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A novel approach to quinazolin-4(3*H*)-one via quinazoline oxidation: an improved synthesis of 4-anilinoquinazolines

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ABSTRACT

A novel strategy to prepare 4-anilinoquinazoline derivatives based on the oxidation of the quinazoline ring is described. Quinazoline oxidation has been investigated and improved, thus leading to an efficient and high yielding method to quinazolin-4(3*H*)-ones. Efficiency of this approach has been evaluated synthesizing four well known tyrosine kinase inhibitors and comparing the obtained yields with those achievable through conventional synthetic methods.

1. Introduction

4-Anilinoquinazolines have been widely studied as anticancer agents for their strong ability to inhibit several receptor tyrosine kinases, such as EGFR or VEGFR-2, often overexpressed or deregulated in many solid tumors.[1,2]

Among 4-anilinoquinazolines, PD153035[3] (1) demonstrated the highest in vitro inhibitory activity, while Erlotinib[4] (2, Tarceva®), Gefitinib[5] (3, Iressa®), and Vandetanib[6] (4, Zactima®) have been recently approved by FDA as anticancer drugs (Fig. 1). They act as ATP-mimetic inhibitors, and in the last few years many publications and patents have dealt with their synthesis, activity, and therapeutic use.

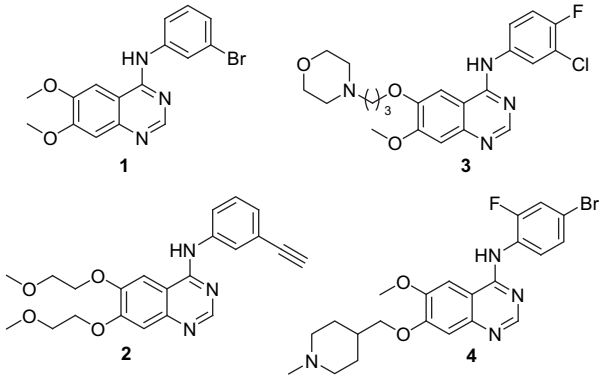
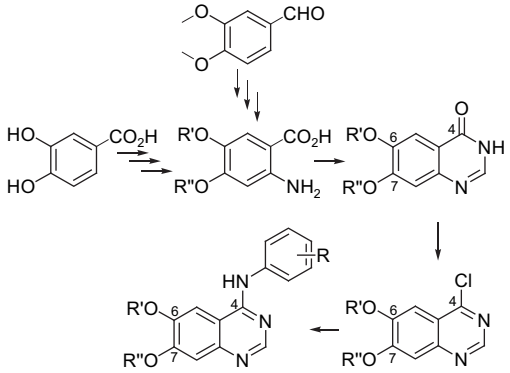


Figure 1. Structure of tyrosine kinase inhibitors.

Despite the widespread utility of this class of compounds, the reported syntheses of 4-anilinoquinazolines require multistep and low-yielding pathways.[7] The key step of the currently known procedures is the synthesis of 6,7-dialkoxyquinazolin-4(3*H*)-one intermediates: these synthons are mainly obtained from non-commercial anthranilic acid derivatives, whose preparation needs several steps, starting from 3,4-dimethoxybenzaldehyde[8] or 3,4-dihydroxybenzoic acid derivatives.[9] The key 6,7-dialkoxyquinazolin-4(3*H*)-ones are then submitted to chlorination at the 4 position and finally the chlorine atom is substituted with the appropriate aniline moiety (Scheme 1).



Scheme 1. Current general synthetic approach.

The major downside of this synthetic route becomes evident when compounds with different substitutions at the 6 and 7 positions have to be obtained, such as in the case of some interesting 4-anilinoquinazolines in clinical trials (see compounds 3–4 in Fig. 1). In any case, the required different substituents at the 6 and 7

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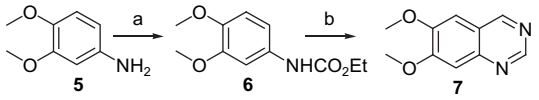
positions should be present at the beginning of the synthetic pathway, given the relative problems for the availability of commercial starting materials, or alternatively they should be introduced in the final step, but with poor chemoselectivity.[10] The overall yield of the reported synthetic strategies is about 30%. Attempts to increase yields through Microwave Assisted Organic Synthesis (MAOS),[11] or designing a novel strategy based on isovanillin as starting material[10] led to modest improvements. Therefore, the identification of novel and general pathways to 4-anilinoquinazolines could be of considerable interest, especially for those with different 6,7-substitutions.

Herein we described a different and more efficient approach for anilinoquinazolines preparation.

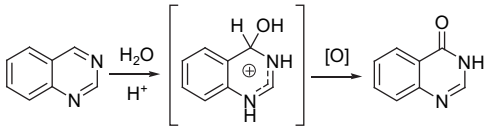
2. Results and discussion

Having in our hands a good strategy to build quinazolines directly from simple anilines,[12] we have undertaken the synthesis of the key 6,7-dialkoxyquinazolin-4(3*H*)-one intermediate via oxidation of the appropriate quinazoline, thus avoiding the preparation of anthranilic acid derivatives. The oxidation of quinazoline nucleus was first reported in the 1960s,[13] but it has not been studied in depth, maybe because of the lack of useful strategies to synthesize quinazoline compounds. Indeed, no synthetic use for this reaction has ever been reported. Thus, we investigated this oxidation reaction, choosing 6,7-dimethoxyquinazoline (**7**) as the reference compound, whose synthesis was achieved by the HMTA/TFA/$K_3Fe(CN)_6$ method[12] starting from 3,4-dimethoxyaniline (**5**) (Scheme 2).



Scheme 2. Reagents and conditions: (a) $ClCO_2Et$, THF, Et_3N, rt, 30 min, 98%; (b) 1. HMTA, TFA, MW, 110 °C, 10 min. 2. KOH aq EtOH, $K_3Fe(CN)_6$, reflux, 4 h, 86%.

Quinazoline oxidation occurs through an acid catalyzed addition of one water molecule to the 3,4-double bond of the quinazoline scaffold followed by subsequent involvement of an oxidizing agent leading to quinazolin-4(3*H*)-one formation (Scheme 3).

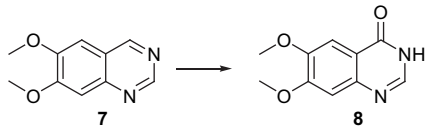


Scheme 3. Proposed mechanism for quinazoline oxidation.

The oxidation mechanism was first reported by Albert,[13] who oxidized quinazoline with both H_2O_2 and CrO_3. However, we found that oxidation of **7** with H_2O_2 both in organic and mineral aqueous acid only afforded 6,7-dimethoxyquinazolin-4(3*H*)-one in a very poor yield (about 19%) and very long reaction times were required (Table 1, Entries 1–6).

The use of CrO_3 instead of H_2O_2 increased the yield to 35% and reduced the reaction time to 5 min (Table 1, Entry 7). To avoid the use of such a toxic compound, other oxidizing agents were tested. The use of $KMnO_4$ was not considered, because oxidation of quinazoline to pyrimidin-4,5-dicarboxylic acid has previously been reported.[14] The use of $NaClO_2$ or a combination of H_5IO_6 with catalytic amounts of CrO_3 led only to traces of the desired compound (Table 1, Entries 8 and 9). The best result was achieved with cerium ammonium nitrate (CAN) in aqueous AcOH at room temperature, more than doubling the yield obtained with CrO_3 (Table 1, entry 10).

