Synthesis of Aroylguanidines by an Unexpected Demethylation–Addition Cascade

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Abstract: A simple and efficient method was developed for the synthesis of *N*-aroyl-*N*′-arylguanidines under mild conditions by an unexpected demethylation–addition cascade reaction of readily available *N*-cyanoimidates with aryl amines. Moreover, 1-aryl-2-aminoquinazolin-4(1*H*)-ones and 2-(arylamino)quinazolin-4(3*H*)-ones can also be prepared by selective cyclization reactions of (2-fluorobenzoyl)- or (2-nitrobenzoyl)guanidines, respectively. This method provided two attractive strategies for the preparation 2-aminoquinazolinones derivatives from inexpensive reactants.

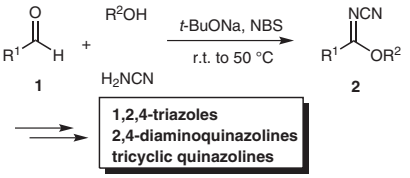
Key words: heterocycles, cyclizations, cascade reactions, amines, quinazolines, ketones

Acylguanidines have attracted a great deal of attention, not only because of the range of significant biological activities that they have shown in medical studies,[1] but also because they are useful building blocks for several natural and therapeutic products of biological significance.[2] Derivatives of acylguanidines are among the most potent inhibitors of Na^+/H^+ exchange[3] and they also have shown remarkable activities as potent $\alpha_v\beta_3$ antagonists,[4] thrombin inhibitors,[5] and histamine H_2 receptors.[6] The usefulness of acylguanidines is highlighted by the range of marketed drugs of this class, which include the sympatholytic guanfacine,[7] the diuretic amiloride,[8] and the Na^+/H^+ exchange inhibitors cariporide[9] and eniporide.[10] Additionally, acylguanidines have also been reported to be potentially useful in the treatment of glaucoma,[11] osteoporosis,[12] and cardiac ischemia and reperfusion,[11,13] as well as acting as antihypertensives,[14] antifungal agents,[15] and plant-protection agents.[16] BMS-344577, an aroylguanidine-based lactam derivative, has progressed to the advanced preclinical development stage because of its potent activity as an inhibitor of blood-coagulation factor Xa.[17] Besides their biological activities, *N*-aroyl-*N*′-arylguanidines have also been used in syntheses of polysubstituted guanidines.[18] Furthermore, several nitrogen-containing heterocycles, including highly bioactive guanosines,[19] can be prepared by using acylguanidines as starting materials.[20–23]

Because of the importance of acylguanidines in various roles, several methods have been reported for their synthesis.[24] However, in comparison with N-polysubstituted acylguanidines, the routes to *N*-acyl-*N*′-arylguanidines are limited to several representative approaches, including reactions of acylcyanamides with aniline hydrochloride in refluxing toluene or xylenes,[25] acylation of guanidines with carbonic acid in the presence of 1,1′-carbonyldimidazole,[21] solid-phase synthesis of disubstituted acylguanidines;[26] and the reaction of acylthioureas with hexamethyldisilazane in the presence of 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide to give acylguanidines.[27] Although these synthetic methods can be used to synthesize *N*-acyl-*N*′-arylguanidines, the poor selectivity of the acylation reaction and the need to protect imino groups represent considerable disadvantages. Other disadvantages include the multistep nature of the reactions, low efficiencies in the preparation of starting materials, and the need for extensive use of condensing agents.

Here we report a convenient method for the synthesis of *N*-aroyl-*N*′-arylguanidines and its application in the preparation of various 2-aminoquinazolinones; the method does not entail any of the problems discussed above.

We have previously shown that oxidative cyanoimidation is a direct and efficient method for the preparation of cyanoimidates **2** (Scheme 1),[28] a class of important organic intermediates for the synthesis of heterocycle derivatives containing several nitrogen atoms.[29]



Scheme 1 Cyanoimidation of aldehydes as a route to nitrogen heterocycles

We recently described a one-pot process for the conversion of methyl *N*-cyano-2-nitrobenzimidates into quinazoline-2,4-diamines and tricyclic quinazolines by iron-mediated reductive cyclization.[30] However, the reactions of aryl amines with cyanoimidates proved not to be an ideal route for the synthesis of *N*′-aryl-substituted quinazolinamines because of the low conversion of the starting materials. To learn more about the scope of this reaction, we chose methyl *N*-cyanonaphthalene-1-carboximidoate (**3k**) as a model substrate, and we studied its condensation with aniline (**4a**) in refluxing methanol. Unfortunately,

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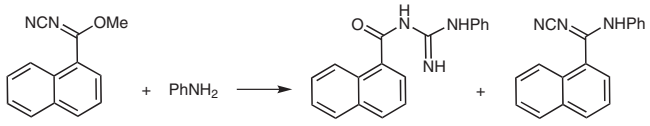
the yield of *N*′-cyano-*N*-phenylnaphthalene-1-carboximidamide (**6k**) was only 24%. However, a second, unexpected, product, *N*-[anilino(imino)methyl]-*N*′-cyanonaphthalene-1-carboximidamide (**5k**) was obtained in 21% yield. We then investigated the effect of various solvents on the reaction. *N*,*N*-Dimethylformamide at 70 °C was found to be the most effective solvent for the condensation reaction to give product **5k**, whereas the reaction gave much lower yields in refluxing chloroform or toluene (Table 1, entries 1–7). On prolonging the reaction time in *N*,*N*-dimethylformamide to 48 hours, we obtained less of the aroylguanidine **5k**, and more of the expected amidine **6k** (entry 8). The temperature also affected the reaction. Increasing the temperature to 90 °C led to a decrease in the yield of **5k** (entry 9). However, the yield of **5k** did not increase and the conversion of the starting material was lower on reducing the temperature to 50 °C (entry 10). The use of three or five equivalents of aniline **4a** (relative to the amount of **3k**) favored the formation of product **5k**, which was obtained 71% and 86% yield, respectively (entries 11 and 12). No improvement in the yield occurred when 0.2 mmol of acetic acid or triethylamine was present as an additive (entries 13 and 14). The optimal conditions are therefore those shown in entry 12.

Table 1 Optimization of the Reaction for Selective Formation of Aroylguanidine **5k**



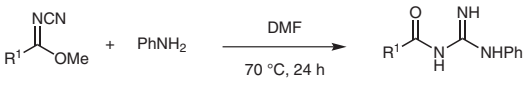
3k **4a** **5k** **6k**

Entry[a]	Solvent	Temp (°C)	Time (h)	Yield (%) of **5k**[b]	Yield (%) of **6k**[b]
1	MeOH	reflux	24	21	24
2	DMF	70	24	52	12
3	DMSO	70	24	46	16
4	$CHCl_3$	reflux	24	31	14
5	toluene	70	24	36	26
6	–	70	24	27	19
7	DMF–H_2O (3:1)	70	24	42	23
8	DMF	70	48	46	18
9	DMF	90	24	34	21
10	DMF	50	24	trace	trace
11[c]	DMF	70	24	71	trace
12[d]	DMF	70	24	86	trace
13[d,e]	DMF	70	24	44	trace
14[d,f]	DMF	70	24	75	trace

[a] Reaction conditions: cyanoimidate **3k** (0.2 mmol), $PhNH_2$ (0.4 mmol), solvent (2 mL).
[b] Isolated yield.
[c] 0.6 mmol $PhNH_2$ was used.
[d] 1.0 mmol $PhNH_2$ was used.
[e] AcOH (0.2 mmol) was used as an additive.
[f] Et_3N (0.2 mmol) was used as an additive.

To test the scope of this reaction system, we examined the reactions of various cyanoimidates under the optimized conditions (Table 2). Almost all the substrates gave the corresponding *N*-aroyl-*N*′-phenylguanidine products in moderate to good yields. We concluded that the method provides a convenient and efficient route for the preparation of *N*-aroylguanidines.

