An Efficient Synthesis of 2-Substituted Quinazolin-4(3*H*)-ones Catalyzed by Iron(III) Chloride

Ramamohan Mekala,[a,b] Raghunadh Akula,[a] Raghavendra Rao Kamaraju,[a] Chandrasekhar Kothapalli Bannoth,[b] Sridhar Regati,[a] Jayaprakash Sarva*[a]

[a] Technology Development Centre, Custom Pharmaceutical Services, Dr. Reddy's Laboratories Ltd, Bollaram Road, Miyapur, Hyderabad, 500049, India
Fax +91(40)44658699; E-mail: sarvaj@drreddys.com

[b] Department of Chemistry, Jawaharlal Nehru Technological University, Anantapur, Andhra Pradesh 515002, India

Received: 22.10.2013; Accepted after revision: 15.01.2014

Abstract: A simple and highly efficient synthesis of 2-substituted quinazolin-4(3*H*)-ones by the iron(III) chloride catalyzed reaction of isatoic anhydride with various amidoxime derivatives was developed. Several aryl and alkyl amidoximes were screened to demonstrate the scope of the methodology.

Key words: heterocycles, polycycles, ketones, catalysis, iron, quinazolinones

Quinazolinones are fused heterocyclic compounds that form building blocks of various natural products and synthetic analogues possessing an extensive array of biological activities.[1] The quinazolinone moiety is an important pharmacophore, and compounds that contain it show a diverse range of pharmacological activities, including anti-inflammatory, antihypertensive, anticancer, anticonvulsant, and antibacterial activities. For example, vasicinone (**1**, Figure 1) is a pyrrolo[2,1-*b*]quinazoline alkaloid, isolated from the aerial parts of adhatoda (*Justica adhatoda*, also known as *Adhatoda vasica* Nees), a plant used extensively in indigenous medicine for treating colds, coughs, bronchitis, and asthma.[2] Methaqualone (**2**) is a hypnotic/sedative that was used for the treatment of insomnia until it was banned and listed as an addictive drug in 1985.[3] Luotonin A (**3**), commonly found in the Chinese plant *Peganum nigellastrum,* is a human DNA topoisomerase I inhibitor and displays cytotoxicity towards the murine leukemia P388 cell line (IC_{50} = 1.8 μg/mL) by stabilizing the topoisomerase I–DNA complex.[4] Benzomalvin A (**4**) is an inhibitor of human neurokinin-1, isolated from a fungal culture of a *Penicillium* species.[5] Rutaecarpine (**5**) is the major alkaloid component of the traditional Chinese herbal drug *Wu-chu-yu* (evodia fruit; *Evodia rutaecarpa*), used extensively as a remedy for headaches, cholera, and dysentery.[6]

Because of their diverse range of pharmacological activities, 2-substituted quinazolin-4(3*H*)-ones have attracted interest from the synthesis community. The common synthetic approach for the preparation of 2-aryl- and 2-alkylquinazolin-4(3*H*)-ones involves two stages: condensation

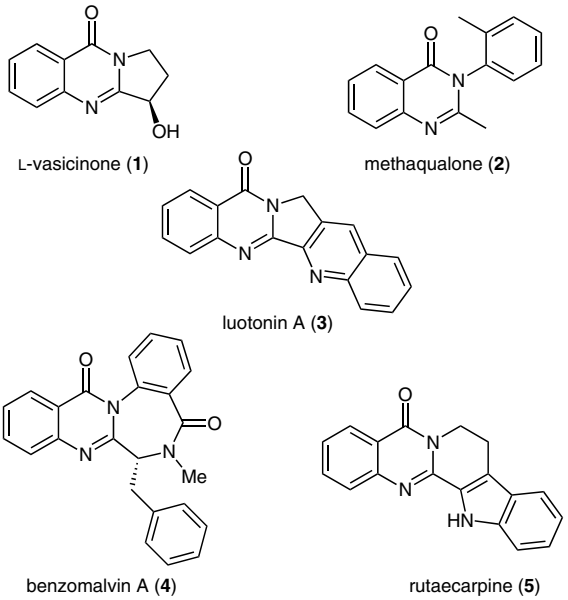
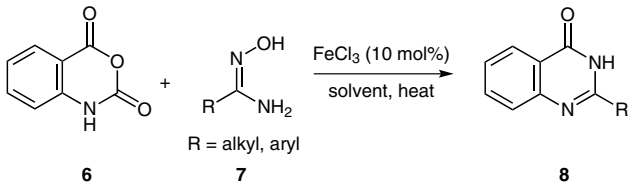


