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Efficient and convenient synthesis of spiroindolinone-quinazolines induced by stannous chloride

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ABSTRACT

An efficient, convenient, one-pot synthesis of 1′*H*-spiro[indoline-3,2′-quinazoline]-2,4′(3′*H*)-dione derivatives was accomplished in good yields via the novel reductive cyclization of 2-nitrobenzamides and isatins mediated by $SnCl_2\cdot 2H_2O$ system. A variety of substrates can participate in the process with good yields, making this methodology have broad applicability. The structure of compound **3c** has been confirmed by X-ray diffraction analysis.

1. Introduction

2,3-Dihydroquinazoline-4(3*H*)-ones and spirooxindole derivatives are important classes of heterocyclic compounds. It has been reported that 2,3-dihydroquinazolin-4(3*H*)-ones possess a broad spectrum of biological and pharmaceutical activities, such as analgesic, antitumor, diuretic, and herbicide activities.[1] In addition, these compounds can easily be oxidized to quinazolin-4(3*H*)-one analogues,[2] which also include important pharmacologically active compounds.[3] Several methods have been reported for the synthesis of 2,3-dihydroquinazolinones.[4–6]

The indole core represents an interesting pharmacophore, which displays the feature of biological and pharmacological properties. Furthermore, the 3′-spirooxindoles formed by sharing of the 3′-carbon atom have been of interest to organic chemists because spirooxindole derivatives are characterized by interesting biological properties.[7] For instances, Spirotryprostain A and B, which have been isolated from the fermentation broth of *Aspergillus fumigatus*, have been identified as novel inhibitors of microtubule assembly.[8] Derivatives of spirooxindole exhibit a range of biological properties, including antimicrobial, antitumoral, antibiotic agents, and inhibitors of human NK-1 receptor.[9] Oxa and azaspiro derivatives are well-known,[9–11] but the preparation of corresponding quinazolinone analogues has been reported by only very few workers. e.g., List et al.[12] reported the synthesis of 1′*H*-spiro-[indoline-3,2′-quinazoline]-2,4′(3′*H*)-dione by reaction of 2-aminobenzamide with isatin. However this method required special catalyst and long reaction time. Recently Mohammadi et al.[13] also reported the synthesis of the same compounds via a three-component cyclocondensation of isatoic anhydride, isatins, and amines using $KAl(SO_4)_2\cdot 12H_2O$ as catalyst. In recent years, our interest has been focused on the usage of $SnCl_2$ reagent. We have previously reported the synthesis of 2-aryl-2*H*-indazoles,[14] 1-hydroxyquinazolinones,[15] quinoxaline derivatives,[16] imidazo[1,2-*c*]quinazoline-5(6*H*)-thione,[17] imidazo[1,2-*c*]quinazolin-5(6*H*)-one,[17] and pyrrolo[1,2-a]quinazoline,[18] respectively, mediated by $SnCl_2$ reagent. As part of our interest in the synthesis of spiroheterocyclic compounds,[19] we report herein the synthesis of 1′*H*-spiro[indoline-3,2′-quinazoline]-2,4′(3′*H*)-dione derivatives via the novel reductive cyclization of 2-nitrobenzamides with isatins mediated by $SnCl_2\cdot 2H_2O$ system.

2. Results and discussion

In a preliminary study, the reaction of 4-chloro-2-nitrobenzamide **1a** with isatin **2a** was chosen as model reaction to optimize the reaction conditions (Scheme 1). The results are summarized in Table 1.

As shown in Table 1, we first examined the effect of different organic solvents (entries 1–4) and concluded that ethanol was the best solvent for this reaction. Then, we also briefly examined the effect of different temperatures and ratio of **1a**/$SnCl_2\cdot 2H_2O$. The results showed that at refluxing temperature the reaction preceded smoothly in high yield. To further evaluate the influence of the ratio of **1a**/$SnCl_2\cdot 2H_2O$, the reaction was carried out in ethanol using a 1:1 to 1:5 ratio of **1a**/$SnCl_2\cdot 2H_2O$ (entries 5, 6, 4, 7, 8), leading to

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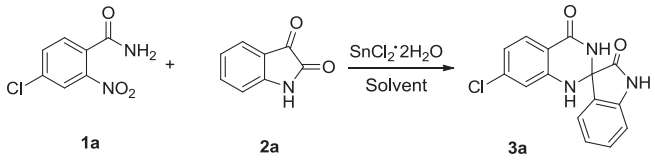


1a 2a 3a

Scheme 1. Model reaction.

Table 1
Optimization of temperature, ratio, and solvents in the synthesis of **3a**

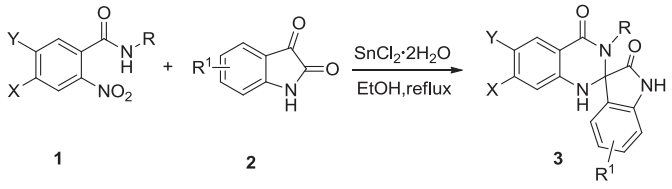
Entry	Solvent	Ratio[a]	Temperature (°C)	Yield[b] (%)
1	CH_3OH	1:3	Reflux	50
2	THF	1:3	Reflux	44
3	$CHCl_3$	1:3	Reflux	57
4	EtOH	1:3	Reflux	71
5	EtOH	1:1	Reflux	23
6	EtOH	1:2	Reflux	45
7	EtOH	1:4	Reflux	83
8	EtOH	1:5	Reflux	80
9	EtOH	1:4	rt	30
10	EtOH	1:4	40	55
11	EtOH	1:4	60	68

[a] Ratio of **1a** and $SnCl_2\cdot 2H_2O$ system.
[b] Isolated yields.

