Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron
Tetrahedron 63 (2007) 451–460

Trifluoroacetic acid: a more effective and efficient reagent for the synthesis of 3-arylmethylene-3,4-dihydro-1*H*-quinolin-2-ones and 3-arylmethyl-2-amino-quinolines from Baylis–Hillman derivatives via Claisen rearrangement☆

Richa Pathak, Sudharshan Madapa and Sanjay Batra*

Medicinal and Process Chemistry Division, Central Drug Research Institute, PO Box 173, Chattar Manzil Palace, Lucknow 226001, Uttar Pradesh, India

Received 3 August 2006; revised 6 October 2006; accepted 19 October 2006
Available online 9 November 2006

Abstract—Trifluoroacetic acid has been discovered to be a highly effective and efficient reagent for the tandem Claisen rearrangement and cyclization reaction to yield 3-arylmethylene-3,4-dihydro-1*H*-quinolin-2-ones from compounds obtained from the S_N2 reaction between anilines and acetyl derivatives of Baylis–Hillman adducts of acrylates in the presence of DABCO. In contrast, similar compounds obtained from the acetyl derivatives of Baylis–Hillman adduct of acrylonitrile on treatment with trifluoroacetic acid directly furnish 3-arylmethyl-2-amino-quinoline via tandem Claisen rearrangement, cyclization and isomerization.

1. Introduction

Recently, the compound R207910 (Fig. 1) from Johnson and Johnson has been described to have significant activity against the drug sensitive and drug-resistant *Mycobacterium tuberculosis*.[1] This compound has been reported to elicit the anti-tubercular activity via a novel mechanistic pathway.[2] The starting substrate for the synthesis of compound R207910, i.e., 3-arylmethyl-2-chloro-quinoline, is afforded by the reaction between aniline and substituted benzenepropionyl chloride followed by heating of the product with $POCl_3$.[3] During our studies toward the exploitation of Baylis–Hillman chemistry for achieving the synthesis of valued intermediates, it occurred to us that 3-arylmethyl-2-chloro-quinolines can be readily synthesized from Baylis–Hillman adducts. Indeed recently, Kim et al. have described elegant synthesis of 3-arylmethylene-3,4-dihydro-1*H*-quinolin-2-one, the precursor for 3-arylmethyl-2-chloro-quinoline, from the acetates of Baylis–Hillman adducts via PPA-mediated Claisen rearrangement.[4] Although, the yields reported for the sequence were high, problems in handling PPA, particularly on large scale runs, prompted the development of a more convenient yet efficient route. Besides, Kim et al.

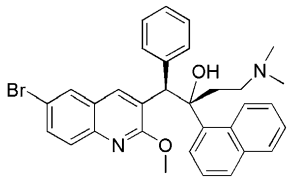


Figure 1. Structure of 207910.

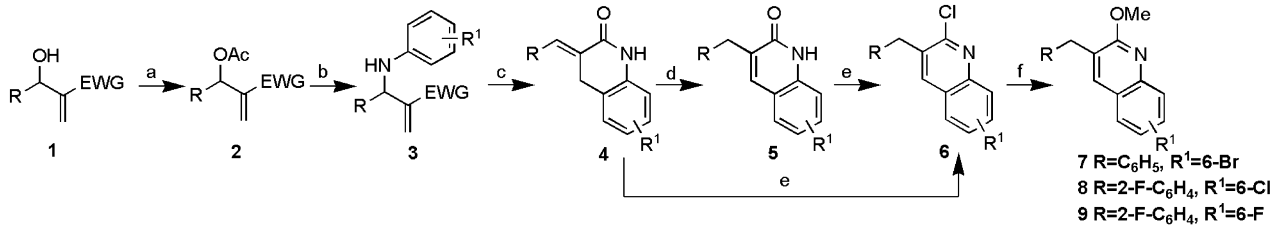
were unsuccessful in obtaining quinoline derivatives when the aniline substrate containing the electron-donating groups such as methoxy or methyl was used. Gratifyingly we have discovered that in the presence of TFA, the Claisen rearrangement proceeds smoothly irrespective of the nature of functional groups present in the aniline and can be performed on large scales. The subsequent isomerization was accomplished in the presence of potassium carbonate in acetone. Interestingly the use of these reagents eliminates the need for column chromatography. We describe herein our results on the efficient synthesis of 3-arylmethylene-3,4-dihydro-1*H*-quinolin-2-one and 3-arylmethyl-2-amino-quinolines.

2. Results and discussion

Synthesis of the title compound is outlined in Scheme 1. In the initial step the Baylis–Hillman adducts **1** from several

☆ CDRI communication no. 7071.
Keywords: Baylis–Hillman; TFA; Claisen rearrangement; 3-Arylmethyl-3,4-dihydro-1*H*-quinolin-2-one; 3-Arylmethyl-2-amino-quinoline.
* Corresponding author. Tel.: +91 522 2262411–18x4368; fax: +91 522 2623405/938; e-mail: batra_san@yahoo.co.uk

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.10.053

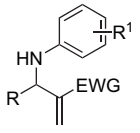


Scheme 1. Reagents and conditions: (a) AcCl, pyridine, CH_2Cl_2, rt, 3 h; (b) substituted anilines, DABCO, THF/H_2O (1:1), rt, 3 h; (c) TFA, 60 °C, 8–14 h; (d) K_2CO_3, acetone, 60 °C, 10–15 min; (e) $POCl_3$, toluene, 120 °C, 30 min; (f) NaOMe, MeOH, reflux, 15 min. (For R and R^1 refer to Table 1.)

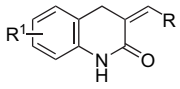
aldehydes were prepared via DABCO-promoted Baylis–Hillman reactions in the absence of solvent. These adducts were acetylated with acetyl chloride in the presence of pyridine in dichloromethane to yield the acetates **2**. Nucleophilic substitution on the acetyl derivatives with anilines in the presence of DABCO led to products **3** in 3 h. Treatment of compounds **3** with neat trifluoroacetic acid at reflux temperature for 8–14 h yielded the 3-arylmethylene-3,4-dihydro-1*H*-quinolin-2-one in good yields. The workup procedure was simple since the evaporation of TFA in vacuo followed by treatment of the residue with saturated sodium bicarbonate gave the products as solids without the need for column chromatography. Subsequent treatment of a few of these compounds with potassium carbonate in acetone at reflux temperature for 10–15 min furnished the isomerized quinolines in almost quantitative yields. During the study several compounds with different ester group were examined and this reaction sequence was found to be general in nature as evident from Table 1. Even the anilines containing methyl or methoxy substitution undergo this reaction, though the yields of the resulting quinolinones were slightly lower. At this stage it occurred to us that a one-pot procedure for the generation of 3-arylmethyl-1*H*-quinolin-2-one might be possible. Accordingly, in a representative reaction instead of treating the reaction mixture obtained after TFA-promoted Claisen rearrangement with sodium bicarbonate, the residue was taken up in acetone and to it was added excess of potassium carbonate and the mixture was heated at reflux temperature for 10 min. Filtration of the inorganic salts followed by evaporation of excess solvent furnished the pure products as solids. However, the overall yield afforded through this one-pot method was significantly less than that obtained during two-step procedure. Treatment of 3-arylmethyl-1*H*-quinolin-2-one **5** with $POCl_3$ yielded the 3-arylmethyl-2-chloro-quinolines in excellent yield. During this investigation we found that the treatment of 3-arylmethylene-3,4-dihydro-1*H*-quinolin-2-ones **4** with $POCl_3$ led to a tandem isomerization and chlorination though here also the yields were less than the two-step process. Unlike the literature report,[3] the reaction of 3-arylmethyl-2-chloro-quinolines with sodium methoxide was complete within 15 min to yield the 3-arylmethyl-2-methoxy-quinolines **7**–**9** in excellent yield, compound **7** being the starting substrate for 207910.

Table 1. Structure and yields of quinolines produced according to Scheme 1

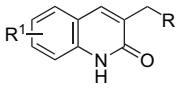
Entry



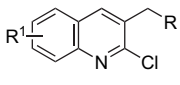
3



4



5

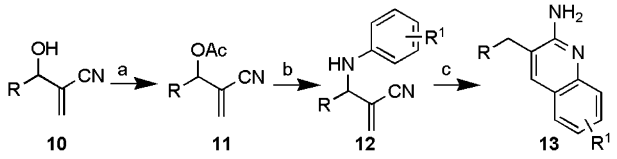


6

	R	R^1	EWG	Yield	R	R^1	Yield	R	R^1	Yield	R	R^1	Yield
1	C_6H_5	H	CO_2Et	85	C_6H_5	H	88	C_6H_5	H	99	C_6H_5	H	66[a]
2	(2-Cl)C_6H_4	H	CO_2Et	80	(2-Cl)C_6H_4	H	71				(2-Cl)C_6H_4	H	71[a]
3	(4-Br)C_6H_4	H	CO_2Et	82	(4-Br)C_6H_4	H	80				(4-Br)C_6H_4	H	85[a]
4	C_6H_5	4-Cl	CO_2Et	76	C_6H_5	6-Cl	88						
5	(2-F)C_6H_4	4-Cl	CO_2Et	81	(2-F)C_6H_4	6-Cl	79	(2-F)C_6H_4	6-Cl	100	(2-F)C_6H_4	6-Cl	97
6	(4-Br)C_6H_4	4-Cl	CO_2Et	80	(4-Br)C_6H_4	6-Cl	85				(4-Br)C_6H_4	6-Cl	82
7	C_6H_5	4-F	CO_2Et	77	C_6H_5	6-F	93						
8	(2-Cl)C_6H_4	4-F	CO_2Et	77	(2-Cl)C_6H_4	6-F	70	(2-Cl)C_6H_4	6-F		(2-Cl)C_6H_4	6-F	68[a]
9	(4-Br)C_6H_4	4-F	CO_2Et	86	(4-Br)C_6H_4	6-F	76	(4-Br)C_6H_4	6-F	100	(4-Br)C_6H_4	6-F	89
10	C_6H_5	4-Br	CO_2Et	64	C_6H_5	6-Br	79	C_6H_5	6-Br	100	C_6H_5	6-Br	97
11	C_6H_5	2-Me	CO_2Et	85	C_6H_5	8-Me	36						
12	C_6H_5	3,4,5-$(OMe)_3$	CO_2Et	65	C_6H_5	5,6,7-$(OMe)_3$	63						
13	Pyrid-2-yl	4-F	CO_2Et	55	Pyridy-2-yl	6-F	68						
14	C_6H_5	4-Me	CO_2Me	86	C_6H_5	6-Me	78	C_6H_5	6-Me	100			
15	(2-Cl)C_6H_4	4-Cl	CO_2Me	82	(2-Cl)C_6H_4	6-Cl	70	(2-Cl)C_6H_4	6-Cl	100			
16	(2-F)C_6H_4	H	CO_2Me	88	(2-F)C_6H_4	H	73	(2-F)C_6H_4	H	100			
17	(2-F)C_6H_4	H	CO_2Bu^t	86	(2-F)C_6H_4	H	53						
18	(2-F)C_6H_4	4-Cl	CO_2Bu^t	81	(2-F)C_6H_4	6-Cl	85						
19	(2-F)C_6H_4	4-F	CO_2Bu^t	81	(2-F)C_6H_4	6-F	85	(2-F)C_6H_4	6-F	100	(2-F)C_6H_4	6-F	81
20	(2-F)C_6H_4	4-OMe	CO_2Bu^t	63	(2-F)C_6H_4	6-OMe	77						

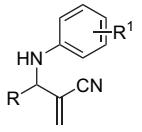
[a] Yields of product directly obtained from compound **4**.