Figure 1 Examples of biologically active quinazolinones

of 2-aminobenzamide with an aliphatic or aromatic aldehyde, and subsequent oxidation with a reagent such as copper(II) chloride, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, potassium permanganate, or manganese dioxide.[7] A one-pot synthesis of quinazolinones from primary alcohols and *o*-aminobenzamides by an iridium-catalyzed dehydrogenation has also been recently reported.[8]

Isatoic anhydride [**6**; 2*H*-3,1-benzoxazine-2,4(1*H*)-dione] has been widely used in syntheses of 2-substituted quinazolinones by condensation with amines and aldehydes in the presence of iodine, silica sulfuric acid, Nafion-H, ionic liquids, or Lewis acids such as gallium(III) triflate. However, these reactions give the corresponding 2,3-dihydroquinazolin-4(1*H*)-ones as major byproducts.[9] As a part of our efforts in the area of total synthesis of quinazolinone-based biologically active molecules, we report a simple, efficient, and high-yielding preparation of 2-substituted quinazolinones **8** by the iron(III) chloride catalyzed reaction of isatoic anhydride (**6**) with amidoxime derivatives **7** (Scheme 1).

SYNLETT 2014, 25, 0821–0826
Advanced online publication: 10.02.2014
DOI: 10.1055/s-0033-1340786; Art ID: ST-2013-D0990-L



Scheme 1 Iron(III) chloride catalyzed synthesis of quinazolinones

We intended to couple isatoic anhydride (**6**) with amidoximes **7** to give the corresponding quinazolinones **8** selectively under mild conditions in the presence of a Lewis acid. Initially, we examined the reaction of isatoic anhydride (**6**) with *N*′-hydroxybenzenecarboximidamide (**7a**) in the presence of various Lewis acids, and the results are summarized in Table 1.

As shown in Table 1, when the reaction was conducted in the absence of a catalyst, a mixture of products was obtained; the desired quinazolinone **8a** was formed as the minor product (28%), with the 1,2,4-oxadiazole derivative **9** as the major product (52%; Table1, entry 1). The base-catalyzed synthesis of 1,2,4-oxadiazole **9** from isatoic anhydride (**6**) and amidoxime **7a** is a known reaction.[10] Because no selectivity was observed in the absence of a catalyst, we carried out reactions in the presence of various Lewis acids (entries 2−6). Among these, the iron(III) chloride catalyzed reaction showed an enhanced selectivity towards the desired product, giving quinazolinone **8a** in 66% yield.

Encouraged by these results, we focused our attention on screening various solvents in an attempt to improve the yield (Table 2). Solvents such as water, *N*-methylpyrrolidin-2-one, methanol, and ethanol were examined, but all were found to be less effective solvents than tetrahydrofuran (entries 1−5). No reaction was observed in toluene or water because of the poor solubility of isatoic anhydride (**6**) and amidoxime **7a** in these solvents. However, the reaction in 1,4-dioxane showed a clean conversion in around four hours, and the isolated yield was improved to 85% (entry 6). From these studies, the optimal conditions were established for the selective formation of 2-aryl quinazolinone derivatives. A plausible mechanism for the formation of the quinazolinones is shown in Scheme 2.