Table 2 Synthesis of *N*-Aroyl-*N*′-Phenylguanidines



3a–j **4a** **5a–j**

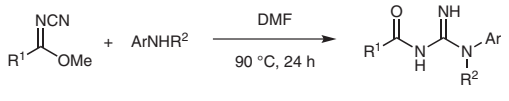
Entry[a]	Cyanoimidate reactant	Product	Yield[b] (%)
1	**3a**, X = H	**5a**	51 (18)[c]
2	**3b**, X = 4-Cl	**5b**	45 (23)[c]
3	**3c**, X = 4-MeO	**5c**	54 (14)[c]
4	**3d**, X = 2-Cl	**5d**	64
5	**3e**, X = 2-Br	**5e**	77
6	**3f**, X = 2-TsO	**5f**	83[d]
7	**3g**, X = 2-Ph	**5g**	76
8	**3h**, X = 2-MeO	**5h**	55
9	**3i**, X = 2,6-Cl_2	**5i**	91[d]
10	**3j**	**5j**	71

[a] Reaction conditions: cyanoimidate **3** (0.5 mmol), $PhNH_2$ (2.5 mmol), DMF (10 mL), 70 °C, 24 h.
[b] Isolated yield.
[c] Yield of *N*-cyanobenzimidamide **6a–c**.
[d] The reaction was performed at 90 °C.

The reactions of secondary aryl amines with cyanoimidates showed better selectivities than those of primary amines, giving moderate to high yields of the corresponding N′,N′-disubstituted *N*-aroylguanidines **5l–z** (Table 3). To achieve complete conversion, it was necessary to use slightly higher reaction temperatures and three equivalents of the secondary aryl amine. Methyl *N*-cyanobenzenecarboximidoate (**3a**) reacted with several nucleophiles, including *N*-methylaniline, indoline and 1,2,3,4-tetrahydroquinoline to give the corresponding products in good yields (entries 1, 2, and 3). We were excited to find that substitution at the 4-position of the aryl

rings was well tolerated (entries 4 and 6). Electron-rich and electron-deficient benzene derivatives and heterocycles participated well in the reaction (entries 4–15). However, the reactions of diphenylamine at 110 °C gave only moderate yields of the desired products because of the low nucleophilicity of this amine (entries 5, 11, and 13). The reaction of imidate **3o** with indoline gave the amidine product **6o** exclusively in 54% yield (entry 16).

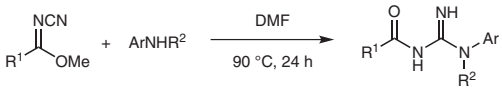
Table 3 Reactions of Cyanoimidates with Secondary Aryl Amines



cyanoimidates **4** **5l–z**

Entry[a]	Cyanoimidate	Product	Yield[b] (%)
1	**3a**	**5l**	78
2	**3a**	**5m**	84
3	**3a**	**5n**	74
4	**3b**	**5o**	80
5[c]	**3b**	**5p**	53
6	**3c**	**5q**	84
7	**3d**	**5r**	79
8	**3d**	**5s**	89
9	**3j**	**5t**	76

Table 3 Reactions of Cyanoimidates with Secondary Aryl Amines (continued)



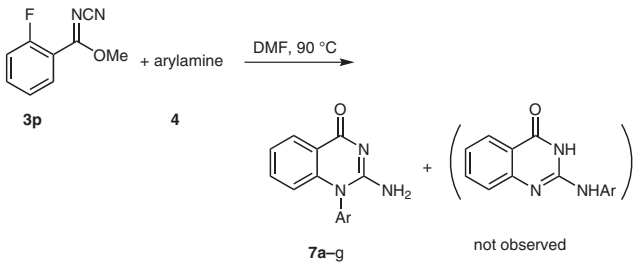
cyanoimidates **4** **5l–z**

Entry[a]	Cyanoimidate	Product	Yield[b] (%)
10	**3k**	**5u**	80
11[c]	**3l**	**5v**	46
12	**3l**	**5w**	94
13[c]	**3m**	**5x**	57
14	**3n**	**5y**	72
15	**3n**	**5z**	81
16	**3o**	**6o**	54

[a] Reaction conditions: cyanoimidate **3** (0.5 mmol), aryl amine (1.5 mmol), DMF (2 mL), 90 °C, 24 h.
[b] Isolated yield.
[c] The reaction was performed at 110 °C.

As part of an attempt to develop simple and efficient methods for synthesizing various bioactive *N*-heterocycles, we tested a novel one-pot approach to 1-aryl-2-aminoquinazolin-4-ones by a tandem intramolecular cyclization. The cascade one-pot reaction of several primary aryl amines with methyl *N*-cyano-2-fluorobenzenecarboximidoate (**3p**) gave the corresponding 1-aryl-2-aminoquinazolin-4-ones **7a**–**g** in moderate to good yields, showing that both electron-withdrawing and electron-donating groups are tolerated in the cascade reaction (Table 4, entries 1–6). However, with a secondary aryl amine, this one-pot reaction did not give the expected cyclization product **7g**, but instead gave the aroylguanidine **5aa** (entry 7).[21]

Table 4 One-pot Synthesis of 2-Amino-1-Arylquinazolinones[a]



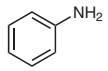
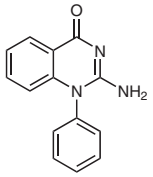
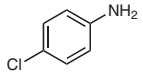
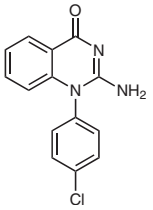
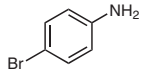
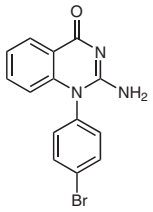
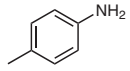
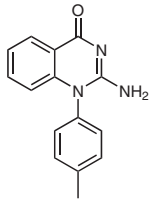
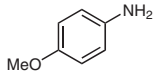
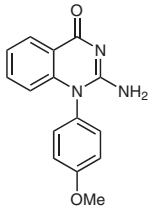
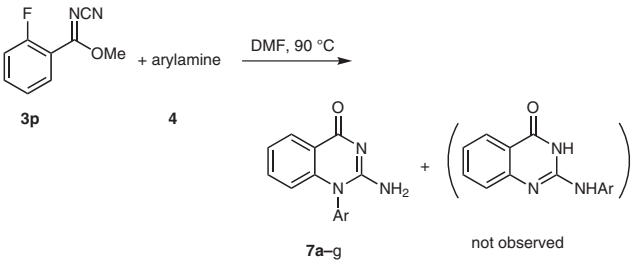
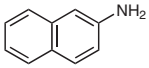
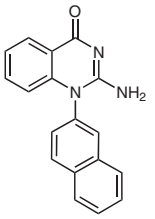
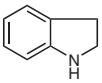
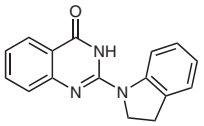
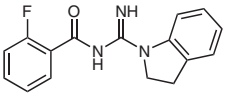
Entry	Aryl amine	Product	Yield (%)[b]
1		**7a** 	72
2		**7b** 	43
3		**7c** 	45
4		**7d** 	71
5		**7e** 	64

Table 4 One-pot Synthesis of 2-Amino-1-Arylquinazolinones[a] (continued)

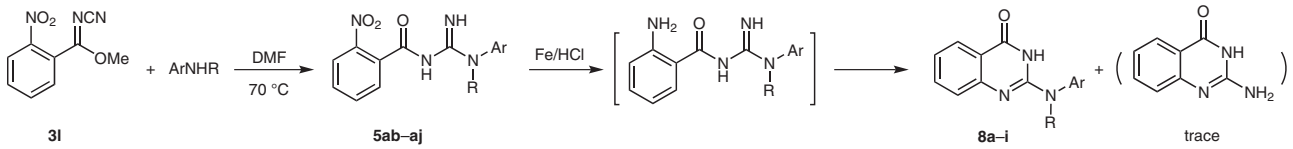


Entry	Aryl amine	Product	Yield (%)[b]
6		**7f** 	76
7		**7g** 	–
		5aa 	56[c]