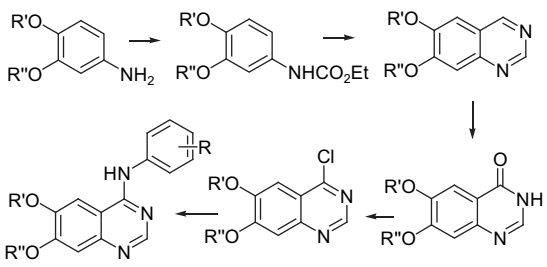
Table 1
Oxidation of 6,7-dimethoxyquinazolin-4(3*H*)-one (**7**)



Entry	Oxidizing agent	Solvent	Temp/°C	Time	Yield (%)
1	H_2O_2	AcOH	rt	48 h	19
2	H_2O_2	AcOH	40	24 h	18
3	H_2O_2	AcOH	80	30 min	0[a]
4	H_2O_2	HCl 2 M	rt	48 h	18
5	H_2O_2	H_2SO_4 2 M	rt	30 min	0[b]
6	H_2O_2	TFA 6 M	rt	30 min	0[a]
7	CrO_3	H_2SO_4/AcOH aq	rt	5 min	35
8	$NaClO_2$	AcOH 6 M	rt	30 min	0[b]
9	H_5IO_6/CrO_3[15]	MeCN/AcOH aq	rt	30 min	0[b]
10	CAN	$AcOH/H_2O$	rt	5 min	86

[a] Complex reaction mixture was obtained.
[b] Only traces of desired quinazolinone were found in the reaction mixture.

Once oxidation conditions were secured, the efficiency of this novel approach to quinazolin-4(3*H*)-one was evaluated synthesizing the four tyrosine kinase inhibitors of Figure 1 and comparing the overall yields with those achievable employing the literature methods. We planned a general synthetic strategy, which is reported in the Scheme 4.



Scheme 4. Novel general synthetic strategy.

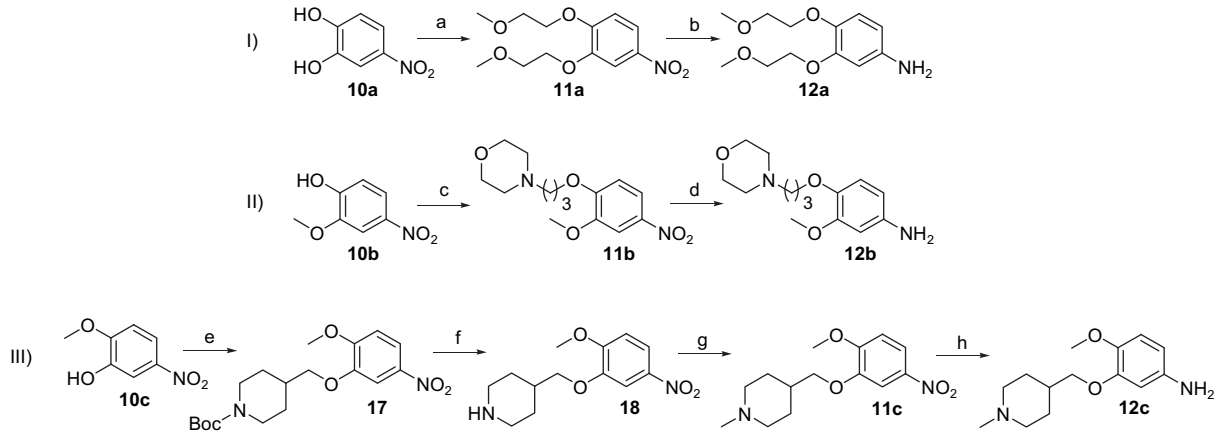
According to this strategy, the starting anilines, substituted with the desired alkoxy functions, were submitted to cyclization, affording the appropriate quinazolines. Quinazolines were oxidized to the key 6,7-dialkoxy-quinazolin-4(3*H*)-ones, which were then converted to the final 4-anilinoquinazoline with the already reported synthetic methods.

The desired alkoxyl functions at the 3 and 4 positions of the aniline ring were introduced on commercial anilines or their precursors, if the appropriate anilines were not commercially available (Scheme 5). Nitrobenzene and nitrocathecol derivatives were used as the starting aniline precursors (i.e. 3,4-dimethoxyaniline for PD153035, 4-nitrocatechol for Erlotinib, 4-nitroguaiacol for Gefitinib, and 2-methoxy-5-nitrophenol for Vandetanib).

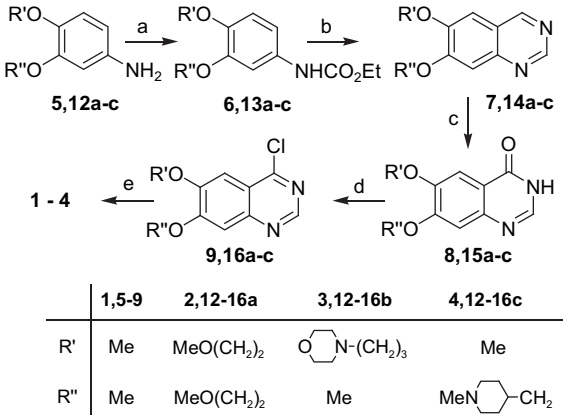
Thus, the corresponding quinazolines were synthesized by the HMTA/TFA/$K_3Fe(CN)_6$ method[12] and oxidized to quinazolin-4(3*H*)-ones with CAN in aqueous AcOH.

Finally, the syntheses of the desired compounds **1**-**4** were completed through a chlorination step with $POCl_3$ or $SOCl_2$, followed by condensation with the suitable aniline substituent (Scheme 6).

It must be pointed out that we did not meet any difficulty with starting material availability. In fact, unlike anthranilic acid derivatives, a large number of anilines or nitrobenzene derivatives with different functional groups in the 3 and 4 positions are commercially available, thus making this synthetic route very attractive for quinazolinone synthesis. For example, the first synthesis of Gefitinib required an initial selective monodemethylation of 6,7-



Scheme 5. Reagents and conditions: (a) 2-methoxyethyl chloride, K_2CO_3, DMF, 150 °C, 8 h, 95%; (b) HCO_2NH_4, 10% Pd/C, EtOH, reflux, 30 min, 98%; (c) 4-(3-chloropropyl)morpholine, K_2CO_3, DMF, 150 °C, 8 h, 95%; (d) HCO_2NH_4, Pd/C, EtOH, reflux, 30 min, 98%; (e) 1-*Boc*-4-(tosyloxymethyl)-piperidine, K_2CO_3, DMF, 150 °C, 8 h, 93%; (f) TFA, CH_2Cl_2, rt, 2 h, 98%; (g) 37% HCHO, HCO_2H, MW, 90 °C, 10 min, 89%; (h) HCO_2NH_4, 10% Pd/C, EtOH, reflux, 30 min, 98%.