Having demonstrated the utility of TFA for Claisen rearrangement for the Baylis–Hillman derivatives of acrylates, we turned our attention to compounds **12** derived from acrylonitrile. It was envisaged that herein the Claisen rearrangement would lead to an intermediate with a free aromatic amino group, which may then attack the cyano group to yield 2-amino quinoline derivatives in a single step. Hence compounds **12** were prepared via the reaction of substituted anilines with the acetates **11** (Scheme 2). Unlike compounds **2**, the nucleophilic substitution reaction takes more than 48 h for completion. Similar treatment of these compounds **12** with TFA led to isolation of a product, which was established to be 2-amino-3-benzyl-quinoline **13** on the basis of spectral analysis. It was interesting to note here that the Claisen rearrangement, cyclization and isomerization occurred in one step. This reaction was found to be general in nature.

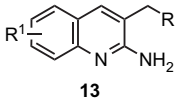


Scheme 2. Reagents and conditions: (a) AcCl, pyridine, rt, 3 h; (b) substituted aniline, DABCO, THF/H_2O (1:1), rt, 48 h; (c) TFA, reflux, 24 h. (For key to R and R^1 refer to Table 2.)

Table 2. Structure and yields of quinolines produced according to Scheme 2



12



13

Entry	R	R^1	Yield	R	R^1	Yield
1	C_6H_5	4-Cl	82	C_6H_5	6-Cl	28
2	2-F-C_6H_4	4-Cl	68	2-F-C_6H_4	6-Cl	48
3	2,4-$(Cl)_2$-C_6H_3	H	73	2,4-$(Cl)_2$-C_6H_3	H	46
4	2,4-$(Cl)_2$-C_6H_3	4-Cl	62	2,4-$(Cl)_2$-C_6H_3	6-Cl	53

3. Conclusions

In summary we have demonstrated that trifluoroacetic acid is an effective and efficient reagent for the synthesis of 3-arylmethylene-3,4-dihydro-1*H*-quinolin-2-ones and 3-arylmethyl-2-amino-quinolines from the derivatives of Baylis–Hillman adducts via tandem Claisen rearrangement followed by cyclization.

4. Experimental

4.1. General

Melting points were recorded on a hot stage melting point apparatus and are uncorrected. The IR spectra were recorded on a FTIR spectrophotometer. The ^1H and ^{13}C NMR spectra were recorded on 200 MHz or 300 MHz spectrometer using TMS as internal standard. The mass spectra were recorded as FAB or LCMS having ES probe. The HRMS spectra were recorded as EI-HRMS.

4.2. General procedure for the preparation of compounds 3 and 12

To a stirred solution of the required acetate (4.0 mmol) (1.0 equiv) in THF/H_2O (10 mL, 50:50, v/v) was added DABCO (6.0 mmol) (1.5 equiv) at room temperature. After 15 min the appropriate aniline (4.8 mmol) was added to the reaction and it was continued for 3 h (48 h when EWG is CN). The solvent was removed in vacuo and the residue was extracted with ethyl acetate (3×50 mL) and water (70 mL). The organic fractions were combined, washed with brine (50 mL), dried (Na_2SO_4), and evaporated to yield the crude product, which was purified via silica gel column chromatography using hexanes/ethyl acetate (90–85:10–15, v/v) to afford pure compounds.

4.2.1. 2-(Phenyl-phenylamino-methyl)-acrylic acid ethyl ester (Table 1, 3, entry 1). Yield: 0.57 g, 85%, as a brown oil; R_f (20% EtOAc/hexane): 0.65; ν_{max} (Neat): 1712 (CO), 3402 (NH) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.21 (t, 3H, J=7.1 Hz, CH_3), 4.15 (q, 2H, J=7.1 Hz, CO_2CH_2), 5.41 (s, 1H, CH), 5.94 (s, 1H, =CH_2), 6.39 (s, 1H, =CH_2), 6.58 (d, 2H, J=7.6 Hz, ArH), 6.72 (t, 1H, J=7.3 Hz, ArH), 7.16 (t, 2H, J=7.4 Hz, ArH), 7.25–7.36 (m, 5H, ArH); mass (ES^+): m/z 281.9 (M^++1). Anal. Calcd. for $C_{18}H_{19}NO_2$ requires: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.65; H, 6.71; N, 5.09.

4.2.2. 2-[(2-Chlorophenyl)-phenylamino-methyl]-acrylic acid ethyl ester (Table 1, 3, entry 2). Yield: 0.90 g, 80%, as a white solid; mp 107–109 °C; R_f (20% EtOAc/hexane): 0.48; ν_{max} (KBr): 1699 (CO), 3382 (NH) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.21 (t, 3H, J=7.2 Hz, CH_3), 4.17 (q, 2H, J=7.2 Hz, CO_2CH_2), 5.78 (s, 1H, CH), 5.85 (s, 1H, =CH_2), 6.42 (s, 1H, =CH_2), 6.55–6.59 (m, 2H, ArH), 6.68–6.75 (m, 1H, ArH), 7.11–7.23 (m, 4H, ArH), 7.37–7.41 (m, 2H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.5, 55.9, 61.4, 113.7, 118.5, 127.5, 127.6, 128.8, 129.4, 129.6, 130.4, 134.5, 138.5, 140.3, 147.0, 166.5; mass (ES^+): m/z 316.0 (M^++1). Anal. Calcd. for $C_{18}H_{18}ClNO_2$ requires: C, 68.46; H, 5.75; N, 4.44. Found: C, 68.11; H, 5.96; N, 4.49.

4.2.3. 2-[(4-Bromophenyl)-phenylamino-methyl]-acrylic acid ethyl ester (Table 1, 3, entry 3). Yield: 1.81 g, 82%, as a brown oil; R_f (20% EtOAc/hexane): 0.5; ν_{max} (Neat): 1747 (CO), 3398 (NH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.25 (t, 3H, J=7.2 Hz, CH_3), 4.18 (q, 2H, J=7.2 Hz, CO_2CH_2), 5.39 (s, 1H, CH), 5.92 (s, 1H, =CH_2), 6.40 (s, 1H, =CH_2), 6.59 (d, 2H, J=7.8 Hz, ArH), 6.75 (d, 2H, J=7.3 Hz, ArH), 7.18 (d, 2H, J=7.6 Hz, ArH), 7.28 (d, 2H, J=3.9 Hz, ArH), 7.48 (d, 2H, J=8.5 Hz, ArH); mass (ES^+): m/z 359.9 (M^++1), 361.9 (M^++3). Anal. Calcd. for $C_{18}H_{18}BrNO_2$ requires: C, 60.01; H, 5.04; N, 3.89. Found: C, 60.08; H, 4.89; N, 3.90.

4.2.4. 2-[(4-Chloro-phenylamino)-phenyl-methyl]-acrylic acid ethyl ester (Table 1, 3, entry 4). Yield: 1.45 g 76%, as a light yellow oil; R_f (15% EtOAc/hexane): 0.42; ν_{max} (Neat): 1715 (CO), 3413 (NH) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.21 (t, 3H, J=7.1 Hz, CH_3), 4.15 (q, 2H, J=7.1 Hz, CO_2CH_2), 5.36 (s, 1H, CH), 5.89 (s, 1H, =CH_2), 6.38 (s, 1H, =CH_2), 6.49 (d, 2H, J=4.6 Hz, ArH), 7.10 (d, 2H,

J=4.6 Hz, ArH), 7.28–7.37 (m, 5H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.8, 57.8, 59.6, 113.3, 121.2, 124.8, 126.2, 126.6, 127.5, 127.7, 138.8, 139.0, 144.0, 164.8; mass (ES^+): m/z 316.0 (M^++1). Anal. Calcd. for $C_{18}H_{18}ClNO_2$ requires: C, 68.46; H, 5.75; N, 4.44. Found: C, 68.60; H, 5.66; N, 4.30.

4.2.5. 2-[(4-Chloro-phenylamino)-(2-fluorophenyl)-methyl]-acrylic acid ethyl ester (Table 1, 3, entry 5). Yield: 1.0 g, 81%, as a brown oil; R_f (15% EtOAc/hexane): 0.53; ν_{max} (Neat): 1721 (CO), 3433 (NH) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.21 (t, 3H, J=7.2 Hz, CH_3), 4.20 (q, 2H, J=7.2 Hz, CO_2CH_2), 4.27 (br s, 1H, NH), 5.67 (s, 1H, CH), 5.84 (s, 1H, =CH_2), 6.40 (s, 1H, =CH_2), 6.50 (d, 2H, J=6.6 Hz, ArH), 7.05–7.14 (m, 4H, ArH), 7.23–7.33 (m, 2H, ArH); mass (ES^+): m/z 333.9 (M^++1), 335.9 (M^++3); HR-EIMS calculated for $C_{18}H_{17}ClFNO_2$: 333.0932. Found: 333.0924.

4.2.6. 2-[(4-Bromophenyl)-(4-chloro-phenylamino)-methyl]-acrylic acid ethyl ester (Table 1, 3, entry 6). Yield: 1.2 g, 80%, as a brown oil; R_f (20% EtOAc/hexane): 0.70; ν_{max} (Neat): 1710 (CO), 3421 (NH) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.24 (t, 3H, J=7.2 Hz, CH_2CH_3), 4.16 (q, 2H, J=7.2 Hz, CH_2CH_3), 5.35 (s, 1H, CH), 5.87 (s, 1H, =CH_2), 6.39 (s, 1H, =CH_2), 6.48 (d, 2H, J=8.9 Hz, ArH), 7.10 (d, 2H, J=8.8 Hz, ArH), 7.24 (d, 2H, J=8.5 Hz, ArH), 7.47 (d, 2H, J=8.5 Hz, ArH); mass (ES^+): m/z 393.9 (M^++1), 395.9 (M^++3). Anal. Calcd. for $C_{18}H_{17}BrClNO_2$ requires: C, 54.78; H, 4.34; N, 3.55. Found: C, 54.71; H, 4.38; N, 3.59.

