H_4$ (**2k**)	**3k**	71
12	**1a** (H, H)	2-$CH_3CH_2C_6H_4$ (**2l**)	**3l**	65
13	**1a** (H, H)	3-$CH_3CH_2C_6H_4$ (**2m**)	**3m**	64
14	**1a** (H, H)	2-$(CH_3)_2CHC_6H_4$ (**2n**)	**3n**	60
15	**1a** (H, H)	4-$NO_2C_6H_4$ (**2o**)	—	trace
16	**1b** (F, H)	4-$CH_3C_6H_4$ (**2b**)	**3o**	88
17	**1c** (Cl, H)	4-$CH_3C_6H_4$ (**2b**)	**3p**	89
18	**1d** (Br, H)	4-$CH_3C_6H_4$ (**2b**)	**3q**	91
19	**1e** (I, H)	4-$CH_3C_6H_4$ (**2b**)	**3r**	35
20	**1f** (CH_3, H)	4-$CH_3C_6H_4$ (**2b**)	**3s**	73
21	**1g** (CH_3CH_2, H)	4-$CH_3C_6H_4$ (**2b**)	**3t**	72
22	**1h** (OCH_3, H)	4-$CH_3C_6H_4$ (**2b**)	**3u**	35
23	**1i** (H, Cl)	4-$CH_3C_6H_4$ (**2b**)	**3v**	88
24	**1j** (H, CH_3)	4-$CH_3C_6H_4$ (**2b**)	**3w**	72
25	**1b** (F, H)	C_6H_5 (**2a**)	**3x**	87
26	**1e** (I, H)	C_6H_5 (**2a**)	**3y**	43
27	**1c** (Cl, H)	4-$(CH_3)_2CHC_6H_4$ (**2p**)	**3z**	89
28	**1g** (CH_3CH_2, H)	4-FC_6H_4 (**2f**)	**3aa**	90
29	**1g** (CH_3CH_2, H)	4-ClC_6H_4 (**2g**)	**3ab**	87

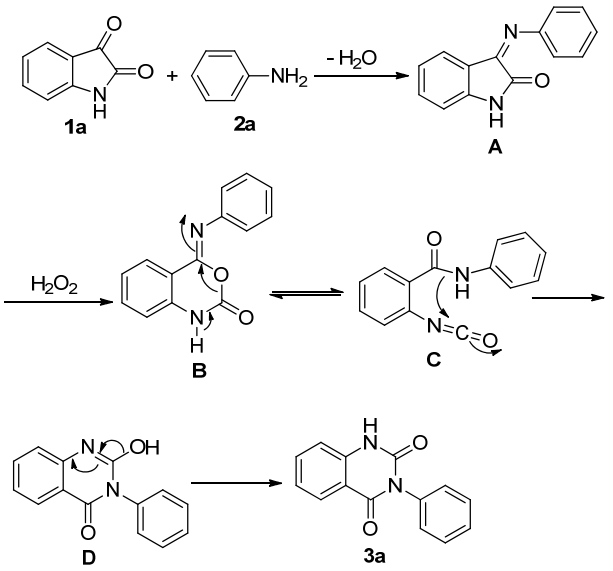
Continued

Entry	R^1, R^2	R^3	Product	Yield[b]/%
30	**1h** (OCH_3, H)	4-$CH_3CH_2C_6H_4$ (**2c**)	**3ac**	38
31	**1a** (H, H)	*n*-Bu (**2q**)	—	trace
32	**1a** (H, H)	CH_3CH_2 (**2r**)	—	trace
33	**1a** (H, H)	2-pyridyl (**2s**)	—	trace
34	**1a** (H, H)	2,6-$(CH_3)_2C_6H_3$ (**2t**)	—	trace
35	**1a** (H, H)	2-CH_3-6-BrC_6H_3 (**2u**)	—	trace

[a] Reaction conditions: isatins **1** (0.1 mmol), arylamines **2** (0.1 mmol) and hydrogen peroxide (0.03 mL, 30%), $NaHCO_3$ (0.12 mmol) at room temperature in MeOH (1.5 mL) for 8 h. [b] Isolated yields.

2a as shown in Scheme 2. Initially, the intermediate **A** is produced by the Knoevenagel condensation between isatin **1a** and arylamine **2a** in the presence of $NaHCO_3$. Subsequently, the intermediate **B** was generated from the intermediate **A** via the Baeyer-Villiger oxidation with hydrogen peroxide. Then, the intermediate **D** was afforded from the intramolecular nucleophilic addition of the isocyanate carboxamide intermediate **C**, which was formed by the rearrangement of intermeditate **B**. Finally, by the stabilization of the intermediate **D**, the final product **3a** was afforded.