	1,5-9	2,12-16a	3,12-16b	4,12-16c
R'	Me	$MeO(CH_2)_2$	O N-$(CH_2)_3$	Me
R''	Me	$MeO(CH_2)_2$	Me	MeN $-CH_2$

Scheme 6. Reagents and conditions: (a) $ClCO_2Et$, THF, Et_3N, rt, 30 min, 98%; (b) 1. HMTA, TFA, MW, 110 °C, 10 min. 2. KOH aq EtOH, $K_3Fe(CN)_6$, reflux, 4 h, 84–91%; (c) CAN, AcOH, rt, 5 min, 86–90%; (d) $POCl_3/Et_3N$ or $SOCl_2$/DMF, reflux, 3 h, 85–98%; (e) 3-ethynylaniline or haloanilines, *i*-PrOH, MW, 80 °C, 15 min, 88–92%.

dimethoxyquinazolin-4(3*H*)-one (achievable from 4,5-dimethoxyanthranilic acid, the only useful commercial anthranilic derivative) and protective acetylation of the 6-hydroxyl group, then chlorination and substitution with the aniline moiety at the 4 position and finally functionalization with morpholino-propyl chain at the 6 position.[16] On the other hand, Vandetanib required a different and more complex approach because selective monodemethylation of 6,7-dimethoxyquinazolin-4(3*H*)-one occurred only at the 6 position, forcing the use of different and less accessible starting products.[2] Applying the new strategy, the selective demethylation or protection of the two oxygenated functions, required in the reported synthesis of Gefitinib and Vandetanib, can be avoided with a considerable simplification of the entire process. In all the cases, the subject compounds were obtained with yields appreciably higher than those achievable via literature methods, thus demonstrating the validity of the new synthetic pathway (Table 2).

Table 2
Overall yields comparison

Compd	Yield (%)	
	Literature[ref]	Isolated
PD153035 (**1**)	17[17]	55
Erlotinib (**2**)	59[16]	60
Gefitinib (**3**)	26,[18] 37,[19] 22,[16] 14[20]	58
Vandetanib (**4**)	28,[2] 29[2]	58

Moreover, all the involved reactions showed total regio- and chemoselectivity and no by-products were found in the reaction mixtures, thus requiring only basic work-up procedures.

3. Conclusions

We have developed a novel synthetic strategy to 4-anilinoquinazoline based on the oxidation of quinazoline intermediates. The efficiency of this approach was evaluated through the synthesis of four well known tyrosine kinases inhibitors, achieving them with overall yields that are higher or at least comparable with those obtained with other literature methods. Moreover, this method used simple work-up procedures and could lead to 6,7-differently substituted derivatives such as Gefitinib or Vandetanib with excellent overall yields. This strategy may represent a valid alternative to anthranilic acid based synthesis of 4-anilinoquinazolines in order to obtain not only known drugs, but also novel compounds in the field of tyrosine kinase inhibitors.

4. Experimental

4.1. General

All chemicals and solvents were analytical grade and used without further purification. Analytical TLC was performed on precoated silica gel plates (Merck 60-F-254, 0.25 mm). Preparative column chromatography was performed using silica gel 60 (0.063–0.100 mm; Merck). Microwave assisted reactions were performed on a CEM Discover® monomode reactor in closed devices with the temperature monitored by a built-in infrared sensor and the automatic control of the power. Melting points were determined on a Gallenkamp MFB-595-010M melting point apparatus and are uncorrected. Elemental analysis were performed on a Perkin-Elmer 2400 analyzer. The IR spectra were recorded on a Perkin-Elmer BX FTIR spectrometer. The ^{1}H NMR spectra were recorded at 300 MHz on a Bruker 300-AMX spectrometer with TMS as an internal standard; chemical shifts are given in ppm and coupling constants in Hertz. Mass spectra were performed on an Applied Biosystem Mariner System 5220 with direct injection of the sample. Compounds **5** and **10a–c** were commercially available. Analytical data for compounds **1**,[3] **2**,[16] **3**,[20] **4**,[2] **8**,[3] **9**,[3] **15a**,[16] **15b**,[20] **15c**,[20] **16a**,[16] **16b**,[2] **16c**[2] were compared with literature data. For these known compounds elemental analyses, ^{1}H NMR and HRMS were reported.

*4.1.1. 3,4-Di(2′-methoxyethoxy)nitrobenzene (**11a**).* A mixture of **10a** (3.1 g, 20.0 mmol), 2-methoxyethyl chloride (4.2 g, 44.0 mmol),

and anhydrous K_2CO_3 (8.3 g, 60.0 mmol) in anhydrous DMF (40.0 mL) was heated at 150 °C for 8 h. After cooling the mixture was diluted with satd NH_4Cl solution (500 mL) and extracted with CH_2Cl_2 (3×200 mL). The organic phase was evaporated under reduced pressure affording the desired product **11a** (5.2 g, 95%) as pale yellow solid; mp 54 °C; IR (KBr) 2930, 2889, 2825, 1588, 1515, 1455, 1340, 1277, 1231, 1129, 1096, 1036, 873 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.89 (1H, dd, J=9.0, 2.7 Hz, 6-H), 7.78 (1H, d, J=2.7 Hz, 2-H), 6.94 (1H, d, J=9.0 Hz, 5-H), 4.27–4.20 (4H, m, 2×OC*H*$_2$CH$_2$OCH$_3$), 3.84–3.78 (4H, m, 2×OCH$_2$C*H*$_2$OCH$_3$), 3.46 (3H, s, OCH_3), 3.45 (3H, s, OCH_3); ^{13}C NMR ($CDCl_3$): δ 154.44, 148.51, 141.57, 118.06, 111.92, 108.92, 70.71, 70.67, 69.03, 68.93, 59.33, 59.28; HRMS (ESI-TOF) for $C_{12}H_{18}NO_6$ $[M+H]^+$: calcd: 272.1129, found: 272.1234. Anal. Calcd for $C_{12}H_{17}NO_6$: C, 53.13; H, 6.32; N, 5.16; Found: C, 53.08; H, 6.36; N, 5.25.

*4.1.2. 3-Methoxy-4-(3′-N-morpholino)propoxynitro-benzene (**11b**).* A mixture of **10b** (3.4 g, 20.0 mmol), 4-(3-chloropropyl)-morpholine (3.6 g, 22.0 mmol), and anhydrous K_2CO_3 (4.1 g, 30.0 mmol) in anhydrous DMF (40.0 mL) was heated at 150 °C for 8 h. After cooling the mixture was diluted with satd NH_4Cl solution (500 mL) and extracted with CH_2Cl_2 (3×200 mL). The organic phase was evaporated under reduced pressure affording the desired product **11b** (5.6 g, 95%) as yellow solid; mp 106 °C; IR (KBr) 2963, 2940, 2815, 1589, 1509, 1469, 1336, 1277, 1238, 1115, 1097, 1031, 862 cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.89 (1H, dd, J=9.0, 2.6 Hz, 6-H), 7.73 (1H, d, J=2.6 Hz, 2-H), 7.18 (1H, d, J=9.0 Hz, 5-H), 4.15 (2H, t, J=6.8 Hz, NCH$_2$CH$_2$C*H*$_2$O), 3.88 (3H, s, OCH_3), 3.59–3.54 (4H, m, C*H*$_2$OC*H*$_2$), 2.41 (2H, t, J=6.8 Hz, NC*H*$_2$CH$_2$CH$_2$O), 2.38–2.33 (4H, m, C*H*$_2$NC*H*$_2$), 1.92 (quint, J=6.8 Hz, 2H, NCH$_2$C*H*$_2$CH$_2$O); ^{13}C NMR (DMSO-d_6): δ 153.91, 148.55, 140.42, 117.56, 111.53, 106.35, 67.17, 66.07, 55.91, 54.50, 53.22, 25.50; HRMS (ESI-TOF) for $C_{14}H_{21}N_2O_5$ $[M+H]^+$: calcd: 297.1445, found: 297.1596. Anal. Calcd for $C_{14}H_{20}N_2O_5$: C, 56.75; H, 6.80; N, 9.45. Found: C, 56.65; H, 6.82; N, 9.48.

