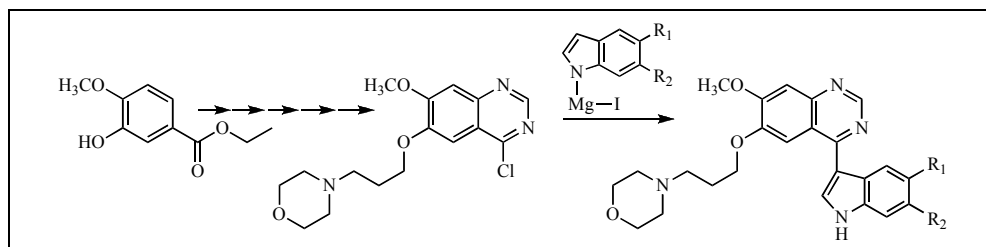


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The epidermal growth factor (EGF) family of membrane receptors has been identified as a key element in the complex signaling network that is utilized by various classes of cell-surface receptors. A new synthetic pathway of 4-(indol-3-yl)quinazolines **15** and **16** is described using cross coupling reactions with quinazoline- and indole moieties. The synthesized compound **15** is a new dual and high potent EGFR- and HER-2-tyrosine kinase inhibitor with excellent cytotoxic properties at different cell lines. Furthermore this substance class shows remarkably strong fluorescence.

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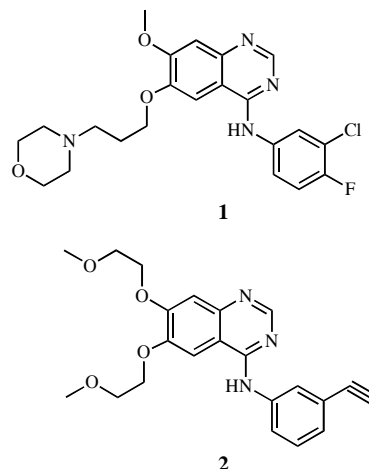
INTRODUCTION

Growth of malignant tumors is mostly caused by a deregulation of the balance between proliferation, survival and death pathways like apoptosis and necrosis.

The Epidermal Growth Factor Receptor (EGFR) is a transmembrane glycoprotein with an extracellular ligand-binding domain and an intracellular domain with tyrosine kinase activity for signal transduction [1]. The receptor is expressed on healthy cells (40-100 EGFR/cell) as well as on malignant tissues (more than 1 000 000 EGFR/cell) [2]. Overexpression of EGFR has been demonstrated in a wide variety of malignant cells, and this increase in receptor levels has been associated with a poor clinical prognosis [3,4].

Thus, therapeutic strategies to inhibit EGFR and EGFR-related pathways have been pursued, including the development of ATP-competitive small molecule inhibitors of the intracellular tyrosine kinase domain of the receptor or inhibitors of downstream effectors of EGFR signalling pathways, like Gefitinib **1** (Iressa®, IC₅₀ 33 nM) and Erlotinib **2** (Tarceva®, IC₅₀ 2 nM) shown in Figure 1 [4,5]. The 4-anilinoquinazoline derivatives are both selective and effective inhibitors of the EGFR kinase. Like Gefitinib and Erlotinib most of the EGFR tyrosine kinase inhibitors have the same 4-anilinoquinazoline skeleton, only the substituents and the side-chains are variable.

On the other hand, the replacement of the aniline structure by an indole nucleus could rigidify the resulting structure through only one single bonding between the indole and the quinazoline nucleus and supposed hydrogen bonding between the indole-NH and the peptide backbone



The 4-anilinoquinazolines Gefitinib **1** and Erlotinib **2**.

Figure 1

could favour specific conformations, which could improve the inhibitory activities of the resulting derivatives.

Therefore, the 4-(indole-3-yl)quinazolines were developed as an active and unique new class of EGFR tyrosine kinase inhibitors [6]. But the previously described synthesis didn't work very well, due to lower overall yield of the total synthesis. We now present a new synthetic route to the desired 4-(indole-3-yl)quinazolines.

