Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron 63 (2007) 9764–9773
Tetrahedron

An efficient synthesis of quinazoline-2,4-dione derivatives with the aid of a low-valent titanium reagent

Da-Qing Shi,[a,b,c,*] Guo-Lan Dou,[b] Zheng-Yi Li,[b] Sai-Nan Ni,[b] Xiao-Yue Li,[b] Xiang-Shan Wang,[b,c] Hui Wu[b,c] and Shun-Jun Ji[a]

[a]*College of Chemistry and Chemical Engineering, Key Laboratory of Organic Synthesis of Jiangsu Province, Suzhou University, Suzhou 215123, PR China*
[b]*Department of Chemistry, Xuzhou Normal University, Xuzhou 221116, PR China*
[c]*The Key Laboratory of Biotechnology on Medical Plants of Jiangsu Province, Xuzhou 221116, PR China*

Received 18 January 2007; revised 4 July 2007; accepted 6 July 2007
Available online 6 August 2007

Abstract—A facile synthetic method using low-valent titanium reagent ($TiCl_4$/Zn system) to promote the novel reductive cyclization of 2-nitrobenzamides and triphosgene is described. Sequentially, a series of quinazoline-2,4-diones were synthesized in good yields.

1. Introduction

Low-valent titanium reagents have exceedingly high ability to promote reductive coupling of carbonyl compounds and are attracting increasing interest in organic synthesis.[1] Recently, we have reported the cyclodimerization of α,β-unsaturated ketones and α,β-unsaturated nitriles promoted by this reagent yielding functional cyclopentanes[2] and cyclopentenes,[3] respectively.

Over the past decade, the synthesis of heterocycles has become one of the important aspects of medicinal chemistry.[4] Among the nitrogen-containing heterocycles, substituted quinazolinones represent the medicinally and pharmaceutically important class of compounds[5] because of their wide range of biological activities such as anticancer, diuretic, anti-inflammatory, anticonvulsant, and antihypertensive activities.[6] 6,7-Dimethoxy-1*H*-quinazoline-2,4-dione is a key intermediate for the production of the following medicines: Prazosin,[7] Bunazosin,[8] and Doxazosin.[9] 7-Chloro-1*H*-quinazoline-2,4-dione (**3a**) is also a key intermediate for the production of medicines such as FK366[10] and KF31327[11] (Fig. 1). The conventional synthesis of quinazoline-2,4-dione is carried out by anthranilic acid with urea,[12] anthranilamide with phosgene,[13] and anthranilic acid with potassium cyanate[14] or chlorosulfonyl isocyanate.[15] Recently, several methods have been developed for synthesizing this heterocyclic system, e.g., Mizuno et al. have reported the simple solvent-free synthesis of 1*H*-quinazoline-2,4-diones using supercritical carbon dioxide and catalytic amount of base.[16] Buckman et al. have reported the solid-phase synthesis of quinazoline-2,4-diones.[17–20] However, these methods suffer from some disadvantages such as drastic conditions, unsatisfactory yields, long-reaction time, high temperature, complex manipulation, and inaccessible starting materials.

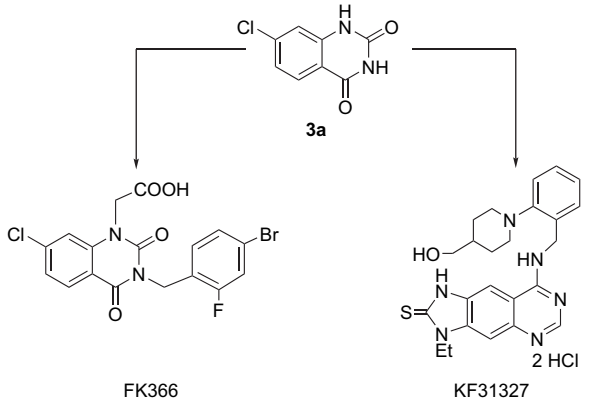
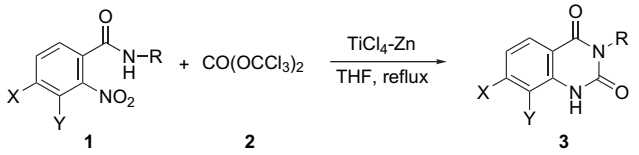


Figure 1. 7-Chloro-1*H*-quinazoline-2,4-dione (**3a**) is a key intermediate for FK366 and KF31327.

Therefore, the development of more efficient methods for preparing this kind of compounds with milder reaction conditions and improved yields is highly desired. Herein, we will describe a new approach to synthesizing quinazoline-2,4-diones via the novel reductive cyclization of 2-nitrobenzamides and triphosgene promoted by $TiCl_4$/Zn system (Scheme 1).

Keywords: Quinazolin-2,4-dione; Low-valent titanium reagent; Synthesis.
* Corresponding author. E-mail: dqshi@263.net

0040–4020/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2007.07.011



Scheme 1. Synthetic route to quinazoline-2,4-dione derivatives.

2. Results and discussion

4-Chloro-2-nitrobenzamide (**1a**) was used as the starting material to synthesize quinazoline-2,4-diones in this experiment. Using low-valent titanium as an inducing reagent, we first chose **3a** and have studied the optimized conditions for its reaction with triphosgene **2**, which gives quinazoline-2,4-diones.

Different low-valent titanium reagent systems were examined first. The comparison of these experiments is summarized in Table 1. We can easily see that $TiCl_4$/Zn system (entry 1) demonstrates superior catalytic activity than the other $TiCl_4$ reagents. To further evaluate the influence of reaction temperature, this type of reaction was carried out at different temperatures (Table 1). The study showed that at room temperature or 40 °C, no reaction took place (Table 1, entries 5 and 6), whereas refluxing gives the highest yield (93%).

Table 1. Optimization of catalyst system and temperature in the synthesis of **3a**

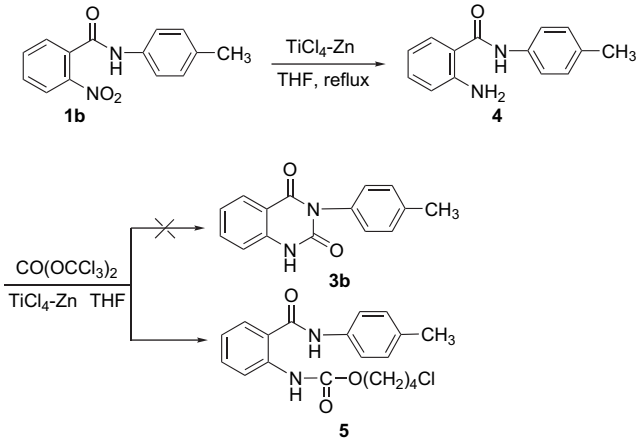
Entry	Catalyst system	Temperature (°C)	Isolated yield (%)
1	$TiCl_4$/Zn	Reflux	93
2	$TiCl_4$/Mg	Reflux	72
3	$TiCl_4$/Al	Reflux	68
4	$TiCl_4$/Fe	Reflux	65
5	$TiCl_4$/Zn	rt	N.R.
6	$TiCl_4$/Zn	40	N.R.
7	$TiCl_4$/Zn	60	60

Table 2. The synthesis of 3-substituted quinazoline-2,4-diones promoted by $TiCl_4$/Zn

Entry	X	Y	R	Isolated yield (%)
3a	Cl	H	H	93
3b	H	H	4-$CH_3C_6H_4$	89
3c	H	H	3-Cl-4-$CH_3C_6H_3$	85
3d	H	H	2,6-$Cl_2C_6H_3$	96
3e	H	H	4-$FC_6H_4CH_2$	95
3f	Cl	H	C_6H_5	91
3g	Cl	H	3-$CH_3C_6H_4$	92
3h	Cl	H	4-FC_6H_4	86
3i	Cl	H	$C_6H_5CH_2$	84
3j	Cl	H	4-$ClC_6H_4CH_2$	93
3k	H	H	4-BrC_6H_4	90
3l	H	CH_3	4-FC_6H_4	92
3m	H	H	Naphthalen-2-yl	91

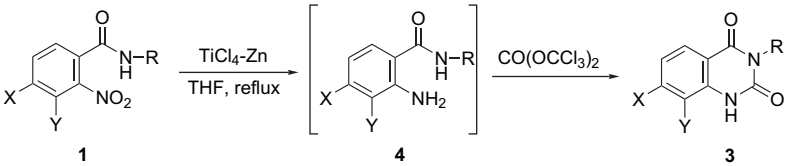
Because the nitro compounds are easy to be reduced to amines by low-valent titanium reagent,[21] we think this reaction may proceed through the intermediate amine **4**. As shown in Scheme 2, the nitro compound was reduced by low-valent titanium to generate amine **4**, which was then reacted with triphosgene to give product **3**.