*4.1.3. 4-Methoxy-3-[(1′-Boc-piperidin-4′-yl)methoxy]-nitrobenzene (**17**).* A mixture of **10c** (3.4 g, 20.0 mmol), 1-*Boc*-4-(tosyloxy-methyl)-piperidine (8.1 g, 22.0 mmol), and anhydrous K_2CO_3 (4.1 g, 30.0 mmol) in anhydrous DMF (40.0 mL) was heated at 150 °C for 8 h. After cooling the mixture was diluted with satd NH_4Cl solution (500 mL) and extracted with CH_2Cl_2 (3×200 mL). The organic phase was evaporated under reduced pressure affording the desired product **17** (6.8 g, 93%) as yellow solid; mp 119 °C; IR (KBr) 2965, 2938, 2874, 1690, 1588, 1507, 1470, 1411, 1347, 1274, 1234, 1174, 1147, 1091, 1016, 859 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.91 (1H, dd, J=8.9, 2.6 Hz, 6-H), 7.72 (1H, d, J=2.6 Hz, 2H), 6.90 (1H, d, J=8.9 Hz, 5-H), 4.26–4.10 (2H, m), 3.96 (3H, s, OCH_3), 3.91 (2H, d, J=5.2 Hz), 2.76 (2H, t, J=12.5 Hz), 2.15–1.99 (1H, m), 1.87 (2H, d, J=12.5 Hz), 1.47 (9H, s, Boc), 1.28 (2H, qd, J=12.5, 5.2 Hz); ^{13}C NMR ($CDCl_3$): δ 154.93, 148.29, 141.35, 117.81, 110.10, 107.76, 79.45, 73.64, 56.39, 35.96, 28.82, 28.45; HRMS (ESI-TOF) for $C_{18}H_{27}N_2O_6$ $[M+H]^+$: calcd: 367.1864, found: 367.1923. Anal. Calcd for $C_{18}H_{26}N_2O_6$: C, 59.00; H, 7.15; N, 7.65. Found: C, 58.95; H, 7.20; N, 7.68.

*4.1.4. 4-Methoxy-3-[(1′-piperidin-4′-yl)methoxy]nitro-benzene (**18**).* A solution of **17** (6.6 g, 18.0 mmol) in TFA (30.0 mL) and CH_2Cl_2 (30 mL) was stirred at room temperature for 2 h. The solution was evaporated under reduced pressure and the solid residue was dissolved in water (100 mL), neutralized with $NaHCO_3$ and extracted with CH_2Cl_2 (3×30 mL). The organic phase was evaporated under reduced pressure and the solid residue was crystallized from *i*-PrOH, giving the compound **18** (4.7 g, 98%) as yellow solid; mp 135 °C; IR (KBr) 3424, 2928, 2851, 1676, 1588, 1511, 1412, 1340, 1277, 1234, 1180, 1136, 1098, 1017, 857, 817 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.90 (1H, dd, J=8.7, 2.5 Hz, 6-H), 7.72 (1H, d, J=2.5 Hz, 2-H), 6.90 (1H, d, J=8.7 Hz, 5-H), 3.95 (3H, s, OCH_3), 3.90 (J=6.5 Hz, d, 2H), 3.20–3.12 (2H, m,), 2.74–2.63 (2H, m), 2.11–1.99 (1H, m), 1.91–1.85 (2H, m), 1.39–1.25 (2H, m); ^{13}C NMR ($CDCl_3$): δ 154.86, 148.10, 141.13, 117.77, 110.03, 107.64, 73.56, 56.20, 45.00, 35.26, 28.60; HRMS (ESI-TOF) for $C_{13}H_{19}N_2O_4$ $[M+H]^+$: calcd: 267.1267, found: 267.1300. Anal. Calcd for $C_{13}H_{18}N_2O_4$: C, 58.63; H, 6.81; N, 10.52. Found: C, 58.58; H, 6.85; N, 10.47.

*4.1.5. 4-Methoxy-3-[(1′-methylpiperidin-4′-yl)methoxy]nitro-benzene (**11c**).* A solution of **18** (4.5 g, 17.0 mmol) in formic acid (15.0 mL) and 37% aqueous formaldehyde (9.0 mL) was microwave irradiated at 90 °C (power set point 100 W; ramp time 2 min; hold time 10 min). After cooling the reaction mixture was diluted with water (150 mL), neutralized with $NaHCO_3$ and extracted with CH_2Cl_2 (3×30 mL). The organic phase was evaporated under reduced pressure, giving the compound **11c** (4.2 g, 89%) as yellow solid; mp 93 °C; IR (KBr) 2936, 2836, 1587, 1512, 1463, 1343, 1273, 1235, 1187, 1139, 1094, 1012, 863, 813 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.91 (1H, dd, J=8.9, 2.7 Hz, 6-H), 7.72 (1H, d, J=2.7 Hz, 2-H), 6.90 (1H, d, J=8.9 Hz, 5-H), 3.97–3.89 (5H, m), 3.03 (2H, d, J=11.8 Hz), 2.39 (3H, s, NCH_3), 2.15 (2H, t, J=11.8 Hz), 1.99–1.88 (3H, m), 1.58 (2H, qd, J=11.8, 2.9 Hz); ^{13}C NMR ($CDCl_3$): δ 154.90, 148.41, 141.37, 117.65, 110.03, 107.64, 73.91, 56.37, 55.31, 46.43, 35.02, 29.09; HRMS (ESI-TOF) for $C_{14}H_{21}N_2O_4$ $[M+H]^+$: calcd: 281.1496, found: 281.1608. Anal. Calcd for $C_{14}H_{20}N_2O_4$: C, 59.99; H, 7.19; N, 9.99. Found: C, 60.01; H, 7.15; N, 9.85.

4.2. General procedure for anilines 12a–c

A mixture of nitrobenzene derivative (**11a–c**) (15.0 mmol), ammonium formate (60.0 mmol) and a catalytic amount of 10% Pd/C in abs. EtOH (100 mL) was stirred under reflux for 30 min. After cooling, the catalyst was filtered off and the clear solution was evaporated under reduced pressure, affording the anilines **12a–c** in quantitative yield (98%).

*4.2.1. 3,4-Di(2′-methoxyethoxy)aniline (**12a**).* Low melting brown solid; mp <40 °C; IR (KBr) 3140, 2816, 1596, 1516, 1229, 1124, 1048, 759 cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.80 (1H, d, J=8.5 Hz, 5-H), 6.54 (1H, d, J=2.5 Hz, 2-H), 6.47 (1H, dd, J=8.5, 2.5 Hz, 6-H), 4.11–4.06 (4H, m, 2×OC*H*$_2$CH$_2$OCH$_3$), 3.76–3.69 (4H, m, 2×OCH$_2$C*H*$_2$OCH$_3$), 3.42 (6H, s, 2×OCH_3); ^{13}C NMR ($CDCl_3$): δ 150.19, 141.81, 141.32, 118.25, 107.44, 103.10, 70.89, 70.13, 68.35, 58.87, 58.79; HRMS (ESI-TOF) for $C_{12}H_{20}NO_4$ $[M+H]^+$: calcd: 242.1387, found: 242.1406. Anal. Calcd for $C_{12}H_{19}NO_4$: C, 59.73; H, 7.94; N, 5.81. Found: C, 59.69; H, 7.99; N, 5.82.