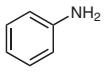
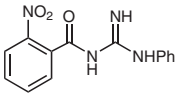
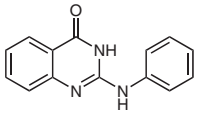
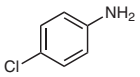
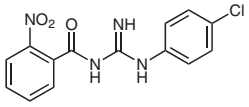
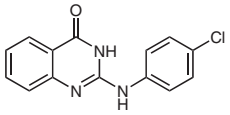
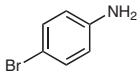
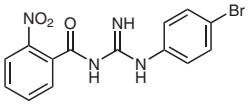
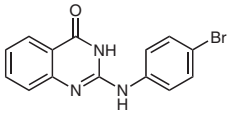
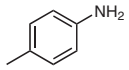
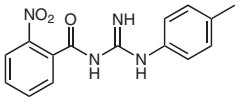
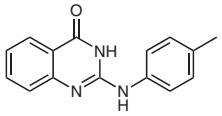
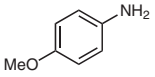
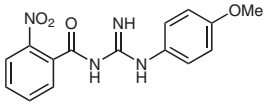
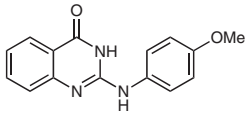
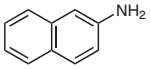
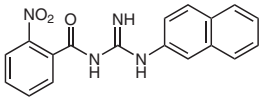
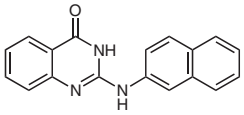
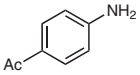
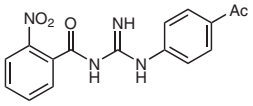
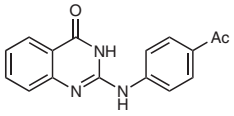
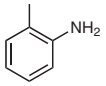
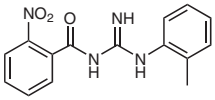
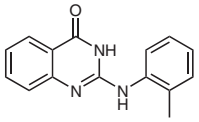
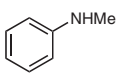
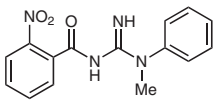
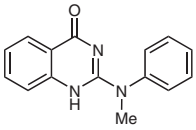
[a] Reaction conditions: carboximidoate **3p** (0.5 mmol), aryl amine **4** (2.5 mmol), DMF (10 mL), 90 °C, 24 h.
[b] Isolated yield.

Moreover, in addition to 1-aryl-2-aminoquinazolin-4-ones, 2-(arylamino)quinazolin-4-ones **8a–i** could be readily prepared through reductive cyclization of the (2-nitroaroyl)guanidines **5ab–aj** formed by reaction of methyl *N*-cyano-2-nitrobenzenecarboximidoate (**3l**) with various aryl amines. Some compounds of type **8** have been the subject of medicinal chemistry studies.[31] Aryl amines bearing electron-withdrawing groups such as 4-chloro, 4-bromo, or 4-acetyl groups gave the corresponding aroylguanidine intermediates **5** in moderate to good yields (Table 5, entries 2, 3, and 7). Similar results were obtained with aniline derivatives substituted with electron-donating groups or with 2-naphthylamine (Table 5, entries 4–6 and 8). *N*-Methylaniline also gave the desired product in excellent yield when three equivalents of this secondary amine were used (Table 5, entry 9). Much to our delight, the resulting (2-nitroaroyl)guanidine derivatives 5**ab–aj** underwent a selective reductive cyclization in the presence of an iron/hydrochloric acid system system[30] to give the corresponding (2-arylamino)quinazolin-4-ones **8a–i** (Table 5).

Table 5 Synthesis of 2-Arylaminoquinazolinones by Cyclization with Iron–Hydrochloric Acid

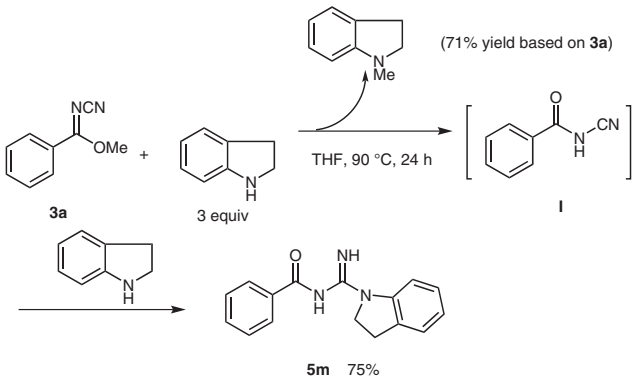


3l 5ab–aj 8a–i trace

Entry[a]	ArNHR	Intermediate product	Yield[b] (%) of **5**	Final product	Yield (%) of **8**
1		**5ab** 	82	**8a** 	77
2		**5ac** 	76	**8b** 	70
3		**5ad** 	80	**8c** 	76
4		**5ae** 	72	**8d** 	84
5		**5af** 	74	**8e** 	81
6		**5ag** 	68	**8f** 	78
7[e]		**5ah** 	52	**8g** 	65
8		**5ai** 	71	**8h** 	75
9[c]		**5aj** 	90	**8i** 	73

[a] Reaction conditions: (1st reaction) methyl *N*-cyano-2-nitrobenzenecarboximidoate (**3l**; 0.5 mmol), aryl amine **4** (2.5 mmol), DMF (10 mL), 70 °C, 24 h; (2nd reaction) aroylguanidine **5ab**–5**aj** (0.1 mmol), Fe (1.8 mmol), concd HCl (0.2 mL), EtOH (10 mL), reflux.
[b] Isolated yield.
[c] The first reaction was performed at 90 °C.

Because the transformation of cyanoimidates serves as a unique route to *N*-aroyl-*N*′-arylguanidines, we were interested in its high selectivity and in the tandem demethylation–condensation process. One possible mechanism involves the hydrolysis of the cyanoimidate, but our preliminary results proved that the addition of water, acid, or base did not promote the formation of the corresponding aroylguanidine. To eliminate the effects of water and the solvent, we examined the reaction of methyl *N*-cyanobenzenecarboximidoate (**3a**) with indoline in anhydrous tetrahydrofuran instead of *N*,*N*-dimethylformamide. The yield of the desired aroylguanidine **5m** was 75% compared with 84% in *N*,*N*-dimethylformamide, and 1-methylindoline was isolated as a byproduct in 71% yield (Scheme 2). We therefore surmised that the reaction might involve demethylation of the cyanoimidate accompanied by methylation of indoline and generation of *N*-cyanobenzamide (**I**), which we were able to characterize by ^{1}H NMR and high-resolution mass spectroscopy. The intermediate *N*-cyanobenzamide (**I**) is readily attacked by the nucleophile indoline and smoothly converted into *N*-[2,3-dihydro-1*H*-indol-1-yl(imino)methyl]benzamide (**5m**).



Scheme 2 Proposed mechanism for the reaction

In summary, we have demonstrated a simple method for the synthesis of *N*-aroyl-*N*′-arylguanidines as an extension of our cyanoimidate research. This synthetic route involves an interesting transformation–condensation cascade in the absence of a condensing agent (as required in many other methods) and it provides a very simple route for the preparation of aroylguanidines from readily available starting materials. Furthermore, *N*-[aryl(imino)methyl]-2-fluorobenzamide products underwent selective cyclization in a one-pot procedure to give the corresponding 1-aryl-2-aminoquinazolin-4-ones. Furthermore, the reductive cyclization of *N*-[aryl(imino)methyl]-2-nitrobenzamide products provides a practical method for the synthesis of 2-(arylamino)quinazolin-4-ones. To the best of our knowledge, these two intramolecular cyclization reactions of *ortho*-substituted aroylguanidines have not been reported before. Further exploration of the synthetic utility of this methodology is currently underway and will be reported in due course.

^{1}H NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 on a Varian Mercury 400-MHz spectrometer with TMS as the internal standard; ^{13}C NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 at 100 Hz. High-resolution mass spectra (ESI) were recorded on an Agilent LC/MSD spectrometer. IR spectra were recorded on a VECTOR22 spectrophotometer. Unless noted otherwise, all the solvents used in the reactions were of analytical grade and were redistilled. Silica gel F_{254} plates were used for TLC and visualized by UV irradiation at 254 nm. Column chromatography was performed on silica gel H (HG/T2354–2010; Qingdao Haiyang Chemical Co., Ltd). The *N*-cyanoimidates were prepared by the procedure described in our previous work.[28]

N-Aroylguanidines 5a–k and 5ab–ai from Primary Amines; General Procedure

The appropriate *N*-cyanoimidate **3** (0.5 mmol) and aryl amine **4** (2.5 mmol) were dissolved in DMF (10 mL), and the mixture was stirred at 70 °C for 24 h. H_2O (10 mL) was then added and the mixture was extracted with EtOAc (2 × 10 mL). The organic phases were combined, washed with H_2O (3 × 10 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, PE–EtOAc).