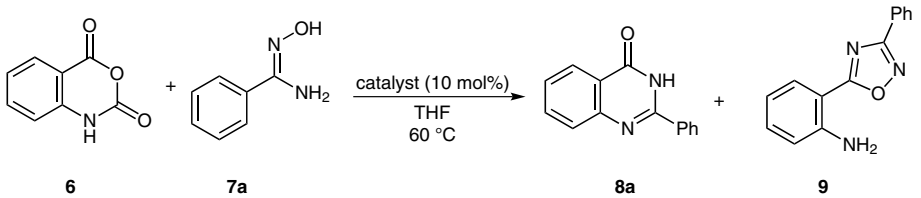
Table 2 Solvent Screening for the Synthesis of Quinazolinone **8a** in the Presence of Iron(III) Chloride (10 mol%)

Entry[a]	Solvent	Temp (°C)	Time (h)	Yield[b] (%)
1	H_2O	100	12	0
2	toluene	110	12	0
3	NMP	150	6	35
4	MeOH	65	30	38
5	EtOH	80	26	61
6	**1,4-dioxane**	**80**	**4**	**85**

[a] Reaction conditions: **6** (1 mmol), **7a** (1.1 mmol), $FeCl_3$ (10 mol%), solvent (2 mL).
[b] Yield of isolated product

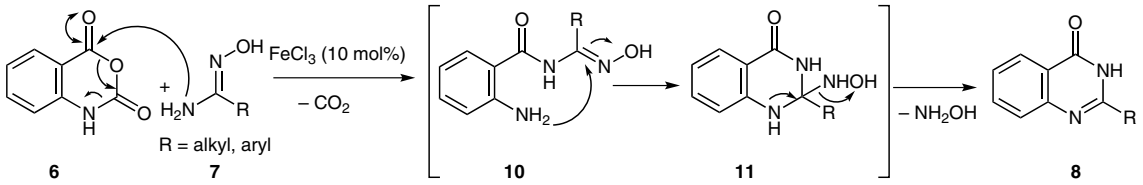
The scope of the method was evaluated by using a variety of substituted aryl amidoximes[11] under the optimized conditions, and the results are shown in Table 3.[12] Gratifyingly, the desired products **8a**–**j** were obtained in high yields in all cases, regardless of the nature of the substituents on the amidoxime. Interestingly, neither electron-donating (methyl, 4-hydroxy, 4-methoxy, 4-amino, or 4-methylsulfanyl) nor electron-withdrawing groups (4-bromo or 4-nitro) on the amidoxime had any effect on the reaction profile and yield (Table 3, entries 1−8). Heteroaromatic

Table 1 Catalyst Screening for the Synthesis of Quinazolinone **8a**



Entry[a]	Catalyst	Time (h)	Yield[b] (%) of **8a**	Yield[b] (%) of **9**
1	no catalyst	12	28	52
2	**$FeCl_3$**	**6**	**66**	–
3	FeF_3	6	61	5
4	$ZnCl_2$	14	52	15
5	$FeCl_3$[c]	10	65	–
6	$TiCl_4$	13	48	20

[a] Reaction conditions: **6** (1 mmol), **7a** (1.1 mmol), catalyst (10 mol%), THF (2 mL), 60 °C.
[b] Yield of isolated product.
[c] Reaction conducted using 5.0 mol% catalyst.



Scheme 2 A plausible mechanism for the formation of quinazolinones **8**

aldoximes also gave the corresponding quinazolinones in good yields (entries 9 and 10).

To check the generality of this process, we also screened several alkyl amidoximes, and the results are shown in Table 4. 2-Cyclopropylethanimidamide, 2,2-dimethylpropanimidamide, and 2-(4-nitrophenyl)ethanimidamide all participated in the reaction as expected and gave the corresponding quinazolinones **8k**–**m** in excellent yields (entries 1−3). It therefore appears that this method provides scope for widespread application in the synthesis of various 2-substituted quinazolin-4(3*H*)-ones.

Table 3 Synthesis of 2-Arylquinazolinone Derivatives **8a–j** under the Optimized Conditions