Scheme 2 Possible reaction mechanism for the formation of the quinazoline-2,4-diones



In the present study, the antibacterial activities of the synthesized compounds were screened against two Gram-negative bacterial strains (*E. coli*, and *K. pneumonia*) and two Gram-positive bacterial strains (*S. epidermidis*, and *S. aureus*) using the Broth microdilution method. The results revealed that the synthesized compounds exhibited antibacterial activity against both *S. epidermidis* and *S. aureus*. The results are summarized in Table 3 and Figure 2. Compared to the standard bacteria against *S. epidermidis*, compound **3t** showed improved activity. In addition, compounds **3p**, **3q**, **3r**, **3t**, **3u** and **3z** showed good antibacterial activity against the *S. aureus* strain which is resistant to most known antibiotics (levofloxacin MIC＝32 μg/mL).

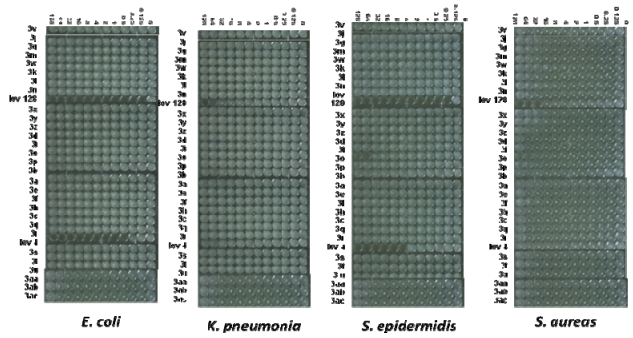


Figure 2 The photos of antibacterial activities with the synthesized compounds.

The quinazoline-2,4-dione skeleton is the core structure of many pharmacological agents and natural alkaloids. It was the substitutions on quinazoline-2,4-dione ring functionality that had distinctive effect on the potency of these compounds against the tested bacterial strains. For instance compound **3t**, with 5-CH_2CH_3 on quinazoline-2,4-dione ring and with 4-CH_3 substituent on the phenyl ring of arylamine was found to be the most active against *S. epidermidis* and good antibacterial activity against *S. aureus*. Similarly, compounds **3p**, **3q**, **3r** and **3z** with halogen groups (Cl, Br, I) on quinazoline-2,4-dione ring were found to have good antibacterial activity against *S. aureus*. Inaddition, compounds **3t**, **3u** with an electron-donating group on quinazoline-2,4-dione ring were also found to have moderate antibacterial activity against *S. aureus*.

Conclusions

In summary, we have developed a green and efficient one-pot synthetic route to prepare quinazoline-2,4-diones from readily available isatins and arylamines using hydrogen peroxide as an oxidant at room temperature. This rearrangement oxidation provided a facile method to the direct synthesis of quinazoline-2,4-diones and exhibited good functional group tolerability, obviating the need for oxidants and only environmentally benign H_2O was released. This reaction is interest-

ing in keeping with the notion of green chemistry because of the use of hydrogen peroxide as the terminal oxidant. The antibacterial activity of all compounds was also evaluated for both Gram-negative and Gram-positive bacteria. Some of the testing compounds inhibited the growth of the *Staphylococcus aureus*, which could potentially solve the problem of multidrug resistance.

Table 3 The MIC of all compounds against bacteria (μg/mL)

Comp.	HPLC purity/%	*S. epidermidis*	*E. coli*	*S. aureus*	*K. pneumoniae*
3a	97.95	>128	>128	>128	>128
3b	96.19	>128	>128	>128	>128
3c	100	>128	>128	>128	>128
3d	100	>128	>128	>128	>128
3e	100	>128	>128	>128	>128
3f	98.06	>128	>128	>128	>128
3g	100	>128	>128	>128	>128
3h	100	>128	>128	>128	>128
3i	98.08	>128	>128	>128	>128
3j	100	>128	>128	>128	>128
3k	91.31	>128	>128	>128	>128
3l	97.84	>128	>128	>128	>128
3m	100	>128	>128	>128	>128
3n	99.78	>128	>128	>128	>128
3o	100	>128	>128	>128	>128
3p	98.05	>128	>128	64	>128
3q	100	>64	>64	64	>64
3r	100	>128	>128	64	>128
3s	98.64	>128	>128	128	>128
3t	100	64	>128	64	>128
3u	100	>128	>128	64	>128
3v	98.91	>128	>128	>128	>128
3w	100	>128	>128	>128	>128
3x	92.08	>128	>128	>128	>128
3y	92.87	>128	>128	>128	>128
3z	100	>128	>128	32	>128
3aa	100	>128	>128	128	>128
3ab	100	>128	>128	128	>128
3ac	97.16	>128	>128	>128	>128
levofloxacin		0.125	0.002	32	64

Experimental

Chemistry

Unless otherwise specified, all reagents and starting materials were purchased from commercial sources and used as received, and the solvents were purified and dried by standard procedures. The chromatography solvents were technical grade and distilled prior to use. Flash chromatography was performed using 200−300 mesh silica gel with the indicated solvent system according to standard techniques. The ^{1}H and ^{13}C NMR data were recorded on 400 MHz NMR spectrometers, unless otherwise specified. Chemical shifts (δ) in parts per million are reported relative to the residual signals of chloroform (δ 7.26 for ^{1}H and 76.1 for ^{13}C). Multiplicities are described as s (singlet), d (doublet), t (triplet), q (quartet), or m (multiplet), and coupling constants (J) are reported in hertz. HRMS analysis with a quadrupole time-of-flight mass spectrometer yielded ion mass/charge (m/z) ratios in atomic mass units. IR spectra were measured as dry films (KBr), and peaks are reported in terms of wave number (cm^{-1}).