4.2.7. 2-[(4-Fluoro-phenylamino)-phenyl-methyl]-acrylic acid ethyl ester (Table 1, 3, entry 7). Yield: 1.12 g, 77%, as a brown oil; R_f (20% EtOAc/hexane): 0.58; ν_{max} (Neat): 1712 (CO), 3401 (NH) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.24 (t, 3H, J=7.1 Hz, CH_3), 4.17 (q, 2H, J=7.1 Hz, CO_2CH_2), 5.36 (s, 1H, CH), 5.92 (t, 1H, J=1.0 Hz, =CH_2), 6.40 (s, 1H, =CH_2), 6.51–6.56 (m, 2H, ArH), 6.88 (t, 2H, J=8.6 Hz, ArH), 7.30–7.40 (m, 5H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.4, 60.0, 61.3, 114.7, 114.8, 115.8, 116.2, 126.4, 127.9, 128.2, 129.1, 140.8, 141.0, 143.5, 154.1, 158.8, 166.6; mass (ES^+): m/z 299.9 (M^++1); HR-EIMS calculated for $C_{18}H_{18}FNO_2$: 299.1322. Found: 299.1328.

4.2.8. 2-[(2-Chlorophenyl)-(4-fluoro-phenylamino)-methyl]-acrylic acid ethyl ester (Table 1, 3, entry 8). Yield: 0.68 g, 77%, as a brown oil; R_f (20% EtOAc/hexane): 0.58; ν_{max} (Neat): 1714 (CO), 3400 (NH) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.24 (t, 3H, J=7.2 Hz, CH_3), 4.13 (br s, 1H, NH), 4.20 (q, 2H, J=7.2 Hz, CO_2CH_2), 5.78 (s, 1H, CH), 5.81 (s, 1H, =CH_2), 6.45 (s, 1H, =CH_2), 6.49–6.55 (m, 2H, ArH), 6.85–6.90 (m, 2H, ArH), 7.23–7.28 (m, 2H, ArH), 7.39–7.45 (m, 2H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.7, 54.8, 59.7, 112.9, 114.2, 114.5, 125.8, 126.0, 127.0, 127.7, 128.7, 132.8, 136.6, 138.5, 141.7, 153.3, 156.4, 164.7; mass (ES^+): m/z 334.1 (M^++1); HR-EIMS calculated for $C_{18}H_{17}ClFNO_2$: 333.0932. Found: 333.0930.

4.2.9. 2-[(4-Bromophenyl)-(4-fluoro-phenylamino)-methyl]-acrylic acid ethyl ester (Table 1, 3, entry 9). Yield: 1.9 g, 86%, as a brown oil; R_f (20% EtOAc/hexane): 0.53; ν_{max} (Neat): 1707 (CO), 3419 (NH) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.25 (t, 3H, J=7.1 Hz, CH_3), 4.18 (q, 2H, J=7.1 Hz, CH_2), 5.31 (s, 1H, CH), 5.90 (s, 1H, =CH_2), 6.40 (s, 1H, =CH_2), 6.49–6.54 (m, 2H, ArH), 6.88 (t, 2H, J=6.4 Hz, ArH), 7.27 (d, 2H, J=7.3 Hz, ArH), 7.48 (d, 2H, J=6.6 Hz, ArH); mass (ES^+): m/z 377.9 (M^++1), 379.9 (M^++3); HR-EIMS calculated for $C_{18}H_{17}BrFNO_2$: 377.0427. Found: 377.0431.

4.2.10. 2-[(4-Bromo-phenylamino)-phenyl-methyl]-acrylic acid ethyl ester (Table 1, 3, entry 10). Yield: 1.50 g, 75%, as a light yellow oil; R_f (20% EtOAc/hexane): 0.8; ν_{max} (Neat): 1709 (CO), 3398 (NH) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.23 (t, 3H, J=7.1 Hz, CH_3), 4.17 (q, 2H, J=7.1 Hz, CO_2CH_2), 5.38 (s, 1H, CH), 5.92 (s, 1H, =CH_2), 6.40 (s, 1H, =CH_2), 6.46–6.50 (m, 2H, ArH), 7.23–7.26 (m, 3H, ArH), 7.28–7.32 (m, 4H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.0, 58.0, 59.9, 108.5, 114.0, 125.0, 126.4, 126.9, 127.7, 128.7, 130.8, 139.0, 139.2, 144.7, 165.0; mass (ES^+): m/z 359.9 (M^++1), 361.9 (M^++3); HR-EIMS calculated for $C_{18}H_{18}BrNO_2$: 359.0521. Found: 359.0527.

4.2.11. 2-(Phenyl-*o*-tolylamino-methyl)-acrylic acid ethyl ester (Table 1, 3, entry 11). Yield: 0.4 g, 85%, as brown oil; R_f (20% EtOAc/hexane): 0.66; ν_{max} (Neat): 1705 (CO), 3429 (NH) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.21 (t, 3H, J=7.2 Hz, CH_3), 2.15 (s, 3H, CH_3), 4.04–4.20 (q merged with br s, 3H, CO_2CH_2, and NH), 5.47 (s, 1H, CH), 5.90 (s, 1H, =CH_2), 6.38 (s, 1H, =CH_2), 6.50 (d, 1H, J=8.2 Hz, ArH), 6.71 (t, 1H, J=7.0 Hz, ArH), 7.06 (d, 2H, J=7.1 Hz), 7.31–7.38 (m, 5H, ArH); mass (ES^+): m/z 296.0 (M^++1). Anal. Calcd. for $C_{19}H_{21}NO_2$ requires: C, 77.26; H, 7.17; N, 4.74. Found: C, 77.14; H, 7.26; N, 4.91.

4.2.12. 2-[Phenyl-(3,4,5-trimethoxy-phenylamino)-methyl]-acrylic acid ethyl ester (Table 1, 3, entry 12). Yield: 1.95 g, 65%, as a brown oil; R_f (20% EtOAc/hexane): 0.41; ν_{max} (Neat): 1713 (CO), 3383 (NH) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.24 (t, 3H, J=7.1 Hz, CH_3), 3.77 (s, 3H, OCH_3), 3.78 (s, 6H, 2×OCH_3), 4.17 (q, 2H, J=3.9 Hz, CO_2CH_2), 5.40 (s, 1H, CH), 5.85 (s, 2H, ArH), 5.97 (s, 1H, =CH_2), 6.41 (s, 1H, =CH_2), 7.28–7.38 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 12.8, 54.6, 58.1, 59.6, 59.8, 89.9, 124.7, 126.1, 126.5, 127.5, 129.1, 139.3, 139.4, 142.3, 152.5, 165.0; mass (ES^+): m/z 371.9 (M^++1). Anal. Calcd. for $C_{21}H_{25}NO_5$ requires: C, 67.91; H, 6.78; N, 3.77. Found: C, 68.12; H, 6.89; N, 3.59.

4.2.13. 2-[(4-Fluoro-phenylamino)-pyridin-3-yl-methyl]-acrylic acid ethyl ester (Table 1, 3, entry 13). Yield: 1.38 g, 55%, as a brown oil; R_f (30% EtOAc/hexane): 0.54; ν_{max} (Neat): 1707 (CO), 3407 (NH) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.23 (t, 3H, J=7.1 Hz, CH_3), 4.16 (q, 2H, J=7.1 Hz, CH_2), 5.37 (d, 1H, J=3.7 Hz, CH), 5.95 (s, 1H, =CH_2), 6.44 (s, 1H, =CH_2), 6.49–6.56 (m, 2H, ArH), 6.88 (t, 2H, J=8.7 Hz, ArH), 7.29–7.32 (m, 1H, ArH), 7.71 (d, 1H, J=7.8 Hz, ArH), 8.55 (d, 1H, J=3.9 Hz, ArH), 8.65 (s, 1H, ArH); mass (ES^+): m/z 301.1 (M^++1); HR-EIMS calculated for $C_{17}H_{17}FN_2O_2$: 300.1274. Found: 300.1266.

4.2.14. 2-(Phenyl-*p*-tolylamino-methyl)-acrylic acid methyl ester (Table 1, 3, entry 14). Yield: 3.1 g, 86%, as a brown oil; R_f (20% EtOAc/hexane): 0.69; ν_{max} (Neat): 1719 (CO), 3402 (NH) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.23 (s, 3H, CH_3), 3.70 (s, 3H, CH_3), 4.04 (br s, 1H, NH), 5.37 (s, 1H, CH), 5.97 (s, 1H, $=CH_2$), 6.38 (s, 1H, $=CH_2$), 6.50 (d, 2H, J=8.4 Hz, ArH), 6.97 (d, 2H, J=8.4 Hz, ArH), 7.26–7.39 (m, 5H, ArH); mass (ES^+): m/z 282.2 (M^++1). Anal. Calcd. for $C_{18}H_{19}NO_2$ requires: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.60; H, 6.75; N, 5.10.

4.2.15. 2-[(2-Chlorophenyl)-(4-chloro-phenylamino)-methyl]-acrylic acid methyl ester (Table 1, 3, entry 15). Yield: 1.90 g, 82%, as a brown oil; R_f (20% EtOAc/hexane): 0.70; ν_{max} (Neat): 1718 (CO), 3408 (NH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.76 (s, 3H, CH_3), 4.21 (br s, 1H, NH), 5.78 (s, 1H, $=CH_2$), 5.81 (d, 1H, J=5.2 Hz, CH), 6.44 (s, 1H, $=CH_2$), 6.50 (d, 2H, J=8.8 Hz, ArH), 7.10 (d, 2H, J=8.8 Hz, ArH), 7.22–7.28 (m, 2H, ArH), 7.36–7.46 (m, 2H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 50.9, 54.3, 113.12, 121.4, 125.8, 126.4, 126.9, 127.8, 128.8, 132.8, 136.1, 138.0, 143.8, 165.1; mass (ES^+): m/z 335.9 (M^++1), 337.9 (M^++3). Anal. Calcd. for $C_{17}H_{15}Cl_2NO_2$ requires: C, 60.73; H, 4.50; N, 4.17. Found: C, 60.50; H, 4.66; N, 3.98.