N-[Anilino(imino)methyl]benzamide (5a)

Yellow powder; yield: 61 mg (51%); mp 108–110 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.36 (s, 1 H), 8.14 (d, *J* = 6.8 Hz, 2 H), 7.56 (d, *J* = 8.0 Hz, 2 H), 7.49–7.37 (m, 5 H), 7.12 (t, *J* = 7.6 Hz, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 176.3, 159.4, 138.8, 138.5, 131.3, 129.1, 128.9, 128.1, 123.9, 122.1.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{14}H_{14}N_3O$: 240.1137; found: 240.1138.

N′-Cyano-*N*-phenylbenzenecarboximidamide (6a)

White powder; yield: 20 mg (18%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.89 (s, 1 H), 7.76–7.74 (m, 4 H), 7.69–7.64 (m, 3 H), 7.43 (t, *J* = 7.6 Hz, 1 H), 7.24 (t, *J* = 7.6 Hz, 1 H).

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{14}H_{12}N_3$: 222.1031; found: 222.1024.

N-[Anilino(imino)methyl]-4-chlorobenzamide (5b)

White powder; yield: 61 mg (45%); mp 178–181 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.38 (s, 1 H), 8.08 (d, *J* = 8.4 Hz, 2 H), 7.51–7.48 (m, 4 H), 7.39 (t, *J* = 7.6 Hz, 2 H), 7.13 (t, *J* = 7.6 Hz, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 175.2, 159.6, 138.3, 137.7, 136.1, 130.7, 129.1, 128.2, 124.0, 122.3.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{14}H_{13}ClN_3O$: 274.0747; found: 274.0751.

N-[Anilino(imino)methyl]-4-methoxybenzamide (5c)

Yellow powder; yield: 73 mg (54%); mp 152–154 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.33 (br s, 1 H), 8.08 (d, *J* = 8.8 Hz, 2 H), 7.56 (d, *J* = 7.6 Hz, 2 H), 7.38 (t, *J* = 8.4 Hz, 2 H), 7.16–7.09 (m, 1 H), 6.97 (d, *J* = 8.8 Hz, 2 H), 3.80 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 176.1, 162.0, 159.2, 138.8, 131.3, 130.9, 129.1, 123.7, 122.0, 113.4, 55.5.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{15}H_{16}N_3O_2$: 270.1243; found: 270.1246.

N-[Anilino(imino)methyl]-2-chlorobenzamide (5d)

White powder; yield: 87 mg (64%); mp 186–188 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.48 (br s, 1 H), 7.63 (dd, *J* = 6.8, 2.0 Hz, 1 H), 7.45–7.42 (m, 3 H), 7.37–7.31 (m, 4 H), 7.10 (t, *J* = 7.2 Hz, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 177.4, 159.3, 140.1, 138.2, 130.4, 130.2, 129.8, 129.2, 126.9, 124.2, 122.4, 122.0.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{14}H_{13}ClN_3O$: 274.0747; found: 274.0752.

Anal. Calcd for $C_{14}H_{12}ClN_3O$: C, 61.43; H, 4.42; Cl, 12.95; N, 15.35. Found: C, 61.48; H, 4.53; Cl, 13.08; N, 15.39.

***N*-[Anilino(imino)methyl]-2-bromobenzamide (5e)**
Yellow powder; yield: 122 mg (77%); mp 184–187 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.74 (br s, 1 H), 7.54 (dd, *J* = 7.6, 1.6 Hz, 1 H), 7.39 (d, *J* = 8.0 Hz, 1 H), 7.31–7.27 (m, 2 H), 7.21–7.16 (m, 2 H), 7.07–7.03 (m, 1 H), 6.95 (d, *J* = 7.6 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.4, 159.9, 140.5, 135.6, 133.1, 130.1, 129.7, 129.3, 128.8, 126.7, 125.0, 119.7.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{14}H_{13}BrN_3O$: 318.0242; found: 318.0239.

2-({[Anilino(imino)methyl]amino}carbonyl)phenyl Tosylate (5f)
Yellow powder; yield: 170 mg (83%); mp 166–168 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.86–7.84 (m, 1 H), 7.76 (d, *J* = 8.4 Hz, 2 H), 7.43 (t, *J* = 7.8 Hz, 2 H), 7.38–7.20 (m, 8 H), 7.02–7.00 (m, 1 H), 3.41 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.5, 166.6, 159.0, 146.3, 145.4, 138.4, 134.9, 131.9, 130.9, 130.8, 130.0, 129.0, 128.4, 127.1, 123.6, 121.7, 21.3.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{21}H_{20}N_3O_4S$: 410.1175; found: 410.1176.

***N*-[Anilino(imino)methyl]biphenyl-2-carboxamide (5g)**
White powder; yield: 120 mg (76%); mp 135–137 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67 (d, *J* = 7.2 Hz, 1 H), 7.44–7.25 (m, 11 H), 7.15 (t, *J* = 7.2 Hz, 2 H), 6.92 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 180.3, 158.6, 141.7, 141.0, 139.3, 138.5, 130.0, 129.0, 128.8, 128.6, 128.5, 128.2, 127.0, 126.9, 123.4, 121.7.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{20}H_{18}N_3O$: 316.1450; found: 316.1447.

***N*-[Anilino(imino)methyl]-2-methoxybenzamide (5h)**
Yellow powder; yield: 74 mg (55%); mp 140–142 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71–7.51 (m, 5 H), 7.41 (t, *J* = 7.6 Hz, 2 H), 7.24 (t, *J* = 7.6 Hz, 1 H), 7.13–7.05 (m, 2 H), 3.93 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 177.2, 157.1, 141.6, 131.7, 129.9, 129.2, 123.2, 122.0, 120.3, 115.8, 114.1, 112.3, 55.9.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{15}H_{16}N_3O_2$: 270.1243; found: 270.1244.

***N*-[Anilino(imino)methyl]-2,6-dichlorobenzamide (5i)**
Yellow powder; yield: 140 mg (91%); mp 158–160 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.65 (br s, 1 H), 9.06 (br s, 1 H), 7.45 (d, *J* = 8.4 Hz, 2 H), 7.37–7.31 (m, 6 H), 7.13 (t, *J* = 6.6 Hz, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 175.2, 159.6, 140.4, 137.5, 130.3, 129.6, 129.3, 128.1, 124.7, 122.7.

HRMS (ESI): *m/z* [M + H] calcd for $C_{14}H_{12}Cl_2N_3O$: 308.0357; found: 308.0361.

***N*-[Anilino(imino)methyl]-6-bromo-1,3-benzodioxole-5-carboxamide (5j)**
Yellow powder; yield: 128 mg (71%); mp 198–200 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.41 (s, 1 H), 7.44 (d, *J* = 8.0 Hz, 2 H), 7.33 (t, *J* = 7.8 Hz, 2 H), 7.23 (s, 1 H), 7.17 (s, 1 H), 7.10 (t, *J* = 7.4 Hz, 2 H), 6.21 (s, 1 H), 6.09 (s, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 177.0, 159.2, 148.6, 146.8, 138.3, 135.0, 129.1, 124.1, 122.3, 113.1, 111.0, 109.8, 102.3.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{15}H_{13}BrN_3O_3$: 362.0140; found: 362.0145.

***N*-[Anilino(imino)methyl]-1-naphthamide (5k)**
Yellow powder; yield: 124 mg (86%); mp 138–140 °C.

IR (KBr): 3449, 3244, 1587, 1551, 1455, 1408, 1331, 1305 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.46 (br s, 1 H), 8.84 (d, *J* = 9.2 Hz, 1 H), 8.07–7.94 (m, 3 H), 7.56–7.50 (m, 5 H), 7.34 (t, *J* = 7.8 Hz, 2 H), 7.01 (t, *J* = 7.2 Hz, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 179.0, 158.6, 136.7, 136.1, 133.1, 130.4, 130.2, 129.3, 129.0, 127.9, 126.7, 126.2, 126.0, 125.9, 124.4, 124.3, 114.9, 107.4.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{18}H_{16}N_3O$: 290.1293; found: 290.1296.