General procedure for the synthesis of 1*H*-quinazoline-2,4-dione derivatives 3

To a solution of isatin **1** (0.1 mmol) and aryamine **2** (0.1 mmol) in MeOH (1.5 mL), $NaHCO_3$ (0.12 mmol) and hydrogen peroxide (0.03 mL, 30%) were added and the resulting mixture was stirred for 8 h at room temperature. Upon the completion of this reaction (monitored by TLC), the mixture was evaporated in vacuum, diluted with CH_2Cl_2 (3×10 mL), and washed by brine. Organic layers were combined, dried over Na_2SO_4, filtered, and evaporated in a vacuum. The residue was purified by flash column chromatography on silica gel (300−400 mesh) with CH_2Cl_2 and MeOH (20∶1, *V*/*V*) as eluting solvent to give the desired products **3**.

3-Phenylquinazoline-2,4(1*H*,3*H*)-dione (3a)[9] White solid. m.p. 267−269 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.54 (s, 1H), 7.94 (t, J=7.2 Hz, 1H), 7.72−7.67 (m, 1H), 7.50−7.40 (m, 3H), 7.33 (d, J=6.8 Hz, 2H), 7.24 (t, J=7.6 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 162.6, 150.6, 140.3, 136.2, 135.6, 129.5, 129.2, 128.5, 128.0, 122.9, 115.7, 114.8; IR (KBr) v: 3198, 3144, 1732, 1648, 1491, 1438, 1404, 1275, 1170, 758, 702, 692, 661, 577, 547 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{11}N_2O_2$ ($[M+H]^+$) 239.0821, found 239.0809.

3-*p*-Tolylquinazoline-2,4(1*H*,3*H*)-dione (3b)[9] White solid. m.p. 265−267 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.94−7.92 (m, 1H), 7.71−7.67 (m, 1H), 7.28 (d, J=8.4 Hz, 2H), 7.24 (d, J=8.4 Hz, 2H), 7.19−7.16 (m, 2H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 162.7, 150.7, 140.3, 137.91, 135.6, 133.5, 129.7, 129.2, 128.0, 122.9, 115.7, 114.8, 21.2; IR (KBr) v: 3200, 3144, 1731, 1650, 1604, 1513, 1492, 1440, 1405, 1275, 1168, 812, 759, 692, 651, 518 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{13}N_2O_2$ ($[M+H]^+$) 253.0977, found 253.0971.

3-(4-Ethylphenyl)quinazoline-2,4(1*H*,3*H*)-dione (3c) Yellow solid. m.p. 288−290 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.52 (s, 1H), 7.94 (d, J=8.0 Hz, 1H), 7.71 (t, J=7.2 Hz, 1H), 7.31 (d, J=8.0 Hz, 2H), 7.23 (t, J=8.4 Hz, 4H), 2.69 (m, 2H), 1.25 (t, J=7.6 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 162.7, 150.7, 144.1, 140.2, 135.6, 133.7, 129.3, 128.6, 128.0, 122.9, 115.6, 114.7, 28.3, 16.0; IR (KBr) v: 3066, 2932, 1723, 1666, 1609, 1489, 1445, 1401, 1288, 1151, 870, 825,

755, 671, 508 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{15}N_2O_2$ ($[M+H]^+$) 267.1134, found 267.1122.

3-(4-Methoxyphenyl)quinazoline-2,4(1*H*,3*H*)-dione (3d) White soild. m.p. 298−300 ℃. ^1H NMR (400 MHz, DMSO-d_6) δ: 11.64 (s, 1H), 7.95 (d, J=7.6 Hz, 1H), 7.71 (t, J=6.8 Hz, 1H), 7.32−7.22 (m, 4H), 7.03 (d, J=8.0 Hz, 2H), 3.82 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 162.8, 159.2, 150.8, 140.3, 135.5, 130.4, 128.6, 127.9, 122.8, 115.7, 114.7, 114.4, 55.7; IR (KBr) v: 3439, 2938, 1720, 1660, 1513, 1490, 1447, 1405, 1249, 1175, 1030, 827, 760, 669, 539 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{13}N_2O_3$ ($[M+H]^+$) 269.0926, found 269.0924.

3-(3-Methoxyphenyl)quinazoline-2,4(1*H*,3*H*)-dione (3e)[9] White solid. m.p. 256−258 ℃; ^1H NMR (400 MHz, DMSO-d_6) δ: 11.52 (s, 1H), 7.93−7.91 (m, 1H), 7.69 (t, J=3.6 Hz, 1H), 7.38 (t, J=6.4 Hz, 1H), 7.23−7.19 (m, 2H), 6.99−6.97 (m, 1H), 6.93 (t, J=1.6 Hz, 1H), 6.88−6.86 (m, 1H), 3.75 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 162.5, 160.1, 150.5, 140.2, 137.3, 135.6, 129.8, 128.1, 122.9, 121.7, 115.6, 115.3, 114.7, 114.2, 55.7; IR (KBr) v: 3440, 3197, 3065, 3001, 1736, 1659, 1606, 1492, 1405, 1383, 1286, 1249, 1156, 1030, 825, 760, 696, 539 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{13}N_2O_3$ ($[M+H]^+$) 269.0926, found 269.0924.