4.2.16. 2-[(2-Fluorophenyl)-phenylamino-methyl]-acrylic acid methyl ester (Table 1, 3, entry 16). Yield: 1.50 g, 88%, as a white solid; mp 89–91 °C; R_f (20% EtOAc/hexane): 0.54; ν_{max} (KBr): 1709 (CO), 3403 (NH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.76 (s, 3H, CH_3), 4.32 (br s, 1H, NH), 5.83 (s, 1H, CH), 5.96 (s, 1H, $=CH_2$), 6.46 (s, 1H, $=CH_2$), 6.64–6.67 (m, 2H, ArH), 6.75–6.80 (m, 1H, ArH), 7.08–7.23 (m, 4H, ArH), 7.27–7.35 (m, 1H, ArH), 7.39–7.45 (m, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 50.7, 51.2, 112.2, 114.4, 114.7, 116.9, 123.1, 125.6, 126.3, 127.4, 128.0, 128.2, 138.2, 145.2, 157.7, 161.2, 165.2; mass (ES^+): m/z 286.0 (M^++1); HR-EIMS calculated for $C_{17}H_{16}FNO_2$: 285.1165. Found: 285.1158.

4.2.17. 2-[(2-Fluorophenyl)-phenylamino-methyl]-acrylic acid *tert*-butyl ester (Table 1, 3, entry 17). Yield: 2.4 g, 86%, as a white solid; mp 85–87 °C; R_f (15% EtOAc/hexane): 0.72; ν_{max} (KBr): 1699 (CO), 3401 (NH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.40 (s, 9H, 3×CH_3), 5.73 (s, 1H, CH), 5.81 (s, 1H, $=CH_2$), 6.35 (s, 1H, $=CH_2$), 6.63 (d, 2H, J=7.7 Hz, ArH), 6.75 (t, 1H, J=7.3 Hz), 7.06–7.22 (m, 4H, ArH), 7.26–7.33 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 26.6, 51.1, 80.1, 112.1, 114.2, 114.5, 116.7, 123.0, 124.3, 126.7, 126.9, 127.9, 128.1, 139.9, 145.4, 157.6, 160.9, 164.0; mass (ES^+): m/z 327.9 (M^++1); HR-EIMS calculated for $C_{20}H_{22}FNO_2$: 327.1635. Found: 327.1644.

4.2.18. 2-[(4-Chlorophenylamino)-(2-fluorophenyl)-methyl]-acrylic acid *tert*-butyl ester (Table 1, 3, entry 18). Yield: 2.0 g, 81%, as a brown solid; mp 102–104 °C; R_f (15% EtOAc/hexane): 0.76; ν_{max} (KBr): 1700 (CO), 3337 (NH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.40 (s, 9H, 3×CH_3), 4.23 (br s, 1H, NH), 5.67 (s, 1H, CH), 5.76 (s, 1H, $=CH_2$), 6.34 (s, 1H, $=CH_2$), 6.54 (d, 2H, J=8.7 Hz, ArH), 7.06–7.15 (m, 4H, ArH), 7.26–7.36 (m, 2H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.6, 51.3, 80.2, 113.0, 114.2, 114.5, 121.3, 123.0, 124.4, 126.5, 127.1, 127.8, 128.2, 139.6, 143.9, 157.6, 160.9, 163.9; mass (ES^+): m/z 361.9 (M^++1); HR-EIMS calculated for $C_{20}H_{21}ClFNO_2$: 361.1245. Found: 361.1243.

4.2.19. 2-[(2-Fluorophenyl)-(4-fluoro-phenylamino)-methyl]-acrylic acid *tert*-butyl ester (Table 1, 3, entry 19). Yield: 2.1 g, 81%, as a yellow solid; mp 82–84 °C; R_f (15% EtOAc/hexane): 0.74; ν_{max} (KBr): 1696 (CO), 3398 (NH) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.40 (s, 9H, 3×CH_3), 5.64 (s, 1H, CH), 5.77 (s, 1H, $=CH_2$), 6.34 (s, 1H, $=CH_2$), 6.54–6.57 (m, 2H, ArH), 6.85–6.91 (m, 2H, ArH), 7.05–7.15 (m, 2H, ArH), 7.25–7.38 (m, 2H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.6, 51.7, 80.2, 112.9, 113.0, 114.2, 114.5, 123.0, 124.3, 126.7, 127.2, 128.1, 139.8, 141.7, 153.2, 156.4, 157.6, 160.9, 164.0; mass (ES^+): m/z 345.9 (M^++1); HR-EIMS calculated for $C_{20}H_{21}F_2NO_2$: 345.1540. Found: 345.1544.

4.2.20. 2-[(2-Fluorophenyl)-(4-methoxy-phenylamino)-methyl)]-acrylic acid *tert*-butyl ester (Table 1, 3, entry 20). Yield: 1.10 g, 63%, as a brown oil; R_f (20% EtOAc/hexane): 0.71; ν_{max} (Neat): 1711 (CO), 3419 (NH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.39 (s, 9H, 3×CH_3), 3.75 (s, 3H, OCH_3), 5.63 (s, 1H, CH), 5.79 (s, 1H, $=CH_2$), 6.33 (s, 1H, $=CH_2$), 6.58 (d, 2H, J=8.9 Hz, ArH), 6.77 (d, 2H, J=8.9 Hz, ArH), 7.06–7.15 (m, 2H, ArH), 7.23–7.41 (m, 2H, ArH); mass (ES^+): m/z 358.9 (M^++1). Anal. Calcd. for $C_{21}H_{24}FNO_3$ requires: C, 70.57; H, 6.77; N, 3.92. Found: C, 70.48; H, 6.59; N, 4.11.

4.2.21. 2-[(4-Chloro-phenylamino)-phenyl-methyl]-acrylonitrile (Table 2, 12, entry 1). Yield: 1.45 g, 82%, as a brown oil; R_f (20% EtOAc/hexane): 0.56; ν_{max} (Neat): 2225 (CN), 3391 (NH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.15 (d, 1H, J=3.9 Hz, NH) 5.02 (d, 1H, J=5.1 Hz, CH), 6.11 (s, 1H, $=CH_2$), 6.15 (s, 1H, $=CH_2$), 6.56 (d, 2H, J=8.8 Hz, ArH), 7.17 (d, 2H, J=8.8 Hz, ArH), 7.42–7.48 (m, 5H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 60.2, 113.5, 115.0, 116.0, 122.4, 122.8, 126.0, 127.7, 127.8, 128.1, 129.8, 136.5, 143.0; mass (ES^+): m/z 268.0 (M^+). Anal. Calcd. for $C_{16}H_{13}ClN_2$ requires: C, 71.51; H, 4.88; N, 10.42. Found: C, 71.77; H, 5.02; N, 10.61.

4.2.22. 2-[(4-Chloro-phenylamino)-(2-fluorophenyl)-methyl]-acrylonitrile (Table 2, 12, entry 2). Yield: 1.1 g, 68%, as a brown oil; R_f (20% EtOAc/hexane): 0.51; ν_{max} (Neat): 2226 (CN), 3386 (NH) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 4.17 (d, 1H, J=5.8 Hz, NH), 5.35 (d, 1H, J=5.8 Hz, CH), 6.08 (s, 1H, $=CH_2$), 6.13 (s, 1H, $=CH_2$), 6.57–6.63 (m, 3H, ArH), 7.08–7.19 (m, 3H, ArH), 7.35–7.39 (m, 2H, ArH); mass (ES^+): m/z 287.0 (M^++1). Anal. Calcd. for $C_{16}H_{12}ClFN_2$ requires: C, 67.02; H, 4.22; N, 9.77. Found: C, 66.92; H, 4.09; N, 9.97.

4.2.23. 2-[(2,4-Dichlorophenyl)-phenylamino-methyl]-acrylonitrile (Table 2, 12, entry 3). Yield: 1.6 g, 73%, as a brown oil; R_f (20% EtOAc/hexane): 0.5; ν_{max} (Neat): 2247 (CN), 3425 (NH) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 4.09 (d, 1H, J=4.6 Hz, CHN*H*), 5.49 (d, 1H, J=5.0 Hz, C*H*NH), 6.07 (s, 1H, $=CH_2$), 6.16 (s, 1H, $=CH_2$), 6.55 (d, 2H, J=7.4 Hz, ArH), 6.79 (t, 1H, J=7.2 Hz, ArH), 7.15–7.32 (m, 3H, ArH), 7.39–7.48 (m, 2H, ArH); mass (FAB^+): m/z 303 (M^++1). Anal. Calcd. for $C_{16}H_{12}Cl_2N_2$

requires: C, 63.38; H, 3.99; N, 9.24. Found: C, 63.41; H, 4.19; N, 9.41.

4.2.24. 2-[(4-Chloro-phenylamino)-(2,4-dichloro-phenyl-methyl]-acrylonitrile (Table 2, 12, entry 4). Yield: 1.6 g, 62%, as a brown oil; R_f (20% EtOAc/hexane): 0.61; ν_{max} (Neat): 2223 (CN), 3386 (NH) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 4.08 (d, 1H, J=4.8 Hz, NH), 5.01 (d, 1H, J=5.2 Hz, CH), 6.12 (s, 1H, =CH_2), 6.14 (s, 1H, =CH_2), 6.48–6.62 (m, 2H, ArH), 6.74–6.80 (m, 3H, ArH), 7.35 (d, 1H, J=2.6 Hz, ArH), 7.58 (d, 1H, J=2.6 Hz, ArH); mass (ES^+): m/z 337.2 (M^++1), 339.2 (M^++1). Anal. Calcd. for $C_{16}H_{11}Cl_3N_2$ requires: C, 56.92; H, 3.28; N, 8.30. Found: C, 56.94; H, 3.10; N, 8.14.

4.3. General procedure for the preparation of compounds 4 and 13

To a vessel containing the appropriate aniline (2.5 mmol) was added TFA (5 mL) (amount of TFA was kept between 5 and 8 mL for all compounds in the range 1.0–3.0 g) and the mixture was refluxed for 8–14 h. On completion (monitored by TLC), the reaction mixture was poured into ice cold water and neutralized with saturated $NaHCO_3$ solution. The suspension formed was filtered and washed with ethyl acetate to afford the product **4** in 30–94% yield. However, for compounds **13** the crude product obtained after usual workup were purified via silica gel column chromatography using hexane/ethyl acetate (35:65, v/v) as eluent.

4.3.1. 3-Benzylidene-3,4-dihydro-1*H*-quinolin-2-one (Table 1, 4, entry 1). Yield: 1.2 g, 88%, as a white solid; mp 177–179 °C; R_f (25% EtOAc/hexane): 0.42; ν_{max} (KBr): 1669 (CO), 3444 (NH) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 4.08 (s, 2H, CH_2), 6.86–6.93 (m, 2H, ArH), 7.09–7.17 (m, 2H, ArH), 7.36–7.54 (m, 5H, ArH), 7.66 (s, 1H, =CH), 10.35 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 29.1, 114.0, 120.0, 121.2, 126.3, 127.1, 127.2, 127.7, 129.1, 134.3, 134.4, 135.9, 163.2; mass (FAB^+): m/z 236 (M^++1). Anal. Calcd. for $C_{16}H_{13}NO$ requires: C, 81.68; H, 5.57; N, 5.95. Found: C, 81.82; H, 5.69; N, 5.63.