3a in 23%, 45%, 71%, 83%, and 80% yields, respectively. We concluded the best ratio of **1a**/$SnCl_2\cdot 2H_2O$ was 1:4.

With the optimized conditions in hand, we then performed the reaction of a variety of 2-nitrobenzamides **1** and isatins **2** via $SnCl_2\cdot 2H_2O$ system. The results are summarized in Table 2.

Table 2
Synthesis of spiroindolinone-quinazoline derivatives **3**



1 2 3

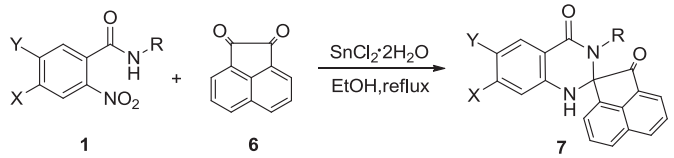
Entry	X	Y	R	R^1	Products	Isolated yield (%)
1	Cl	H	H	H	**3a**	83
2	Cl	H	4-FC_6H_4	H	**3b**	85
3	Cl	H	4-FC_6H_4	4-Cl	**3c**	82
4	H	Cl	H	H	**3d**	91
5	H	Cl	4-$CH_3C_6H_4$	5-Br	**3e**	86
6	H	Cl	3-$CH_3C_6H_4$	4-Br	**3f**	72
7	H	H	4-ClC_6H_4	5-Cl	**3g**	81
8	H	H	4-ClC_6H_4	5-Br	**3h**	86
9	H	H	4-ClC_6H_4	4-Br	**3i**	85
10	H	H	4-FC_6H_4	4-Br	**3j**	82
11	H	H	4-$CH_3C_6H_4$	4-Cl	**3k**	75
12	H	H	4-$CH_3C_6H_4$	4-Br	**3l**	86
13	H	CH_3	H	4-Cl	**3m**	82
14	H	CH_3	H	4-Br	**3n**	84
15	CF_3	H	H	H	**3o**	87
16	CF_3	H	4-$CH_3C_6H_4$	H	**3p**	82

As shown in Table 2, we were pleased to find that the method was applicable to a broad substrate scope on both substituted 2-nitrobenzamides and isatins. It can be seen that this protocol can be applied not only to the 2-nitrobenzamides with electron-withdrawing groups (such as halide and trifluoromethyl groups) or electron-donating groups (such as alkyl groups) but also to *N*-substituted-2-nitrobenzamides under the same conditions, which highlighted the wide scope of this reaction. Meanwhile, it was particularly noteworthy that the effects of different isatins were also investigated. 4-Substituted and 5-substituted isatins can also give moderate to good yields.

Encouraged by these results, we then focused our attention on the reaction of bis(2-nitrobenzamides) **4** with isatins **2**. To our delight, the desired product bis(spiroindolinone-quinazoline) **5** was obtained (Scheme 2).

As expected, when the isatin **2** was replaced by acenaphthylene-1,2-dione **6**, another series of 1′*H*,2*H*-spiro[acenaphthylene-1,2′-quinazoline]-2,4′(3′*H*)-dione **7** were obtained under the same reaction conditions. The results are summarized in Table 3.

Table 3
Synthesis of **7** from 2-nitrobenzamides **1** and acenaphthylene-1,2-diones **6**



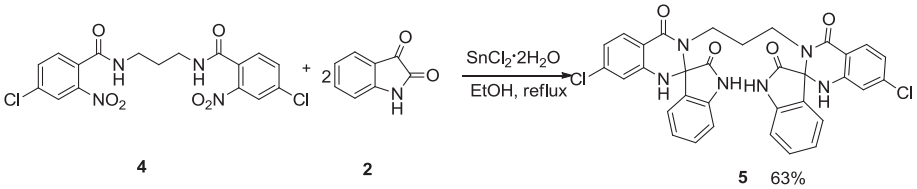
1 6 7

Entry	X	Y	R	Products	Isolated yield (%)
1	Cl	H	H	**7a**	80
2	H	H	4-FC_6H_4	**7b**	73
3	H	CH_3	H	**7c**	78
4	H	H	H	**7d**	83
5	H	H	4-BrC_6H_4	**7e**	69
6	H	H	$C_6H_5CH_2$	**7f**	82

Similarly, it can be seen that either 2-nitrobenzamides or *N*-substituted ones were well tolerated. They all reacted well with acenaphthylene-1,2-diones under the optimized conditions, and the corresponding products were obtained in moderate yields. No remarkable electronic effects on the reaction were observed.

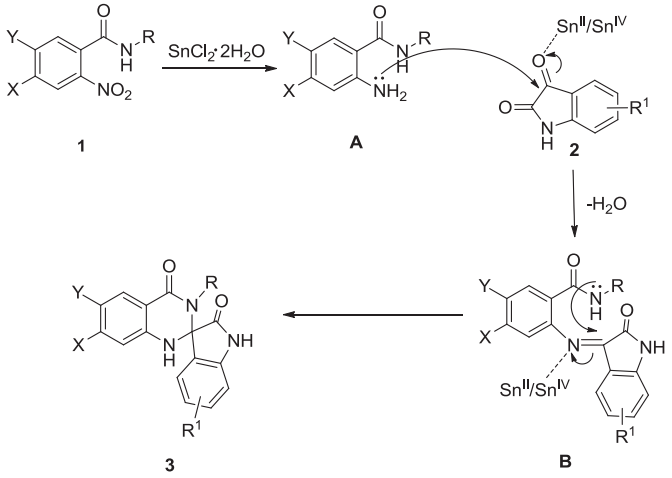
Although the detailed mechanism of the above reaction has not been clarified yet, the formation of spiroindolinone-quinazoline derivatives **3** can be explained by a possible mechanism presented in Scheme 3. In the initial step, 2-nitrobenzamides **1** was reduced by tin(II) chloride to 2-aminobenzamide **A** and Sn(II) was oxidated to Sn(IV). The 2-aminobenzamide **A** then reacted with isatins **2** with the aid of Sn(IV) or excess Sn(II) to give the intermediate **B**. Finally, products **3** were formed by attack of the amino group onto the central carbon atom of the imine mediated by Sn(IV) or excess Sn(II).