*4.2.2. 3-Methoxy-4-(3′-N-morpholino)propoxyaniline (**12b**).* Brown solid; mp 75 °C; IR (KBr) 3181, 1598, 1514, 1459, 1228, 1132, 1111, 1030, 761 cm^{-1}; ^1H NMR (DMSO-d_6): δ 6.62 (1H, d, J=8.5 Hz, 5-H), 6.24 (1H, d, J=2.5 Hz, 2-H), 6.03 (1H, dd, J=8.5, 2.5 Hz, 6-H), 3.80 (2H, t, J=6.8 Hz, NCH$_2$CH$_2$C*H*$_2$O), 3.66 (3H, s, OCH_3), 3.58–3.53 (4H, m, C*H*$_2$OC*H*$_2$), 2.42–2.31 (6H, m, NC*H*$_2$CH$_2$CH$_2$O and C*H*$_2$NC*H*$_2$), 1.76 (2H, quint, J=6.8 Hz, NCH$_2$C*H*$_2$CH$_2$O); ^{13}C NMR (DMSO-d_6): δ 150.36, 143.69, 138.92, 116.84, 105.16, 99.92, 68.21, 66.16, 55.13, 55.01, 53.33, 26.25; HRMS (ESI-TOF) for $C_{14}H_{23}N_2O_3$ $[M+H]^+$: calcd: 267.1703, found: 267.1656. Anal. Calcd for $C_{14}H_{22}N_2O_3$: C, 63.13; H, 8.33; N, 10.52. Found: C, 63.08; H, 8.35; N, 10.48.

*4.2.3. 4-Methoxy-3-[(1′-methylpiperidin-4′-yl)methoxy]aniline (**12c**).* Brown solid; mp 42 °C; IR (KBr) 3145, 1602, 1516, 1349, 1235, 1132, 1080, 1021, 760 cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.71 (1H, d, J=8.2 Hz, 5-H), 6.30–6.24 (2H, m, 2-H and 6-H), 5.30 (2H, br s, NH_2), 3.92–3.83 (2H, m), 3.76 (3H, s, OCH_3), 3.61–3.51 (2H, m), 2.75 (3H, s, NCH_3), 2.70–2.55 (2H, m), 2.18–2.01 (3H, m), 1.97–1.80 (2H, m); ^{13}C NMR ($CDCl_3$): δ 150.34, 145.22, 140.87, 115.54, 108.91, 103.64, 72.60, 56.15,

55.13, 46.93, 35.40, 29.56; HRMS (ESI-TOF) for $C_{14}H_{23}N_2O_2$ $[M+H]^+$: calcd: 251.1754, found: 251.1888. Anal. Calcd for $C_{14}H_{22}N_2O_2$: C, 67.17; H, 8.86; N, 11.19. Found: C, 67.12; H, 8.88; N, 11.23.

4.3. General procedure for carbamates 6 and 13a–c

A mixture of aniline (**5**, **12a**–**c**) (10.0 mmol), ethyl chloroformate (20.0 mmol), and Et_3N (20.0 mmol) in anhydrous THF (200 mL) was stirred at room temperature for 30 min. The solid was filtered off and the solvent was evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 (200 mL) and the organic layer was washed with water (2×100 mL). The organic phase was evaporated under reduced pressure to give the title compounds in quantitative yield (98%).

*4.3.1. Ethyl (3,4-dimethoxyphenyl)carbamate (**6**).* Brown solid; mp 45 °C; IR (KBr) 3323, 2974, 2938, 2840, 1693, 1605, 1520, 1452, 1417, 1232, 1168, 1135, 1074, 1023, 845 cm^{-1}; ^1H NMR (DMSO-d_6): δ 9.39 (1H, br s, NH), 7.16 (1H, d, J=1.7, 2-H), 6.93 (1H, dd, J=9.2 Hz, 1.7, 6-H), 6.85 (1H, d, J=9.2 Hz, 5-H), 4.09 (2H, q, J=7.1 Hz, $CO_2CH_2CH_3$), 3.70 (3H, s, OCH_3), 3.69 (3H, s, OCH_3), 1.23 (3H, t, J=7.1 Hz, $CO_2CH_2CH_3$); ^{13}C NMR (DMSO-d_6): δ 153.51, 148.62, 144.18, 132.71, 122.32, 112.28, 59.84, 55.72, 55.25, 14.46; HRMS (ESI-TOF) for $C_{11}H_{16}NO_4$ $[M+H]^+$: calcd: 226.1074, found: 226.1106. Anal. Calcd for $C_{11}H_{15}NO_4$: C, 58.66; H, 6.71; N, 6.22. Found: C, 58.71; H, 6.72; N, 6.18.

*4.3.2. Ethyl [3,4-di(2′-methoxyethoxy)phenyl]carbamate (**13a**).* Brown solid; mp <40 °C; IR (KBr) 3316, 2980, 2933, 2889, 1690, 1609, 1515, 1455, 1227, 1124, 1054, 857, 777 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.18 (1H, d, J=2.5 Hz, 2-H), 6.86 (1H, d, J=8.4 Hz, 5-H), 6.76 (1H, dd, J=8.4, 2.5 Hz, 6-H), 6.49 (1H, br s, NH), 4.20 (2H, q, J=7.1 Hz, $CO_2CH_2CH_3$), 4.17–4.09 (4H, m, 2×$OCH_2CH_2OCH_3$), 3.80–3.71 (4H, m, 2×$OCH_2CH_2OCH_3$), 3.44 (6H, s, 2×OCH_3), 1.30 (3H, t, J=7.1 Hz, $CO_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$): δ 164.46, 159.36, 149.00, 145.11, 115.54, 112.51, 107.17, 70.83, 70.71, 69.07, 68.22, 60.79, 58.83, 58.77, 14.32; HRMS (ESI-TOF) for $C_{15}H_{24}NO_6$ $[M+H]^+$: calcd: 314.1598, found: 314.153. Anal. Calcd for $C_{15}H_{23}NO_6$: C, 57.50; H, 7.40; N, 4.47. Found: C, 57.42; H, 7.38; N, 4.51.

*4.3.3. Ethyl [3-methoxy-4-(3′-N-morpholino)propoxyphenyl]-carbamate (**13b**).* Brown solid; mp 81 °C; IR (KBr) 3307, 2957, 2933, 2810, 1697, 1628, 1604, 1521, 1462, 1409, 1264, 1236, 1139, 1117, 1071, 1035, 862, 798 cm^{-1}; ^1H NMR (DMSO-d_6): δ 9.39 (1H, br s, NH), 7.16 (1H, d, J=1.8 Hz, 2-H), 6.90 (1H, dd, J=8.7, 1.8 Hz, 6-H), 6.84 (1H, d, J=8.7 Hz, 5-H), 4.09 (2H, q, J=7.1 Hz, $CO_2CH_2CH_3$), 3.91 (2H, t, J=6.8 Hz, $NCH_2CH_2CH_2O$), 3.70 (3H, s, OCH_3), 3.59–3.53 (4H, m, CH_2OCH_2), 2.43–2.31 (6H, m, $NCH_2CH_2CH_2O$ and CH_2NCH_2), 1.82 (2H, quint, J=6.8 Hz, $NCH_2CH_2CH_2O$), 1.23 (3H, t, J=7.1 Hz, $CO_2CH_2CH_3$); ^{13}C NMR (DMSO-d_6): δ 153.47, 149.02, 143.37, 114.05, 110.12, 105.58, 67.02, 66.10, 59.82, 55.33, 54.82, 53.27, 25.98, 14.45; HRMS (ESI-TOF) for $C_{17}H_{27}N_2O_5^+$ $[M+H]^+$: calcd: 339.1914, found: 339.2005. Anal. Calcd for $C_{17}H_{26}N_2O_5$: C, 60.34; H, 7.74; N, 8.28. Found: C, 60.29; H, 7.77; N, 8.26.