To prove this point, we chose **1b** as starting material. Compound **1b** was firstly reduced to 2-amino-*N*-(4-methylphenyl)-benzamide (**4**) by low-valent titanium reagent, which was isolated and identified by spectral data. Then intermediate **4** was reacted with triphosgene under the same conditions. To our surprise, 4-chlorobutyl 2-(*p*-tolylcarbamoyl)phenylcarbamate **5** was obtained (yield: 73%) as our final product (Scheme 3), while the one we desired, **3b**, was not detected. This indicated that in this reaction the nitro compound was not simply reduced to amines.



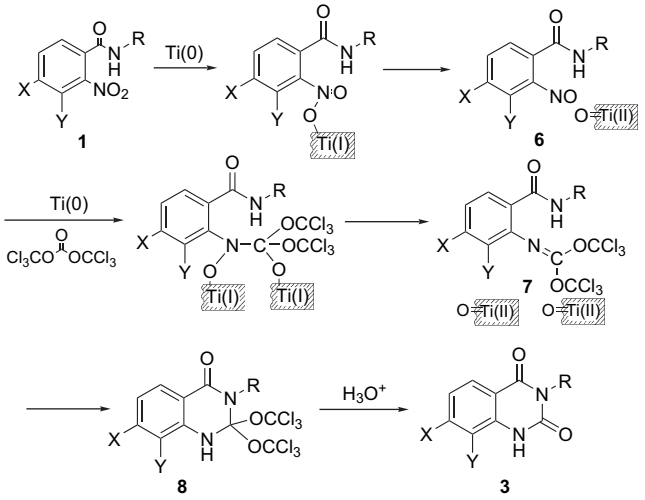
Scheme 3.

According to literature,[22] we suppose the following mechanism to explain this reaction. $TiCl_4$ is reduced by Zn dust to give low-valent titanium species. In the initial step, **1** was



Scheme 2.

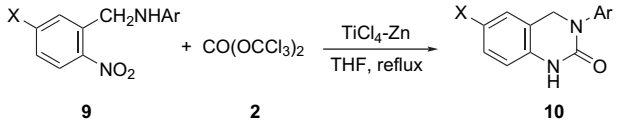
reduced by low-valent titanium to nitroso-compound **6**. Then reductive nitroso-compound **6** reacted with triphosgene and gave the intermediate **7**. Then **8** was obtained by addition, and the product **3** was obtained by hydrolysis (Scheme 4).



Scheme 4. Supposed reaction mechanism.

In order to apply this reaction to a library synthesis, 3,4-dihydroquinazolin-2(1*H*)-ones and imidazo[1,2-*c*]quinazolin-5(6*H*)-ones were synthesized similarly from the corresponding 2-nitrobenzyl amines and 2-(2-nitrophenyl)-imidazoles.

When 2-nitrobenzyl amines **9** and triphosgene **2** were treated with low-valent titanium reagent under the same reaction conditions, the reductive cyclization products 3,4-dihydro-3-arylquinazolin-2(1*H*)-ones **10** were obtained in good yields (Scheme 5). The results are summarized in Table 3.

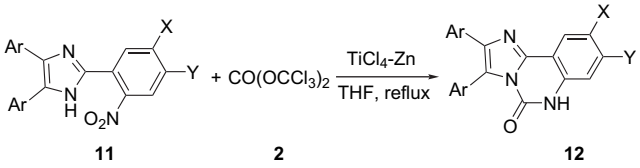


Scheme 5.

Table 3. The synthesis of 3,4-dihydro-3-arylquinazolin-2(1*H*)-ones promoted by $TiCl_4$/Zn

Entry	X	Ar	Isolated yield (%)
10a	H	C_6H_5	86
10b	H	4-FC_6H_4	78
10c	H	4-ClC_6H_4	83
10d	H	3-Cl-4-$CH_3C_6H_3$	87
10e	H	4-BrC_6H_4	74
10f	H	4-$CH_3C_6H_4$	71
10g	H	3-Cl-4-FC_6H_3	73
10h	Cl	4-FC_6H_4	92
10i	Cl	4-$CH_3OC_6H_4$	91
10j	Cl	4-BrC_6H_4	89
10k	Cl	4-ClC_6H_4	81
10l	Cl	C_6H_5	77
10m	Cl	4-$CH_3C_6H_4$	91
10n	Cl	3-Cl-4-FC_6H_3	72

Moreover, treatment of 2-(2-nitrophenyl)imidazoles **11** and triphosgene **2** with $TiCl_4$/Zn in anhydrous THF under the same reaction condition afforded imidazo[1,2-*c*]quinazolin-5(6*H*)-ones **12** in moderate to good yields (Scheme 6). The results are summarized in Table 4.



Scheme 6.

Table 4. The synthesis of imidazo[1,2-*c*]quinazolin-5(6*H*)-ones promoted by $TiCl_4$/Zn

Entry	X	Y	Ar	Isolated yield (%)
12a	H	H	C_6H_5	75
12b	H	H	4-$CH_3C_6H_4$	74
12c	H	H	4-$CH_3OC_6H_4$	86
12d	H	H	4-BrC_6H_4	94
12e	H	H	4-FC_6H_4	85
12f	Cl	H	C_6H_5	82
12g	Cl	H	4-$CH_3C_6H_4$	75
12h	Cl	H	4-$CH_3OC_6H_4$	88
12i	Cl	H	4-BrC_6H_4	90
12j	Cl	H	4-FC_6H_4	89
12k	CH_3O	CH_3O	C_6H_5	83
12l	CH_3O	CH_3O	4-BrC_6H_4	72

All the structures of **3**, **10**, and **12** were identified by IR, ^{1}H NMR, and elemental analysis, and the structures of **10c** and **12f** were further confirmed by X-ray analysis (Figs. 2 and 3).[23,24]

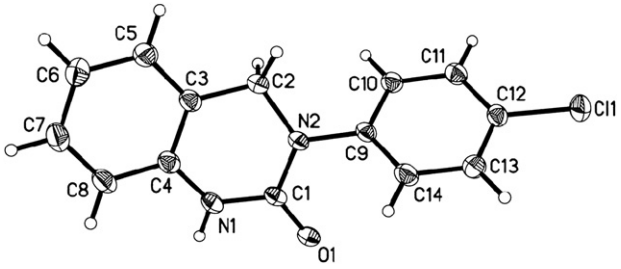


Figure 2. ORTEP diagram of **10c**.

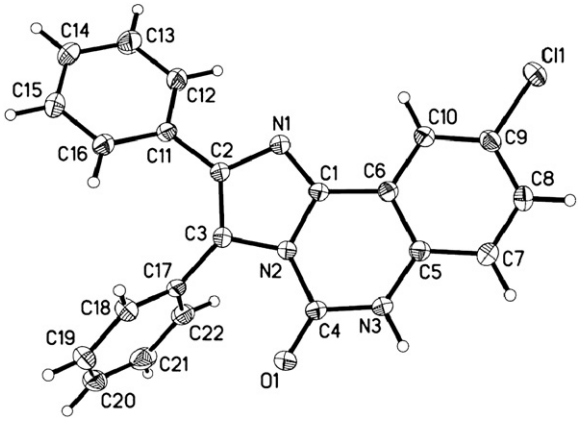


Figure 3. ORTEP diagram of **12f**.

3. Conclusion

In summary, a series of quinazoline-2,4-diones, 3,4-dihydroquinazolin-2(1*H*)-ones, and imidazo[1,2-*c*]quinazolin-5(6*H*)-ones were synthesized via low-valent titanium ($TiCl_4$/Zn system) induced reductive cyclization of 2-nitrobenzamide, 2-nitrobenzyl amines, and 2-(2-nitrophenyl)imidazoles with triphosgene, respectively. The new method has advantages such as easily accessible starting materials, convenient manipulation, and moderate to high yields. More importantly, using this described method, 7-chloro-1*H*-quinazoline-2,4-dione (**3a**), which is a key intermediate for medicines (FK366, Zenarestat, and KF31327), was synthesized in 93% yield.