All the structures of products **3**, **5**, and **7** were characterized by IR, ^{1}H NMR, ^{13}C NMR, and HRMS spectra. The structure of **3c** was further confirmed by X-ray diffraction analysis. The molecular structure of the product **3c** is shown in Fig. 1.



4 2 5 63%

Scheme 2. Synthesis of compounds **5** from bis(2-nitrobenzamides) **4** and isatins **2**.



Scheme 3. Proposed reaction mechanism.

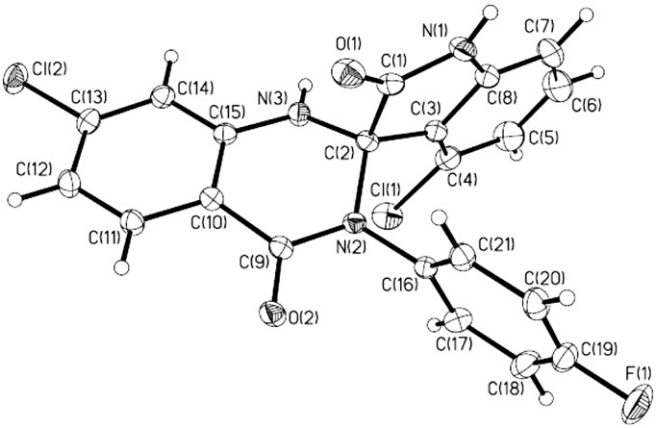


Fig. 1. The crystal structure of compound **3c**.

3. Conclusion

In conclusion, a series of 1′*H*-spiro[indoline-3,2′-quinazoline]-2,4′(3′*H*)-diones and 1′*H*,2*H*-spiro[acenaphthylene-1,2′-quinazoline]-2,4′(3′*H*)-diones were synthesized by the reaction of 2-nitrobenzamides with isatins and acenaphthylene-1,2-diones, respectively, mediated by $SnCl_2\cdot 2H_2O$ system. A variety of substrates can participate in the process with moderate to good yields. Our protocol is characterized by (i) faster reaction times, (ii) accessible materials and handy manipulation (only one pot), and (iii) isolation of products via simple recrystallization to give higher purities.

4. Experimental section

4.1. General

Melting points were determined in open capillaries and uncorrected. IR spectra were recorded on a Varian F-1000 spectrometer in KBr pellet. ^{1}H NMR and ^{13}C NMR spectra were obtained from a solution in DMSO-d_6 with Me_4Si as internal standard using Varian Invoa-400 MHz or Invoa-300 MHz spectrometer. HRMS analyses were carried out using TOF-MS or GCT-TOF instrument. X-ray crystallographic analysis was performed with a Rigaku Mercury CCD/AFC diffractometer.

4.2. General procedure for the synthesis of 4, 5, and 7

A solution of 2-nitrobenzamides **1** or bis(2-nitrobenzamides) **4** (1 mmol), isatins **2** or acenaphthylene-1,2-diones **6** (1 mmol), and $SnCl_2\cdot 2H_2O$ (4 mmol) in EtOH (5 mL) was stirred at reflux for 3–5 h. After this period, the TLC analysis of the mixture showed the reaction to be completed. The mixture was quenched with 3% HCl (10 mL) and filtered to yield a crude product, which was purified by recrystallization from 95% ethanol and DMF.

*4.2.1. 7′-Chloro-1′H-spiro[indoline-3,2′-quinazoline]-2,4′(3′H)-dione (**3a**).* Yellow powder; mp: >300 °C. IR (KBr) ν: 3309, 3207, 3073, 2831, 1729, 1668, 1612, 1475, 1394, 1296, 1206, 1079, 915, 764, 663 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 6.62 (s, 1H, ArH), 6.69 (dd, J_1=8.4 Hz, 1H, J_2=1.8 Hz, ArH), 6.85 (d, J=7.5 Hz, 1H, ArH), 7.06 (t, J=7.5 Hz, 1H, ArH), 7.33 (t, J=7.5 Hz, 1H, ArH), 7.48 (d, J=7.2 Hz, 1H, ArH), 7.55 (d, J=5.1 Hz, 1H, ArH), 7.59 (s, 1H, NH), 8.46 (s, 1H, NH), 10.35 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 71.6, 110.9, 113.6, 114.0, 117.8, 123.1, 126.2, 129.4, 129.5, 131.8, 138.5, 142.8, 148.6, 163.9, 176.5. HRMS found: m/z 300.0559 (M+H), calcd for $C_{15}H_{11}N_3O_2^{35}Cl$: M+H, 300.0540.