*4.3.4. Ethyl {4-methoxy-3-[(1′-methylpiperidin-4′-yl)methoxy]-phenyl}carbamate (**13c**).* Brown solid; mp <40 °C; IR (KBr) 3309, 2950, 1697, 1604, 1515, 1466, 1413, 1231, 1134, 1070, 1026, 770 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.16 (1H, d, J=2.4 Hz, 2-H), 6.78 (1H, d, J=8.7 Hz, 5-H), 6.72 (1H, dd, J=8.7, 2.4 Hz, 6-H), 4.19 (2H, q, J=7.1 Hz, $CO_2CH_2CH_3$), 3.86–3.77 (5H, m), 2.91 (2H, d, J=11.4 Hz), 2.30 (3H, s, NCH_3), 2.05–1.94 (2H, m), 1.93–1.82 (3H, m), 1.41 (2H, qd, J=11.4, 2.6 HZ), 1.28 (3H, t, J=7.1 Hz, $CO_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$): δ 163.25, 157.23, 148.24, 131.90, 125.37, 112.37, 72.58, 60.89, 56.27, 53.76, 50.29, 45.26, 30.21, 14.40; HRMS (ESI-TOF) for $C_{17}H_{27}N_2O_4^+$ $[M+H]^+$: calcd: 323.1965, found: 323.1938. Anal. Calcd for $C_{17}H_{26}N_2O_4$: C, 63.13; H, 8.41; N, 8.66. Found: C, 63.29; H, 8.45; N, 8.65.

4.4. General procedure for quinazolines 7 and 14a–c

All the quinazolines were synthesized accordingly to previously reported method.[12] Generally, a mixture of ethyl carbamate (**6**, **13a**–**c**) (10.0 mmol) and hexamethylene-tetramine (10.0 mmol) in TFA (30 mL) was microwave irradiated at 110 °C (power set point 80 W; ramp time 1 min; hold time 10 min). After cooling the mixture was diluted with aqueous ethanolic (water/EtOH: 1/1) 10% KOH (300 mL), added with $K_3Fe(CN)_6$ (80.0 mmol) and stirred to reflux for 4 h. After cooling the mixture was diluted with water (300 mL) and extracted with CH_2Cl_2 (3×200 mL). The organic phase was evaporated under reduced pressure to give the quinazoline **7** and **14a**–**c**.

*4.4.1. 6,7-Dimethoxyquinazoline (**7**).* Yield 1.6 g; 86%; yellow solid; mp 138 °C; IR (KBr) 2931, 1670, 1615, 1503, 1432, 1358, 1325, 1232, 1151, 1093, 999, 851 cm^{-1}; ^1H NMR (DMSO-d_6): δ 9.29 (1H, s, 4-H), 9.07 (1H, s, 2-H), 7.48 (1H, s, 5-H or 8-H), 7.35 (1H, s, 5-H or 8-H), 3.98 (3H, s, OCH_3), 3.94 (3H, s, OCH_3); ^{13}C NMR (DMSO-d_6): δ 156.71, 155.88, 153.41, 150.10, 147.15, 120.58, 105.93, 104.49, 56.06, 55.79; HRMS (ESI-TOF) for $C_{10}H_{11}N_2O_2$ $[M+H]^+$: 191.0815, found: 191.1002. Anal. Calcd for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.10; H, 5.32; N, 14.75.

*4.4.2. 6,7-Di(2′-methoxyethoxy)quinazoline (**14a**).* Yield 2.5 g; 91%; yellow solid; mp 114 °C; IR (KBr) 2926, 1676, 1564, 1506, 1459, 1372, 1325, 1233, 1129, 1033, 859 cm^{-1}; ^1H NMR ($CDCl_3$): δ 9.10 (2H, s, 4-H and 2-H), 7.28 (1H, s, 5-H or 8-H), 7.11 (1H, s, 5-H or 8-H), 4.33–4.24 (4H, m, 2×$OCH_2CH_2OCH_3$), 3.89–3.82 (4H, m, 2×$OCH_2CH_2OCH_3$), 3.47 (3H, s, OCH_3), 3.46 (3H, s, OCH_3); ^{13}C NMR ($CDCl_3$): δ 156.75, 155.89, 154.05, 150.17, 147.98, 121.04, 107.42, 105.50, 70.64, 70.39, 68.75, 68.61, 59.39, 59.36; HRMS (ESI-TOF) for $C_{14}H_{19}N_2O_4$ $[M+H]^+$: calcd: 279.1339, found: 279.1398. Anal. Calcd for $C_{14}H_{18}N_2O_4$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.39; H, 6.55; N, 10.10.

*4.4.3. 7-Methoxy-6-(3′-N-morpholino)propoxyquinazoline (**14b**).* Yield 2.5 g; 84%; yellow solid; mp 116 °C; IR (KBr) 2953, 1671, 1616, 1500, 1469, 1357, 1324, 1230, 1149, 1116, 1012, 860 cm^{-1}; ^1H NMR (DMSO-d_6): δ 9.29 (1H, s, 4-H), 9.06 (1H, s, 2-H), 7.49 (1H, s, 5-H or 8-H), 7.35 (1H, s, 5-H or 8-H), 4.18 (2H, t, J=6.8 Hz, $NCH_2CH_2CH_2O$), 3.99 (3H, s, OCH_3), 3.60–3.55 (4H, m, CH_2OCH_2), 2.46 (2H, t, J=6.8 Hz, $NCH_2CH_2CH_2O$), 2.41–2.35 (4H, m, CH_2NCH_2), 1.98 (2H, quint, J=6.8 Hz, $NCH_2CH_2CH_2O$); ^{13}C NMR (DMSO-d_6): δ 156.77, 156.00, 153.40, 149.41, 147.06, 120.63, 106.00, 105.21, 66.84, 66.10, 56.11, 54.69, 53.27, 25.52; HRMS (ESI-TOF) for $C_{16}H_{22}N_3O_3$ $[M+H]^+$: 304.0656, found: 304.1012. Anal. Calcd for $C_{16}H_{21}N_3O_3$: C, 63.35; H, 6.98; N, 13.85. Found: C, 63.30; H, 6.98; N, 13.92.

*4.4.4. 6-Methoxy-7-[(1′-methylpiperidin-4′-yl)methoxy]quinaz-oline (**14c**).* Yield 2.6 g; 90%; yellow solid; mp 120 °C; IR (KBr) 2933, 1616, 1578, 1500, 1456, 1357, 1326, 1232, 1153, 1099, 1001, 868 cm^{-1}; ^1H NMR ($CDCl_3$): δ 9.14 (1H, s, 4-H), 9.13 (1H, s, 2-H), 7.27 (1H, s, 5-H or 8-H), 7.09 (1H, s, 5-H or 8-H), 4.06 (2H, d, J=6.2 Hz), 4.01 (3H, s, OCH_3), 3.04 (2 h, d, J=11.2 Hz), 2.39 (3H, s, NCH_3), 2.16 (2H, t, J=11.2 Hz), 2.04–1.91 (3H, m), 1.62 (2H, qd, J=11.2, 3.0 Hz); ^{13}C NMR ($CDCl_3$): δ 156.51, 155.81, 153.86, 150.99, 147.93, 120.89, 107.03, 103.80, 73.69, 56.15, 55.24, 46.37, 34.68, 28.99; HRMS (ESI-TOF) for $C_{16}H_{22}N_3O_2$ $[M+H]^+$: 288.1707, found: 288.1695. Anal. Calcd for $C_{16}H_{21}N_3O_2$: C, 66.88; H, 7.37; N, 14.62. Found: C, 66.95; H, 7.41; N, 14.55.