3-(4-Fluorophenyl)quinazoline-2,4(1*H*,3*H*)-dione (3f) White solid. m.p. 290−292 ℃; ^1H NMR (400 MHz, DMSO-d_6) δ: 11.55 (s, 1H), 7.94 (d, J=7.6 Hz, 1H), 7.71 (t, J=8.0 Hz, 1H), 7.41−7.37 (m, 2H), 7.33 (t, J=8.8 Hz, 2H), 7.24 (t, J=8.0 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 163.2 (d, $^1J_{CF}$=53.7 Hz), 160.8, 150.7, 140.2, 135.6, 132.4 (d, $^1J_{CF}$=3.9 Hz), 131.7 (d, $^3J_{CF}$=8.6 Hz), 128.0, 122.9, 116.2, 115.9 (d, $^2J_{CF}$=25.4 Hz), 114.7; IR (KBr) v: 3201, 3145, 1732, 1647, 1508, 1441, 1402, 1276, 1237, 1170, 832, 692, 652, 507 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{10}FN_2O_2$ ($[M+H]^+$) 257.0726, found 257.0720.

3-(4-Chlorophenyl)quinazoline-2,4(1*H*,3*H*)-dione (3g)[9] White solid. m.p. 295−297 ℃; ^1H NMR (400 MHz, DMSO-d_6) δ: 11.57 (s, 1H), 7.94 (d, J=7.6 Hz, 1H), 7.72−7.68 (m, 1H), 7.56 (d, J=8.8 Hz, 2H), 7.39 (d, J=8.8 Hz, 2H), 7.24 (t, J=8.0 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 162.6, 150.5, 140.3, 135.7, 135.1, 133.2, 131.5, 129.3, 128.0, 123.0, 115.7, 114.7; IR (KBr) v: 3199, 3062, 1732, 1648, 1492, 1440, 1405, 1275, 1169, 1092, 1016, 820, 761, 739, 691, 603, 514 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{10}ClN_2O_2$ ($[M+H]^+$) 273.0431, found 273.0423.

3-(3-Chlorophenyl)quinazoline-2,4(1*H*,3*H*)-dione (3h) White solid. m.p. 283−285 ℃; ^1H NMR (400 MHz, DMSO-d_6) δ: 11.59 (s, 1H), 7.94 (d, J=6.0 Hz, 1H), 7.71 (t, J=5.8 Hz, 1H) 7.51 (d, J=4.4 Hz, 3H), 7.34 (t, J=6.4 Hz, 1H), 7.24 (t, J=6.0 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 162.5, 150.5, 140.3, 137.7, 135.7, 133.3, 130.8, 129.8, 128.7, 128.6, 128.0, 123.0, 115.7, 114.8; IR (KBr) v: 3240, 3199, 3145, 1735, 1725, 1604, 1491, 1441, 1405, 1275, 1166, 1091, 761, 603 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{10}ClN_2O_2$ ($[M+H]^+$) 273.0431, found 273.0423.

3-(4-Bromophenyl)quinazoline-2,4(1*H*,3*H*)-dione (3i)[9] White solid. m.p. 297−299 ℃; ^1H NMR (400 MHz, DMSO-d_6) δ: 9.74 (s, 1H), 7.95−7.93 (m, 1H), 7.72−7.67 (m, 3H), 7.33−7.31 (m, 2H), 7.25−7.21 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 162.5, 150.4, 140.2, 135.6, 135.5, 132.2, 131.8, 127.9, 122.9, 121.6, 115.7, 114.7; IR (KBr) v: 3438, 3065, 2937, 1723, 1670, 1489, 1448, 1404, 1282, 1154, 1068, 1012, 820, 758, 728, 591 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{10}BrN_2O_2$ ($[M+H]^+$) 316.9926, found 316.9919.

3-(4-Iodophenyl)quinazoline-2,4(1*H*,3*H*)-dione (3j) White solid. m.p. > 300 ℃. ^1H NMR (400 MHz, DMSO-d_6) δ: 11.56 (s, 1H), 7.94 (d, J=7.2 Hz, 1H), 7.85 (d, J=7.2 Hz, 2H), 7.69 (d, J=6.8 Hz, 1H), 7.23 (d, J=7.2 Hz, 2H), 7.16 (d, J=7.2 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 162.5, 150.4, 140.2, 138.2, 136.1, 135.7, 131.9, 128.0, 123.0, 115.7, 114.7, 94.7; IR (KBr) v: 3062, 2934, 1722, 1668, 1616, 1487, 1448, 1404, 1290, 1153, 1006, 871, 814, 757, 723, 582 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{10}IN_2O_2$ ($[M+H]^+$) 364.9787, found 364.9775.