*4.2.2. 7′-Chloro-3′-(4-fluorophenyl)-1′H-spiro[indoline-3,2′-quinazoline]-2,4′(3′H)-dione (**3b**).* Yellow powder; mp: >300 °C. IR (KBr) ν: 3265, 3169, 2998, 2809, 1739, 1625, 1506, 1357, 1225, 1084, 936, 847, 755, 682 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 6.69–6.80 (m, 3H, ArH), 6.98–7.21 (m, 6H, ArH), 7.62–7.68 (m, 2H, ArH), 7.94 (s, 1H, NH), 10.54 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 77.0, 111.0, 113.8, 113.9, 116.1, 116.4, 118.4, 123.0, 127.1, 127.3, 130.1, 131.8, 134.5, 139.0, 142.3, 147.9, 160.0, 163.6, 175.8. HRMS found: m/z 393.0679 (M$^+$), calcd for $C_{21}H_{13}N_3O_2F^{35}Cl$: M, 393.0680.

*4.2.3. 4,7′-Dichloro-3′-(4-fluorophenyl)-1′H-spiro[indoline-3,2′-quinazoline]-2,4′(3′H)-dione (**3c**).* Yellow powder; mp: >300 °C. IR (KBr) ν: 3260, 2927, 2850, 1744, 1644, 1513, 1352, 1228, 1175, 1088, 923, 835, 770, 619 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 6.65–6.68 (m, 2H, ArH), 6.75 (d, J=8.4 Hz, 1H, ArH), 7.02 (d, J=8.4 Hz, 1H, ArH), 7.07–7.15 (m, 4H, ArH), 7.24 (t, J=8.0 Hz, 1H, ArH), 7.65 (d, J=8.4 Hz, 1H, ArH), 8.06 (s, 1H, NH), 10.83 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 77.8, 110.1, 112.2, 113.3, 116.2, 116.5, 117.9, 123.9, 124.0, 130.1, 131.1, 131.2, 132.3, 133.6, 133.8, 139.2, 144.1, 147.6, 160.2, 162.8, 174.9. HRMS found: m/z 427.0282 (M$^+$), calcd for $C_{21}H_{12}^{35}Cl_2FN_3O_2$: M, 427.0291.

*4.2.4. 6′-Chloro-1′H-spiro[indoline-3,2′-quinazoline]-2,4′(3′H)-dione (**3d**).* Yellow powder; mp: 276–278 °C. IR (KBr): ν: 3299, 3194, 3078, 2832, 1726, 1665, 1650, 1511, 1475, 1393, 1293, 1207, 1108, 895, 826, 760, 664 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 6.62 (d, J=8.7 Hz, 1H, ArH), 6.84 (d, J=7.8 Hz, 1H, ArH), 7.04 (t, J=7.5 Hz, 1H, ArH), 7.25 (dd, J_1=8.7 Hz, J_2=2.4 Hz, 1H, ArH), 7.32 (t, J=7.8 Hz, 1H, ArH), 7.48 (s, 1H, NH), 7.50 (t, J=2.7 Hz, 2H, ArH), 8.53 (s, 1H, NH), 10.33 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 71.5, 110.9, 116.4, 116.5, 121.5, 123.1, 126.2, 126.6, 129.5, 131.7, 133.7, 142.8, 146.3, 163.6, 176.5. HRMS found: m/z 299.0464 (M$^+$), calcd for $C_{15}H_{10}N_3O_2^{35}Cl$: M, 299.0462.

*4.2.5. 5-Bromo-6′-chloro-3′-p-tolyl-1′H-spiro[indoline-3,2′-quinazoline]-2,4′(3′H)-dione (**3e**).* Yellow powder; mp: 294–297 °C. IR (KBr): ν: 3243, 3080, 2924, 2860, 1737, 1639, 1509, 1355, 1249, 1182, 1094, 882, 818, 692, 532 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 6.63 (d, J=8.4 Hz, 1H, ArH), 6.73 (d, J=8.4 Hz, 1H, ArH), 6.92 (d, J=7.6 Hz, 2H, ArH), 7.06 (d, J=7.6 Hz, 2H, ArH), 7.35–7.37 (m, 2H, ArH), 7.60 (s, 1H, ArH), 7.81 (s, 1H, ArH), 7.86 (s, 1H, NH), 10.60 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 21.2, 76.9, 113.0, 114.5, 116.5, 116.8, 122.2, 127.2, 129.6, 129.8, 130.1, 134.0, 134.2, 134.4, 135.5, 138.1, 141.7, 145.3, 163.1, 175.7. HRMS found: m/z 467.0044 (M$^+$), calcd for $C_{22}H_{15}^{79}Br^{35}ClN_3O_2$: M, 467.0036.

*4.2.6. 4-Bromo-6′-chloro-3′-m-tolyl-1′H-spiro[indoline-3,2′-quinazoline]-2,4′(3′H)-dione (**3f**).* Yellow powder; mp: 282–284 °C. IR (KBr) ν: 3239, 2998, 2921, 2876, 1734, 1669, 1632, 1521, 1445, 1351,

1181, 1098, 903, 817, 695, 533 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ_H 2.17 (s, 3H, CH_3), 6.66 (d, J=7.2 Hz, 1H, ArH), 6.69 (d, J=8.8 Hz, 1H, ArH), 6.88 (d, J=7.6 Hz, 1H, ArH), 6.93 (s, 1H, ArH), 7.04 (d, J=7.6 Hz, 1H, ArH), 7.10–7.18 (m, 3H, ArH), 7.34 (dd, J_1=8.8 Hz, J_2=2.8 Hz, 1H, ArH), 7.57 (s, 1H, ArH), 7.93 (s, 1H, NH), 10.74 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 21.4, 78.5, 110.5, 114.4, 116.2, 121.3, 121.4, 126.0, 127.0, 127.1, 129.2, 129.6, 129.8, 133.5, 133.9, 134.3, 137.6, 138.7, 144.6, 145.6, 163.0, 175.2. HRMS found: m/z 467.0028 (M^+), calcd for $C_{22}H_{15}N_3O_2^{35}Cl^{79}Br$: M, 467.0036.