4.5. General procedure for quinazolin-4(3*H*)-ones 8 and 15a–c

To a solution of quinazoline (**7**, **14a**–**c**) (5.0 mmol) in AcOH (2.0 mL) a solution of CAN (20.0 mmol) in water (24.0 mL) was

added dropwise. Starting from quinazoline **7**, a white precipitate was formed, which was collected affording the compound **8**. Starting from quinazolines **14a–c**, the reaction mixture was neutralized with 4 M NaOH solution and evaporated under reduced pressure. The solid residue was adsorbed over anhydrous Na_2SO_4 and extracted in soxhlet (solvent: acetone) for 24 h. The organic phase was evaporated under reduced pressure and the solid residue was purified by column chromatography (eluent: CH_2Cl_2/MeOH, 80/20), giving the title compounds.

4.5.1. 6,7-Dimethoxyquinazolin-4(3H)-one[3] (***8***). Yield 1.2 g; 86%; white solid; ^{1}H NMR (DMSO-d_6): δ 7.98 (1H, s, 2-H), 7.43 (1H, s, 5-H or 8-H), 7.11 (1H, s, 5-H or 8-H), 3.90 (3H, s, OCH_3), 3.87 (3H, s, OCH_3); HRMS (ESI-TOF) for $C_{10}H_{11}N_2O_3$ $[M+H]^+$: 207.0770, found: 207.0802. Anal. Calcd for $C_{10}H_{10}N_2O_3$: C, 58.25; H, 4.89; N, 13.59. Found: C, 58.23; H, 4.82; N, 13.65.

4.5.2. 6,7-Di(2′-methoxyethoxy)quinazolin-4(3H)-one[16] (***15a***). Yield 1.3 g; 88%; white solid; ^{1}H NMR (DMSO-d_6): δ 7.97 (1H, s, 2-H), 7.45 (1H, s, 5-H or 8-H), 7.13 (1H, s, 5-H or 8-H), 4.26–4.16 (4H, m, 2×OC*H*$_2$CH$_2$OCH$_3$), 3.73–3.67 (4H, m, 2×OCH$_2$C*H*$_2$OCH$_3$), 3.32 (6H, s, 2×OCH_3); HRMS (ESI-TOF) for $C_{14}H_{19}N_2O_5$ $[M+H]^+$: 295.1294, found: 295.1276. Anal. Calcd for $C_{14}H_{18}N_2O_5$: C, 57.13; H, 6.16; N, 9.52. Found: C, 57.17; H, 6.19; N, 9.65.

4.5.3. 7-Methoxy-6-(3′-N-morpholino)propoxyquinazolin-4(3H)-one[20] (***15b***). Yield 1.4 g; 87%; white solid; ^{1}H NMR (DMSO-d_6): δ 7.97 (1H, s, 2-H), 7.42 (1H, s, 5-H or 8-H), 7.12 (1H, s, 5-H or 8-H), 4.09 (2H, t, J=6.8 Hz, NCH$_2$CH$_2$C*H*$_2$O), 3.89 (3H, s, OCH_3), 3.60–3.55 (4H, m, C*H*$_2$OC*H*$_2$), 2.60–2.20 (6H, m, NC*H*$_2$CH$_2$CH$_2$O and C*H*$_2$NC*H*$_2$), 1.91 (2H, quint, J=6.8 Hz, NCH$_2$C*H*$_2$CH$_2$O); HRMS (ESI-TOF) for $C_{16}H_{22}N_3O_4$ $[M+H]^+$: 320.1610, found: 320.1634. Anal. Calcd for $C_{16}H_{21}N_3O_4$: C, 60.17; H, 6.63; N, 13.16. Found: C, 60.20; H, 6.68; N, 13.15.

4.5.4. 6-Methoxy-7-[(1′-methylpiperidin-4′-yl)methoxy]quinazolin-4(3H)-one[20] (***15c***). Yield 1.4 g; 90%; white solid; ^{1}H NMR (DMSO-d_6): δ 7.99 (1H, s, 2-H), 7.45 (1H, s, 5-H or 8-H), 7.13 (1H, s, 5-H or 8-H), 4.00 (2H, d, J=6.2 Hz), 3.90 (3H, s, OCH_3), 2.80 (2H, d, J=11.2 Hz), 2.20 (3H, s, NCH_3), 1.90 (2H, t, J=11.2 Hz), 1.85–1.70 (3H, m), 1.30–1.45 (2H, m); HRMS (ESI-TOF) for $C_{16}H_{22}N_3O_3$ $[M+H]^+$: 304.1661, found: 304.1639. Anal. Calcd for $C_{16}H_{21}N_3O_3$: C, 63.35; H, 6.98; N, 13.85. Found: C, 63, 42; H, 7.01; N, 13.85.

4.6. General procedure for 4-chloroquinazolin-4(3*H*)-ones 9 and 16a–b

A suspension of quinazolinone (**8**, **15a–b**) (2.0 mmol) in $POCl_3$ (4.0 mL) and Et_3N (1.0 mL) was heated to reflux for 3 h. After cooling the mixture was concentrated under reduced pressure and the solid residue was dissolved in EtOAc (50 mL) and washed with satd $NaHCO_3$ solution (2×20 mL). The organic phase was evaporated under reduced pressure affording the title compounds.

4.6.1. 4-Chloro-6,7-dimethoxyquinazoline[3] (***9***). Yield 0.38 g; 85%; yellow solid; ^{1}H NMR ($CDCl_3$): δ 8.86 (s, 1H, 2-H), 7.38 (s, 1H, 5-H or 8-H), 7.32 (s, 1H, 5-H or 8-H), 4.05 (s, 6H, 2×OCH_3); HRMS (ESI-TOF) for $C_{10}H_{10}ClN_2O_2$ $[M+H]^+$: 225.0431, found: 225.0401. Anal. Calcd for $C_{10}H_9ClN_2O_2$: C, 53.47; H, 4.04; Cl, 15.78; N, 12.47. Found: C, 53.50; H, 4.11; Cl, 15.83; N, 12.44.

4.6.2. 4-Chloro-6,7-di(2′-methoxyethoxy)quinazoline[16] (***16a***). Yield 0.53 g: 87%; yellow solid; ^{1}H NMR ($CDCl_3$): δ 8.85 (1H, s, 2H), 7.42 (1H, s, 5-H or 8-H), 7.33 (1H, s, 5-H or 8-H), 4.36–4.30 (4H, m, 2×OC*H*$_2$CH$_2$OCH$_3$), 3.91–3.87 (4H, m, 2×OCH$_2$C*H*$_2$OCH$_3$), 3.50 (3H, s, OCH_3), 3.49 (3H, s, OCH_3); HRMS (ESI-TOF) for $C_{14}H_{18}ClN_2O_4$ $[M+H]^+$: 313.0955, found: 313.0983. Anal. Calcd for $C_{14}H_{17}ClN_2O_4$: C, 53.77; H, 5.48; Cl, 11.34; N, 8.96. Found: C, 53.82; H, 5.41; Cl, 11.33; N, 8.98.