4. Experimental

4.1. General

THF was distilled from sodium–benzophenone just prior to use. All the reactions were conducted under N_2 atmosphere. Melting points are uncorrected. IR spectra were recorded on a Tensor 27 spectrometer in KBr with absorptions in cm^{-1}. ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker DPX 400 MHz spectrometer in DMSO-d_6 or $CDCl_3$ solution. *J* values are in hertz. Chemical shifts are expressed in parts per million downfield from internal standard TMS. Microanalyses were carried out on a Perkin–Elmer 2400 II instrument. High-resolution mass spectra were obtained using GCT-TOF instrument. X-ray diffractions were recorded on a Siemens P4 diffractometer.

4.2. General procedure for the synthesis of quinazoline-2,4-diones (3a–3m)

$TiCl_4$ (1.1 mL, 10 mmol) was added dropwise using a syringe to a stirred suspension of zinc powder (1.3 g, 20 mmol) in freshly distilled anhydrous THF (20 mL) at rt under a dry N_2 atmosphere. After completion of the addition, the mixture was refluxed for 2 h. The suspension of the low-valent titanium reagent formed was cooled to rt and a solution of 2-nitrobenzamides (2 mmol) and triphosgene (3 mmol) in THF (10 mL) was added dropwise. The reaction mixture was then refluxed for 2 h under N_2 atmosphere. After this period, the TLC analysis of the mixture showed the completion of this reaction. The mixture was then quenched with 5% HCl (50 mL) and extracted with $ClCH_2CH_2Cl$ (3×50 mL). The extracts were washed with water (3×50 mL) and dried over anhydrous Na_2SO_4. After evaporation of the solvent under reduced pressure, the crude products were purified by recrystallization from 95% ethanol.

4.2.1. 7-Chloroquinazoline-2,4-dione (3a). Yellow crystals, mp >300 °C.

IR (KBr, ν, cm^{-1}): 3304, 3175, 3052, 2839, 1742, 1684, 1618, 1498, 1479, 1430, 1366, 1336, 1286, 1226, 1150, 1082, 1019, 933, 863, 828, 793, 768, 754.

^1H NMR (DMSO-d_6) δ: 7.19 (d, J=1.6 Hz, 1H, ArH), 7.22 (dd, J_1=2.0 Hz, J_2=8.4 Hz, 1H, ArH), 7.88 (d, J=8.4 Hz, 1H, ArH), 11.26 (s, 1H, NH), 11.41 (s, 1H, NH).

Anal. Calcd for $C_8H_5ClN_2O_2$: C 48.88, H 2.56, N 14.25; found: C 48.95, H 2.51, N 14.34.

4.2.2. 3-(4-Methylphenyl)quinazoline-2,4-dione (3b). Colorless crystals, mp 268–269 °C.

IR (KBr, ν, cm^{-1}): 3202, 3071, 2932, 1721, 1667, 1613, 1512, 1489, 1450, 1404, 1288, 1149, 872, 818, 756, 710.

^1H NMR ($CDCl_3$) δ: 2.44 (s, 3H, CH_3), 6.98 (d, J=7.8 Hz, 1H, ArH), 7.17–7.24 (m, 3H, ArH), 7.34 (d, J=8.1 Hz, 2H, ArH), 7.59 (t, J=7.8 Hz, 1H, ArH), 8.15 (d, J=8.1 Hz, 1H, ArH), 9.16 (s, 1H, NH).

Anal. Calcd for $C_{15}H_{12}N_2O_2$: C 71.42, H 4.79, N 11.10; found: C 71.53, H 4.72, N 11.19.

4.2.3. 3-(3-Chloro-4-methylphenyl)quinazoline-2,4-dione (3c). Yellow crystals, mp 289–290 °C.

IR (KBr, ν, cm^{-1}): 3193, 3129, 3055, 2999, 2933, 1733, 1664, 1605, 1491, 1448, 1409, 1277, 1248, 1148, 1052, 1022, 997, 904, 870, 808, 755, 702, 673.

^1H NMR (DMSO-d_6) δ: 2.40 (s, 3H, CH_3), 7.21–7.25 (m, 3H, ArH), 7.45–7.48 (m, 2H, ArH), 7.69–7.73 (m, 1H, ArH), 7.94 (d, J=7.2 Hz, 1H, ArH), 11.57 (s, 1H, NH).

Anal. Calcd for $C_{15}H_{11}ClN_2O_2$: C 62.84, H 3.87, N 9.77; found: C 62.97, H 3.83, N 9.82.

4.2.4. 3-(2,6-Dichlorophenyl)quinazoline-2,4-dione (3d). Yellow crystals, mp >300 °C.

IR (KBr, ν, cm^{-1}): 3202, 3139, 3084, 3000, 2939, 1723, 1683, 1618, 1604, 1570, 1490, 1461, 1444, 1401, 1283, 1249, 1203, 1158, 1105, 871, 823, 795, 779, 756, 691, 679.

^1H NMR (DMSO-d_6) δ: 7.29–7.33 (m, 2H, ArH), 7.57 (dd, J_1=7.2 Hz, J_2=8.8 Hz, 1H, ArH), 7.69–7.72 (m, 2H, ArH), 7.77–7.82 (m, 1H, ArH), 7.80 (d, J=8.0 Hz, 1H, ArH), 11.93 (s, 1H, NH).

Anal. Calcd for $C_{14}H_8Cl_2N_2O_2$: C 54.75, H 2.63, N 9.12; found: C 54.81, H 2.58, N 9.16.

4.2.5. 3-(4-Fluorobenzyl)quinazoline-2,4-dione (3e). Colorless crystals, mp 248–250 °C.

IR (KBr, ν, cm^{-1}): 3186, 3056, 2907, 1709, 1655, 1602, 1567, 1509, 1493, 1456, 1426, 1407, 1354, 1339, 1302, 1274, 1222, 1160, 1091, 961, 943, 857, 829, 790, 758, 692, 681.

^1H NMR (DMSO-d_6) δ: 5.07 (s, 2H, CH_2), 7.11–7.16 (m, 2H, ArH), 7.19–7.24 (m, 2H, ArH), 7.37–7.40 (m, 2H, ArH), 7.66–7.70 (m, 1H, ArH), 7.95 (d, J=8.0 Hz, 1H, ArH), 11.55 (s, 1H, NH).

Anal. Calcd for $C_{15}H_{11}FN_2O_2$: C 66.66, H 4.10, N 10.37; found: C 66.59, H 4.15, N 10.44.

4.2.6. 7-Chloro-3-phenylquinazoline-2,4-dione (3f). Yellow crystals, mp >300 °C.

IR (KBr, ν, cm^{-1}): 3185, 3067, 1731, 1650, 1614, 1484, 1429, 1369, 1335, 1258, 1170, 1088, 943, 869, 834, 761, 738, 697.

^1H NMR (DMSO-d_6) δ: 7.25–7.34 (m, 4H, ArH), 7.41–7.51 (m, 3H, ArH), 7.95 (d, J=8.4 Hz, 1H, ArH), 11.68 (s, 1H, NH).

Anal. Calcd for $C_{14}H_9ClN_2O_2$: C 61.66, H 3.33, N 10.27; found: C 61.91, H 3.03, N 10.02.

4.2.7. 7-Chloro-3-(3-methylphenyl)quinazoline-2,4-dione (3g). Yellow crystals, mp >300 °C.

IR (KBr, ν, cm^{-1}): 3227, 3183, 3069, 2920, 2865, 1735, 1652, 1602, 1485, 1428, 1369, 1335, 1261, 1180, 1159, 1088, 1058, 943, 870, 833, 814, 762, 726, 699, 684.

^1H NMR (DMSO-d_6) δ: 2.35 (s, 3H, CH_3), 7.09–7.14 (m, 2H, ArH), 7.22–7.29 (m, 3H, ArH), 7.34–7.39 (m, 1H, ArH), 7.94 (d, J=8.4 Hz, 1H, ArH), 11.68 (s, 1H, NH).

^{13}C NMR (DMSO-d_6) δ: 20.95, 113.51, 114.72, 122.84, 126.16, 128.80, 129.02, 129.53, 129.83, 135.55, 138.41, 139.66, 141.05, 150.24, 161.66.

Anal. Calcd for $C_{15}H_{11}ClN_2O_2$: C 62.84, H 3.87, N 9.77; found: C 62.98, H 3.62, N 9.65.

4.2.8. 7-Chloro-3-(4-fluorophenyl)quinazoline-2,4-dione (3h). Pale yellow crystals, mp >300 °C.

IR (KBr, ν, cm^{-1}): 3184, 3079, 1733, 1651, 1616, 1509, 1485, 1435, 1373, 1338, 1279, 1261, 1238, 1226, 1169, 1155, 1089, 943, 872, 835, 763, 733, 657.