RESULTS AND DISCUSSION

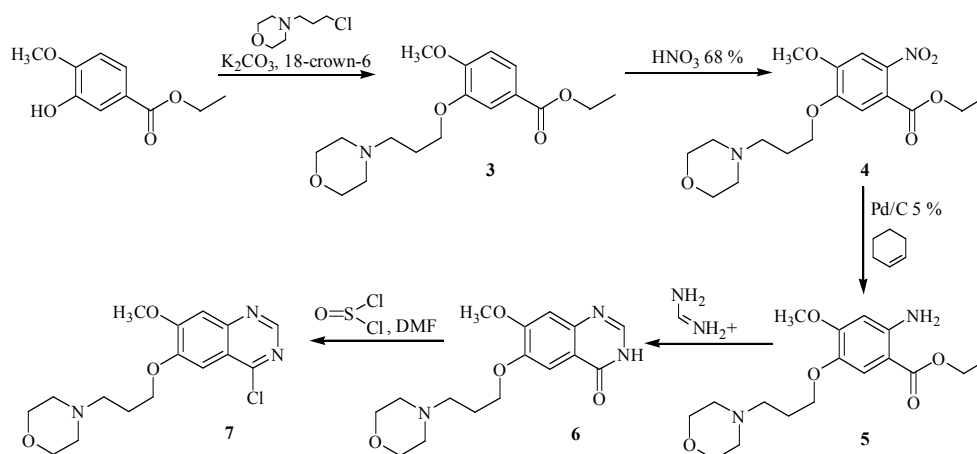
The 4-(indole-3-yl)quinazolines **15** and **16** were synthesized by cross coupling reactions of appropriately

substituted quinazolines and indoles.

An improved process for the preparation of Gefitinib (Iressa®) by Natco Pharma Limited starts with 3-hydroxy-4-methoxybenzene carbaldehyde and needs 8 steps to give the desired quinazoline unit **7** [7]. Another 7-step synthetic route described by Wang *et al.* starts with the same educt [8]. The quinazoline **7** was received by our new synthetic pathway affording 5 steps starting with ethyl (3-hydroxy-4-methoxy)benzoate (Scheme 1) [9]. After introduction

compound **4** in quantitative yield. Interestingly in this case the nitro group of the benzene ring is introduced ortho to the ester group. The nitro compound **4** was reduced by palladium/charcoal in the presence of cyclohexene to give the anthranilic acid ester **5**. The following cyclization with formamidine acetate led to the desired quinazoline-4-one derivative **6** [10-12]. After that chlorination of compound **6** takes place in position 4 with thionyl chloride in the presence of dimethyl formamide [13]. The only reaction product

Scheme 1

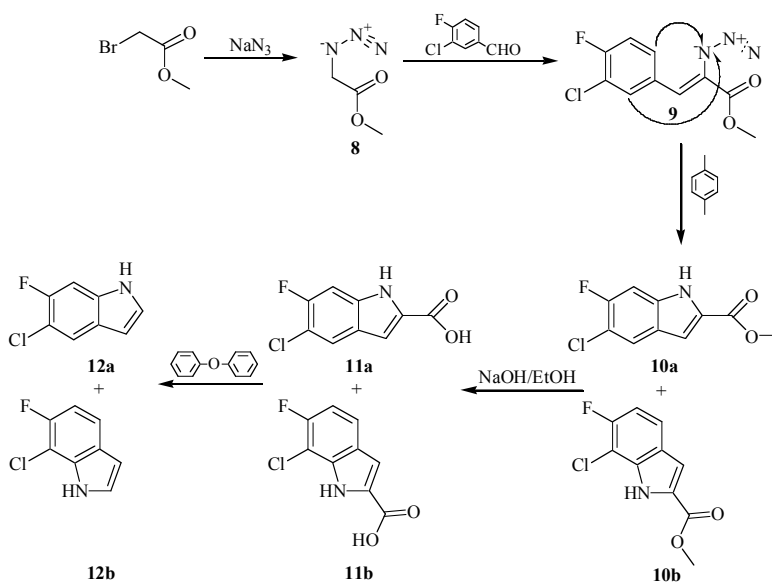


of the morpholinopropoxy side chain in the presence of potassium carbonate and 18-crown-6 the resulting compound **3** was nitrated by 68 % nitric acid to give

observed was the corresponding 4-chloro compound **7**.