3-*o*-Tolylquinazoline-2,4(1*H*,3*H*)-dione (3k) White solid. m.p. 253−255 ℃; ^1H NMR (400 MHz, DMSO-d_6) δ: 11.62 (s, 1H), 7.99 (d, J=7.2 Hz, 1H), 7.73 (t, J=7.2 Hz, 1H), 7.38−7.24 (m, 6H), 2.08 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 162.2, 150.1, 140.3, 136.1, 135.7, 135.3, 130.8, 129.6, 128.8, 128.0, 127.0, 123.0, 115.7, 114.5, 17.4; IR (KBr) v: 3201, 3147, 2359, 1731, 1651, 1493, 1436, 1399, 1271, 1170, 877, 757, 717, 576 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{13}N_2O_2$ ($[M+H]^+$) 253.0977, found 253.0971.

3-(2-Ethylphenyl)quinazoline-2,4(1*H*,3*H*)-dione (3l) White solid. m.p. 274−275 ℃; ^1H NMR (400 MHz, DMSO-d_6) δ: 11.63 (s, 1H), 7.99 (d, J=7.6 Hz, 1H), 7.75 (t, J=7.6 Hz, 1H), 7.41−7.24 (m, 6H), 2.42−2.37 (m, 2H), 1.08 (t, J=7.6 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 162.5, 150.4, 141.4, 140.3, 135.7, 134.7, 129.7, 129.1, 129.0, 128.0, 127.0, 123.0, 115.7, 114.4, 23.9, 14.4; IR (KBr) v: 3248, 3203, 2360, 1731, 1651, 1492, 1436, 1398, 1272, 1169, 879, 755, 662, 579 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{15}N_2O_2$ ($[M+H]^+$) 267.1134, found 267.1122.

3-(3-Ethylphenyl)quinazoline-2,4(1*H*,3*H*)-dione White solid. m.p. 289−291 ℃; ^1H NMR (400 MHz, DMSO-d_6) δ: 11.52 (s, 1H), 7.93 (d, J=6.8 Hz, 1H), 7.71−7.67 (m, 1H), 7.39 (t, J=6.2 Hz, 1H), 7.26−7.20 (m, 3H), 7.14 (s, 1H), 7.11 (d, J=6.4 Hz, 1H), 2.66−2.62 (m, 2H), 1.21 (t, J=6.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 150.6, 144.9, 140.2, 136.1, 135.6, 129.1, 128.6, 128.0, 127.9, 126.7, 122.9, 115.6, 114.7, 28.2, 15.7; IR (KBr) v: 3250, 3201, 2365, 1736, 1657, 1492, 1436, 1390, 1255, 1160, 889, 755, 652, 573 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{15}N_2O_2$ ($[M+H]^+$) 267.1134, found 267.1122.

3-(2-Isopropylphenyl)quinazoline-2,4(1*H*,3*H*)-dione (3n) White solid. m.p. 248−250 ℃; ^1H NMR (400 MHz, DMSO-d_6) δ: 11.62 (s, 1H), 7.99 (d, J=7.6

Hz, 1H), 7.75 (t, J=7.6 Hz, 1H), 7.49−7.42 (m, 2H), 7.33−7.22 (m, 4H), 2.73−2.69 (m, 1H), 1.14 (d, J=6.8 Hz, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 162.7, 150.5, 146.3,140.3, 135.7, 133.7, 129.5, 129.3, 128.1, 126.8, 126.5, 123.0, 115.7, 114.4, 28.3, 23.7; IR (KBr) v: 3255, 2967, 1732, 1651, 1617, 1492, 1435, 1400, 1269, 1169, 753, 693, 662, 531 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{17}N_2O_2$ ([M+H]$^+$) 281.1290, found 281.1281.

6-Fluoro-3-*p*-tolylquinazoline-2,4(1*H*,3*H*)-dione (3o) White solid. m.p. 255−257 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.56 (s, 1H), 7.64−7.59 (m, 2H), 7.28 (t, J=7.6 Hz, 3H), 7.18 (d, J=8.8 Hz, 2H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 162.0 (d, $^3J_{CF}$=3.9 Hz), 159.0 (d, $^1J_{CF}$=238.5 Hz), 150.4, 138.0, 136.9, 133.4, 129.7, 129.1, 123.7 (d, $^2J_{CF}$=24.6 Hz), 118.0 (d, $^3J_{CF}$=8.2 Hz), 115.9 (d, $^2J_{CF}$=11.2 Hz), 113.1 (d, $^2J_{CF}$=23.3 Hz), 21.2; IR (KBr) v: 3197, 1737, 1647, 1512, 1378, 1272, 1142, 903, 831, 773, 682, 654, 516 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{12}FN_2O_2$ ([M+H]$^+$) 271.0883, found 271.0880.