^1H NMR (DMSO-d_6) δ: 7.27–7.30 (m, 2H, ArH), 7.33 (d, J=8.8 Hz, 2H, ArH), 7.38–7.41 (m, 2H, ArH), 7.94 (d, J=8.8 Hz, 1H, ArH), 11.69 (s, 1H, NH).

Anal. Calcd for $C_{14}H_8ClFN_2O_2$: C 57.85, H 2.77, N 9.64; found: C 58.04, H 2.59, N 9.48.

4.2.9. 3-Benzyl-7-chloroquinazoline-2,4-dione (3i). Colorless crystals, mp 268–269 °C.

IR (KBr, ν, cm^{-1}): 3264, 3192, 3064, 2970, 2883, 1713, 1668, 1617, 1598, 1441, 1384, 1350, 1251, 1084, 1072, 960, 863, 834, 779, 768, 740, 696, 686.

^1H NMR (DMSO-d_6) δ: 5.07 (s, 2H, CH_2), 7.21–7.32 (m, 7H, ArH), 7.94 (d, J=8.4 Hz, 1H, ArH), 11.67 (s, 1H, NH).

Anal. Calcd for $C_{15}H_{11}ClN_2O_2$: C 62.84, H 3.87, N 9.77; found: C 62.79, H 3.92, N 9.71.

4.2.10. 3-(4-Chlorobenzyl)-7-chloroquinazoline-2,4-dione (3j). Colorless crystals, mp 269–271 °C.

IR (KBr, ν, cm^{-1}): 3188, 3037, 2975, 2881, 1715, 1661, 1596, 1489, 1439, 1382, 1352, 1331, 1298, 1252, 1159, 1124, 1082, 1019, 960, 950, 860, 838, 806, 774, 760, 685.

^1H NMR (DMSO-d_6) δ: 5.05 (s, 2H, CH_2), 7.22 (d, J=1.6 Hz, 1H, ArH), 7.27 (dd, J_1=1.6 Hz, J_2=8.4 Hz, 1H, ArH), 7.33–7.39 (m, 4H, ArH), 7.94 (d, J=8.4 Hz, 1H, ArH), 11.68 (s, 1H, NH).

Anal. Calcd for $C_{15}H_{10}Cl_2N_2O_2$: C 56.10, H 3.14, N 8.72; found: C 56.23, H 3.08, N 8.85.

4.2.11. 3-(4-Bromophenyl)quinazoline-2,4-dione (3k). Pale yellow crystals, mp >300 °C.

IR (KBr, ν, cm^{-1}): 3250, 3134, 3065, 3002, 2936, 2893, 1723, 1669, 1606, 1489, 1441, 1403, 1281, 1243, 1153, 1068, 1011, 871, 819, 758, 728, 689, 680.

^1H NMR (DMSO-d_6) δ: 7.23–7.26 (m, 2H, ArH), 7.33 (d, J=8.4 Hz, 2H, ArH), 7.68–7.74 (m, 3H, ArH), 7.95 (d, J=7.6 Hz, 1H, ArH), 11.61 (s, 1H, NH).

^{13}C NMR (DMSO-d_6) δ: 114.48, 115.43, 121.44, 122.73, 127.75, 131.62, 131.97, 135.33, 135.46, 139.99, 150.18, 162.28.

Anal. Calcd for $C_{14}H_9BrN_2O_2$: C 53.02, H 2.86, N 8.83; found: C 53.25, H 2.73, N 8.96.

4.2.12. 8-Methyl-3-(4-fluorophenyl)quinazoline-2,4-dione (3l). Colorless crystals, mp 269–271 °C.

IR (KBr, ν, cm^{-1}): 3241, 3087, 1721, 1659, 1512, 1474, 1412, 1327, 1265, 1227, 1149, 833, 802, 756.

^1H NMR (DMSO-d_6) δ: 2.35 (s, 3H, CH_3), 7.15–7.31 (m, 5H, ArH), 7.49 (d, J=7.2 Hz, 1H, ArH), 8.03 (d, J=7.8 Hz, 1H, ArH), 8.62 (s, 1H, NH).

Anal. Calcd for $C_{15}H_{11}FN_2O_2$: C 66.66, H 4.10, N 10.37; found: C 66.72, H 3.97, N 10.20.

4.2.13. 3-(Naphthalen-2-yl)quinazoline-2,4-dione (3m). Pale yellow crystals, mp 268–269 °C.

IR (KBr, ν, cm^{-1}): 3254, 3058, 1721, 1669, 1619, 1602, 1489, 1432, 1398, 1268, 1158, 1032, 884, 794, 756.

^1H NMR (DMSO-d_6) δ: 7.26–7.32 (m, 2H, ArH), 7.46–7.60 (m, 6H, ArH), 7.94–7.98 (m, 1H, ArH), 8.04–8.10 (m, 2H, ArH), 11.70 (s, 1H, NH).

Anal. Calcd for $C_{18}H_{12}N_2O_2$: C 74.99, H 4.20, N 9.72; found: C 75.16, H 4.28, N 9.63.

4.3. Synthesis of 2-amino-*N*-(4-methylphenyl)benzamide 4

$TiCl_4$ (1.1 mL, 10 mmol) was added dropwise using a syringe to a stirred suspension of zinc powder (1.3 g, 20 mmol) in freshly distilled anhydrous THF (20 mL) at rt under a dry N_2 atmosphere. After completion of the addition, the mixture was refluxed for 2 h. The suspension of the low-valent titanium reagent formed was cooled to rt and a solution of 2-nitro-*N*-(4-methylphenyl)benzamide (5 mmol) in THF (10 mL) was added dropwise. The reaction mixture was then stirred for 1 h at rt under N_2. After this period, the

TLC analysis of the mixture showed the reaction to be completed. The reaction mixture was quenched with 3% HCl (100 mL) and extracted with $ClCH_2CH_2Cl$ (3×50 mL). The combined extracts were washed with water (3×50 mL) and dried over anhydrous Na_2SO_4. After evaporation of the solvent under reduced pressure, the crude product was purified by recrystallization from 95% ethanol. Yield 92%, colorless crystals, mp 140–141 °C.

IR (KBr, ν, cm^{-1}): 3466, 3362, 3275, 3053, 1635, 1580, 1538, 1406, 1316, 1281, 1256, 1152, 815, 747, 693.

^1H NMR (DMSO-d_6) δ: 2.28 (s, 3H, CH_3), 6.30 (s, 2H, NH_2), 6.59 (t, J=7.6 Hz, 1H, ArH), 6.75 (d, J=8.0 Hz, 1H, ArH), 7.13–7.21 (m, 3H, ArH), 7.58–7.62 (m, 3H, ArH), 9.90 (s, 1H, NH).

HRMS: found: m/z 226.1111 (M^+), calcd for $C_{14}H_{14}N_2O$: M, 226.1106.

4.4. Synthesis of 4-chlorobutyl 2-(*p*-tolylcarbamoyl)-phenylcarbamate 5

$TiCl_4$ (1.1 mL, 10 mmol) was added dropwise using a syringe to a stirred suspension of zinc powder (1.3 g, 20 mmol) in freshly distilled anhydrous THF (20 mL) at rt under a dry N_2 atmosphere. After completion of the addition, the mixture was refluxed for 2 h. The suspension of the low-valent titanium reagent formed was cooled to rt and a solution of 2-amino-*N*-(4-methylphenyl)benzamide (2 mmol) and triphosgene (3 mmol) in THF (10 mL) was added dropwise. The reaction mixture was then refluxed for 1 h under N_2 atmosphere. After this period, the TLC analysis of the mixture showed the reaction to be completed. The reaction mixture was quenched with 5% HCl (50 mL) and extracted with $ClCH_2CH_2Cl$ (3×50 mL). The combined extracts were washed with water (3×50 mL) and dried over anhydrous Na_2SO_4. After evaporation of the solvent under reduced pressure, the crude product was purified by recrystallization from 95% ethanol. Yield 73%, colorless crystals, mp 96–98 °C.

IR (KBr, ν, cm^{-1}): 3307, 2966, 1707, 1665, 1602, 1586, 1522, 1451, 1403, 1326, 1248, 1214, 1095, 1060, 818, 741, 696.

^1H NMR (DMSO-d_6) δ: 1.72–1.81 (m, 4H, 2×CH_2), 2.30 (s, 3H, CH_3), 3.67 (t, J=6.4 Hz, 2H, CH_2), 4.11 (t, J=6.4 Hz, 2H, CH_2), 7.16–7.21 (m, 3H, ArH), 7.52–7.61 (m, 3H, ArH), 7.82 (d, J=8.0 Hz, 1H, ArH), 8.09 (d, J=8.0 Hz, 1H, ArH), 10.22 (s, 1H, NH), 10.37 (s, 1H, NH).