4.6.3. 4-Chloro-7-methoxy-6-(3′-N-morpholino)propoxyquinazoline[2] (***16b***). Yield 0.62 g; 91%; yellow solid; ^{1}H NMR ($CDCl_3$): δ 8.86 (1H, s, 2H), 7.39 (1H, s, 5-H or 8-H), 7.33 (1H, s, 5-H or 8-H), 4.28 (2H, t, J=6.8 Hz, NCH$_2$CH$_2$C*H*$_2$O), 4.05 (3H, s, OCH_3), 3.80–3.68 (4H, m, C*H*$_2$OC*H*$_2$), 2.60 (2H, t, J=6.8 Hz, NC*H*$_2$CH$_2$CH$_2$O), 2.55–2.46 (4H, m, C*H*$_2$NC*H*$_2$), 2.14 (2H, quint, J=6.8 Hz, NCH$_2$C*H*$_2$CH$_2$O); HRMS (ESI-TOF) for $C_{16}H_{21}ClN_3O_3$ $[M+H]^+$: 338.1271, found: 338.1299. Anal. Calcd for $C_{16}H_{20}ClN_3O_3$: C, 56.89; H, 5.97; Cl, 10.50; N, 12.44. Found: C, 56.93; H, 5.96; Cl, 10.57; N, 12.48.

4.6.4. 4-Chloro-6-methoxy-7-[(1′-methylpiperidin-4′-yl)methoxy]quinazoline (***16c***). A solution of **15c** (0.6 g, 2.0 mmol) and DMF (50 μL) in $SOCl_2$ (5 mL) was heated to reflux for 1 h. After cooling the mixture was concentrated under reduced pressure and the solid was triturated with diethyl ether (10 mL), filtered and dried under vacuum. The solid residue was dissolved in EtOAc (50 mL) and washed with satd $NaHCO_3$ aqueous solution (2×20 mL). The organic phase was evaporated under reduced pressure giving the compound **16c**[2] (0.63 g, 98%) as yellow solid; ^{1}H NMR (DMSO-d_6): δ 8.90 (1H, s, 2H), 7.46 (1H, s, 5-H or 8-H), 7.41 (1H, s, 5-H or 8-H), 4.12 (2H, d, J=6.2 Hz), 4.02 (3H, s, OCH_3), 2.85 (2H, d, J=11.2 Hz), 2.25 (3H, s, NCH_3), 2.00 (2H, t, J=11.2 Hz), 1.90–1.75 (3H, m), 1.30–1.50 (2H, m); HRMS (ESI-TOF) for $C_{16}H_{21}ClN_3O_2$ $[M+H]^+$: 322.1322, found: 322.1309. Anal. Calcd for $C_{16}H_{20}ClN_3O_2$: C, 59.72; H, 6.26; Cl, 11.02; N, 13.06. Found: C, 59.70; H, 6.31; Cl, 11.11; N, 13.00.

4.7. General procedure for 4-anilinoquinazolines 1–4

A mixture of 4-chloroquinazoline (**9**, **16a–c**) (0.5 mmol) and the appropriate aniline (0.5 mmol) in *i*-PrOH was microwave irradiated at 80 °C (power set point 60 W; ramp time 1 min; hold time 15 min). After cooling other 0.5 mmol of aniline were added and the mixture was microwave irradiated at 80 °C for another cycle. After cooling, the obtained precipitate was collected by filtration, dissolved in satd $NaHCO_3$ solution (50 mL) and extracted with CH_2Cl_2 (3×50 mL). The organic phase was evaporated under reduced pressure, giving the title compound.

4.7.1. PD153035[3] (***1***). Yield 0.16 g; 88%; light yellow solid; mp 188 °C; ^{1}H NMR (DMSO-d_6): δ 9.58 (1H, s, 2-H), 8.53 (1H, s, 5-H or 8-H), 8.16 (1H, t, J=1.9 Hz, HAr), 7.92–7.85 (1H, m, HAr), 7.83 (1H, s, NH), 7.36 (1H, t, J=8.0 Hz, HAr), 7.31–7.25 (1H, m, HAr), 7.21 (1H, s, 5-H or 8-H), 3.98 (3H, s, OCH_3), 3.95 (3H, s, OCH_3); HRMS (ESI-TOF) for $C_{16}H_{15}BrN_3O_2$ $[M+H]^+$: 360.0348, found: 360.0372. Anal. Calcd for $C_{16}H_{14}BrN_3O_2$: C, 53.35; H, 3.92; Br, 22.18; N, 11.67. Found: C, 53.26; H, 4.01; Br, 22.13; N, 11.64.

4.7.2. Erlotinib[16] (***2***). Yield 0.07 g; 91%; light yellow solid; mp 158 °C; ^{1}H NMR ($CDCl_3$): δ 8.60 (1H, s, 2-H), 7.96 (1H, br s, NH), 7.85 (1H, s, 5-H or 8-H), 7.76–7.70 (1H, m, HAr), 7.42–7.36 (3H, m, HAr), 7.12 (1H, s, 5-H or 8-H), 4.21–4.13 (4H, m, 2×OC*H*$_2$CH$_2$OCH$_3$), 3.78–3.73 (4H, m, 2×OCH$_2$C*H*$_2$OCH$_3$), 3.40 (6H, s, 2×OCH_3), 3.08 (1H, s, CH); HRMS (ESI-TOF) for $C_{22}H_{24}N_3O_4$ $[M+H]^+$: 394.1767, found: 394.1790. Anal. Calcd for $C_{22}H_{23}N_3O_4$: C, 67.16; H, 5.89; N, 10.68. Found: C, 67.19; H, 5.92; N, 10.74.

4.7.3. Gefitinib[20] (***3***). Yield 0.08 g; 92%; light yellow solid; mp 193 °C; ^{1}H NMR (DMSO-d_6): δ 8.60 (1H, s, 2-H), 8.22 (1H, dd, J=6.6, 3.0 Hz, HAr), 7.95–7.80 (2H, m, HAr), 7.55 (1H, t, J=8.8 Hz, HAr), 7.31 (1H, s, 5-H or 8-H), 4.29 (2H, t, J=6.2 Hz, NCH$_2$CH$_2$C*H*$_2$O), 4.04 (3H, s, OCH_3), 3.72–3.64 (4H, m, C*H*$_2$OC*H*$_2$), 2.63–2.40 (6H, m, NC*H*$_2$CH$_2$CH$_2$O and C*H*$_2$NC*H*$_2$), 2.10 (2H, quint, J=6.8 Hz,

$NCH_2CH_2CH_2O$); HRMS (ESI-TOF) for $C_{22}H_{25}ClFN_4O_3$ $[M+H]^+$: 447.1599, found: 447.1623. Anal. Calcd for $C_{22}H_{24}ClFN_4O_3$: C, 59.13; H, 5.41; Cl, 7.93; N, 12.54. Found: C, 59.19; H, 5.47; Cl, 7.83; N, 12.51.

4.7.4. Vandetanib[2] (***4***). Yield 0.08 g; 89%; light yellow solid; mp 242 °C; ^{1}H NMR (DMSO-d_6): δ 8.38 (1H, s, 2-H), 7.80 (1H, s, 5-H or 8-H), 7.68 (1H, dd, J=6.5, 2.3 Hz, HAr), 7.55 (1H, t, J=2.3 Hz, HAr), 7.48 (1H, d, J=6.5 Hz, HAr), 7.20 (1H, s, 5-H or 8-H), 4.02 (2H, d, J=6.2 Hz), 3.95 (3H, s, OCH_3), 2.80 (2H, d, J=11.2 Hz), 2.19 (3H, s, NCH_3), 1.90 (2H, t, J=11.2 Hz), 1.90–1.70 (3H, m), 1.30–1.45 (2H, m); HRMS (ESI-TOF) for $C_{22}H_{25}BrFN_4O_2$ $[M+H]^+$: 475.1145, found: 475.1167. Anal. Calcd for $C_{22}H_{24}BrFN_4O_2$: C, 55.59; H, 5.09; Br, 16.81; N, 11.79. Found: C, 55.63; H, 5.06; Br, 16.85; N, 11.79.

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