6-Chloro-3-*p*-tolylquinazoline-2,4(1*H*,3*H*)-dione (3p) White solid. m.p. 291−293 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.66 (s, 1H), 7.85 (d, J=2.4 Hz, 1H), 7.75−7.72 (m, 1H), 7.28−7.23 (m, 3H), 7.19 (d, J=8.0 Hz, 2H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 161.7, 150.4, 139.0, 138.0, 135.3, 133.2, 129.7, 129.0, 126.8, 117.8, 116.1, 21.1; IR (KBr) v: 3055, 1722, 1674, 1604, 1479, 1440, 1380, 1284, 1152, 830, 778, 729, 668, 533, 515 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{12}ClN_2O_2$ ([M + H]$^+$) 287.0587, found 287.0579.

6-Bromo-3-*p*-tolylquinazoline-2,4(1*H*,3*H*)-dione (3q) White solid. m.p. 267−269 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.66 (s, 1H), 7.99 (d, J=2.4 Hz, 1H), 7.87−7.84 (m, 1H), 7.28 (d, J=8.0 Hz, 2H), 7.19−7.17 (m, 3H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 161.6, 150.4, 139.4, 138.1, 138.0, 133.2, 129.8, 129.7, 129.0, 118.0, 116.6, 114.3, 21.1; IR (KBr) v: 3447, 3195, 1716, 1670, 1613, 1503, 1399, 1316, 1270, 1164, 1141, 1054, 882, 779, 669, 518 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{12}BrN_2O_2$ ([M + H]$^+$) 331.0082, found 331.0073.

6-Iodo-3-*p*-tolylquinazoline-2,4(1*H*,3*H*)-dione (3r) White solid. m.p.＞300 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.62 (s, 1H), 8.16 (d, J=2.0 Hz, 1H), 7.99−7.97 (m, 1H), 7.28 (d, J=8.0 Hz, 2H), 7.18 (d, J=8.0 Hz, 2H), 7.06 (d, J=8.8 Hz, 1H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 161.5, 150.4, 143.5, 139.7, 137.9, 135.8, 133.2, 129.7, 129.0, 118.0, 116.9, 85.5, 21.1; IR (KBr) v: 3246, 1716, 1670, 1609, 1514, 1490, 1427, 1366, 1270, 1159, 823, 759, 716, 656, 518 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{12}IN_2O_2$ ([M+H]$^+$) 378.9943, found 378.9936.

6-Methyl-3-*p*-tolylquinazoline-2,4(1*H*,3*H*)-dione (3s)[9] White solid. m.p. 285−287 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.42 (s, 1H), 7.73 (s, 1H), 7.52−7.49 (m, 1H), 7.27 (d, J=8.0 Hz, 2H), 7.17−7.12 (m, 3H), 2.36 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 162.7, 150.6, 138.1, 137.8, 136.5, 133.6, 132.1, 129.7, 129.2, 127.4, 115.6, 114.5, 21.2, 20.7; IR (KBr) v: 3217, 2919, 1731, 1651, 1514, 1435, 1380, 1275, 1194, 821, 758, 654, 563, 512 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{15}N_2O_2$ ([M + H]$^+$) 267.1134, found 267.1124.

6-Ethyl-3-*p*-tolylquinazoline-2,4(1*H*,3*H*)-dione (3t) White solid. m.p. 248−250 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.45 (s, 1H), 7.77 (s, 1H), 7.59−7.56 (m, 1H), 7.28 (d, J=8.4 Hz, 2H), 7.19 (m, J=8.0 Hz, 3H), 2.70−2.64 (m, 2H), 2.38 (s, 3H), 1.22 (t, J=7.6 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 162.7, 150.7, 138.5, 138.3, 137.8, 135.6, 133.6, 129.7, 129.2, 126.3, 115.7, 114.6, 27.8, 21.2, 16.1; IR (KBr) v: 3120, 2960, 1731, 1651, 1513, 1436, 1386, 1274, 1189, 839, 756, 656, 512 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{17}N_2O_2$ ([M+H]$^+$) 281.1290, found 281.1280.

6-Methoxy-3-*p*-tolylquinazoline-2,4(*1H*,3*H*)-dione (3u) White solid. m.p. 241−243 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.41 (s, 1H), 7.38−7.34 (m, 2H), 7.30 (d, J=8.4 Hz, 2H), 7.21 (t, J=8.4 Hz, 3H), 3.81 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 162.5, 155.1, 150.4, 137.8, 134.4, 133.7, 129.7, 129.6, 129.2, 124.4, 117.3, 115.2, 109.1, 56.0, 21.1; IR (KBr) v: 3251, 2925, 1716, 1662, 1505, 1442, 1361, 1270, 1149, 1025, 827, 763, 683, 657, 567, 514 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{15}N_2O_3$ ([M + H]$^+$) 283.1083, found 283.1072.