HRMS: found: m/z 360.1228 (M^+), calcd for $C_{19}H_{21}{}^{35}ClN_2O_3$: M, 360.1241.

4.5. General procedure for the synthesis of 3,4-dihydroquinazolin-2(1*H*)-ones (10a–10n)

$TiCl_4$ (1.1 mL, 10 mmol) was added dropwise using a syringe to a stirred suspension of zinc powder (1.3 g, 20 mmol) in freshly distilled anhydrous THF (20 mL) at rt under a dry N_2 atmosphere. After completion of the addition, the mixture was refluxed for 2 h. The suspension of the low-valent titanium reagent formed was cooled to rt and a solution of 2-nitrobenzyl amines (2 mmol) and triphosgene (3 mmol) in THF (10 mL) was added dropwise. The reaction mixture was then refluxed for 0.5 h under N_2. After this period, the TLC analysis of the mixture showed the reaction to be completed. The reaction mixture was quenched with 5% HCl (50 mL) and extracted with $ClCH_2CH_2Cl$ (3×50 mL). The combined extracts were washed with water (3×50 mL) and dried over anhydrous Na_2SO_4. After evaporation of the solvent under reduced pressure, the crude product was purified by recrystallization from 95% ethanol.

4.5.1. 3-Phenyl-3,4-dihydroquinazolin-2(1*H*)-one (10a). Yellow crystals, mp 188–189 °C.

IR (KBr, ν, cm^{-1}): 3199, 3063, 2913, 1663, 1598, 1492, 1428, 1321, 1298, 1266, 1209, 1171, 1154, 1034, 872, 769, 750, 701.

^1H NMR (DMSO-d_6) δ: 4.82 (s, 2H, CH_2), 6.88–6.94 (m, 2H, ArH), 7.16–7.24 (m, 3H, ArH), 7.37–7.39 (m, 4H, ArH), 9.59 (s, 1H, NH).

Anal. Calcd for $C_{14}H_{12}N_2O$: C 74.98, H 5.39, N 12.49; found: C 75.06, H 5.36, N 12.53.

4.5.2. 3-(4-Fluorophenyl)-3,4-dihydroquinazolin-2(1*H*)-one (10b). Pale yellow crystals, mp 200–202 °C.

IR (KBr, ν, cm^{-1}): 3207, 3066, 2911, 1670, 1598, 1509, 1470, 1440, 1426, 1411, 1320, 1296, 1263, 1215, 1155, 840, 793, 750.

^1H NMR (DMSO-d_6) δ: 4.82 (s, 2H, CH_2), 6.87 (d, J=8.0 Hz, 1H, ArH), 6.91–6.94 (m, 1H, ArH), 7.15–7.24 (m, 4H, ArH), 7.40–7.43 (m, 2H, ArH), 9.60 (s, 1H, NH).

Anal. Calcd for $C_{14}H_{11}FN_2O$: C 69.41, H 4.58, N 11.56; found: C 69.54, H 4.52, N 11.61.

4.5.3. 3-(4-Chlorophenyl)-3,4-dihydroquinazolin-2(1*H*)-one (10c). Colorless crystals, mp 208–210 °C.

IR (KBr, ν, cm^{-1}): 3206, 3072, 2918, 1671, 1600, 1485, 1470, 1423, 1397, 1319, 1297, 1257, 1225, 1160, 1089, 1012, 837, 800, 756.

^1H NMR (DMSO-d_6) δ: 4.81 (s, 2H, CH_2), 6.88 (d, J=8.0 Hz, 1H, ArH), 6.91–6.95 (m, 1H, ArH), 7.16–7.22 (m, 2H, ArH), 7.38–7.46 (m, 4H, ArH), 9.66 (s, 1H, NH).

Anal. Calcd for $C_{14}H_{11}ClN_2O$: C 65.00, H 4.29, N 10.83; found: C 65.12, H 4.24, N 10.75.

4.5.4. 3-(3-Chloro-4-methylphenyl)-3,4-dihydroquinazolin-2(1*H*)-one (10d). Pale yellow crystals, mp 185–187 °C.

IR (KBr, ν, cm^{-1}): 3211, 3064, 2992, 2918, 1672, 1604, 1566, 1485, 1473, 1419, 1382, 1307, 1261, 1216, 1161, 1045, 1016, 994, 863, 817, 735, 664.

^1H NMR (DMSO-d_6) δ: 2.33 (s, 3H, CH_3), 4.81 (s, 2H, CH_2), 6.88 (d, J=7.6 Hz, 1H, ArH), 6.91–6.95 (m, 1H, ArH), 7.16–7.21 (m, 2H, ArH), 7.27 (d, J=8.0 Hz, 1H, ArH), 7.35 (d, J=8.4 Hz, 1H, ArH), 7.47 (s, 1H, ArH), 9.64 (s, 1H, NH).

Anal. Calcd for $C_{15}H_{13}ClN_2O$: C 66.06, H 4.80, N 10.27; found: C 66.18, H 4.74, N 10.16.

4.5.5. 3-(4-Bromophenyl)-3,4-dihydroquinazolin-2(1*H*)-one (10e). Pale yellow crystals, mp 287–289 °C.

IR (KBr, ν, cm^{-1}): 3203, 3067, 2916, 1667, 1603, 1587, 1574, 1489, 1463, 1427, 1398, 1319, 1301, 1267, 1224, 1071, 1009, 833, 798, 756, 728.

^1H NMR (DMSO-d_6) δ: 4.81 (s, 2H, CH_2), 6.88 (d, J=7.6 Hz, 1H, ArH), 6.93 (t, J=7.2 Hz, 1H, ArH), 7.16–7.21 (m, 2H, ArH), 7.36 (d, J=8.4 Hz, 2H, ArH), 7.56 (d, J=8.4 Hz, 2H, ArH), 9.68 (s, 1H, NH).

Anal. Calcd for $C_{14}H_{11}BrN_2O$: C 55.47, H 3.66, N 9.24; found: C 55.53, H 3.71, N 9.29.

4.5.6. 3-(4-Methylphenyl)-3,4-dihydroquinazolin-2(1*H*)-one (10f). Pale yellow crystals, mp 220–222 °C.

IR (KBr, ν, cm^{-1}): 3214, 3069, 2913, 1692, 1606, 1512, 1423, 1306, 1253, 1217, 1161, 1111, 1035, 1020, 1003, 974, 931, 859, 808, 784.

^1H NMR (DMSO-d_6) δ: 2.31 (s, 3H, CH_3), 4.77 (s, 2H, CH_2), 6.86–6.93 (m, 2H, ArH), 7.15–7.26 (m, 6H, ArH), 9.53 (s, 1H, NH).

^{13}C NMR (DMSO-d_6) δ: 20.73, 50.57, 113.49, 118.77, 121.42, 125.17, 125.71, 128.14, 129.10, 134.64, 137.61, 140.20, 157.39.

Anal. Calcd for $C_{15}H_{14}N_2O$: C 75.61, H 5.92, N 11.76; found: C 75.72, H 5.88, N 11.83.

4.5.7. 3-(3-Chloro-4-fluorophenyl)-3,4-dihydroquinazolin-2(1*H*)-one (10g). Yellow crystals, mp 171–172 °C.

IR (KBr, ν, cm^{-1}): 3206, 3068, 2990, 2921, 1694, 1604, 1505, 1470, 1445, 1425, 1404, 1312, 1257, 1240, 1218, 1157, 1059, 1014, 857, 810, 794, 738, 716.

^1H NMR (DMSO-d_6) δ: 4.83 (s, 2H, CH_2), 6.88 (d, J=7.6 Hz, 1H, ArH), 6.92–6.96 (m, 1H, ArH), 7.16–7.26 (m, 2H, ArH), 7.40–7.46 (m, 2H, ArH), 7.65–7.67 (m, 1H, ArH), 9.69 (s, 1H, NH).

Anal. Calcd for $C_{14}H_{10}ClFN_2O$: C 60.77, H 3.64, N 10.12; found: C 60.88, H 3.57, N 10.20.

4.5.8. 6-Chloro-3-(4-fluorophenyl)-3,4-dihydroquinazolin-2(1*H*)-one (10h). Colorless crystals, mp 164–166 °C.