*4.2.7. 5-Chloro-3′-(4-chlorophenyl)-1′H-spiro[indoline-3,2′-quinazoline]-2,4′(3′H)-dione (**3g**).* Yellow powder; mp: 268–270 °C. IR (KBr) ν: 3326, 3280, 3103, 2838, 2718, 1737, 1647, 1483, 1355, 1275, 1185, 1091, 870, 813, 634 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ_H 6.70 (d, J=8.4 Hz, 2H, ArH), 6.78 (t, J=7.6 Hz, 1H, ArH), 7.08 (d, J=8.4 Hz, 2H, ArH), 7.25 (dd, J_1=8.4 Hz, J_2=2.0 Hz, 1H, ArH), 7.31–7.36 (m, 3H, ArH), 7.67 (d, J=7.6 Hz, 1H, ArH), 7.73 (d, J=2.4 Hz, 1H, ArH), 7.74 (s, 1H, NH), 10.64 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 77.0, 112.4, 114.8, 118.6, 126.9, 127.2, 128.1, 129.4, 129.5, 131.6, 131.8, 132.0, 133.0, 134.6, 137.4, 141.2, 146.4, 164.0, 175.7. HRMS found: m/z 409.0396 (M^+), calcd for $C_{21}H_{13}N_3O_2^{35}Cl_2$: M, 409.0385.

*4.2.8. 5-Bromo-3′-(4-chlorophenyl)-1′H-spiro[indoline-3,2′-quinazoline]-2,4′(3′H)-dione (**3h**).* Yellow powder; mp: 256–258 °C. IR (KBr) ν: 3326, 3267, 3091, 2832, 1737, 1658, 1484, 1355, 1276, 1186, 1092, 870, 813, 758, 660 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ_H 6.65 (d, J=8.4 Hz, 1H, ArH), 6.71 (d, J=8.0 Hz, 1H, ArH), 6.78 (t, J=7.2 Hz, 1H, ArH), 7.07 (d, J=8.0 Hz, 2H, ArH), 7.31–7.39 (m, 4H, ArH), 7.68 (d, J=7.6 Hz, 1H, ArH), 7.71 (s, 1H, ArH), 7.80 (s, 1H, NH), 10.60 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 77.0, 113.0, 114.5, 114.9, 118.7, 128.2, 129.6, 129.9, 130.0, 131.8, 131.9, 133.1, 134.5, 134.7, 137.5, 141.7, 146.5, 164.1, 175.7. HRMS found: m/z 452.9876 (M^+), calcd for $C_{21}H_{13}^{79}Br^{35}ClN_3O_2$: M, 452.9880.

*4.2.9. 4-Bromo-3′-(4-chlorophenyl)-1′H-spiro[indoline-3,2′-quinazoline]-2,4′(3′H)-dione (**3i**).* Yellow powder; mp: 280–282 °C. IR (KBr) ν: 3344, 3060, 2930, 1751, 1615, 1507, 1487, 1448, 1362, 1266, 1175, 1090, 817, 778, 613, 516 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ_H 6.64–6.73 (m, 3H, ArH), 7.08–7.17 (m, 4H, ArH), 7.28–7.31 (m, 1H, ArH), 7.35 (t, J=7.6 Hz, 2H, ArH), 7.64 (t, J=6.4 Hz, 1H, ArH), 7.74 (d, J=6.4 Hz, 1H, NH), 10.72 (d, J=6.4 Hz, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 78.2, 110.1, 112.6, 113.9, 117.4, 121.0, 125.5, 126.7, 127.7, 129.1, 130.8, 132.9, 133.2, 134.4, 136.6, 144.2, 146.4, 163.3, 174.9. HRMS found: m/z 452.9870 (M^+), calcd for $C_{21}H_{13}N_3O_2^{35}Cl^{79}Br$: M, 452.9880.

*4.2.10. 4-Bromo-3′-(4-fluorophenyl)-1′H-spiro[indoline-3,2′-quinazoline]-2,4′(3′H)-dione (**3j**).* Yellow powder; mp: >300 °C. IR (KBr) ν: 3356, 3280, 2926, 1751, 1626, 1513, 1445, 1368, 1164, 1090, 934, 823, 746, 698 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ_H 6.65–6.68 (m, 2H, ArH), 6.71 (d, J=7.6 Hz, 1H, ArH), 7.11–7.18 (m, 6H, ArH), 7.30 (t, J=8.0 Hz, 1H, ArH), 7.64 (d, J=7.6 Hz, 1H, ArH), 7.73 (s, 1H, NH), 10.71 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_H 78.6, 110.4, 112.8, 114.1, 116.1, 116.4, 117.6, 121.2, 126.0, 127.0, 128.0, 131.3, 131.4, 133.4, 134.2, 134.6, 144.4, 146.7, 160.1, 163.6, 175.2. HRMS found: m/z 437.1072 (M^+), calcd for $C_{21}H_{13}N_3O_2\ F^{79}Br$: M, 437.0175.