The synthesis of the indole moiety is outlined in Scheme 2 [14,15]. The experimental conditions of the

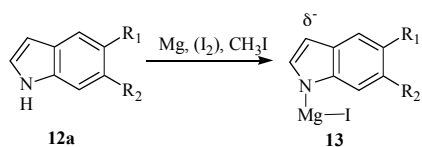
Scheme 2



Synthesis of 5-chloro-6-fluoroindole **13a**

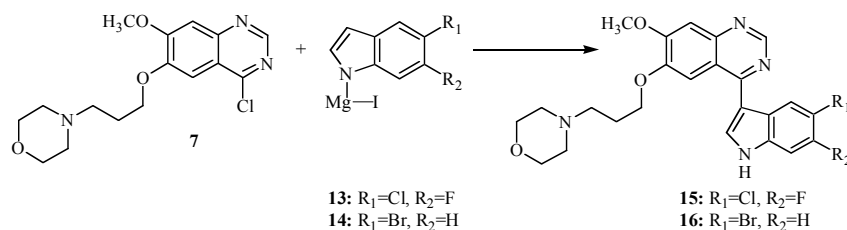
indole synthesis have been changed in details compared to the description of Boes and are outlined in the experimental part [14]. The target 5-chloro-6-fluoro-indole **12a** was synthesized using the Hemetsberger-Knittel reaction [16]. Starting with methylbromoacetate and sodium azide the resulting azido ester **8** was subsequently condensed with 3-chloro-4-fluorobenzaldehyde to give the corresponding azidocinnamate **9**. This intermediate was cyclized by heating with *p*-xylene to afford a mixture of indole-2-carboxylates **10a** and **10b**, which were hydrolyzed in the presence of sodium

better inhibition activity than the Tyrphostin-standard. On the other side remarkable results were observed at a 60 cancer cell lines test performed by the National Cancer Institute (Table 4). Here outstanding activities were obtained against different non-small lung cancer-, CNS cancer-, ovarian cancer-, renal cancer-, colon cancer- and prostate cancer cell lines. It seems to be that the outstanding activity against cancer cell lines are not very well correlated to the results of EGFR/HER-2 tyrosine kinase inhibition tests. Furthermore, the synthesized 4-(indol-3-yl)-quinazolines **15** and **16** show remarkable strong



Activation of position 3 of the indole with help of Grignard compounds

Figure 2



Hetarylation reaction between chlorinated quinazoline and activated indole

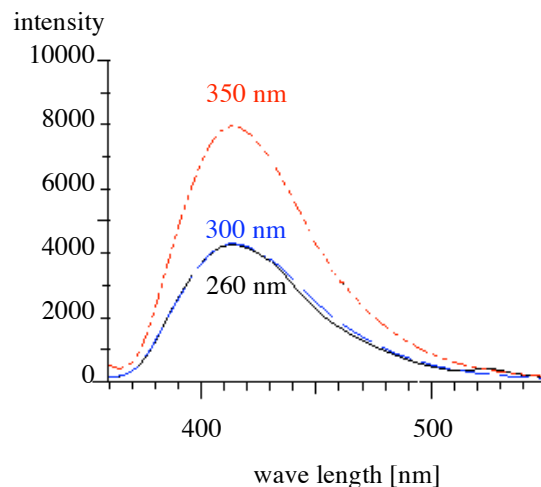
Figure 3

hydroxide to give the indole-2-carboxylic acids **11a** and **11b**. Then the free acid functions were converted to the final indoles **12a** and **12b** by decarboxylation in diphenylether at 260°C. At this stage the separation of **12a** and **12b** was performed by column chromatography. Subsequently the obtained indole **12a** was used in the synthesis leading to the desired 4-(indole-3-yl)-quinazolines **15** and **16**.

The 4-(indole-3-yl)quinazolines **15** and **16** were now synthesized by cross coupling reaction of appropriately substituted indoles, which were converted to the metallated intermediates by use of Grignard compounds and the 4-chlorinated quinazoline **7** (Figure 2 and 3) [17].