IR (KBr, ν, cm^{-1}): 3207, 3087, 2963, 1688, 1600, 1510, 1467, 1443, 1394, 1308, 1274, 1218, 1158, 1083, 928, 824, 806, 741, 709, 672.

^1H NMR (DMSO-d_6) δ: 4.80 (s, 2H, CH_2), 6.87 (d, J=8.4 Hz, 1H, ArH), 7.21–7.26 (m, 4H, ArH), 7.39–7.42 (m, 2H, ArH), 9.73 (s, 1H, NH).

Anal. Calcd for $C_{14}H_{10}ClFN_2O$: C 60.77, H 3.64, N 10.12; found: C 60.84, H 3.59, N 10.23.

4.5.9. 6-Chloro-3-(4-methoxyphenyl)-3,4-dihydroquinazolin-2(1*H*)-one (10i). Colorless crystals, mp 189–190 °C.

IR (KBr, ν, cm^{-1}): 3206, 3086, 2959, 1668, 1604, 1511, 1467, 1441, 1398, 1306, 1247, 1175, 1085, 1032, 927, 826, 749.

^1H NMR (DMSO-d_6) δ: 3.76 (s, 3H, OCH_3), 4.76 (s, 2H, CH_2), 6.85–6.87 (m, 1H, ArH), 6.93–6.96 (m, 2H, ArH), 7.22–7.28 (m, 4H, ArH), 9.63 (s, 1H, NH).

Anal. Calcd for $C_{15}H_{13}ClN_2O_2$: C 62.40, H 4.54, N 9.70; found: C 62.54, H 4.47, N 9.62.

4.5.10. 6-Chloro-3-(4-bromophenyl)-3,4-dihydroquinazolin-2(1*H*)-one (10j). Colorless crystals, mp 228–230 °C.

IR (KBr, ν, cm^{-1}): 3203, 3087, 2936, 1687, 1600, 1492, 1467, 1438, 1391, 1297, 1272, 1218, 1204, 1072, 1008, 927, 826, 806, 732, 709.

^1H NMR (DMSO-d_6) δ: 4.82 (s, 2H, CH_2), 6.88 (d, J=8.4 Hz, 1H, ArH), 7.25–7.28 (m, 2H, ArH), 7.35 (d, J=8.4 Hz, 2H, ArH), 7.57 (d, J=8.4 Hz, 2H, ArH), 9.79 (s, 1H, NH).

Anal. Calcd for $C_{14}H_{10}BrClN_2O$: C 49.81, H 2.99, N 8.30; found: C 49.75, H 3.04, N 8.37.

4.5.11. 6-Chloro-3-(4-chlorophenyl)-3,4-dihydroquinazolin-2(1*H*)-one (10k). Pale yellow crystals, mp 206–208 °C.

IR (KBr, ν, cm^{-1}): 3222, 3095, 2938, 1674, 1593, 1489, 1457, 1442, 1394, 1307, 1273, 1211, 1165, 1093, 1015, 927, 853, 824, 748, 716.

^1H NMR (DMSO-d_6) δ: 4.82 (s, 2H, CH_2), 6.88 (d, J=8.4 Hz, 1H, ArH), 7.24–7.28 (m, 2H, ArH), 7.40 (d, J=8.4 Hz, 2H, ArH), 7.42 (d, J=8.4 Hz, 2H, ArH), 9.79 (s, 1H, NH).

Anal. Calcd for $C_{14}H_{10}Cl_2N_2O$: C 57.36, H 3.44, N 9.56; found: C 57.42, H 3.38, N 9.62.

4.5.12. 6-Chloro-3-phenyl-3,4-dihydroquinazolin-2(1*H*)-one (10l). Colorless crystals, mp 163–164 °C.

IR (KBr, ν, cm^{-1}): 3199, 3084, 2924, 1668, 1597, 1498, 1460, 1432, 1389, 1296, 1221, 1081, 1033, 924, 867, 826, 783, 691.

^1H NMR (DMSO-d_6) δ: 4.82 (s, 2H, CH_2), 6.88 (d, J=8.4 Hz, 1H, ArH), 7.21–7.28 (m, 3H, ArH), 7.34–7.42 (m, 4H, ArH), 9.72 (s, 1H, NH).

Anal. Calcd for $C_{14}H_{11}ClN_2O$: C 65.00, H 4.29, N 10.83; found: C 65.12, H 4.35, N 10.92.

4.5.13. 6-Chloro-3-(4-methylphenyl)-3,4-dihydroquinazolin-2(1*H*)-one (10m). Pale yellow crystals, mp 214–215 °C.

IR (KBr, ν, cm^{-1}): 3195, 3045, 2924, 1670, 1599, 1492, 1467, 1444, 1399, 1304, 1275, 1205, 1084, 927, 878, 819, 747, 718, 668.

^1H NMR (DMSO-d_6) δ: 2.31 (s, 3H, CH_3), 4.78 (s, 2H, CH_2), 6.87 (d, J=8.4 Hz, 1H, ArH), 7.17–7.20 (m, 2H, ArH), 7.23–7.24 (m, 2H, ArH), 7.25–7.28 (m, 2H, ArH), 9.66 (s, 1H, NH).

Anal. Calcd for $C_{15}H_{13}ClN_2O$: C 66.06, H 4.80, N 10.27; found: C 66.14, H 4.76, N 10.09.

4.5.14. 6-Chloro-3-(3-chloro-4-fluorophenyl)-3,4-dihydroquinazolin-2(1*H*)-one (10n). Yellow crystals, mp 251–252 °C.

IR (KBr, ν, cm^{-1}): 3210, 3087, 2952, 1690, 1601, 1503, 1472, 1438, 1390, 1308, 1247, 1218, 878, 813, 729, 698.

^1H NMR (DMSO-d_6) δ: 4.83 (s, 2H, CH_2), 6.88 (d, J=7.6 Hz, 1H, ArH), 7.24–7.27 (m, 2H, ArH), 7.38–7.45 (m, 2H, ArH), 7.64–7.66 (m, 1H, ArH), 9.82 (s, 1H, NH).

Anal. Calcd for $C_{14}H_9Cl_2FN_2O$: C 54.04, H 2.92, N 9.00; found: C 53.96, H 3.04, N 9.05.

4.6. General procedure for the synthesis of imidazo[1,2-*c*]quinazolin-5(6*H*)-ones (12a–12l)

$TiCl_4$ (1.1 mL, 10 mmol) was added dropwise using a syringe to a stirred suspension of zinc powder (1.3 g, 20 mmol) in freshly distilled anhydrous THF (20 mL) at rt under a dry N_2 atmosphere. After completion of the addition, the mixture was refluxed for 2 h. The suspension of the low-valent titanium reagent formed was cooled to rt and a solution of 2-(2-nitrophenyl)imidazoles (2 mmol) and triphosgene (3 mmol) in THF (10 mL) was added dropwise. The mixture was refluxed for 0.5 h (the reaction was monitored by TLC). The reaction mixture was quenched with 10% HCl (50 mL) and extracted with $ClCH_2CH_2Cl$ (3×50 mL). The combined extracts were washed with water (3×50 mL) and dried over anhydrous Na_2SO_4. After evaporation of the solvent under reduced pressure, the crude product was purified by recrystallization from DMF.

4.6.1. 2,3-Diphenylimidazo[1,2-*c*]quinazolin-5(6*H*)-one (12a). Colorless crystals, mp >300 °C.

IR (KBr, ν, cm^{-1}): 3160, 3053, 2925, 1707, 1596, 1554, 1479, 1443, 1378, 1335, 1215, 1073, 803, 779, 750, 696.

^1H NMR (DMSO-d_6) δ: 7.23–7.28 (m, 3H, ArH), 7.35–7.37 (m, 2H, ArH), 7.43–7.47 (m, 5H, ArH), 7.55–7.59 (m, 1H, ArH), 7.62–7.66 (m, 1H, ArH), 7.92–7.96 (m, 1H, ArH), 8.26 (d, J=8.0 Hz, 1H, ArH), 11.74 (s, 1H, NH).

^{13}C NMR (DMSO-d_6) δ: 112.38, 114.27, 114.68, 114.71, 115.66, 118.55, 121.92, 123.15, 123.47, 125.46, 127.52, 127.96, 128.35, 128.44, 130.80, 131.12, 131.38, 133.62, 135.51, 140.17, 143.38, 145.52.

Anal. Calcd for $C_{22}H_{15}N_3O$: C 78.32, H 4.48, N 12.46; found: C 78.43, H 4.42, N 12.52.