***N*-[Anilino(imino)methyl]-2-nitrobenzamide (5ab)**
Light-yellow powder; yield: 116 mg (82%); mp 154–156 °C.

IR (KBr): 3437, 1614, 1564, 1520, 1450, 1394, 1346 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.40 (s, 1 H), 8.97 (br s, 1 H), 7.85–7.80 (m, 2 H), 7.71–7.59 (m, 2 H), 7.41–7.34 (m, 4 H), 7.14–7.12 (m, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 175.2, 159.5, 149.1, 137.8, 135.1, 132.5, 130.6, 130.0, 129.2, 124.4, 123.5, 122.6.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{14}H_{13}N_4O_3$: 285.0988; found: 285.0939.

Anal. Calcd for $C_{14}H_{13}N_4O_3$: C, 59.15; H, 4.25; N, 19.71. Found: C, 59.23; H, 4.39; N, 19.72.

***N*-{[(4-Chlorophenyl)amino](imino)methyl}-2-nitrobenzamide (5ac)**
Light-yellow powder; yield: 121 mg (76%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.43 (s, 1 H), 9.03 (br s, 1 H), 7.82 (t, *J* = 8.6 Hz, 2 H), 7.70 (t, *J* = 7.4 Hz, 1 H), 7.64–7.60 (m, 1 H), 7.44–7.36 (m, 4 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 175.2, 159.3, 149.2, 137.1, 134.8, 132.5, 130.8, 130.0, 129.0, 128.1, 124.1, 123.5.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{14}H_{12}ClN_4O_3$: 319.0598; found: 319.0595.

***N*-{(4-Bromophenyl)amino](imino)methyl}-2-nitrobenzamide (5ad)**
Yellow powder; yield: 145 mg (80%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.42 (s, 1 H), 9.03 (br s, 1 H), 7.84–7.80 (m, 2 H), 7.70 (t, *J* = 7.2 Hz, 1 H), 7.64–7.60 (m, 1 H), 7.50 (d, *J* = 8.8 Hz, 2 H), 7.37 (d, *J* = 8.4 Hz, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 175.1, 159.2, 149.2, 137.5, 134.8, 132.5, 131.8, 130.8, 130.0, 124.4, 123.5, 116.1.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{14}H_{12}BrN_4O_3$: 363.0093; found: 363.0095.

***N*-{Imino[(4-tolyl)amino]methyl}-2-nitrobenzamide (5ae)**
Light-green powder; yield: 107 mg (72%); mp 164–167 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.39 (s, 1 H), 7.83–7.78 (m, 2 H), 7.71–7.67 (m, 1 H), 7.63–7.58 (m, 1 H), 7.25 (t, *J* = 8.0 Hz, 2 H), 7.15 (t, *J* = 8.0 Hz, 2 H), 2.28 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 175.1, 159.7, 149.1, 135.1, 133.8, 132.4, 130.6, 130.0, 129.7, 123.4, 123.0, 122.0, 20.7.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{15}H_{15}N_4O_3$: 299.1144; found: 299.1149.

N-{Imino[(4-methoxyphenyl)amino]methyl}-2-nitrobenzamide (5af)
Yellow powder; yield: 116 mg (74%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.37 (br s, 1 H), 8.92 (br s, 1 H), 7.83–7.78 (m, 2 H), 7.70–7.66 (m, 1 H), 7.60 (dd, *J* = 7.6, 1.2 Hz, 1 H), 7.26 (d, *J* = 8.4 Hz, 2 H), 6.93 (d, *J* = 8.4 Hz, 2 H), 3.75 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 175.0, 160.0, 156.8, 149.1, 135.2, 134.1, 132.4, 130.5, 130.0, 125.2, 123.4, 114.5.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{15}H_{15}N_4O_4$: 315.1093; found: 315.1097.

N-[Imino(2-naphthylamino)methyl]-2-nitrobenzamide (5ag)
Light-yellow powder; yield: 114 mg (68%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.64 (s, 1 H), 9.07 (br s, 1 H), 7.97 (s, 1 H), 7.90–7.83 (m, 5 H), 7.72 (t, *J* = 7.2 Hz, 1 H), 7.65–7.58 (m, 1 H), 7.52–7.42 (m, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 175.3, 159.6, 149.1, 135.5, 135.1, 133.6, 132.6, 130.7, 130.4, 130.0, 128.8, 127.7, 127.6, 126.7, 125.4, 123.5, 122.7, 119.2.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{18}H_{15}N_4O_3$: 335.1144; found: 335.1145.

N-{[(4-Acetylphenyl)amino](imino)methyl}-2-nitrobenzamide (5ah)
Yellow powder; yield: 85 mg (52%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89 (d, *J* = 8.4 Hz, 2 H), 7.75–7.70 (m, 2 H), 7.56 (t, *J* = 7.4 Hz, 1 H), 7.45 (t, *J* = 7.6 Hz, 1 H), 7.19 (d, *J* = 8.4 Hz, 2 H), 2.57 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 196.6, 175.4, 159.0, 149.2, 143.1, 134.8, 132.6, 131.9, 130.8, 130.1, 129.6, 123.5, 120.6, 26.7.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{16}H_{15}N_4O_4$: 327.1093; found: 327.1102.

N-{Imino[(2-tolyl)amino]methyl}-2-nitrobenzamide (5ai)
Yellow powder; yield: 106 mg (71%).

IR (KBr): 3455, 3222, 2923, 2744, 1656, 1609, 1568, 1528, 1480, 1360, 1303 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.31 (br s, 1 H), 8.87 (br s, 1 H), 7.78 (t, *J* = 6.4 Hz, 2 H), 7.66 (t, *J* = 7.4 Hz, 1 H), 7.61–7.58 (m, 1 H), 7.33–7.28 (m, 2 H), 7.24–7.16 (m, 2 H), 7.11 (br s, 1 H), 2.23 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 174.9, 160.4, 149.0, 135.2, 135.0, 133.7, 132.3, 130.9, 130.4, 129.9, 126.9, 126.8, 126.7, 123.3, 17.9.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{15}H_{15}N_4O_3$: 299.1144; found: 299.1146.

Aroylguanidines 5l–z and 5aj from Secondary Aryl Amines; General Procedure
The appropriate *N*-cyanoimidate **3** (0.5 mmol) and secondary aryl amine **4** (1.5 mmol) were dissolved in DMF (2 mL) and the mixture was stirred at 90 °C for 24 h. H_2O (5 mL) was then added and the mixture was extracted with EtOAc (3 × 10 mL). The organic phases were combined, washed with H_2O (3 × 10 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, PE–EtOAc).

N-{Imino[methyl(phenyl)amino]methyl}benzamide (5l)
Dark-gray powder; yield: 99 mg (78%); mp 94–96 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.84 (br s, 1 H), 8.08 (d, *J* = 7.2 Hz, 2 H), 7.51–7.33 (m, 9 H), 3.44 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 175.4, 160.6, 142.9, 139.2, 131.0, 129.8, 128.8, 128.0, 127.50, 127.46, 38.4.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{15}H_{16}N_3O$: 254.1293; found: 254.1298.

N-[2,3-Dihydro-1*H*-indol-1-yl(imino)methyl]benzamide (5m)
Yellow powder; yield: 111 mg (84%); mp 145–147 °C.

IR (KBr): 3499, 3310, 1620, 1590, 1550, 1511 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.04 (br s, 1 H), 8.46 (d, *J* = 7.2 Hz, 1 H), 8.17 (m, 2 H), 7.68–7.48 (m, 3 H), 7.25 (m, 2 H), 6.99 (t, *J* = 6.6 Hz, 1 H), 4.04 (t, *J* = 7.6 Hz, 2 H), 3.18 (d, *J* = 7.4 Hz, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 176.2, 158.7, 142.7, 139.3, 132.6, 131.2, 128.8, 128.3, 127.2, 125.1, 122.9, 117.4, 47.8, 26.9.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{16}H_{16}N_3O$: 266.1293; found: 266.1299.