4.3.2. 3-(2-Chlorobenzylidene)-3,4-dihydro-1*H*-quinolin-2-one (Table 1, 4, entry 2). Yield: 0.48 g, 71%, as a white solid; mp 196–198 °C; R_f (20% EtOAc/hexane): 0.4; ν_{max} (KBr): 1672 (CO), 3428 (NH) cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): δ 3.96 (s, 2H, CH_2), 6.88–6.96 (m, 2H, ArH), 7.13–7.23 (m, 2H, ArH), 7.38–7.51 (m, 2H, ArH), 7.57–7.60 (m, 2H, ArH), 7.67 (s, 1H, =CH), 10.50 (s, 1H, NH); mass (ES^+): m/z 270.2 (M^++1); HR-EIMS calculated for $C_{16}H_{12}ClNO$: 269.0607. Found: 269.0604.

4.3.3. 3-(4-Bromobenzylidene)-3,4-dihydro-1*H*-quinolin-2-one (Table 1, 4, entry 3). Yield: 1.04 g, 80%, as a pale yellow solid; mp 238–240 °C; R_f (20% EtOAc/hexane): 0.38; ν_{max} (KBr): 1676 (CO), 3407 (NH) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 4.06 (d, 2H, J=1.8 Hz, CH_2), 6.88–6.93 (m, 2H, ArH), 7.10–7.19 (m, 2H, ArH), 7.46–7.52 (m, 2H, ArH), 7.59 (s, 1H, =CH), 7.66–7.74 (m, 2H, ArH), 10.38 (s, 1H, NH); ^{13}C NMR (50 MHz, DMSO-d_6): δ 35.4, 120.4, 126.2, 127.5, 127.7, 132.7, 133.7, 134.4, 136.7, 137.1, 137.5, 139.5, 139.9, 142.2, 169.3; mass (FAB^+): m/z 314 (M^++1). Anal. Calcd. for $C_{16}H_{12}BrNO$ requires: C, 61.17; H, 3.85; N, 4.46. Found: C, 61.15; H, 3.84; N, 4.41.

4.3.4. 3-Benzylidene-6-chloro-3,4-dihydro-1*H*-quinolin-2-one (Table 1, 4, entry 4). Yield: 1.2 g, 88%, as a yellow solid; mp 235–237 °C; R_f (20% EtOAc/hexane): 0.36; ν_{max} (KBr): 1668 (CO), 3415 (NH) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 4.12 (d, 2H, J=2.0 Hz, CH_2), 6.89–6.92 (m, 1H, ArH), 7.17–7.20 (m, 1H, ArH), 7.30 (s, 1H, ArH), 7.41–7.55 (m, 5H, ArH), 7.65 (s, 1H, =CH), 10.49 (s, 1H, NH); mass (ES^+): m/z 270.1 (M^++1); HR-EIMS calculated for $C_{16}H_{12}ClNO$: 269.0607. Found: 269.0595.

4.3.5. 6-Chloro-3-(2-fluorobenzylidene)-3,4-dihydro-1*H*-quinolin-2-one (Table 1, 4, entry 5). Yield: 0.81 g, 79%, as a yellow solid; mp 197–199 °C; R_f (20% EtOAc/hexane): 0.39; ν_{max} (KBr): 1666 (CO), 3428 (NH) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 3.85 (s, 2H, CH_2), 7.11–7.21 (m, 2H, ArH), 7.27–7.34 (m, 3H, ArH), 7.45–7.49 (m, 1H, ArH), 7.56 (s, 1H, ArH), 7.72 (s, 1H, =CH), 11.96 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 28.0, 114.3, 114.5, 115.8, 119.5, 123.6, 124.9, 125.6, 127.7, 128.6, 130.6, 132.2, 134.8, 135.8, 160.6; mass (ES^+): m/z 288.2 (M^++1); HR-EIMS calculated for $C_{16}H_{11}ClFNO$: 287.0513. Found: 287.0502.

4.3.6. 3-(4-Bromobenzylidene)-6-chloro-3,4-dihydro-1*H*-quinolin-2-one (Table 1, 4, entry 6). Yield: 0.45 g, 85%, as a pale yellow solid; mp 240–242 °C; R_f (20% EtOAc/hexane): 0.36; ν_{max} (KBr): 1674 (CO), 3408 (NH) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 3.80 (s, 2H, CH_2), 7.23–7.31 (m, 4H, ArH), 7.46–7.49 (m, 2H, ArH), 7.68–7.72 (m, 2H, =CH, ArH), 11.92 (s, 1H, NH); ^{13}C NMR (50 MHz, DMSO-d_6): δ 34.1, 121.8, 121.9, 127.1, 130.3, 130.4, 130.7, 133.2, 133.3, 133.4, 133.8, 135.3, 138.0, 155.1, 158.2; mass (ES^+): m/z 349 (M^++1). Anal. Calcd. for $C_{16}H_{11}BrClNO$ requires: C, 55.12; H, 3.18; N, 4.02. Found: C, 55.10; H, 3.15; N, 4.00.

4.3.7. 3-Benzylidene-6-fluoro-3,4-dihydro-1*H*-quinolin-2-one (Table 1, 4, entry 7). Yield: 0.95 g, 93%, as a light yellow solid; mp 220–222 °C; R_f (25% EtOAc/hexane): 0.43; ν_{max} (KBr): 1668 (CO), 3433 (NH) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 4.11 (d, 2H, J=1.5 Hz, CH_2), 6.89–6.98 (m, 2H, ArH), 7.07–7.11 (m, 1H, ArH), 7.38–7.54 (m, 5H, ArH), 7.65 (t, 1H, J=2.1 Hz, =CH), 10.38 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 29.0, 112.7, 113.0, 113.8, 114.1, 115.1, 121.9, 126.3, 127.8, 129.1, 132.4, 134.1, 134.6, 155.1, 158.2, 162.8; mass (FAB^+): m/z 254 (M^++1); HR-EIMS calculated for $C_{16}H_{12}FNO$: 253.0903. Found: 253.0896.

4.3.8. 3-(2-Chlorobenzylidene)-6-fluoro-3,4-dihydro-1*H*-quinolin-2-one (Table 1, 4, entry 8). Yield: 0.60 g, 70%, as a white solid; mp 185–187 °C; R_f (25% EtOAc/hexane): 0.37; ν_{max} (KBr): 1674 (CO), 3426 (NH) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 3.91 (s, 2H, CH_2), 6.80–6.88 (m, 3H, ArH), 7.35 (br s, 3H, ArH), 7.46–7.49 (m, 1H, ArH), 7.93 (s, 1H, ArH), 8.68 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 28.8, 112.8, 113.1, 113.7, 114.1, 115.3, 122.0, 126.4, 128.7, 129.5, 130.0, 131.1, 132.4, 155.1, 158.3, 162.6; mass (ES^+): m/z 288.2 (M^++1); HR-EIMS calculated for $C_{16}H_{11}ClFNO$: 287.0513. Found: 287.0514.

4.3.9. 3-(4-Bromobenzylidene)-6-fluoro-3,4-dihydro-1*H*-quinolin-2-one (Table 1, 4, entry 9). Yield: 1.0 g, 76%, as an off white solid; mp 215–217 °C; R_f (20% EtOAc/hexane): 0.39; ν_{max} (KBr): 1670 (CO), 3436 (NH) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 4.07 (s, 2H, CH_2), 6.87–7.01 (m, 2H, ArH), 7.05–7.09 (m, 1H, ArH), 7.22–7.34 (m, 2H, ArH), 7.45–7.49 (m, 3H, ArH), 7.59 (s, 1H, =CH), 7.65 (d, 2H, J=8.3 Hz, ArH), 10.44 (s, 1H, NH); mass (ES^+): m/z 332.1 (M+1), 334.1 (M+1); HR-EIMS calculated for $C_{16}H_{11}BrFNO$: 331.0008. Found: 331.0007.

4.3.10. 3-Benzylidene-6-bromo-3,4-dihydro-1*H*-quinolin-2-one (Table 1, 4, entry 10). Yield: 0.52 g, 79%, as a white solid; mp 221–223 °C; R_f (20% EtOAc/hexane): 0.31; ν_{max} (KBr): 1670 (CO), 3404 (NH) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 3.81 (s, 2H, CH_2), 7.15–7.27 (m, 5H, ArH), 7.52–7.56 (m, 1H, ArH), 7.62 (s, 1H, ArH), 7.78 (d, 1H, J=1.7 Hz, =CH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 39.5, 117.2, 120.8, 125.0, 130.1, 132.3, 132.8, 133.2, 135.9, 138.5, 139.5, 140.9, 143.3, 165.5; mass (ES^+): m/z 314.1 (M^++1), 316.1 (M^++3); HR-EIMS calculated for $C_{16}H_{12}BrNO$: 313.0102. Found: 313.0106.

4.3.11. 3-Benzylidene-8-methyl-3,4-dihydro-1*H*-quinolin-2-one (Table 1, 4, entry 11). Yield: 0.45 g, 36%, as a pale yellow solid; mp 172–174 °C; R_f (20% EtOAc/hexane): 0.31; ν_{max} (KBr): 1624 (CO), 3422 (NH) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.28 (s, 3H, CH_3), 4.09 (s, 2H, CH_2), 6.84–7.00 (m, 3H, ArH), 7.15–7.44 (m, 4H, ArH), 7.79–7.84 (m, 2H, =CH, ArH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 17.1, 31.0, 121.5, 123.0, 126.5, 127.5, 128.3, 128.9, 129.4, 130.3, 132.2, 134.7, 135.8, 137.8, 166.1; mass (ES^+): m/z 250.2 (M^++1). Anal. Calcd. for $C_{17}H_{15}NO$ requires: C, 81.90; H, 6.06; N, 5.62. Found: C, 81.92; H, 6.08; N, 5.66.

4.3.12. 3-Benzylidene-5,6,7-trimethoxy-3,4-dihydro-1*H*-quinolin-2-one (Table 1, 4, entry 12). Yield: 0.55 g, 63%, as a yellow solid; mp 134–136 °C; R_f (20% EtOAc/hexane): 0.43; ν_{max} (KBr): 1671 (CO), 3421 (NH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.82 (s, 3H, CH_3), 3.85 (s, 3H, CH_3), 3.91 (s, 3H, CH_3), 4.01 (d, 2H, J=2.0 Hz CH_2), 6.35 (s, 1H, ArH), 7.36–7.41 (m, 1H, ArH), 7.44–7.53 (m, 4H, ArH), 7.94 (s, 1H, =CH), 9.96 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.6, 54.8, 59.4, 59.7, 94.2, 105.3, 125.3, 127.3, 127.4, 128.8, 130.8, 134.2, 136.2, 136.4, 149.7, 151.6, 164.9; mass (FAB^+): m/z 326 (M^++1). Anal. Calcd. for $C_{19}H_{19}NO_4$ requires: C, 70.14; H, 5.89; N, 4.31. Found: C, 69.88; H, 6.06; N, 4.52.