The structures of compounds **3-16** were confirmed by ¹H-NMR, IR, mass spectra and elemental analysis. Compound **16** was subjected to EGFR- and **15** was subjected to EGFR- and HER-2-tyrosine kinase inhibition activity tests as well as *in vitro* anticancer testing. The pharmacological results outlined in Table 3 show that compound **16** and **17** exhibit a weaker activity against EGFR and HER-2 than Gefitinib and Erlotinib, but have a

fluorescences in the ultraviolet light, comparable with that of quinine-sulphate (Figure 4, 5 and Table 1, 2) [18].

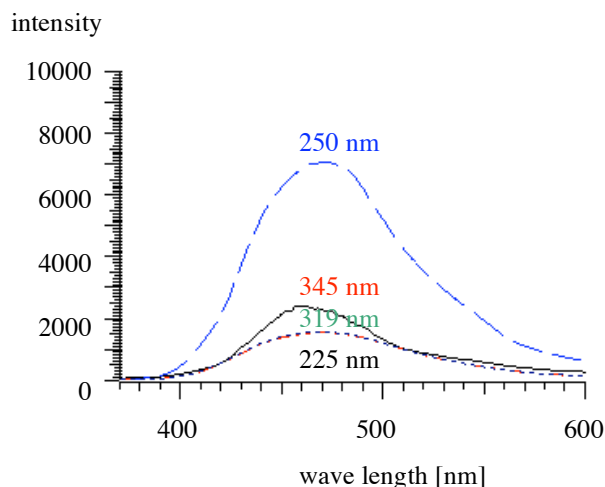


fluorescence spectrum of compound **15** at a concentration of 5 μ M

Figure 4

Table 1

excitation [nm]	emission [nm]	intensity
260	413,8	4258
300	413,8	4268
350	413,6	7948

data of fluorescence spectrum of compound **15**

fluorescence spectrum of comparison quinine sulphate at a concentration of 5 µM

Figure 5

Table 2

excitation [nm]	emission [nm]	intensity
225	461,4	2416
250	470,6	7089
319	468,6	1542
345	468,6	1556

data of fluorescence spectrum of comparison quinine sulphate

Table 3

compound	EGFR-TK-Inhibition (IC ₅₀ or inhibition at a concentration of 100 nM)	HER-2-TK-Inhibition at a concentration of 100 nM
15	333 nM (62 %)	19 %
16	131 nM (26 %)	not tested
Tyrphostin 47	1.1 µM	5.7 µM
Gefitinib	33 nM	> 3.7 µM
Erlotinib	2 nM	134,5 nM

EGFR- and HER-TK inhibition of compound **15**, **16** the reference Tyrphostin, Gefitinib and Erlotinib [4-5, 18]

EXPERIMENTAL

Ethyl 4-methoxy-3-(3-morpholin-4-ylpropoxy)-benzoate (3). A mixture of ethyl-3-hydroxy-4-methoxybenzoate (1.00 g, 5.10 mmol), 4-(3-chloropropyl)morpholin (1 mL), potassium carbonate anhydrous (2.00 g), 18-crown-6 (0.20 g) in

Table 4

cell line	GI ₅₀ (mol) of compound 15
<i>non-small lung cancer</i>	
EKVX	8.97x10 ⁻⁸
HOP-92	5.04x10 ⁻⁷
NCI-H322M	3.80x10 ⁻⁸
<i>CNS cancer</i>	
SNB-75	4.93x10 ⁻⁸
<i>ovarian cancer</i>	
IGR-OV-1	1.08x10 ⁻⁷
SK-OV-3	5.92x10 ⁻⁷
<i>renal cancer</i>	
A498	2.90x10 ⁻⁶
ACHN	2.15x10 ⁻⁷
TK-10	9.76x10 ⁻⁸
<i>colon cancer</i>	
HT29	3.76x10 ⁻⁶
<i>prostate cancer</i>	
PC-3	4.90x10 ⁻⁷