N-[3,4-Dihydroquinolin-1(2*H*)-yl(imino)methyl]benzamide (5n)
Yellow powder; yield: 103 mg (74%); mp 104–107 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.19 (br s, 1 H), 8.11–8.09 (m, 2 H), 7.57 (d, *J* = 8.0 Hz, 1 H), 7.49–7.39 (m, 3 H), 7.26–7.20 (m, 2 H), 7.13–7.09 (m, 1 H), 3.91 (t, *J* = 6.2 Hz, 2 H), 2.73 (t, *J* = 6.4 Hz, 2 H), 1.95–1.89 (m, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 175.9, 160.3, 153.8, 139.1, 138.0, 132.8, 131.1, 128.9, 128.0, 126.0, 125.4, 124.7, 44.7, 26.5, 23.9.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{17}H_{18}N_3O$: 280.1450; found: 280.1451.

4-Chloro-N-[2,3-dihydro-1*H*-indol-1-yl(imino)methyl]benzamide (5o)
Gray powder; yield: 120 mg (80%); mp 163–165 °C.

IR (KBr): 3448, 1611, 1589, 1522, 744 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.20–8.17 (m, 2 H), 8.10 (br s, 1 H), 7.41–7.83 (m, 2 H), 7.28–7.24 (m, 3 H), 7.04 (t, *J* = 7.2 Hz, 1 H), 4.14 (t, *J* = 8.4 Hz, 2 H), 3.22 (t, *J* = 8.4 Hz, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 175.0, 158.6, 142.5, 138.1, 136.0, 132.6, 130.6, 128.4, 127.2, 125.1, 123.0, 117.3, 47.9, 26.9.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{16}H_{15}ClN_3O$: 300.0904; found: 300.0910.

4-Chloro-N-[(diphenylamino)(imino)methyl]benzamide (5p)
White needle crystals; yield: 92 mg (53%); mp 168–171 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.29 (br s, 1 H), 7.89 (d, *J* = 8.4 Hz, 2 H), 7.45–7.25 (m, 12 H), 5.34 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.4, 160.2, 141.6, 137.2, 136.9, 130.6, 129.5, 128.1, 128.0, 127.3.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{20}H_{17}ClN_3O$: 350.1060; found: 350.1061.

N-[2,3-Dihydro-1*H*-indol-1-yl(imino)methyl]-4-methoxybenzamide (5q)
Yellow powder; yield: 124 mg (84%); mp 166–169 °C.

IR (KBr): 3364, 1604, 1541, 1254, 1032 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.01 (br s, 1 H), 8.44 (d, *J* = 7.2 Hz, 1 H), 8.12 (d, *J* = 8.0 Hz, 2 H), 7.25 (m, 2 H), 7.02–7.00 (m, 3 H), 4.03 (d, *J* = 7.6 Hz, 2 H), 3.82 (s, 3 H), 3.18 (d, *J* = 7.2 Hz, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 176.0, 161.8, 158.5, 142.8, 132.6, 131.8, 130.6, 127.1, 125.1, 122.8, 117.3, 113.5, 55.5, 47.8, 26.9.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{17}H_{18}N_3O_2$: 296.1399; found: 296.1396.

2-Chloro-*N*-{imino[methyl(phenyl)amino]methyl}benzamide (5r)
Yellow needle crystals; yield: 113 mg (79%); mp 183–185 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.81 (br s, 1 H), 7.93–7.91 (m, 1 H), 7.50 (t, *J* = 7.8 Hz, 2 H), 7.42–7.39 (m, 2 H), 7.33–7.27 (m, 4 H), 3.49 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 177.7, 160.2, 141.1, 139.0, 132.1, 130.9, 130.4, 130.1, 128.5, 127.2, 126.2, 38.6, 29.6.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{15}H_{15}ClN_3O$: 288.0904; found: 288.0901.

2-Chloro-*N*-[2,3-dihydro-1*H*-indol-1-yl(imino)methyl]benzamide (5s)
White powder; yield: 133 mg (89%); mp 144–146 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.13 (s, 1 H), 7.85–7.83 (m, 1 H), 7.42–7.39 (m, 1 H), 7.31–7.28 (m, 2 H), 7.21–7.16 (m, 2 H), 7.01 (m, 1 H), 4.09 (t, *J* = 8.2 Hz, 2 H), 3.20 (t, *J* = 8.4 Hz, 2 H).

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{16}H_{15}ClN_3O$: 300.0904; found: 300.0906.

Anal. Calcd for $C_{16}H_{15}ClN_3O$: C, 64.11; H, 4.71, Cl, 11.83; N, 14.02. Found: C, 64.51; H, 4.85, Cl, 11.82; N, 14.00.

6-Bromo-*N*-{imino[methyl(phenyl)amino]methyl}-1,3-benzodioxole-5-carboxamide (5t)
White powder; yield: 143 mg (76%); mp 187–190 °C.

IR (KBr): 3448, 3374, 2938, 1592, 1560, 1529, 1451, 1361 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.83 (s, 1 H), 7.52–7.48 (m, 2 H), 7.42–7.39 (m, 1 H), 7.33–7.28 (m, 2 H), 7.05 (s, 1 H), 6.00 (s, 2 H), 3.49 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 177.3, 160.1, 149.0, 146.7, 141.2, 130.4, 128.5, 127.3, 113.7, 112.7, 111.1, 101.8, 38.6, 29.6.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{16}H_{15}BrN_3O_3$: 376.0297; found: 376.0295.

***N*-{[Benzyl(phenyl)amino](imino)methyl}-1-naphthamide (5u)**
Yellow needle crystals; yield: 152 mg (80%); mp 151–153 °C.

IR (KBr): 3469, 2922, 2852, 1626, 1594, 1566, 1522, 1454, 1416, 1353, 1314 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.19 (s, 1 H), 9.00 (t, *J* = 2.8 Hz, 1 H), 8.22 (d, *J* = 6.8 Hz, 1 H), 7.90–7.83 (m, 2 H), 7.54–7.14 (m, 12 H), 7.15 (d, *J* = 7.2 Hz, 2 H), 5.22 (s, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 180.5, 160.3, 139.6, 137.7, 137.2, 133.9, 131.2, 130.6, 130.3, 129.2, 128.7, 128.6, 128.5, 128.4, 128.3, 128.1, 127.4, 127.1, 126.9, 126.3, 125.4, 124.7, 117.4, 112.7, 53.9.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{25}H_{22}N_3O$: 380.1763; found: 380.1769.

***N*-[(Diphenylamino)(imino)methyl]-2-nitrobenzamide (5v)**
White powder; yield: 83 mg (46%); mp 178–181 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.08 (br s, 1 H), 7.71 (d, *J* = 8.0 Hz, 1 H), 7.58 (d, *J* = 7.6 Hz, 1 H), 7.46 (t, *J* = 7.2 Hz, 1 H), 7.43–7.39 (m, 4 H), 7.33–7.29 (m, 6 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 174.5, 160.5, 149.3, 142.1, 134.4, 131.9, 130.7, 130.1, 129.7, 128.4, 127.4, 123.2.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{20}H_{17}N_4O_3$: 361.1301; found: 361.1305.

***N*-[2,3-Dihydro-1*H*-indol-1-yl(imino)methyl]-2-nitrobenzamide (5w)**
Yellow powder; yield: 146 mg (94%); mp 148–151 °C.

IR (KBr): 3455, 1626, 1606, 1589, 1519, 1481, 1347 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92 (dd, *J* = 7.6, 1.2 Hz, 2 H), 7.82 (br s, 1 H), 7.72 (d, *J* = 7.6 Hz, 1 H), 7.60 (t, *J* = 7.6 Hz, 1 H), 7.51 (t, *J* = 7.6 Hz, 1 H), 7.23–7.17 (m, 2 H), 7.02 (d, *J* = 7.6 Hz, 1 H), 4.09 (d, *J* = 8.4 Hz, 2 H), 3.18 (d, *J* = 8.4 Hz, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 174.7, 158.1, 149.2, 142.2, 135.4, 132.6, 130.6, 129.8, 127.1, 125.1, 123.6, 123.3, 117.6, 110.5, 47.8, 26.8.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{16}H_{15}N_4O_3$: 311.1144; found: 311.1142.

***N*-[(Diphenylamino)(imino)methyl]-4-nitrobenzamide (5x)**
White powder; yield: 103 mg (57%); mp 179–182 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.24 (br s, 1 H), 8.14–8.07 (m, 4 H), 7.48–7.44 (m, 4 H), 7.40–7.34 (m, 6 H), 5.44 (br s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 173.6, 160.8, 142.3, 129.9, 129.7, 129.4, 128.6, 127.5, 123.3, 116.9.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{20}H_{17}N_4O_3$: 361.1301; found: 361.1306.