4.3.13. 6-Fluoro-3-pyridin-3-yl-methylene-3,4-dihydro-1*H*-quinolin-2-one (Table 1, 4, entry 13). Yield: 0.52 g, 68%, as a pale yellow solid; mp 186–188 °C; R_f (20% EtOAc/hexane): 0.3; ν_{max} (KBr): 1659 (CO), 3431 (NH) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 3.86 (s, 2H, CH_2), 7.28–7.38 (m, 3H, ArH), 7.43–7.49 (m, 1H, ArH), 7.68–7.73 (m, 2H, ArH), 8.42 (d, 1H, J=3.7 Hz, ArH), 8.54 (s, 1H, =CH), 11.90 (s, 1H, NH); mass (FAB^+): m/z 255 (M^++1); HR-EIMS calculated for $C_{15}H_{11}FN_2O$: 254.0855. Found: 254.0856.

4.3.14. 3-Benzylidene-6-methyl-3,4-dihydro-1*H*-quinolin-2-one (Table 1, 4, entry 14). Yield: 2.07 g, 78%, as a yellow solid; mp 215–217 °C; R_f (20% EtOAc/hexane): 0.28; ν_{max} (KBr): 1669 (CO), 3431 (NH) cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): δ 2.49 (s, 3H, CH_3), 4.04 (s, 2H, CH_2), 6.77 (d, 1H, J=7.9 Hz, ArH), 6.91–6.97 (t, 2H, J=7.8 Hz, ArH), 7.39–7.54 (m, 5H, ArH), 7.61 (s, 1H, =CH), 10.28 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 19.5, 29.1, 98.7, 113.9, 119.8, 126.7, 127.0, 127.3, 127.7, 129.1, 130.1, 133.4, 134.2, 134.3, 163.1; mass (ES^+): m/z 250.2 (M^++1). Anal. Calcd. for $C_{17}H_{15}NO$ requires: C, 81.90; H, 6.06; N, 5.62. Found: C, 82.05; H, 6.01; N, 5.51.

4.3.15. 6-Chloro-3-(2-chlorobenzylidene)-3,4-dihydro-1*H*-quinolin-2-one (Table 1, 4, entry 15). Yield: 1.40 g, 70%, as a white solid; mp 215–217 °C; R_f (20% EtOAc/hexane): 0.37; ν_{max} (KBr): 1674 (CO), 3406 (NH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.94 (s, 2H, CH_2), 7.29–7.34 (m, 4H, ArH), 7.43–7.49 (m, 3H, ArH), 7.69 (d, 1H, J=1.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 37.2, 120.6, 124.3, 129.6, 130.4, 131.2, 132.3, 133.3, 133.4, 135.3, 136.7, 137.3, 139.4, 140.3, 140.5, 165.4; mass (ES^+): m/z 304.2 (M^++1), 306.2 (M^++3). Anal. Calcd. for $C_{16}H_{11}Cl_2NO$ requires: C, 63.18; H, 3.65; N, 4.60. Found: C, 62.93; H, 3.88; N, 4.48.

4.3.16. 3-(2-Fluorobenzylidene)-3,4-dihydro-1*H*-quinolin-2-one (Table 1, 4, entry 16). Yield: 0.52 g, 73%, as a light yellow solid; mp 182–183 °C; R_f (20% EtOAc/hexane): 0.31; ν_{max} (KBr): 1667 (CO), 3422 (NH) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 3.97 (d, 2H, J=1.4 Hz, CH_2), 6.89–6.94 (m, 2H, ArH), 7.10–7.15 (m, 2H, ArH), 7.29–7.34 (m, 2H, ArH), 7.45–7.47 (m, 1H, ArH), 7.54–7.62 (m, 2H, ArH and =CH), 10.38 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 29.1, 114.1, 114.7, 115.0, 119.9, 120.9, 123.7, 126.4, 126.5, 127.2, 129.5, 130.0, 135.9, 157.5, 160.8, 162.7; mass (ES^+): m/z 254.2 (M^++1); HR-EIMS calculated for $C_{16}H_{12}FNO$: 253.0903. Found: 253.0902.

4.3.17. 6-Fluoro-3-(2-fluorobenzylidene)-3,4-dihydro-1*H*-quinolin-2-one (Table 1, 4, entry 19). Yield: 0.8 g 85%, as a white solid; mp 215–217 °C; R_f (20% EtOAc/hexane): 0.34; ν_{max} (KBr): 1672 (CO), 3424 (NH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.96 (d, J=1.0 Hz, 2H, CH_2), 6.84–6.91 (m, 3H, ArH), 7.15–7.28 (m, 2H, ArH), 7.37–7.45 (m, 2H, ArH), 7.90 (s, 1H, =CH), 9.40 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 29.2, 112.8, 113.0, 113.4, 114.5, 114.8, 115.1, 121.7, 122.7, 127.4, 129.3, 129.6, 131.1, 157.5, 160.9, 164.1; mass (ES^+): m/z 272.2 (M^++1); HR-EIMS calculated for $C_{16}H_{11}F_2NO$: 271.0809. Found: 271.0811.

4.3.18. 3-(2-Fluorobenzylidene)-6-methoxy-3,4-dihydro-1*H*-quinolin-2-one (Table 1, 4, entry 20). Yield: 0.61 g, 77%, as a white solid; mp 180–182 °C; R_f (20% EtOAc/hexane): 0.34; ν_{max} (KBr): 1658 (CO), 3419 (NH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.72 (s, 3H, CH_3), 3.90 (s, 2H, CH_2), 6.62–6.67 (m, 2H, ArH), 6.82–6.85 (m, 1H, ArH), 7.09–7.15 (m, 1H, ArH), 7.19–7.24 (m, 1H, ArH), 7.32–7.39 (m, 2H, ArH), 7.74 (s, 1H, =CH), 9.88 (s, 1H, CONH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 34.2, 59.0, 116.5, 119.6, 125.6, 126.7, 127.5, 132.5, 133.6, 133.8, 133.9, 134.0, 158.6, 162.2, 165.5, 168.0; mass (ES^+): m/z 284.2

(M^++1). Anal. Calcd. for $C_{17}H_{14}FNO_2$ requires: C, 72.07; H, 4.98; N, 4.94. Found: C, 71.88; H, 5.16; N, 5.13.

4.3.19. 3-Benzyl-6-chloro-quinolin-2-ylamine (Table 2, 13, entry 1). Yield: 0.17 g, 28%, as a yellow solid; mp 157–159 °C; R_f (30% EtOAc/hexane): 0.49; ν_{max} (KBr): 3462 (NH_2) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 3.95 (s, 2H, CH_2), 6.44 (s, 2H, NH_2), 7.26–7.32 (m, 5H, ArH), 7.44 (t, 2H, J=2.5 Hz, ArH), 7.59 (s, 1H, ArH), 7.66 (s, 1H, ArH); mass (ES^+): m/z 368.2 (M^++1), 370.2 (M^++3). Anal. Calcd. for $C_{16}H_{13}ClN_2$ requires: C, 71.51; H, 4.88; N, 10.42. Found: C, 71.66; H, 5.11; N, 10.13.

4.3.20. 6-Chloro-3-(2-fluorobenzyl)-quinolin-2-ylamine (Table 2, 13, entry 2). Yield: 0.43 g, 48%, as a yellow solid; mp 204–206 °C; R_f (20% EtOAc/hexane): 0.41; ν_{max} (KBr): 3430 (NH_2) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.97 (s, 2H, CH_2), 4.57 (br s, 2H, NH_2), 7.10–7.16 (m, 3H, ArH), 7.31–7.34 (m, 1H, ArH), 7.46–7.64 (m, 4H, ArH); mass (ES^+): m/z 287.3 (M^++1). Anal. Calcd. for $C_{16}H_{12}ClFN_2$ requires: C, 67.02; H, 4.22; N, 9.77. Found: C, 67.10; H, 4.17; N, 9.52.

4.3.21. 3-(2,4-Dichlorobenzyl)-quinolin-2-ylamine (Table 2, 13, entry 3). Yield: 0.21 g, 46%, as a yellow solid; mp 286–288 °C; R_f (20% EtOAc/hexane): 0.3; ν_{max} (KBr): 3432 (NH) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 3.98 (s, 2H, CH_2), 7.26–7.29 (m, 1H, ArH), 7.36 (d, 2H, J=6.2 Hz, ArH), 7.46 (s, 1H, =CH), 7.58–7.61 (m, 1H, ArH), 7.78 (d, 1H, J=2.0 Hz, ArH), 7.88 (d, 1H, J=8.5 Hz, ArH); mass (FAB^+): m/z 303 (M^++1); HR-EIMS calculated for $C_{16}H_{12}Cl_2N_2$: 302.0378. Found: 302.0366.

4.3.22. 6-Chloro-3-(2,4-dichlorobenzyl)-quinolin-2-ylamine (Table 2, 13, entry 4). Yield: 0.79 g, 53%, as a yellow solid; mp 228–230 °C; R_f (20% EtOAc/hexane): 0.45; ν_{max} (KBr): 3442 (NH_2) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 3.98 (s, 2H, CH_2), 6.58 (br s, 2H, NH_2), 7.21 (s, 1H, ArH), 7.32–7.35 (m, 1H, ArH), 7.42–7.49 (m, 3H, ArH), 7.65 (d, 1H, J=2.2 Hz, ArH), 7.67 (d, 1H, J=2.1 Hz, ArH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 32.8, 121.5, 123.0, 124.2, 125.0, 125.7, 126.8, 127.9, 128.1, 131.4, 131.9, 132.8, 133.8, 134.1, 144.4, 156.4; mass (ES^+): m/z 337.3 (M^++1). Anal. Calcd. for $C_{16}H_{11}Cl_3N_2$ requires: C, 56.92; H, 3.28; N, 8.30. Found: C, 60.21; H, 3.50; N, 8.12.

4.4. General procedure for the preparation of compound 5

To a solution of the appropriate 3-arylmethylene-3,4-dihydro-1*H*-quinolin-2-one (3.2 mmol) in acetone (10 mL) was added anhydrous K_2CO_3 (0.9 g, 6.4 mmol) (2.0 equiv) and the mixture refluxed for 15 min. Thereafter acetone was removed under reduced pressure, the residue was diluted with water, and the formed suspension was filtered and dried under vacuum to yield the pure compound.

4.4.1. 3-Benzyl-1*H*-quinolin-2-one (Table 1, 5, entry 1). See Ref. 4.