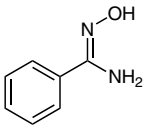
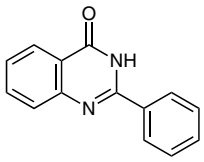
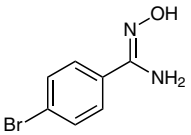
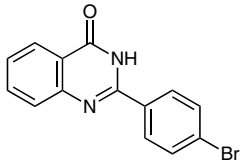
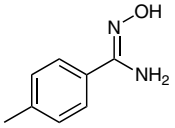
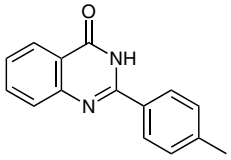
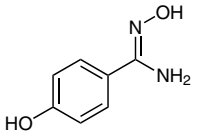
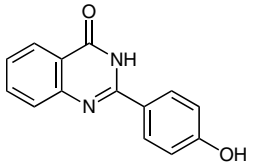
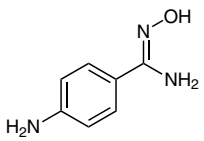
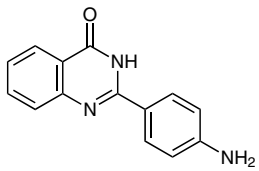
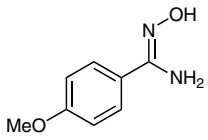
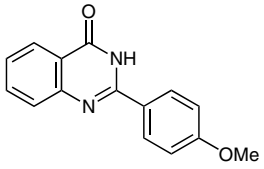
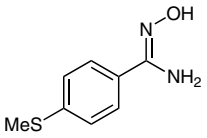
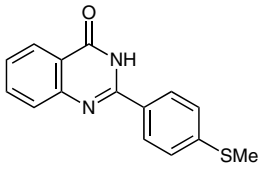
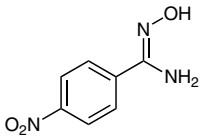
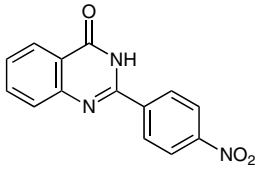
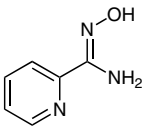
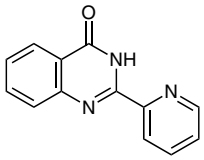
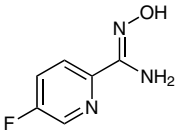
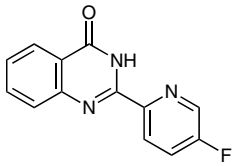
Entry[a]	Amidoxime	Product	Time (h)	Yield[b] (%)
1	 **7a**	 **8a**	6.0	84.6
2	 **7b**	 **8b**	8.0	80.4
3	 **7c**	 **8c**	6.0	83.2
4	 **7d**	 **8d**	9.0	80.0
5	 **7e**	 **8e**	8.0	78.2

Table 3 Synthesis of 2-Arylquinazolinone Derivatives **8a–j** under the Optimized Conditions (continued)

Entry[a]	Amidoxime	Product	Time (h)	Yield[b] (%)
6	 **7f**	 **8f**	2.0	90.1
7	 **7g**	 **8g**	3.0	93.2
8	 **7h**	 **8h**	5.0	84.0
9	 **7i**	 **8i**	6.0	79.2
10	 **7j**	 **8j**	7.0	80.2

[a] Reaction conditions: **6** (1 mmol), **7** (1.1 mmol), $FeCl_3$ (10 mol%), 1,4-dioxane (10 mL), 80 °C.
[b] Yield of isolated product.

Table 4 Synthesis of 2-Alkylquinazolinone Derivatives **8k**–**m** Under the Optimized Conditions

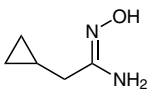
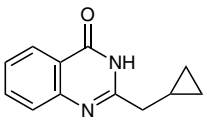
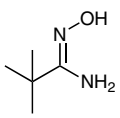
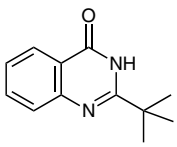
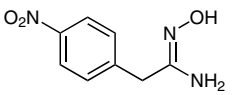
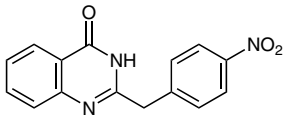
Entry[a]	Amidoxime **7**	Product	Time (h)	Yield[b] (%)
1	 **7k**	 **8k**	4.0	91.0
2	 **7l**	 **8l**	3.0	89.0

Table 4 Synthesis of 2-Alkylquinazolinone Derivatives **8k**–**m** Under the Optimized Conditions (continued)

Entry[a]	Amidoxime **7**	Product	Time (h)	Yield[b] (%)
3	 **7m**	 **8m**	4.0	89.0

[a] Reaction conditions: **6** (1 mmol), amidoxime **7** (1.1 mmol), $FeCl_3$ (10 mol%), 1,4-dioxane (10 mL), 80 °C.
[b] Yield of isolated product.