***N*-{[Benzyl(phenyl)amino](imino)methyl}thiophene-2-carboxamide (5y)**
Yellow powder; yield: 121 mg (72%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.50 (br s, 1 H), 7.63–7.62 (m, 2 H), 7.49–7.21 (m, 10 H), 7.11–7.09 (m, 1 H), 6.77 (br s, 1 H), 5.20 (s, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 171.3, 160.0, 145.4, 140.1, 138.0, 131.1, 130.0, 129.9, 128.5, 128.4, 128.1, 127.93, 127.90, 127.4, 53.4.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{19}H_{18}N_3OS$: 336.1171; found: 336.1177.

***N*-{Imino[methyl(phenyl)amino]methyl}thiophene-2-carboxamide (5z)**
Yellow powder; yield: 105 mg (81%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.49 (br s, 1 H), 7.62–7.57 (m, 2 H), 7.49 (m, 2 H), 7.39–7.37 (m, 3 H), 7.08–7.06 (m, 2 H), 3.40 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 171.0, 160.0, 145.5, 142.5, 130.9, 129.8, 129.7, 127.8, 127.52, 127.46, 38.3.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{13}H_{14}N_3OS$: 260.0858; found: 260.082.

(2,3-Dihydro-1*H*-indol-1-ylmethylene)cyanamide (6o)
Yellow powder; yield: 46 mg (54%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.94 (s, 1 H), 7.24 (m, 1 H), 7.17 (t, *J* = 6.0 Hz, 2 H), 7.08–7.06 (m, 1 H), 4.07 (t, *J* = 8.0 Hz, 2 H), 3.17 (t, *J* = 8.0 Hz, 2 H).

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{10}H_{10}N_3$: 172.0875; found: 172.0869.

***N*-{Imino[methyl(phenyl)amino]methyl}-2-nitrobenzamide (5aj)**
Yellow powder; yield: 134 mg (90%); mp 155–158 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.39 (s, 1 H), 7.85 (d, *J* = 7.6 Hz, 1 H), 7.73 (d, 7.2 Hz, 1 H), 7.67–7.58 (m, 2 H), 7.49 (t, *J* = 7.6 Hz, 2 H), 7.39–7.35 (m, 3 H), 7.07 (br s, 1 H), 3.30 (s, 3 H).

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{15}H_{15}N_4O_3$: 299.1144; found: 299.1150.

1-Aryl-2-Aminoquinazolin-4(1*H*)-ones (7a–f) and *N*-[2,3-Dihydro-1*H*-indol-1-yl(imino)methyl]-2-fluorobenzamide (5aa); General Procedure
The appropriate *N*-cyanoimidate **3** (0.5 mmol) and aryl amine **4** (2.5 mmol) were dissolved in DMF (10 mL) and the mixture was stirred

at 90 °C for 24 h. The resulting mixture was purified by flash column chromatography (silica gel, CH_2Cl_2 then CH_2Cl_2–MeOH).

2-Amino-1-phenylquinazolin-4(1*H*)-one (7a)
Gray powder; yield: 85 mg (72%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.99 (dd, *J* = 7.8, 1.0 Hz, 1 H), 7.71–7.63 (m, 3 H), 7.49 (d, *J* = 6.8 Hz, 2 H), 7.46–7.42 (m, 1 H), 7.24 (t, *J* = 7.4 Hz, 1 H), 6.71 (br s, 2 H), 6.30 (d, *J* = 8.4 Hz, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 168.0, 155.9, 142.5, 135.7, 132.8, 131.4, 130.4, 129.5, 127.0, 123.3, 118.2, 115.1.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{14}H_{12}N_3O$: 238.0980; found: 238.0988.

2-Amino-1-(4-chlorophenyl)quinazolin-4(1*H*)-one (7b)
White powder; yield: 58 mg (43%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.99–7.97 (m, 1 H), 7.74 (d, *J* = 8.8 Hz, 2 H), 7.55 (d, *J* = 8.8 Hz, 2 H), 7.47–7.43 (m, 1 H), 7.26–7.22 (m, 1 H), 6.75 (br s, 2 H), 6.35 (d, *J* = 8.0 Hz, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 167.9, 155.8, 142.4, 135.0, 134.7, 132.9, 131.7, 131.5, 127.0, 123.3, 118.2, 115.1.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{14}H_{11}ClN_3O$: 272.0591; found: 272.0593.

2-Amino-1-(4-bromophenyl)quinazolin-4(1*H*)-one (7c)
White powder; yield: 71 mg (45%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.98 (d, *J* = 7.6 Hz, 1 H), 7.88 (d, *J* = 8.4 Hz, 2 H), 7.49–7.43 (m, 3 H), 7.25 (t, *J* = 7.4 Hz, 1 H), 6.84 (br s, 2 H), 6.36 (d, *J* = 8.4 Hz, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 167.9, 155.6, 142.3, 135.1, 134.4, 132.9, 131.9, 127.0, 123.8, 123.4, 118.1, 115.1.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{14}H_{11}BrN_3O$: 316.0085; found: 316.0086.

2-Amino-1-(4-tolyl)quinazolin-4(1*H*)-one (7d)
White powder; yield: 89 mg (71%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.99 (d, *J* = 6.8 Hz, 1 H), 7.51–7.43 (m, 3 H), 7.36 (d, *J* = 8.0 Hz, 2 H), 7.24 (t, *J* = 7.4 Hz, 1 H), 6.34 (d, *J* = 8.4 Hz, 1 H), 2.45 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 167.7, 155.8, 142.6, 140.0, 133.0, 132.9, 131.8, 129.2, 127.0, 123.3, 118.1, 115.2, 21.1.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{15}H_{14}N_3O$: 252.1137; found: 252.1132.

2-Amino-1-(4-methoxyphenyl)quinazolin-4(1*H*)-one (7e)
White powder; yield: 85 mg (64%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.97 (dd, *J* = 7.6, 1.2 Hz, 1 H), 7.47–7.43 (m, 1 H), 7.40 (d, *J* = 8.8 Hz, 2 H), 7.25–7.20 (m, 3 H), 6.36 (d, *J* = 8.4 Hz, 1 H), 3.86 (s, 3 H).

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{15}H_{14}N_3O_2$: 268.1086; found: 268.1080.

2-Amino-1-(2-naphthyl)quinazolin-4(1*H*)-one (7f)
Gray powder; yield: 109 mg (76%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.24 (d, *J* = 8.8 Hz, 1 H), 8.16 (s, 1 H), 8.12 (d, *J* = 8.0 Hz, 1 H), 8.07–8.01 (m, 2 H), 7.71–7.64 (m, 2 H), 7.53 (dd, *J* = 8.4, 1.6 Hz, 1 H), 7.40 (t, *J* = 8.0 Hz, 1 H), 7.24 (t, *J* = 7.4 Hz, 1 H), 6.35 (d, *J* = 8.4 Hz, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 167.9, 156.0, 142.6, 134.2, 133.6, 133.0, 132.9, 131.5, 129.2, 128.6, 128.2, 127.7, 127.1, 127.0, 126.4, 123.4, 118.1, 115.3.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{18}H_{14}N_3O$: 288.1137; found: 288.1142.

***N*-[2,3-Dihydro-1*H*-indol-1-yl(imino)methyl]-2-fluorobenzamide (5aa)**
White powder; yield: 80 mg (56%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.25 (br s, 1 H), 8.03 (t, *J* = 7.2 Hz, 1 H), 7.42–7.38 (br s, 1 H), 7.23–7.16 (m, 3 H), 7.13–7.08 (m, 1 H), 7.00 (t, *J* = 7.2 Hz, 1 H), 4.04 (t, *J* = 8.2 Hz, 2 H), 3.16 (t, *J* = 8.2 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.2, 162.7, 158.1, 141.8, 132.0, 131.9, 131.6, 127.5, 124.9, 123.5, 123.4, 117.0, 116.7, 116.4, 47.6, 27.2.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{16}H_{15}FN_3O$: 284.1199; found: 288.1196.