4.4.2. 6-Chloro-3-(2-fluorobenzyl)-1*H*-quinolin-2-one (Table 1, 5, entry 5). Yield: 0.5 g, 100%, as a white solid; mp 235–236 °C; R_f (20% EtOAc/hexane): 0.37; ν_{max} (KBr): 1656 (CO), 3426 (NH) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 3.85 (s, 2H, CH_2), 7.14–7.20 (m, 2H, ArH), 7.26–7.33 (m, 3H, ArH), 7.45–7.49 (m, 1H, ArH), 7.55 (s, 1H, ArH), 7.71 (d, 1H, J=1.9 Hz, ArH), 11.95 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 27.9, 114.3, 114.5, 115.8, 119.5, 123.5, 124.8, 124.9, 125.6, 127.7, 128.6, 130.5, 132.1, 134.7, 135.8, 160.6; mass (ES^+): m/z 288.2 (M^++1), 290.2 (M^++3); HR-EIMS calculated for $C_{16}H_{11}ClFNO$: 287.0513. Found: 287.0516.

4.4.3. 3-(4-Bromobenzyl)-6-fluoro-1*H*-quinolin-2-one (Table 1, 5, entry 9). Yield: 0.17 g, 100%, as a pale yellow solid; mp >250 °C; R_f (20% EtOAc/hexane): 0.37; ν_{max} (KBr): 1662 (CO), 3425 (NH) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 3.81 (s, 2H, CH_2), 7.23 (d, 2H, J=8.3 Hz, ArH), 7.31–7.34 (m, 2H, ArH), 7.44–7.49 (m, 3H, ArH), 7.66 (s, 1H, ArH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 34.2, 111.2, 111.5, 115.8, 116.5, 116.8, 118.5, 119.1, 130.3, 133.3, 133.9, 135.2, 138.1, 154.6, 157.7, 160.6; mass (ES^+): m/z 332.1 (M^++1); HR-EIMS calculated for $C_{16}H_{11}BrFNO$: 331.0008. Found: 331.0012.

4.4.4. 3-Benzyl-6-bromo-1*H*-quinolin-2-one (Table 1, 5, entry 10). Yield: 0.52 g, 100%, as a white solid; mp >250 °C; R_f (20% EtOAc/hexane): 0.3; ν_{max} (KBr): 1670 (CO), 3399 (NH) cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 3.81 (s, 2H, CH_2), 7.18–7.27 (m, 6H, ArH), 7.54–7.57 (m, 1H, ArH), 7.64 (s, 1H, ArH), 7.80 (d, 1H, J=2.1 Hz, ArH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 35.5, 113.4, 116.9, 121.1, 126.2, 128.4, 128.9, 129.4, 132.0, 134.6, 135.7, 137.0, 139.4, 161.6; mass (ES^+): m/z 314.1 (M^++1), 316.1 (M^++3); HR-EIMS calculated for $C_{16}H_{12}BrNO$: 313.0102. Found: 313.0102.

4.4.5. 3-Benzyl-6-methyl-1*H*-quinolin-2-one (Table 1, 5, entry 14). Yield: 0.50 g, 100%, as a white solid; mp 224–225 °C; R_f (20% EtOAc/hexane): 0.3; ν_{max} (KBr): 1646 (CO), 3431 (NH) cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 2.31 (s, 3H, CH_3), 3.82 (s, 2H, CH_2), 7.18–7.35 (m, 8H, ArH), 7.58 (s, 1H, ArH), 11.69 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 24.3, 39.5, 118.6, 123.2, 130.0, 130.8, 132.2, 132.8, 134.6, 137.1, 139.9, 140.4, 143.7, 165.7; mass (ES^+): m/z 250.2 (M^++1). Anal. Calcd. for $C_{17}H_{15}NO$ requires: C, 81.90; H, 6.06; N, 5.62. Found: C, 82.16; H, 5.93; N, 5.69.

4.4.6. 6-Chloro-3-(2-chlorobenzyl)-1*H*-quinolin-2-one (Table 1, 5, entry 15). Yield: 0.60 g, 100%, as a white solid; mp 229–231 °C; R_f (20% EtOAc/hexane): 0.35; ν_{max} (KBr): 1662 (CO), 3429 (NH) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 3.93 (s, 2H, CH_2), 7.28–7.37 (m, 4H, ArH), 7.41–7.48 (m, 3H, ArH), 7.68 (d, 1H, J=2.1 Hz); ^{13}C NMR (75 MHz, DMSO-d_6): δ 32.4, 115.9, 119.5, 124.8, 125.6, 126.5, 127.6, 128.5, 130.6, 131.9, 132.6, 134.7, 135.5, 135.8, 160.7; mass (ES^+): m/z 304.2 (M^++1), 306.1 (M^++3). Anal. Calcd. for $C_{16}H_{11}Cl_2NO$ requires: C, 63.18; H, 3.65; N, 4.60. Found: C, 63.04; H, 3.89; N, 4.78.

4.4.7. 3-(2-Fluorobenzyl)-1*H*-quinolin-2-one (Table 1, 5, entry 16). Yield: 0.20 g, 100%, as a white solid; mp 197–199 °C; R_f (20% EtOAc/hexane): 0.3; ν_{max} (KBr): 1662 (CO), 3427 (NH) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6):

δ 4.07 (s, 2H, CH_2), 7.06–7.35 (m, 5H, ArH), 7.39–7.49 (m, 4H, ArH), 11.49 (s, 1H, NH); ^{13}C NMR (50 MHz, DMSO-d_6): δ 29.1, 115.2, 115.8, 119.5, 122.1, 124.7, 126.2, 127.7, 128.8, 129.9, 131.8, 131.9, 137.0, 138.3, 162.0, 163.4; mass (ES^+): *m/z* 254.1 (M^++1); HR-EIMS calculated for $C_{16}H_{12}FNO$: 253.0903. Found: 253.0902.

4.4.8. 6-Fluoro-3-(2-fluorobenzyl)-1*H*-quinolin-2-one (Table 1, 5, entry 19). Yield: 1.0 g, 100%, as a white solid; mp 219–221 °C; R_f (20% EtOAc/hexane): 0.32; ν_{max} (KBr): 1657 (CO), 3414 (NH) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.86 (s, 2H, CH_2), 7.11–7.21 (m, 2H, ArH), 7.26–7.33 (m, 4H, ArH), 7.45–7.53 (m, 2H, ArH), 11.86 (br s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 28.0, 111.5, 114.5, 115.8, 116.9, 119.0, 123.5, 125.0, 127.7, 130.6, 132.2, 133.8, 134.9, 157.7, 160.5, 161.4; mass (ES^+): *m/z* 272.2 (M^++1); HR-EIMS calculated for $C_{16}H_{11}F_2NO$: 271.0809. Found: 271.0805.

4.5. General procedure for the preparation of compound 6

To a round bottom flask containing 2-quinolone (3.2 mmol) (1.0 equiv) was added $POCl_3$ (5.8 mL, 63.9 mmol) and the mixture refluxed for 30 min. After completion of the reaction, reaction mixture was poured in ice cold water and basified with $NaHCO_3$ solution to pH 8–8.5 and extracted with ethyl acetate (3×50 mL). These organic fractions were combined, washed with brine (50 mL), dried (Na_2SO_4), and evaporated in vacuo to yield the crude product, which was purified by silica gel column chromatography using hexanes/ethyl acetate (95–90:5–10, v/v) to furnish the pure compounds in 82–97% yield.

*One-pot procedure from compound **4***: to a vessel containing the appropriate aniline (2.5 mmol) was added TFA (5 mL) and this mixture was heated at reflux for 8–14 h. On completion (as monitored by TLC), the excess TFA was evaporated in vacuo and the residue was taken in 10 mL of acetone. To this solution K_2CO_3 (1.19 g, 8.62 mmol) was added and the mixture was heated at reflux for 15 min. The solvent was removed, water was added to the residue, and the separated solid was filtered and dried to furnish the pure products.

4.5.1. 3-Benzyl-2-chloro-quinoline (Table 1, 6, entry 1). Yield: 0.035 g, 66%, as a yellow solid; mp 156–158 °C; R_f (10% EtOAc/hexane): 0.81; ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.11 (s, 2H, CH_2), 6.84 (d, 2H, *J*=7.6 Hz, ArH), 6.97 (t, 1H, *J*=7.2 Hz, ArH), 7.17 (d, 2H, *J*=8.8 Hz, ArH), 7.45 (s, 4H, ArH), 7.88 (s, 1H, ArH), 8.68 (s, 1H, ArH); mass (ES^+): *m/z* 254.2 (M^++1). Anal. Calcd. for $C_{16}H_{12}ClN$ requires: C, 75.74; H, 4.77; N, 5.52. Found: C, 75.72; H, 4.73; N, 5.49.

4.5.2. 2-Chloro-3-(2-chlorobenzyl)-quinoline (Table 1, 6, entry 2). Yield: 0.20 g, 71%, as a yellow solid; mp 107–109 °C; R_f (15% EtOAc/hexane): 0.61; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.36 (s, 2H, CH_2), 7.18–7.21 (m, 1H, ArH), 7.23–7.32 (m, 3H, ArH), 7.46–7.55 (m, 2H, ArH), 7.66–7.73 (m, 3H, ArH), 8.04 (d, 1H, *J*=9.0 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 36.8, 115.4, 123.0, 126.5, 127.0, 129.6, 128.5, 129.9, 130.4, 131.2, 133.3, 134.8, 136.5, 145.3, 150.1, 164.4; mass (ES^+): *m/z* 288.3 (M^++1), 290.2 (M+3). Anal. Calcd. for $C_{16}H_{11}Cl_2N$ requires: C, 66.69; H, 3.85; N, 4.86. Found: C, 66.45; H, 4.03; N, 4.99.

4.5.3. 3-(4-Bromobenzyl)-2-chloro-quinoline (Table 1, 6, entry 3). Yield: 0.18 g, 85%, as a yellow solid; mp 144–146 °C; R_f (5% EtOAc/hexane): 0.61; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.19 (s, 2H, CH_2), 7.13 (d, 2H, *J*=8.3 Hz, ArH), 7.48 (d, 2H, *J*=8.3 Hz, ArH), 7.52–7.57 (m, 1H, ArH), 7.69–7.75 (m, 2H, ArH), 7.81 (s, 1H, ArH), 8.03 (d, 1H, *J*=8.3 Hz, ArH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 37.3, 119.4, 125.9, 126.1, 126.9, 128.8, 129.6, 130.6, 135.8, 136.9, 145.3, 150.0; mass (ES^+): *m/z* 332.3 (M^++1), 334.2 (M^++3). Anal. Calcd. for $C_{16}H_{11}BrClN$ requires: C, 57.77; H, 3.33; N, 4.21. Found: C, 57.75; H, 3.31; N, 4.19.