*4.2.11. 4-Chloro-3′-p-tolyl-1′H-spiro[indoline-3,2′-quinazoline]-2,4′(3′H)-dione (**3k**).* Yellow powder; mp: 296–298 °C. IR (KBr) ν: 3338, 3043, 2927, 1751, 1624, 1513, 1485, 1448, 1374, 1272, 1175, 939, 815, 744, 695, 516 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ_H 2.18 (s, 3H, CH_3), 6.62 (t, J=10.0 Hz, 2H, ArH), 6.69 (t, J=7.6 Hz, 1H, ArH), 6.93–6.98 (m, 3H, ArH), 7.03 (d, J=7.6 Hz, 2H, ArH), 7.18 (t, J=8.0 Hz, 1H, ArH), 7.27 (t, J=7.6 Hz, 1H, ArH), 7.63 (d, J=8.0 Hz, 1H, ArH), 7.68 (s, 1H, NH), 10.66 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 21.2, 78.0, 110.0, 113.6, 114.2, 117.8, 123.9, 124.9, 128.1, 128.9, 129.9, 132.4, 133.2, 134.5, 135.6, 138.1, 144.3, 146.7, 163.7, 175.4. HRMS found: m/z 389.0917 (M^+), calcd for $C_{22}H_{16}N_3O_2^{35}Cl$: M, 389.0931.

*4.2.12. 4-Bromo-3′-p-tolyl-1′H-spiro[indoline-3,2′-quinazoline]-2,4′(3′H)-dione (**3l**).* Yellow powder; mp: 278–280 °C. IR (KBr) ν: 3344, 3040, 2921, 1751, 1621, 1510, 1486, 1368, 1266, 1169, 1025, 934, 806, 744, 613 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ_H 2.20 (s, 3H, CH_3), 6.64 (d, J=8.0 Hz, 2H, ArH), 6.69 (t, J=7.6 Hz, 1H, ArH), 6.98 (d, J=8.4 Hz, 2H, ArH), 7.04 (d, J=8.4 Hz, 2H, ArH), 7.09–7.16 (m, 2H, ArH), 7.28 (t, J=7.6 Hz, 1H, ArH), 7.63 (d, J=7.2 Hz, 1H, ArH), 7.67 (s, 1H, NH), 10.64 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 21.1, 78.5, 110.3, 113.1, 114.0, 117.5, 121.3, 126.4, 126.9, 128.0, 129.0, 129.8, 133.2, 134.4, 135.4, 137.9, 144.4, 146.6, 163.5, 175.4. HRMS found: m/z 433.0424 (M^+), calcd for $C_{22}H_{16}N_3O_2^{79}Br$: M, 433.0426.

*4.2.13. 4-Chloro-6′-methyl-1′H-spiro[indoline-3,2′-quinazoline]-2,4′(3′H)-dione (**3m**).* Yellow powder; mp: 287–289 °C. IR (KBr) ν: 3237, 3018, 2921, 1743, 1647, 1523, 1449, 1370, 1253, 1172, 1095, 918, 819, 782, 656 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ_H 2.19 (s, 3H, CH_3), 6.48 (d, J=8.4 Hz, 1H, ArH), 6.80 (d, J=7.6 Hz, 1H, ArH), 7.04 (d, J=8.0 Hz, 2H, ArH), 7.16 (s, 1H, ArH), 7.32 (t, J=8.0 Hz, 1H, ArH), 7.40 (s, 1H, NH), 8.32 (s, 1H, NH), 10.52 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 20.7, 72.5, 109.7, 113.7, 114.1, 123.7, 125.9, 126.3, 127.4, 132.3, 132.8, 134.7, 144.6, 145.0, 164.0, 175.9. HRMS found: m/z 313.0620 (M^+), calcd for $C_{16}H_{12}N_3O_2^{35}Cl_2$: M, 313.0618.

*4.2.14. 4-Bromo-6′-methyl-1′H-spiro[indoline-3,2′-quinazoline]-2,4′(3′H)-dione (**3n**).* Yellow powder; mp: 278–280 °C. IR (KBr) ν: 3238, 3023, 2922, 1742, 1645, 1525, 1447, 1372, 1258, 1171, 1095, 912, 816, 656 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ_H 2.18 (s, 3H, CH_3), 6.48 (d, J=8.0 Hz, 1H, ArH), 6.83 (d, J=7.6 Hz, 1H, ArH), 7.03 (d, J=8.4 Hz, 1H, ArH), 7.12 (s, 1H, ArH), 7.18–7.24 (m, 2H, ArH), 7.39 (s, 1H, NH), 8.27 (s, 1H, NH), 10.47 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 20.7, 73.2, 110.2, 113.6, 114.1, 120.9, 125.8, 126.8, 127.4, 127.8, 133.0, 134.7, 145.0, 145.1, 164.0, 176.0. HRMS found: m/z 357.0110 (M^+), calcd for $C_{16}H_{12}N_3O_2^{79}Br$: M, 357.0113.

*4.2.15. 7′-(Trifluoromethyl)-1′H-spiro[indoline-3,2′-quinazoline]-2,4′(3′H)-dione (**3o**).* Yellow powder; mp: 264–266 °C. IR (KBr) ν: 3297, 3195, 3078, 2832, 1724, 1664, 1650, 1518, 1476, 1394, 1293, 1209, 1108, 896, 826, 760, 670 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ_H 6.86–6.89 (m, 2H, ArH), 6.96–6.99 (m, 1H, ArH), 7.08 (t, J=0.66 Hz, 1H, ArH), 7.34 (t, J=5.4 Hz, 1H, ArH), 7.51 (t, J=5.7 Hz, 1H, ArH), 7.71 (s, 1H, NH), 7.77–7.80 (m, 1H, ArH), 8.65 (s, 1H, NH), 10.39 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ_c 76.0, 115.5, 115.6, 118.6, 122.7, 127.8, 130.9, 133.4, 133.8, 136.5, 147.5, 152.4, 168.1, 181.0. HRMS found: m/z 334.0812 $(M+H)^+$, calcd for $C_{16}H_{11}F_3N_3\ O_2$: M+H, 334.0804].