Results of growth inhibition (GI) testing of compound **15** at different cell lines

acetonitrile was heated under reflux for 4 hours. After filtration the solvent was evaporated and the crude product was washed with *n*-hexane. There was obtained 1.60 g (97.7 %) of a white solid. mp: 56-59 °C; ¹H-NMR (DMSO-*d*₆): δ 7.60 (dd, 1H, ³J=8.48 Hz, ⁴J=1.88 Hz, H6), 7.45 (d, 1H, ⁴J=1.81 Hz, H2), 7.07 (d, 1H, ³J=8.50 Hz, H5), 4.28 (q, 2H, J=7.12 Hz, CH₂), 4.03 (t, 2H, J=6.57 Hz, H1'), 3.83 (s, 3H, OCH₃), 3.58 (m, 4H, J=7.23 Hz, H2', H6'), 2.42 (t, 2H, J=7.01 Hz, H3'), 2.38 (m, 4H, J=7.14 Hz, H3', H5'), 1.88 (m, 2H, J=6.99 Hz, H2'), 1.30 (t, 3H, J=7.10 Hz, CH₃); MS: *m/z* 322.9 (M⁺). Anal. Calcd. for C₁₇H₂₅NO₅: C: 63.14; H: 7.79; N: 4.33. Found: C: 63.20; H: 7.77; N: 4.21.

Ethyl 4-methoxy-5-(3-morpholin-4-ylpropoxy)-2-nitrobenzoate (4). **3** (1.00 g, 3.09 mmol) was added to cooled nitric acid (65 %, 25 mL) in portions and stirred under cooling for 2.5 hours. The reaction mixture was put into ice water. After that sodium hydroxide (10 %) was added with a pH > 8. The mixture was extracted with dichloromethane. After evaporation of the solvent the crude product was washed with ethyl acetate/*n*-hexane. There was obtained 1.10 g (96.8 %) of a yellow oil. ¹H-NMR (DMSO-*d*₆): δ 7.63 (s, 1H, H6), 7.31 (s, 1H, H3), 4.28 (q, 2H, J=7.12 Hz, CH₂), 4.17 (t, 2H, J=6.60 Hz, H1'), 3.91 (s, 3H, OCH₃), 3.56 (m, 4H, J=7.23 Hz, H2', H6'), 2.40 (t, 2H, J=6.99 Hz, H3'), 2.36 (m, 4H, J=7.20 Hz, H3', H5'), 1.90 (m, 2H, J=7.00 Hz, H2'), 1.26 (t, 3H, J=7.08 Hz, CH₃); MS: *m/z* 368.0 (M⁺). Anal. Calcd. for C₁₇H₂₄N₂O₇: C: 55.43; H: 6.57; N: 7.60. Found: C: 55.49; H: 6.66; N: 7.66.

Ethyl 2-amino-4-methoxy-5-(3-morpholin-4-ylpropoxy)-benzoate (5). **4** (5.50 g, 14.93 mmol), palladium/carbon (5 %, 3.2 g) and cyclohexene (57 mL) in ethanol (570 mL) were heated under reflux for 2 h. After filtration and evaporation of the solvent the crude product was washed with *n*-hexane. There was obtained 4.65 g (92.0 %) of a white solid. mp: 72-74 °C; ¹H-NMR (DMSO-*d*₆): δ 7.15 (s, 1H, H6), 6.44 (s, 2H, NH₂), 6.34 (s, 1H, H3), 4.19 (q, 2H, J=7.09 Hz, CH₂), 3.82 (t, 2H, J=6.64 Hz,

H1''), 3.74 (s, 3H, OCH₃), 3.57 (m, 4H, J=7.21 Hz, H2', H6'), 2.38 (t, 2H, J=7.02 Hz, H3''), 2.35 (m, 4H, J=7.19 Hz, H3', H5'), 1.80 (m, 2H, J=7.01 Hz, H2''), 1.28 (t, 3H, J=7.08 Hz, CH₃); MS: *m/z* 338.1 (M⁺). Anal. Calcd. for C₁₇H₂₆N₂O₅: C: 60.34; H: 7.74; N: 8.28. Found: C: 60.30; H: 7.75; N: 8.33.