In conclusion, we have developed an efficient iron(III) chloride catalyzed synthesis of 2-substituted quinazolinones from isatoic anhydride (**6**) and various amidoximes **7** in good to excellent yields. The reaction proceeds under mild conditions without needing an expensive catalyst, and it provides the desired quinazolinones with high selectivity. Extension of this method to the synthesis of various biologically active quinazolinone derivatives is in progress and will be reported in due course.

Acknowledgment

The authors are grateful to Dr. Upadhya Timmanna and Dr. Vilas H. Dahanukar for their constant encouragement, support, and useful discussions. We also thank the analytical department of Dr. Reddy's Laboratories for providing timely support.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

References and Notes

(1) (a) Mhaske, S. B.; Argade, N. P. *Tetrahedron* **2006**, *62*, 9787. (b) Sharma, P. C.; Kaur, G.; Pahza, R.; Sharma, A.; Rajak, H. *Curr. Med. Chem.* **2011**, *18*, 4786. (c) Arora, R.; Kapoor, A.; Gill, N. S.; Rana, A. C. *Int. Res. J. Pharm.* **2011**, *2*, 22. (d) Reisch, J.; Kamal, G. M.; Gunaherath, G. *J. Nat. Prod.* **1989**, *52*, 404. (e) Liu, J.-F.; Wilson, C. J.; Ye, P.; Sprague, K.; Sargent, K.; Si, Y.; Beletsky, G.; Yohannes, D.; Ng, S.-C. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 686. (f) Liu, J.-F.; Kaselj, M.; Isome, Y.; Ye, P.; Sargent, K.; Sprague, K.; Cherrak, D.; Wilson, C. J.; Si, Y.; Yohannes, D.; Ng, S.-C. *J. Comb. Chem.* **2006**, *8*, 7. (g) Ma, C.; Li, Y.; Niu, S.; Zhang, H.; Liu, X.; Che, Y. *J. Nat. Prod.* **2011**, *74*, 32. (h) Nett, M.; Hertweck, C. *J. Nat. Prod.* **2011**, *74*, 2265.

(2) Liu, J.-F.; Ye, P.; Sprague, K.; Sargent, K.; Yohannes, D.; Baldino, C. M.; Wilson, C. J. *Org. Lett.* **2005**, *7*, 3363.

(3) (a) Chenard, B. L.; Menniti, F. S.; Pagnozzi, M. J.; Shenk, K. D.; Ewing, F. E.; Welch, W. M. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1203. (b) Bhogal, N.; Balls, M. *Curr. Drug Discovery Technol.* **2008**, *5*, 250.

(4) (a) Ma, Z. Z.; Hano, Y.; Nomura, T.; Chen, Y. J. *Heterocycles* **1997**, *46*, 541. (b) Cagir, A.; Jones, S. H.; Gao, R.; Eisenhauer, B. M.; Hecht, S. M. *J. Am. Chem. Soc.* **2003**, *125*, 13628.

(5) Sun, H. H.; Barrow, C. J.; Sedlock, D. M.; Gillum, A. M.; Copper, R. *J. Antibiot.* **1994**, *47*, 515.

(6) (a) Chen, A. L.; Chen, K. K. *J. Am. Pharm. Assoc.* **1933**, *22*, 716. (b) Hibino, S.; Choshi, T. *Nat. Prod. Rep.* **2001**, *18*, 66. (c) Deng, P.-Y.; Ye, F.; Cai, W.-J.; Tan, G.-S.; Hu, C.-P.; Deng, H.-W.; Li, Y.-J. *J. Hypertens.* **2004**, *22*, 1819.