8-Chloro-3-*p*-tolylquinazoline-2,4(1*H*,3*H*)-dione (3v) White solid. m.p. 245−247 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.06 (s, 1H), 7.94 (d, J=7.6 Hz, 1H), 7.85 (d, J=7.6 Hz, 1H), 7.29−7.19 (m, 5H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 161.9, 150.4, 138.0, 137.1, 135.4, 133.3, 129.8, 129.0, 127.1, 123.5, 119.1, 116.9, 21.1; IR (KBr) v: 3191, 2913, 1726, 1642, 1605, 1498, 1441, 1380, 1288, 1511, 920, 830, 776, 725, 667, 532, 512 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{12}ClN_2O_2$ ([M+H]$^+$) 287.0587, found 287.0584.

8-Methyl-3-*p*-tolylquinazoline-2,4(1*H*,3*H*)-dione (3w) Yellow solid. m.p. 282−284 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.78 (s, 1H), 7.84 (d, J=7.2 Hz, 1H), 7.55 (d, J=7.2 Hz, 1H), 7.31 (d, J=8.0 Hz, 2H), 7.22 (d, J=8.4 Hz, 2H), 7.16 (t, J=7.6 Hz, 1H), 2.43 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 162.7, 150.9, 138.5, 137.9, 136.5, 133.5, 129.7, 129.1, 125.81, 124.4, 122.6, 114.9, 21.1, 17.5; IR (KBr) v: 3223, 3053, 1735, 1648, 1482, 1433, 1380, 1336, 1224, 1150, 835, 758, 709, 563, 515 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{15}N_2O_2$ ([M+H]$^+$) 267.1134, found 267.1125.

7-Fluoro-3-phenylquinazoline-2,4(1*H*,3*H*)-dione (3x) White solid. m.p. 283−285 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.41 (s, 1H), 7.71−7.57 (m, 2H), 7.49 (t, J=6.8 Hz, 2H), 7.43 (t, J=7.6 Hz, 1H), 7.31 (d, J=7.2 Hz, 2H), 7.25−7.18 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 162.1 (d, $^3J_{CF}$=3.5 Hz), 158.8 (d, $^1J_{CF}$=238.6 Hz), 150.7, 137.8, 136.2, 129.4, 129.2, 128.5, 123.6 (d, $^2J_{CF}$=24.7 Hz), 118.4 (d, $^3J_{CF}$=7.7 Hz), 115.8 (d, $^3J_{CF}$=8.2 Hz), 112.9 (d, $^2J_{CF}$=23.9 Hz); IR

(KBr) *v*: 3077, 2924, 1731, 1669, 1490, 1441, 1379, 1287, 1135, 830, 774, 713, 674, 547 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{10}FN_2O_2$ ($[M+H]^+$) 257.0726, found 257.0717.

6-Iodo-3-phenylquinazoline-2,4(1*H*,3*H*)-dione (3y) White solid. m.p. 289−291 ℃. ^1H NMR (400 MHz, DMSO-d_6) δ: 11.66 (s, 1H), 8.16 (s, 1H), 8.01−7.98 (m, 1H), 7.50−7.42 (m, 3H), 7.32 (d, J=7.2 Hz, 2H), 7.07 (d, J=8.4 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 161.4, 150.4, 143.6, 139.8, 135.9, 135.8, 129.4, 129.2, 128.6, 118.0, 116.9, 85.6; IR (KBr) *v*: 3220, 1744, 1639 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{10}IN_2O_2$ ($[M+H]^+$) 364.9787, found 364.9779.

6-Chloro-3-(4-isopropylphenyl)quinazoline-2,4-(1*H*,3*H*)-dione (3z) White solid. m.p. 260−262 ℃; ^1H NMR (400 MHz, DMSO-d_6) δ: 11.70 (s, 1H), 7.88 (d, J=2.4 Hz, 1H), 7.78−7.76 (m, 1H), 7.38 (d, J=8.4 Hz, 2H), 7.27−7.22 (m, 3H), 2.99−2.96 (m, 1H), 1.28 (d, J=6.8 Hz, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 161.7, 150.4, 148.7, 139.1, 135.4, 133.5, 129.1, 127.1, 126.8, 126.8, 117.8, 116.2, 33.6, 24.2; IR (KBr) *v*: 3268, 2913, 1734, 1670, 1510, ,1459, 1380, 1197, 894, 778, 677, 583, 536 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{16}ClN_2O_2$ ($[M+H]^+$) 315.0900, found 315.0891.

6-Ethyl-3-(4-fluorophenyl)quinazoline-2,4(1*H*,3*H*)-dione (3aa) White solid. m.p. 254−256 ℃; ^1H NMR (400 MHz, DMSO-d_6) δ: 11.48 (s, 1H), 7.75 (s, 1H), 7.57 (d, J=6.8 Hz, 1H), 7.39−7.28 (m, 4H), 7.17 (d, J=8.4 Hz, 1H), 2.69−2.62 (m, 2H), 1.18 (t, J=7.6 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 162.7, 160.7 (d, $^1J_{CF}$=242.8 Hz), 150.6, 138.5, 138.3, 135.6, 132.4 (d, $^3J_{CF}$=3.0 Hz), 131.6 (d, $^3J_{CF}$=9.2 Hz), 126.2, 116.1, 115.9 (d, $^2J_{CF}$=16.4 Hz), 114.5, 27.8, 16.0; IR (KBr) *v*: 3252, 2962, 1725, 1666, 1431, 1431, 1388, 1274, 1223, 1187, 1153, 837, 760, 657, 509 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{14}FN_2O_2$ ($[M+H]^+$) 285.1039, found 285.1030.