4.6.2. 2,3-Di(4-methylphenyl)imidazo[1,2-*c*]quinazolin-5(6*H*)-one (12b). Yellow crystal, mp >300 °C.

IR (KBr, ν, cm^{-1}): 3165, 3065, 2933, 1708, 1594, 1549, 1516, 1489, 1445, 1398, 1371, 1335, 1325, 1271, 1206, 1184, 1104, 960, 937, 833, 818, 745, 694.

^1H NMR (DMSO-d_6) δ: 2.26 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 7.08 (d, J=8.0 Hz, 2H, ArH), 7.23 (d, J=8.0 Hz, 2H, ArH), 7.30 (d, J=8.0 Hz, 2H, ArH), 7.33–7.37 (m, 4H, ArH), 7.44 (d, J=8.0 Hz, 1H, ArH), 8.24 (d, J=7.2 Hz, 1H, ArH), 11.70 (s, 1H, NH).

Anal. Calcd for $C_{24}H_{19}N_3O$: C 78.88, H 5.24, N 11.50; found: C 78.94, H 5.18, N 11.57.

4.6.3. 2,3-Di(4-methoxyphenyl)imidazo[1,2-*c*]quinazolin-5(6*H*)-one (12c). Yellow crystal, mp >300 °C.

IR (KBr, ν, cm^{-1}): 3161, 3054, 2935, 2832, 1708, 1602, 1555, 1516, 1489, 1458, 1442, 1401, 1376, 1338, 1289, 1248, 1173, 1031, 831, 809, 779, 746, 691.

^1H NMR (DMSO-d_6) δ: 3.73 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 6.85 (d, J=8.8 Hz, 2H, ArH), 6.98 (d, J=8.8 Hz, 2H, ArH), 7.31–7.35 (m, 4H, ArH), 7.42 (d, J=8.8 Hz, 2H, ArH), 7.52–7.56 (m, 1H, ArH), 8.23 (d, J=7.6 Hz, 1H, ArH), 11.65 (s, 1H, NH).

Anal. Calcd for $C_{24}H_{19}N_3O_3$: C 72.53, H 4.82, N 10.57; found: C 72.48, H 4.87, N 10.64.

4.6.4. 2,3-Di(4-bromophenyl)imidazo[1,2-*c*]quinazolin-5(6*H*)-one (12d). Colorless crystals, mp >300 °C.

IR (KBr, ν, cm^{-1}): 3171, 3072, 2927, 1711, 1593, 1548, 1475, 1392, 1369, 1337, 1071, 1006, 958, 832, 744, 728.

^1H NMR (DMSO-d_6) δ: 7.33–7.43 (m, 6H, ArH), 7.53 (d, J=8.4 Hz, 2H, ArH), 7.58 (t, J=8.0 Hz, 1H, ArH), 7.64 (d, J=8.4 Hz, 2H, ArH), 8.25 (d, J=8.0 Hz, 1H, ArH), 11.79 (s, 1H, NH).

Anal. Calcd for $C_{22}H_{13}Br_2N_3O$: C 53.36, H 2.65, N 8.49; found: C 53.42, H 2.69, N 8.53.

4.6.5. 2,3-Di(4-fluorophenyl)imidazo[1,2-*c*]quinazolin-5(6*H*)-one (12e). Colorless crystals, mp >300 °C.

IR (KBr, ν, cm^{-1}): 3160, 3097, 2929, 2867, 1707, 1599, 1556, 1514, 1488, 1397, 1375, 1326, 1267, 1215, 1164, 1091, 1015, 847, 819, 779, 751, 740, 691.

^1H NMR (DMSO-d_6) δ: 7.15 (t, J=8.8 Hz, 2H, ArH), 7.27 (t, J=8.8 Hz, 2H, ArH), 7.33–7.38 (m, 2H, ArH), 7.47–7.52 (m, 4H, ArH), 7.57 (t, J=8.0 Hz, 1H, ArH), 8.25 (d, J=8.4 Hz, 1H, ArH), 11.75 (s, 1H, NH).

Anal. Calcd for $C_{22}H_{13}F_2N_3O$: C 70.77, H 3.51, N 11.25; found: C 70.84, H 3.49, N 11.30.

4.6.6. 9-Chloro-2,3-diphenylimidazo[1,2-*c*]quinazolin-5(6*H*)-one (12f). Pale yellow crystal, mp >300 °C.

IR (KBr, ν, cm^{-1}): 3208, 3044, 2919, 1718, 1594, 1553, 1500, 1475, 1435, 1364, 1311, 1211, 1169, 1076, 1020, 918, 879, 834, 816, 766, 751, 696.

^1H NMR (DMSO-d_6) δ: 7.23–7.29 (m, 3H, ArH), 7.43–7.47 (m, 5H, ArH), 7.59–7.66 (m, 3H, ArH), 7.92–7.94 (m, 1H, ArH), 8.17–8.19 (m, 1H, ArH), 11.86 (s, 1H, NH).

Anal. Calcd for $C_{22}H_{14}ClN_3O$: C 71.07, H 3.80, N 11.30; found: C 71.12, H 3.85, N 11.36.

4.6.7. 9-Chloro-2,3-di(4-methylphenyl)imidazo[1,2-*c*]quinazolin-5(6*H*)-one (12g). Colorless crystals, mp >300 °C.

IR (KBr, ν, cm^{-1}): 3215, 3038, 2917, 1710, 1592, 1549, 1476, 1438, 1384, 1365, 1327, 1268, 1161, 1076, 1007, 911, 867, 839, 821, 753, 735, 712.

^1H NMR (DMSO-d_6) δ: 2.27 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 7.08 (d, J=8.0 Hz, 2H, ArH), 7.23 (d, J=7.6 Hz, 2H, ArH), 7.31 (d, J=8.0 Hz, 2H, ArH), 7.35–7.37 (m, 3H, ArH), 7.59 (dd, J_1=2.0 Hz, J_2=8.4 Hz, 1H, ArH), 8.17 (d, J=2.0 Hz, 1H, ArH), 11.81 (s, 1H, NH).

Anal. Calcd for $C_{24}H_{18}ClN_3O$: C 72.09, H 4.54, N 10.51; found: C 72.16, H 4.58, N 10.46.

4.6.8. 9-Chloro-2,3-di(4-methoxyphenyl)imidazo[1,2-*c*]quinazolin-5(6*H*)-one (12h). Colorless crystals, mp >300 °C.

IR (KBr, ν, cm^{-1}): 3208, 3090, 2955, 2834, 1701, 1612, 1553, 1518, 1482, 1448, 1365, 1287, 1246, 1170, 1067, 1037, 907, 867, 841, 827, 751, 741.

^1H NMR (DMSO-d_6) δ: 3.73 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 6.85 (d, J=8.8 Hz, 2H, ArH), 6.99 (d, J=8.8 Hz, 2H, ArH), 7.34–7.36 (m, 3H, ArH), 7.42 (d, J=8.8 Hz, 2H, ArH), 7.58 (dd, J_1=1.6 Hz, J_2=8.8 Hz, 1H, ArH), 8.15 (d, J=1.6 Hz, 1H, ArH), 11.78 (s, 1H, NH).

Anal. Calcd for $C_{24}H_{18}ClN_3O_3$: C 66.75, H 4.20, N 9.73; found: C 66.82, H 4.16, N 9.81.

4.6.9. 9-Chloro-2,3-di(4-bromophenyl)imidazo[1,2-*c*]quinazolin-5(6*H*)-one (12i). Pale yellow crystals, mp >300 °C.

IR (KBr, ν, cm^{-1}): 3216, 3041, 2919, 1715, 1596, 1549, 1493, 1473, 1435, 1362, 1331, 1069, 1006, 841, 826, 799, 752, 734, 699.

^1H NMR (DMSO-d_6) δ: 7.36–7.42 (m, 5H, ArH), 7.52 (d, J=8.4 Hz, 2H, ArH), 7.59–7.62 (dd, J_1=2.0 Hz, J_2=8.8 Hz, 1H, ArH), 7.64 (d, J=8.4 Hz, 2H, ArH), 8.17 (d, J=2.0 Hz, 1H, ArH), 11.91 (s, 1H, NH).

Anal. Calcd for $C_{22}H_{12}Br_2ClN_3O$: C 49.89, H 2.28, N 7.93; found: C 50.01, H 2.25, N 7.98.

4.6.10. 9-Chloro-2,3-di(4-fluorophenyl)imidazo[1,2-*c*]quinazolin-5(6*H*)-one (12j). Colorless crystals, mp >300 °C.