(7) (a) Hisano, T.; Ichikawa, M.; Nakagawa, A.; Tsuji, M. *Chem. Pharm. Bull.* **1975**, *23*, 1910. (b) Mitobe, Y.; Ito, S.; Mizutani, T.; Nagase, T.; Sato, N.; Tokita, S. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4075. (c) Balakumar, C.; Lamba, P.; Kishore, D. P.; Narayana, B. L.; Rao, K. V.; Rajwinder, K.; Rao, A. R.; Shireesha, B.; Narsaiah, B. *Eur. J. Med. Chem.* **2010**, *45*, 4904. (d) Abdel-Jalil, R. J.; Aldoqum, H. M.; Ayoub, M. T.; Voelter, W. *Heterocycles* **2005**, *65*, 2061.

(8) Zhou, J.; Fang, J. *J. Org. Chem.* **2011**, *76*, 7730.

(9) (a) Lingaiah, B. V.; Ezikiela, G.; Yakaiaha, T.; Reddy, G. V.; Rao, P. S. *Synlett* **2006**, 2507. (b) Chen, J.; Wu, D.; He, F.; Liu, M.; Wu, H.; Ding, J.; Su, W. *Tetrahedron Lett.* **2008**, *49*, 3814. (c) Zeng, L.-Y.; Cai, C. *J. Heterocycl. Chem.* **2010**, *47*, 1035. (d) Wang, X.-S.; Yang, K.; Zhang, M.-M.; Yao, C.-S. *Synth. Commun.* **2010**, *40*, 2633. (e) Salehi, P.; Dabiri, M.; Zolfigolc, M. A.; Baghbanzadeh, M. *Tetrahedron Lett.* **2005**, *46*, 7051.

(10) Draghici, B.; El-Gendy, B. El-D. M.; Katritzky, A. R. *Synthesis* **2012**, *44*, 547.

(11) (a) Agirbas, H.; Sumengen, D.; Durust, Y.; Durust, N. *Synth. Commun.* **1992**, *22*, 209. (b) Durust, Y.; Akcan, M.; Martiskainen, O.; Siirola, E.; Pihlaja, K. *Polyhedron* **2008**, *27*, 999. (c) Hussein, A. Q. *Heterocycles* **1987**, *26*, 163. (d) Rai, N. P.; Narayanaswamy, V. K.; Govender, T.; Manuprasad, B. K.; Shashikanth, S.; Arunachalam, P. N. *Eur. J. Med. Chem.* **2010**, *45*, 2677.

(12) **2-Substituted Quinazolin-4(3*H*)-ones 8a–m; General Procedure**
The appropriate amidoxime **7** (1.1 mmol) and $FeCl_3$ (10 mol%) were added sequentially to a solution of isatoic anhydride (**6**; 1 mmol.) in 1,4-dioxane (10 mL), and the mixture was stirred at 80 °C for 2–9 h until the reaction was complete (TLC). The mixture was then diluted with EtOAc (10 mL) and washed with H_2O (2 × 5 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a crude product that was purified by column chromatography (silica gel, 30% EtOAc–hexanes). All new compounds gave satisfactory analytical and spectroscopic results.
2-(4-Aminophenyl)quinazolin-4(3*H*)-one (8e)
Yellow solid; yield: 284 mg (78%); mp 250–254 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 5.83 (s, 2 H, NH_2), 6.62 (d, *J* = 8.8 Hz, 2 H, ArH), 7.40 (t, *J* = 6.9 Hz, 1 H, ArH), 7.61 (d, *J* = 8.3 Hz, 1 H, ArH), 7.76 (t, *J* = 6.8 Hz, 1 H, ArH), 7.95 (d, *J* = 8.8 Hz, 2 H, ArH), 8.08 (dd, *J* = 6.9, 1 Hz, 1 H, ArH), 12.06 (br s, 1 H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 113.0, 121.5, 125.3, 125.8, 126.9, 128.7, 129.1, 134.4, 149.6, 152.2, 152.4, 162.4; MS: *m/z* = 238.1 [M + H]; HRMS (ESI): *m/z* [M + H] calcd for $C_{14}H_{12}N_3O$: 238.0980; found: 238.0969.