*4.2.16. 3′-(4-Methylphenyl)-7′-(trifluoromethyl)-1′H-spiro[indoline-3,2′-quinazoline]-2,4′(3′H)-dione (**3p**).* Yellow powder; mp: >300 °C. IR (KBr) ν: 3311, 3210, 3073, 2834, 1727, 1669, 1612, 1470, 1395, 1213, 1077, 925, 665, 771 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ_H 2.18 (s, 3H, CH_3), 6.66 (s, 1H, ArH), 6.88–7.02 (m, 6H, ArH), 7.17 (s, 1H, ArH), 7.35 (d, J=7.2 Hz, 1H, ArH), 7.58 (s, 1H, ArH), 7.85 (s, 1H, NH), 7.94–8.03 (m, 1H, ArH), 10.52 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 25.9, 81.5, 115.7, 119.0, 180.7, 167.9, 151.7, 147.1, 142.9, 142.5, 140.3, 140.1, 138.6, 136.5, 134.6, 134.1, 131.9, 127.7, 127.5, 126.4, 122.9, 122.6, 193.2. HRMS found: m/z 424.1267 $(M+H)^+$, calcd for $C_{23}H_{17}F_2N_2O_2$: M+H, 424.1274.

*4.2.17. Compound **5**.* Yellow powder; mp: 237–239 °C. IR (KBr) ν: 3258, 3108, 2935, 1735, 1611, 1476, 1320, 1185, 1081, 923, 850, 755, 683 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ_H 1.27–1.52 (m, 2H, CH_2), 2.31–2.38 (m, 2H, CH_2), 3.01–3.14 (m, 2H, CH_2), 6.60 (s, 2H, ArH), 6.73 (d, J=8.0 Hz, 2H, ArH), 6.92 (d, J=7.6 Hz, 2H, ArH), 7.05 (t,

J=7.6 Hz, 2H, ArH), 7.33–7.39 (m, 4H, ArH), 7.58 (d, J=8.4 Hz, 2H, ArH), 7.61 (s, 2H, 2×NH), 10.58 (s, 2H, 2×NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 28.5, 41.5, 75.9, 111.5, 113.5, 113.9, 118.2, 123.3, 126.5, 127.1, 129.7, 132.2, 138.4, 142.8, 147.4, 163.7, 175.6. HRMS found: m/z 639.1311 (M+H), calcd for $C_{33}H_{24}N_6O_4^{35}Cl_2$: M+H, 639.1314.

*4.2.18. 7′-Chloro-1′H,2H-spiro[acenaphthylene-1,2′-quinazoline]-2,4′(3′H)-dione (**7a**).* Yellow powder; mp: 249–251 °C. IR (KBr) ν: 3350, 3259, 2930, 2876, 1899, 1720, 1675, 1598, 1487, 1337, 1203, 1101, 931, 868, 673, 545 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 6.59 (d, J=2.0 Hz, 1H, ArH), 6.75 (dd, J_1=8.4 Hz, J_2=2.0 Hz, 1H, ArH), 7.66 (d, J=8.4 Hz, 1H, ArH), 7.73 (s, 1H, NH), 7.85 (t, J=7.6 Hz, 1H, ArH), 7.86–7.89 (m, 1H, ArH), 7.90–7.93 (m, 1H, ArH), 8.03 (d, J=6.8 Hz, 1H, ArH), 8.16 (d, J=8.0 Hz, 1H, ArH), 8.39 (d, J=8.4 Hz, 1H, ArH), 8.61 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 74.6, 113.5, 114.0, 118.1, 122.6, 123.6, 127.3, 128.7, 129.7, 129.9, 130.0, 130.6, 133.0, 138.0, 138.7, 141.6, 148.4, 163.6, 200.8. HRMS found: m/z 334.0516 (M$^+$), calcd for $C_{19}H_{11}N_2O_2^{35}Cl$: M, 334.0509.

*4.2.19. 3′-(4-Fluorophenyl)-1′H,2H-spiro[acenaphthylene-1,2′-quinazoline]-2,4′(3′H)-dione (**7b**).* Yellow powder; mp: >300 °C. IR (KBr) ν: 3338, 3290, 3068, 2998, 1737, 1644, 1507, 1485, 1351, 1255, 1158, 1067, 885, 829, 741, 661, 528 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 6.66 (d, J=8.0 Hz, 1H, ArH), 6.81 (t, J=8.0 Hz, 1H, ArH), 6.88 (t, J=8.4 Hz, 2H, ArH), 6.95 (s, 2H, ArH+NH), 7.33 (t, J=8.4 Hz, 1H, ArH), 7.70–7.76 (m, 2H, ArH), 7.83 (t, J=7.6 Hz, 2H, ArH), 7.99 (d, J=7.6 Hz, 2H, ArH), 8.02 (d, J=2.4 Hz, 1H, ArH), 8.27 (d, J=8.4 Hz, 1H, ArH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 79.9, 114.6, 115.1, 115.8, 116.1, 118.6, 123.4, 124.1, 127.2, 128.2, 128.7, 129.4, 129.6, 130.2, 131.9, 132.0, 133.1, 133.2, 134.5, 134.9, 135.9, 141.3, 146.5, 164.3, 200.8. HRMS found: m/z 394.1120 (M$^+$), calcd for $C_{25}H_{15}N_2O_2F$: M, 394.1118.