IR (KBr, ν, cm^{-1}): 3221, 3043, 2920, 1712, 1596, 1550, 1488, 1436, 1408, 1364, 1329, 1223, 1157, 1059, 840, 811, 753, 741.

^1H NMR (DMSO-d_6) δ: 7.15 (t, J=8.8 Hz, 2H, ArH), 7.28 (t, J=8.8 Hz, 2H, ArH), 7.37 (d, J=8.4 Hz, 1H, ArH), 7.46–7.52 (m, 4H, ArH), 7.60 (dd, J_1=2.4 Hz, J_2=8.8 Hz, 1H, ArH), 8.17 (d, J=2.4 Hz, 1H, ArH), 11.88 (s, 1H, NH).

Anal. Calcd for $C_{22}H_{12}ClF_2N_3O$: C 64.80, H 2.97, N 10.30; found: C 64.87, H 3.02, N 10.36.

4.6.11. 8,9-Dimethoxy-2,3-diphenylimidazo[1,2-*c*]quinazolin-5(6*H*)-one (12k). Colorless crystals, mp >300 °C.

IR (KBr, ν, cm^{-1}): 3198, 3056, 2998, 2934, 1725, 1667, 1612, 1560, 1507, 1441, 1413, 1389, 1349, 1279, 1217, 1177, 1133, 1101, 1022, 999, 786, 743, 709, 697.

^1H NMR (DMSO-d_6) δ: 3.84 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 6.90 (s, 1H, ArH), 7.21–7.28 (m, 3H, ArH), 7.41–7.47 (m, 7H, ArH), 7.61 (s, 1H, ArH), 11.50 (s, 1H, NH).

Anal. Calcd for $C_{24}H_{19}N_3O_3$: C 72.53, H 4.82, N 10.57; found: C 72.64, H 4.86, N 10.63.

4.6.12. 8,9-Dimethoxy-2,3-di(4-bromophenyl)imidazo[1,2-*c*]quinazolin-5(6*H*)-one (12l). Pale yellow crystals, mp >300 °C.

IR (KBr, ν, cm^{-1}): 3163, 3010, 2929, 1703, 1668, 1628, 1572, 1506, 1474, 1438, 1420, 1392, 1357, 1282, 1237, 1219, 1135, 1109, 1069, 1009, 828, 788, 753, 715.

^1H NMR (DMSO-d_6) δ: 3.84 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 6.89 (s, 1H, ArH), 7.39 (d, J=8.0 Hz, 4H, ArH), 7.50 (d, J=8.0 Hz, 2H, ArH), 7.58 (s, 1H, ArH), 7.61 (d, J=8.0 Hz, 2H, ArH), 11.59 (s, 1H, NH).

Anal. Calcd for $C_{24}H_{17}Br_2N_3O_3$: C 51.92, H 3.09, N 7.57; found: C 51.96, H 3.04, N 7.61.

Acknowledgements

We are grateful to the National Natural Science Foundation of China (20472062 and 20672079), the Natural Science Foundation of Jiangsu Province (BK2006048), and the Natural Science Foundation of Jiangsu Education Department (06KJA15007) for financial support.

References and notes

1. (a) McMurry, J. E. *Acc. Chem. Res.* **1974**, *7*, 281; (b) McMurry, J. E. *Acc. Chem. Res.* **1983**, *16*, 405; (c) McMurry, J. E. *Chem. Rev.* **1989**, *89*, 1513; (d) Lenoir, D. *Synthesis* **1989**, 883; (e) Fürstner, A.; Bogdanovi, B. *Angew. Chem., Int. Ed.* **1996**, *35*, 2443; (f) Shi, D. Q.; Chen, J. X.; Chai, W. Y.; Chen, W. X.; Kao, T. Y. *Tetrahedron Lett.* **1993**, *34*, 2963.
2. Zhou, L. H.; Shi, D. Q.; Gao, Y.; Shen, W. B.; Dai, G. Y.; Chen, W. X. *Tetrahedron Lett.* **1997**, *38*, 2729.

3. Zhou, L. H.; Tu, S. J.; Shi, D. Q.; Dai, G. Y.; Chen, W. X. *Synthesis* **1998**, 851.
4. Ondheim, K.; Benneche, T. *Advances in Heterocyclic Chemistry*; Gilchrist, T. L., Gribble, G. W., Eds.; Pergamon: Oxford, 1999; Vol. 11, p 21.
5. (a) Bonola, G.; Da Re, P.; Magistretti, M. J.; Massarani, E.; Setnikar, I. *J. Med. Chem.* **1968**, *11*, 1136; (b) Okumura, K.; Oine, T.; Yamada, Y.; Hayashi, G.; Nakama, M. *J. Med. Chem.* **1968**, *11*, 348.
6. (a) Chan, J. H.; Hong, J. S.; Kuyper, L. F.; Jones, M. L.; Baccanari, D. P.; Tansik, R. L.; Boytos, C. M.; Rudolph, S. K.; Brown, A. D. *J. Heterocycl. Chem.* **1997**, *34*, 145; (b) Gackenheimer, S. L.; Schaus, J. M.; Gehlert, D. R. *J. Pharmacol. Exp. Ther.* **1996**, *732*, 113; (c) Dempcy, R. O.; Skibo, E. B. *Biochemistry* **1991**, *30*, 8480; (d) Campbell, S. F.; Davey, M. J. *Drug Des. Deliv.* **1986**, 83; (e) Imagawa, J.; Sakai, K. *Eur. J. Pharmacol.* **1986**, *131*, 257.
7. *Merck Index*; Merck: Whitehouse Station, NJ, 1996; Vol. 12, p 7897.
8. *Merck Index*; Merck: Whitehouse Station, NJ, 1996; Vol. 12, p 1512.
9. *Merck Index*; Merck: Whitehouse Station, NJ, 1996; Vol. 12, p 3489.
10. (a) Goto, S.; Tsuboi, H.; Kagara, K. *Chem. Express* **1993**, *8*, 761; (b) Kagara, K.; Goto, S.; Tsuboi, H. Japanese Patent 25,767, 1989; *Chem. Abstr.* **1989**, *111*, 97274.
11. Mohri, S. *J. Synth. Org. Chem. Jpn.* **2001**, *59*, 514.
12. (a) Pastor, G. J.; Blanchard, C.; Montginoul, C.; Torreilles, E.; Giral, L.; Texier, A. *Bull. Soc. Chim. Fr.* **1975**, 1331; (b) Khalifa, M.; Osman, A. N.; Ibrahim, M. G.; Ossman, A. R. E.; Ismail, M. A. *Pharmazie* **1982**, *37*, 115.
13. Michman, M.; Patai, S.; Wiesel, Y. *Org. Prep. Proced. Int.* **1978**, *10*, 13.
14. Lange, N. A.; Sheibley, F. E. *Org. Synth.* **1943**, *2*, 79.
15. Vorbrueggen, H.; Krolikiewicz, K. *Tetrahedron* **1994**, *50*, 6549.
16. (a) Mizuno, T.; Iahino, Y. *Tetrahedron* **2002**, *58*, 3155; (b) Mizuno, T.; Iwai, T.; Ishino, Y. *Tetrahedron Lett.* **2004**, *45*, 7073.
17. Buckman, B. O.; Mohan, R. *Tetrahedron Lett.* **1996**, *37*, 4439.
18. Gordeev, M. F.; Hui, H. C.; Gordon, E. M.; Patel, D. V. *Tetrahedron Lett.* **1997**, *38*, 1729.
19. Smith, A. L.; Thomson, C. G.; Leeson, P. D. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1483.
20. Choo, H. P.; Kim, M.; Lee, S. K.; Kim, S. W.; Chung, I. K. *Bioorg. Med. Chem. Lett.* **2002**, *10*, 517.
21. Ceorge, J.; Chandraseharan, S. *Synth. Commun.* **1983**, *13*, 495.
22. Li, J.; Shi, D. Q.; Chen, W. X. *Heterocycles* **1997**, *45*, 2381.
23. Crystallographic data for the structures of **10c** and **12f** have been deposited at the Cambridge Crystallographic Data Centre, deposit numbers are CCDC-255898 and CCDC-255904, respectively. Copies of available material can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk).
24. (a) Shi, D. Q.; Li, Z. Y.; Shi, C. L.; Wang, X. S.; Zhang, Q. Y. *Acta Crystallogr.* **2004**, *E60*, o2011; (b) Shi, D. Q.; Li, Z. Y.; Shi, C. L.; Zhuang, Q. Y.; Wang, X. S.; Zhang, Y. *Acta Crystallogr.* **2004**, *E60*, o2032.