3-(4-Chlorophenyl)-6-ethylquinazoline-2,4(1*H*,3*H*)-dione (3ab) White solid. m.p. 265−267 ℃; ^1H NMR (400 MHz, DMSO-d_6) δ: 7.75 (s, 1H), 7.55 (d, J=8.4 Hz, 3H), 7.36 (d, J=8.4 Hz, 2H), 7.18 (d, J=8.0 Hz, 1H), 2.67-2.62 (m, 2H), 1.18 (t, J=7.6 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 162.7, 150.6, 138.8, 138.3, 135.5, 135.3, 133.0, 131.4, 129.2, 126.1, 116.1, 114.5, 27.8, 16.0; IR (KBr) *v*: 3052, 2973, 1736, 1479, 1469, 1380, 1280, 1197, 1019, 920, 799, 677, 583, 515 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{14}ClN_2O_2$ ($[M+H]^+$) 301.0744, found 301.0733.

3-(4-Ethylphenyl)-6-methoxyquinazoline-2,4(1*H*,3*H*)-dione (3ac) White solid. m.p. 286−288 ℃; ^1H NMR (400 MHz, DMSO-d_6) δ: 11.56 (s, 1H), 7.37−7.27 (m, 5H), 7.21 (d, J=4.4 Hz, 2H), 3.81 (s, 3H), 2.71−2.66 (m, 2H), 1.26 (t, J=7.6 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 162.5, 155.0, 150.4, 143.9, 134.4, 133.8, 129.2, 128.5, 124.4, 117.4, 115.1, 108.9, 56.0, 28.2, 15.9; IR (KBr) *v*: 3438, 2964, 1723, 1660, 1513, 1492, 1436, 1360, 1283, 1149, 1027, 761, 567 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{17}N_2O_3$ ($[M+H]^+$) 297.1239, found 297.1230.

Biological assays

The bacterial strain of *Staphylococcus aureus* (Identification number: WXI-004) was obtained from WuXi AppTec (Shanghai) Co., Ltd. Other bacterial strains, such as *Staphylococcus epidermidis* (Identification number: ATCC 35984), *Escherichia coli* (Identification number: ATCC 25922), and *Klebsiella pneumoniae* (Identification number: ATCC BAA-1898), were obtained from American Type Culture Collection (ATCC).

Preparing compound testing plates

Testing compounds were balanced and transferred into 1.5 mL sterile centrifuge tubes. Pure DMSO (Sigma D5879-1L, 12.8 mg/mL) was used to dissolve the compounds. This stock solution was made and used on the day of testing. On the day of testing, 980μCAMHB (Cation-adjusted Muller Hinton Broth, BD-212322) was added into column 1 of a 96-deep well plate (Corning-3960) and rest of the wells were filled with 500 μL CAMHB. An aliquot of 20 μL stock solution was added into a well in column 1 and mixed by pipetting. Then, 500 μL of the solution from well 1 was transferred to well 2, and mixed by pipetting, and 2-fold serial dilution was performed so forth until well 11. The well 12 contained only CAMHB. Aliquots of 100 μL solution were replicating transferred into 4 U-bottom 96-well testing plates (Corning-3788), one for each strain. The residue solution was transferred to another 96-well testing plate for observing compounds precipitation. This plate was not inoculated with bacteria. For some stock solutions in which the compounds were prepared in 6.4 mg/mL, the volume was adjusted accordingly.

Preparing bacterial inoculum

A day prior to the testing, –80 ℃ bacterial glycerol stocks were streaked onto MHAII (Muller Hinton II Agar, BD-211438) plates. The plates were incubated at 37 ℃ for 20 h. On the day of testing, single colonies were picked from the plate and suspended in 5 mL of sterile saline. A turbidity meter (Siemens MicroScan Turbidity Meter) was used to adjust the turbidity to 0.5 McFarland standard, which is equivalent to a bacterial density of ~1.0×10^8 CFU/mL. The bacteria/saline suspension was diluted another 100× in a CAMHB to 1.0×10^6 CFU/mL. This was used as the inoculum.

Minimum inhibitory concentration (MIC) test

An aliquot of 100 μL bacterial inoculum was transferred into each well of the compound testing plates. Each testing plate was inoculated with a single strain to prevent cross contamination. The final testing concentrations were 128, 64, 32, 16, 8, 4, 2, 1, 0.5, 0.25, 0.125 and 0 μg/mL. The starting bacterial density was ~5×10^5 CFU/mL. The testing plates were incubated at 37 ℃ for 20 h before the MICs were read.

Determining the MIC

After the 20 h incubation, the MICs were evaluated by visual observation. Based on the CLSI-M7, the MIC is defined as the minimum compound concentration that completely or significantly inhibits the growth of bacterium.

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