*4.2.20. 6′-Methyl-1′H,2H-spiro[acenaphthylene-1,2′-quinazoline]-2,4′(3′H)-dione (**7c**).* Yellow powder; mp: 258–260 °C. IR (KBr) ν: 3387, 3188, 2918, 1720, 1649, 1604, 1502, 1351, 1252, 1186, 1064, 897, 829, 741, 548 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 2.23 (s, 3H, CH_3), 6.49 (d, J=8.0 Hz, 1H, ArH), 7.07 (dd, J_1=8.0 Hz, J_2=3.2 Hz, 1H, ArH), 7.28 (s, 1H, ArH), 7.49 (s, 1H, NH), 7.81–7.86 (m, 2H, ArH), 7.89 (t, J=7.6 Hz, 1H, ArH), 8.00 (d, J=6.8 Hz, 1H, ArH), 8.13 (dd, J_1=7.2 Hz, J_2=1.6 Hz, 1H, ArH), 8.36 (d, J=8.0 Hz, 1H, ArH), 8.44 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 20.8, 74.7, 114.5, 115.1, 122.3, 123.2, 126.7, 127.0, 127.7, 129.2, 129.8, 129.9, 130.6, 132.8, 134.9, 138.7, 141.4, 145.1, 164.6, 201.1. HRMS (ESI) found: m/z 315.1128, calcd for $C_{20}H_{15}N_2O_2$: [M+H]$^+$, 315.1134.

*4.2.21. 1′H,2H-Spiro[acenaphthylene-1,2′-quinazoline]-2,4′(3′H)-dione (**7d**).* Yellow powder; mp: 238–240 °C. IR (KBr) ν: 3384, 3248, 3040, 2927, 1732, 1658, 1607, 1521, 1493, 1368, 1339, 1147, 1090, 840, 786, 669, 548 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 6.57 (d, J=8.0 Hz, 1H, ArH), 6.72 (t, J=7.6 Hz, 1H, ArH), 7.24 (t, J=8.4 Hz, 1H, ArH), 7.46 (s, 1H, NH), 7.67 (d, J=8.0 Hz, 1H, ArH), 7.71–7.91 (m, 3H, ArH), 8.00 (d, J=6.8 Hz, 1H, ArH), 8.14 (d, J=8.0 Hz, 1H, ArH), 8.37 (d, J=8.0 Hz, 1H, ArH), 8.49 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 74.7, 114.4, 115.0, 118.1, 122.4, 123.3, 127.1, 127.7, 129.0, 129.8, 129.9, 130.6, 132.8, 134.2, 138.6, 141.5, 147.3, 164.4, 201.0. HRMS found: m/z 300.0891 (M$^+$), calcd for $C_{19}H_{12}N_2O_2$: M, 300.0899.

*4.2.22. 3′-(4-Bromophenyl)-1′H,2H-spiro[acenaphthylene-1,2′-quinazoline]-2,4′(3′H)-dione (**7e**).* Yellow powder; mp: 257–259 °C. IR (KBr) ν: 3236, 3097, 2938, 1723, 1661, 1601, 1527, 1487, 1246, 1186, 1098, 894, 834, 755, 656, 519 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 6.66 (d, J=8.4 Hz, 1H, ArH), 6.81 (t, J=7.6 Hz, 1H, ArH), 6.88 (s, 2H, ArH+NH), 7.26 (d, J=8.0 Hz, 2H, ArH), 7.33 (t, J=7.6 Hz, 1H, ArH), 7.70–7.76 (m, 2H, ArH), 7.84 (t, J=8.0 Hz, 2H, ArH), 7.95 (d, J=4.8 Hz, 1H, ArH), 8.01 (d, J=8.4 Hz, 2H, ArH), 8.28 (d, J=8.0 Hz, 1H, ArH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 79.8, 114.7, 115.2, 118.8, 121.3, 123.7, 124.2, 127.4, 128.3, 128.8, 129.6, 129.8, 130.4, 132.1, 132.3, 133.4, 134.7, 135.9, 136.2, 138.2, 141.5, 146.5, 164.2, 200.7. HRMS found: m/z 454.0315 (M$^+$), calcd for $C_{25}H_{15}N_2O_2^{79}Br$: M, 454.0317.

*4.2.23. 3′-Benzyl-1′H,2H-spiro[acenaphthylene-1,2′-quinazoline]-2,4′(3′H)-dione (**7f**).* Yellow powder; mp: 163–165 °C. IR (KBr) ν: 3250, 3074, 3029, 2967, 1734, 1621, 1573, 1516, 1433, 1260, 1158, 1076, 868, 834, 698, 548 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 4.27 (d, J=15.6 Hz, 1H, CH), 4.41 (d, J=15.6 Hz, 1H, CH), 6.58 (t, J=6.8 Hz, 3H, ArH), 6.80 (t, J=7.6 Hz, 1H, ArH), 6.92 (t, J=7.6 Hz, 2H, ArH), 7.00 (t, J=7.6 Hz, 1H, ArH), 7.28 (t, J=8.4 Hz, 1H, ArH), 7.63 (s, 1H, NH), 7.70–7.75 (m, 2H, ArH), 7.75–7.80 (m, 3H, ArH), 8.14 (dd, J_1=7.2 Hz, J_2=1.6 Hz, 1H, ArH), 8.33 (d, J=7.6 Hz, 1H, ArH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 46.6, 78.6, 114.5, 115.5, 118.6, 123.3, 123.7, 127.4, 127.6, 128.1, 128.3, 128.5, 129.0, 129.4, 129.6, 130.6, 133.0, 134.2, 135.3, 137.9, 141.8, 146.5, 164.6, 200.4. HRMS found: m/z 390.1374 (M$^+$), calcd for $C_{26}H_{18}N_2O_2$: M, 390.1368].

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