2-(Arylamino)quinazolin-4-ones 8a–i; General Procedure
Fe (1.8 mmol) and concd HCl (0.2 mL) were added to a soln of aroylguanidine **5** (0.1 mmol) in EtOH (10 mL). The resulting mixture was refluxed for 2 h then filtered through kieselguhr. The solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography (silica gel, CH_2Cl_2–MeOH).

2-Anilinoquinazolin-4(3*H*)-one (8a)
White powder; yield: 18 mg (77%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.83 (s, 1 H), 8.68 (s, 1 H), 7.88 (d, *J* = 8.0 Hz, 1 H), 7.76 (d, *J* = 8.4 Hz, 2 H), 7.66 (t, *J* = 7.6 Hz, 1 H), 7.42 (d, *J* = 8.0 Hz, 1 H), 7.36 (t, *J* = 8.0 Hz, 2 H), 7.24 (t, *J* = 7.6 Hz, 1 H), 7.05 (t, *J* = 7.6 Hz, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 161.9, 147.6, 139.2, 134.7, 129.1, 126.2, 125.6, 123.3, 122.8, 119.5, 118.6, 115.9.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{14}H_{12}N_3O$: 238.0980; found: 238.0986.

2-[(4-Chlorophenyl)amino]quinazolin-4(3*H*)-one (8b)
Light-yellow powder; yield: 19 mg (70%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.88 (s, 1 H), 8.82 (s, 1 H), 7.97 (dd, *J* = 8.0, 1.2 Hz, 1 H), 7.78 (d, *J* = 8.4 Hz, 2 H), 7.69–7.64 (m, 1 H), 7.42–7.39 (m, 3 H), 7.26–7.23 (m, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 162.0, 150.0, 147.5, 138.2, 134.7, 128.9, 126.3, 126.2, 125.6, 123.5, 121.1, 118.7.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{14}H_{11}ClN_3O$: 272.0591; found: 272.0587.

2-[(4-Bromophenyl)amino]quinazolin-4(3*H*)-one (8c)
Yellow powder; yield: 24 mg (76%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.88 (s, 1 H), 8.82 (s, 1 H), 7.98 (d, *J* = 7.6 Hz, 1 H), 7.73 (d, *J* = 8.0 Hz, 2 H), 7.67–7.63 (m, 1 H), 7.51 (d, *J* = 8.8 Hz, 2 H), 7.40 (d, *J* = 8.4 Hz, 1 H), 7.24 (t, *J* = 7.4 Hz, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 161.8, 150.0, 147.4, 138.7, 134.7, 131.8, 126.2, 125.6, 123.5, 121.5, 118.7, 114.2.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{14}H_{11}BrN_3O$: 316.0085; found: 316.0086.

2-[(4-Tolyl)amino]quinazolin-4(3*H*)-one (8d)
Light-yellow powder; yield: 21 mg (84%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.80 (s, 1 H), 8.58 (s, 1 H), 7.96 (dd, *J* = 7.6, 0.8 Hz, 1 H), 7.66–7.60 (m, 3 H), 7.38 (t, *J* = 8.0 Hz, 1 H), 7.16 (d, *J* = 8.0 Hz, 2 H), 2.28 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 162.0, 148.7, 148.2, 136.0, 134.8, 132.4, 129.6, 126.3, 124.4, 123.4, 120.5, 118.2, 20.7.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{15}H_{14}N_3O$: 252.1137; found: 252.1136.

2-[(4-Methoxyphenyl)amino]quinazolin-4(3*H*)-one (8e)
White powder; yield: 22 mg (81%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.82 (s, 1 H), 8.54 (s, 1 H), 7.95 (dd, *J* = 8.0, 1.2 Hz, 1 H), 7.64–7.60 (m, 3 H), 7.34 (d, *J* = 8.0 Hz, 1 H), 7.20 (t, *J* = 7.4 Hz, 1 H), 6.95–6.93 (m, 2 H), 3.75 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 162.3, 155.4, 149.8, 148.3, 134.6, 131.9, 126.2, 124.9, 123.0, 121.9, 118.3, 114.3, 55.5.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{15}H_{14}N_3O_2$: 268.1086; found: 268.1080.

2-(2-Naphthylamino)quinazolin-4(3*H*)-one (8f)
White powder; yield: 22 mg (78%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.97 (s, 1 H), 8.95 (s, 1 H), 8.54 (s, 1 H), 8.01 (d, *J* = 8.0 Hz, 1 H), 7.91–7.85 (m, 3 H), 7.71–7.66 (m, 2 H), 7.54–7.47 (m, 2 H), 7.40 (t, *J* = 7.4 Hz, 1 H), 7.26 (t, *J* = 7.4 Hz, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 161.9, 153.7, 150.2, 147.7, 136.8, 134.7, 133.9, 129.6, 128.7, 127.7, 127.5, 126.7, 126.2, 125.8, 124.6, 123.5, 120.7, 115.1.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{18}H_{14}N_3O$: 288.1137; found: 288.1140.

2-(4-Acetylphenylamino)quinazolin-4(3*H*)-one (8g)
Yellow powder; yield: 18 mg (65%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.95 (s, 1 H), 9.14 (s, 1 H), 8.00–7.86 (m, 5 H), 7.69 (t, *J* = 7.2 Hz, 1 H), 7.46 (d, *J* = 8.0 Hz, 1 H), 7.28 (t, *J* = 7.4 Hz, 1 H), 2.54 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 201.4, 166.6, 154.6, 151.9, 148.6, 139.6, 135.8, 134.7, 131.0, 130.7, 128.7, 123.2, 44.6, 31.5.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{16}H_{14}N_3O_2$: 280.1086; found: 280.1087.

2-(2-Tolylamino)quinazolin-4(3*H*)-one (8h)
Yellow powder; yield: 19 mg (75%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.27 (s, 1 H), 8.11 (s, 1 H), 7.97–7.95 (m, 2 H), 7.62 (t, *J* = 7.6 Hz, 1 H), 7.32 (d, *J* = 8.0 Hz, 1 H), 7.25–7.19 (m, 3 H), 7.05 (t, *J* = 7.2 Hz, 1 H), 2.27 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 162.1, 150.4, 148.2, 137.0, 134.6, 130.5, 129.2, 126.5, 126.1, 125.4, 123.8, 123.0, 122.7, 118.5, 18.1.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{15}H_{14}N_3O$: 252.1137; found: 252.1136.

2-[Methyl(phenyl)amino]quinazolin-4(3*H*)-one (8i)
Yellow powder; yield: 18 mg (73%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.99 (s, 1 H), 7.94 (d, *J* = 7.6 Hz, 1 H), 7.61 (m, 1 H), 7.45–7.43 (m, 2 H), 7.35–7.34 (m, 4 H), 7.19 (t, *J* = 7.4 Hz, 1 H), 3.41 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 162.7, 150.7, 150.4, 144.2, 134.5, 131.4, 129.8, 126.6, 126.2, 125.3, 122.9, 117.9, 39.9.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{15}H_{14}N_3O$: 252.1137; found: 252.1130.

1-Methylindoline[32]
Brown oil; yield: 95 mg (71%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.08–7.07 (m, 2 H), 6.67 (t, *J* = 7.6 Hz, 1 H), 6.49 (t, *J* = 8.0 Hz, 1 H), 3.28 (t, *J* = 8.0 Hz, 2 H), 2.94 (t, *J* = 8.0 Hz, 2 H), 2.75 (s, 3 H).

MS (ESI): *m/z* [M + H]$^+$ calcd for $C_9H_{12}N$: 134.1; found: 134.1.

***N*-Cyanobenzamide (I)**[33]
White solid; yield: 34 mg (23%); mp 134–136 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.91 (d, 2 H, *J* = 7.6 Hz), 7.61 (t, 1 H, *J* = 7.6 Hz), 7.48 (t, 2 H, *J* = 7.6 Hz).

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_8H_7N_2O$: 147.0558; found: 147.0566.

Methyl Cyanoimidoformate (3o)[29e]
Colorless oil; yield: 11.63g (85%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.66 (s, 1 H), 3.72 (s, 3 H).

MS (ESI): *m/z* [M + H]$^+$ calcd for $C_3H_5N_2O$: 85.0; found: 85.0.

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

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