2-[4-(Methylsulfanyl)phenyl]quinazolin-4(3*H*)-one (8g)
White solid; yield: 383 mg (93%); mp 237–239 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.55 (s, 3 H, SCH_3), 7.40 (d, *J* = 8.4 Hz, 2 H, ArH), 7.50 (t, *J* = 7.2 Hz, 1 H, ArH), 7.72 (d, *J* = 7.6 Hz, 1 H, ArH), 7.83 (t, *J* = 7.6 Hz, 1 H, ArH), 8.13–8.16 (m, 3 H, ArH), 12.48 (br s, 1 H, NH); ^{13}C NMR (400 MHz, DMSO-d_6): δ = 14.1, 120.8, 125.1, 125.8, 126.4, 127.4, 128.0, 128.6, 134.6, 143.0, 148.7, 151.78, 162.2; MS: *m/z* = 269.0 [M + H]; HRMS (ESI): *m/z* [M + H] calcd for $C_{15}H_{13}N_2OS$: 269.07486; found: 269.07446.

2-(5-Fluoropyridin-2-yl)quinazolin-4(3*H*)-one (8j)
Brown solid; yield: 296 mg (80%); mp 180–183 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.51–7.56 (m, 1 H, ArH), 7.61–7.65 (m, 1 H, ArH), 7.77–7.80 (m, 2 H, ArH), 8.35 (d, *J* = 7.4 Hz, 1 H, ArH), 8.51 (d, *J* = 2.9 Hz, 1 H, ArH), 8.63 (dd, *J* = 8.8, 4.8 Hz, 1 H, ArH), 10.76 (br s, 1 H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 122.2, 123.7 (d, *J* = 5.4 Hz), 124.4 (d, *J* = 18.4 Hz), 126.7, 127.4, 127.9, 134.6, 137.2 (d, *J* = 25.2 Hz), 144.7, 147.9, 148.9, 161.1 (d, *J* = 260.0 Hz), 161.3; MS: *m/z* = 242.1 [M + H]; HRMS (ESI): *m/z* [M + H] calcd for $C_{13}H_9N_3OF$: 242.0730; found: 242.0722.

2-(Cyclopropylmethyl)quinazolin-4(3*H*)-one (8k)
White solid; yield: 279 mg (91%); mp 210–213 °C; ^{1}H NMR (400 MHz,, $CDCl_3$): δ = 0.38–0.42 (m, 2 H, CH_2), 0.70–0.73 (m, 2 H, CH_2), 1.14–1.21 (m, 1 H, CH), 2.70 (d, *J* = 7.6 Hz, 2 H, CH_2), 7.26–7.49 (m, 1 H, ArH), 7.68 (d, *J* = 7.6 Hz, 1 H, ArH), 7.74–7.79 (m, 1 H, ArH), 8.28 (dd, *J* = 6.8, 1.2 Hz, 1 H, ArH), 10.20 (br s, 1 H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 4.2, 9.2, 39.2, 120.8, 125.7, 126.0, 126.8, 134.3, 149.0, 157.2, 161.8; MS: *m/z* = 201.1 [M + H]; HRMS (ESI): *m/z* [M + H] calcd for $C_{12}H_{13}N_2O$: 201.1028; found: 201.1037.

2-(4-Nitrobenzyl)quinazolin-4(3*H*)-one (8m)
Light-brown solid; yield: 383 mg (89%); mp >300 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 4.11 (s, 2 H, $PhCH_2$), 7.48 (t, *J* = 7.4 Hz, 1 H, ArH), 7.58 (d, *J* = 8.4 Hz, 1 H, ArH), 7.65 (d, *J* = 8.4 Hz, 2 H, ArH), 7.75–7.79 (m, 1 H, ArH), 8.08 (d, *J* = 6.9 Hz, 1 H, ArH), 8.20 (d, *J* = 8.8 Hz, 2 H, ArH), 12.49 (br s, 1 H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 40.7, 121.3, 123.6, 125.7, 126.4, 126.9, 128.3, 128.6, 130.4, 134.4, 144.4, 154.9, 161.7; MS: *m/z* = 282.0 [M + H]; HRMS (ESI): *m/z* [M + H] calcd for $C_{15}H_{12}N_3O_3$: 282.0879; found: 282.0877.