4.5.4. 3-(4-Bromobenzyl)-2,6-dichloro-quinoline (Table 1, 6, entry 6). Yield: 0.15 g, 82%, as yellow solid; mp 151 °C; R_f (5% EtOAc/hexane): 0.58; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.17 (s, 2H, CH_2), 7.11 (d, 2H, *J*=8.3 Hz, ArH), 7.48 (d, 2H, *J*=8.3 Hz, ArH) 7.60–7.64 (m, 3H, ArH), 7.68–7.70 (m, 1H, ArH), 7.93 (d, 1H, *J*=9.0 Hz, ArH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 37.3, 119.6, 124.6, 126.7, 128.5, 129.6, 129.7, 130.7, 131.7, 132.4, 135.4, 135.8, 143.6, 150.3; mass (ES^+): *m/z* 368.2 (M^++1), 370.2 (M^++3). Anal. Calcd. for $C_{16}H_{10}BrCl_2N$ requires: C, 52.35; H, 2.75; N, 3.82. Found: C, 52.59; H, 2.97; N, 4.11.

4.5.5. 2-Chloro-3-(2-chlorobenzyl)-6-fluoro-quinoline (Table 1, 6, entry 8). Yield: 0.19 g, 68%, as yellow solid; mp 109–111 °C; R_f (5% EtOAc/hexane): 0.67; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.35 (s, 2H, CH_2), 7.19–7.22 (m, 1H, ArH), 7.28–7.33 (m, 3H, ArH), 7.43–7.50 (m, 2H, ArH), 7.58 (s, 1H, ArH), 8.00–8.05 (m, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 35.5, 109.0, 109.3, 118.6, 118.9, 126.0, 127.4, 128.7, 129.4, 130.0, 131.2, 133.3, 134.3, 135.7, 157.7, 161.0; mass (ES^+): *m/z* 306.2 (M^++1), 308.2 (M+3); HR-EIMS calculated for $C_{16}H_{10}Cl_2FN$: 305.0174. Found: 305.0175.

4.5.6. 3-(4-Bromobenzyl)-2-chloro-6-fluoro-quinoline (Table 1, 6, entry 9). Yield: 0.14 g, 89%, as a yellow solid; mp 138–140 °C; R_f (5% EtOAc/hexane): 0.62; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.20 (s, 2H, CH_2), 7.13 (d, 2H, *J*=8.2 Hz, ArH), 7.34–7.38 (m, 1H, ArH), 7.44–7.50 (m, 3H, ArH), 7.75 (s, 1H, =CH), 7.99–8.01 (m, 1H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 38.9, 110.5, 111.0, 120.3, 120.8, 121.2, 128.4, 131.1, 132.3, 133.8, 147.1, 137.7, 144.0, 151.0, 158.6, 163.6; mass (ES^+): *m/z* 350.2 (M^++1), 352.2 (M^++3); HR-EIMS calculated for $C_{16}H_{10}BrClFN$: 348.9669. Found: 348.9676.

4.5.7. 3-Benzyl-6-bromo-2-chloro-quinoline (Table 1, 6, entry 10). Yield: 0.51 g, 97%, as a white solid; mp 111–112 °C; R_f (5% EtOAc/hexane): 0.51; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.23 (s, 2H, CH_2), 7.24–7.28 (m, 2H, ArH), 7.31–7.41 (m, 3H, ArH), 7.66 (s, 1H, ArH), 7.72–7.75 (m, 1H, ArH), 7.84–7.88 (m, 2H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 37.8, 119.6, 125.7, 127.2, 127.6, 128.0, 128.5, 132.0, 133.1, 135.6, 136.3, 143.7, 150.7; mass (ES^+): *m/z*

332.2 (M^++1), 334.2 (M^++3); HR-EIMS calculated for $C_{16}H_{11}BrClN$: 330.9763. Found: 330.9769.

4.5.8. 2,6-Dichloro-3-(2-fluorobenzyl)-quinoline (Table 1, 6, entry 18). Yield: 0.31 g, 97%, as a white solid; mp 93–94 °C; R_f (5% EtOAc/hexane): 0.5; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.25 (s, 2H, CH_2), 7.10–7.17 (m, 2H, ArH), 7.20–7.33 (m, 2H, ArH), 7.60–7.63 (m, 1H, ArH), 7.70 (s, 2H, ArH), 7.94 (d, 1H, J=9.0 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 31.1, 114.2, 114.6, 123.2, 124.7, 126.7, 127.8, 128.4, 129.6, 130.0, 130.1, 131.5, 1355.6, 150.3, 158.3, 161.5; mass (ES^+): m/z 306.3 (M^++1), 308.3 (M^++3); HR-EIMS calculated for $C_{16}H_{10}Cl_2FNO$: 305.0174. Found: 305.0178.

4.5.9. 2-Chloro-6-fluoro-3-(2-fluorobenzyl)-quinoline (Table 1, 6, entry 19). Yield: 0.33 g, 81%, as a white solid; mp 85–87 °C; R_f (5% EtOAc/hexane): 0.5; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.26 (s, 2H, CH_2), 7.12–7.17 (m, 2H, ArH), 7.22–7.36 (m, 3H, ArH), 7.45–7.48 (m, 1H, ArH), 7.75 (s, 1H, ArH), 7.99–8.03 (m, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 31.2, 52.4, 115.8, 125.2, 125.4, 125.8, 127.3, 127.8, 128.0, 130.6, 133.2, 134.5, 137.6, 142.9, 159.9, 161.5; mass (ES^+): m/z 290.3 (M^++1), 292.3 (M^++3); HR-EIMS calculated for $C_{16}H_{10}ClF_2N$: 289.0470. Found: 289.0460.

4.6. General procedure for the preparation of compounds 7–9

To a solution of the appropriate 2-chloro-quinoline (1.0 equiv) in dry methanol (10 mL) was added 50% NaOMe (w/v, 10 mL) in methanol and refluxed for 15 min. The solvent was removed in vacuo and the residue was extracted with ethyl acetate (3×50 mL) and water (50 mL). These combined organic fractions were washed with brine (50 mL), dried over Na_2SO_4, and evaporated. The crude product was purified by silica gel column chromatography using hexanes/ethyl acetate (98–95:2–5, v/v) to furnish the pure compounds in 81–97% yield.

4.6.1. 3-Benzyl-6-bromo-2-methoxy-quinoline (7). Yield: 0.51 g, 97%, as a white solid; mp 82–83 °C (lit. 82 °C)[3]; R_f (2% EtOAc/hexane): 0.45; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.05 (s, 2H, CH_2), 4.11 (s, 3H, CH_3), 7.25–7.30 (m, 3H, ArH), 7.33–7.37 (m, 2H, ArH), 7.50 (s, 1H, ArH), 7.61–7.76 (m, 3H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 34.8, 52.4, 115.8, 125.2, 125.4, 125.8, 127.3, 127.8, 128.0, 130.6, 133.2, 134.5, 137.6, 142.9, 159.9; mass (ES^+): m/z 328.2 (M^++1), 330.2 (M^++3); HR-EIMS calculated for $C_{17}H_{14}BrNO$: 327.0259. Found: 327.0260.

4.6.2. 6-Chloro-3-(2-fluorobenzyl)-2-methoxy-quinoline (8). Yield: 0.34 g, 87%, as a white solid; mp 87–89 °C; R_f (2% EtOAc/hexane): 0.63; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.08 (s, 2H, CH_2), 4.11 (s, 3H, CH_3), 7.07–7.14 (m, 2H, ArH), 7.22–7.31 (m, 2H, ArH), 7.49–7.53 (m, 2H, ArH), 7.61 (d, 1H, J=2.3 Hz, ArH), 7.77 (d, 1H, J=8.8 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.0, 52.4, 114.0, 114.3, 122.9, 124.3, 124.6, 124.8, 127.1, 127.5, 128.0, 130.1, 134.5, 142.6, 158.4, 159.7, 161.6; mass (ES^+): m/z 302.2 (M^++1), 304.2 (M^++3); HR-EIMS calculated for $C_{17}H_{13}ClFNO$: 301.0670. Found: 301.0673.

4.6.3. 6-Fluoro-3-(2-fluorobenzyl)-2-methoxy-quinoline (9). Yield: 0.20 g, 81%, as a white solid; mp 91–93 °C; R_f (2% EtOAc/hexane): 0.43; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.08 (s, 2H, CH_2), 4.11 (s, 3H, CH_3), 7.07–7.14 (m, 2H, ArH), 7.22–7.37 (m, 4H, ArH), 7.57 (s, 1H, ArH), 7.80–7.84 (m, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.0, 52.3, 109.1, 114.3, 117.1, 122.9, 124.1, 124.7, 127.1, 127.5, 130.1, 134.7, 141.0, 158.4, 159.4, 161.6; mass (ES^+): m/z 2863 (M^++1); HR-EIMS calculated for $C_{17}H_{13}F_2NO$: 285.0965. Found: 285.0966.

Acknowledgements

Two of the authors (R.P. and S.M.) acknowledge the financial support from CSIR, N. Delhi in the form of fellowship. This work was supported by the financial grant from DST, N. Delhi.

References and notes

1. (a) Cole, S. T.; Alzari, P. M. *Science* **2005**, 306–307; (b) Rubin, E. J. *N. Engl. J. Med.* **2005**, *352*, 933–934; (c) Ji, B.; Jarlier, V. *Antimicrob. Agents Chemother.* **2006**, *50*, 1558–1560.
2. Andries, K.; Verhasselt, P.; Guillemont, J.; Gohlmann, H. W. H.; Neefs, J.-M.; Winkler, H.; Gestel, J. V.; Timmerman, P.; Zhu, M.; Lee, E.; Williams, P.; de Chaffoy, D.; Huitric, E.; Hoffner, S.; Cambau, E.; Truffot-Pernot, C.; Lounis, N.; Jarlier, V. *Science* **2005**, *307*, 223–227.
3. (a) Andries, K. J.; Van Gestel, J. F. E. WO 2005117875, 2005; (b) Van Gestel, J. F. E.; Guillemont, J. E. G.; Venet, M. G.; Poignet, H. J. J.; Decrane, L. F. B.; Vernier, D. F. J.; Odds, F. C. U.S. 2005148581 A1, 2005.
4. Lee, C. G.; Lee, K. Y.; Lee, S.; Kim, J. N. *Tetrahedron* **2005**, *61*, 1493–1499. For other references pertaining to the synthesis of quinoline derivatives from Baylis–Hillman chemistry refer to: Madapa, S.; Singh, V.; Batra, S. *Tetrahedron* **2006**, *62*, 8740–8747 and references cited therein.