7-Methoxy-6-(3-morpholin-4-ylpropoxy)-3H-quinazoline-4-one (6). **5** (1.90 g, 5.61 mmol) and formamidinium acetate (3.19 g, 30.64 mmol) in 2-methoxyethanol (37 mL) were heated under reflux for 8 h. After evaporation of the solvent, liquid ammonia was added and the resulted crystals were isolated. There was obtained 1.24 g (69.2 %) of an ivory-colored solid. mp: 233-236 °C; ¹H-NMR (DMSO-*d*₆): δ 12.08 (s, 1H, NH), 8.00 (s, 1H, H2), 7.45 (s, 1H, H5), 7.15 (s, 1H, H8), 4.14 (t, 2H, J=6.66 Hz, H1'), 3.92 (s, 3H, OCH₃), 3.58 (m, 4H, J=7.22 Hz, H2', H6'), 2.45 (t, 2H, J=7.00 Hz, H3''), 2.38 (m, 4H, J=7.20 Hz, H3', H5'), 1.94 (m, 2H, J=7.01 Hz, H2''); MS: *m/z* 319.0 (M⁺). Anal. Calcd. for C₁₆H₂₁N₃O₄: C: 60.17; H: 6.63; N: 13.16. Found: C: 60.11; H: 6.37; N: 13.35.

4-Chloro-7-methoxy-6-(3-morpholin-4-ylpropoxy)-quinazoline (7). A stirred mixture of **6** (1.00 g, 3.13 mmol), thionyl chloride (25 mL) and *N,N*-dimethylformamide (0.5 mL) was heated at reflux for 4 h. The liquid layer was evaporated. The residue was washed with diethyl ether and dried and give 1.05 g (99.3 %) of a beige solid. mp: 180-181 °C; ¹H-NMR (DMSO-*d*₆): δ 8.93 (s, 1H, H2), 7.49 (s, 1H, H5), 7.45 (s, 1H, H8), 4.33 (t, 2H, J=6.65 Hz, H1''), 4.03 (s, 3H, OCH₃), 3.81 (m, 4H, J=7.20 Hz, H2', H6'), 3.30 (t, 2H, J=6.99 Hz, H3''), 3.10 (m, 4H, J=7.19 Hz, H3', H5'), 2.30 (m, 2H, J=7.05 Hz, H2''); MS: *m/z* 337.0 (M⁺). Anal. Calcd. for C₁₆H₂₃ClN₃O₃: C: 48.99; H: 5.91; N: 10.71. Found: C: 48.82; H: 5.68; N: 10.60.

Methylazidoacetate (8). Sodium azide (44.00 g, 676.81 mmol) and methylbromoacetate (96.90 g, 687.44 mmol) were suspended in *N,N*-dimethylformamide and stirred at ambient temperature for 16 h. The reaction mixture was given into icewater and was extracted with diethylether. The organic layer was washed with water and dried. After evaporation of *N,N*-dimethylformamide, the crude product was distilled under *vacuo* to give 64.20 g (82.4 %) of a colourless oil. ¹H-NMR (DMSO-*d*₆): δ 3.90 (s, 2H, CH₂), 3.81 (s, 3H, OCH₃); MS: *m/z* 115.1 (M⁺).

Methyl-α-azido-3-chloro-4-fluorocinnamate (9). Under cooling sodium (1.35 g) was dissolved in methanol (30 mL). A mixture of 3-chloro-4-fluorobenzaldehyde (4.65 g, 29.33 mmol) and **8** (6.75 g, 58.65 mmol) in methanol (10 mL) was dropwise given to the sodium methanolate. The mixture was stirred at ambient temperature for 3 h. After neutralization with hydrochloric acid (2 *N*) the reaction mixture was extracted with ethyl acetate. The organic layer was washed with water and dried. After evaporation of ethyl acetate at a temperature less than 40 °C the resulting residue was chromatographed on silica gel with ethyl acetate/*n*-hexane (1:3) to give 4.55 g (60.7 %) of white crystals. mp: 58 °C [Lit. 14: 72-74°C]; ¹H-NMR (DMSO-*d*₆): δ 8.13 (dd, ⁴J=2.16 Hz, J_{H-F}=7.42 Hz, 1H, H2), 7.90 (m, 1H, H6), 7.47 (t, ³J=9.01 Hz, 1H, H5), 6.93 (s, 1H, CH aliph), 3.86 (s, 3H, OCH₃); MS: *m/z* 255.1 (M⁺). Anal. Calcd. for C₁₀H₇ClF₂N₃O₂: C: 46.98; H: 2.76; N: 16.44. Found: C: 47.05; H: 2.99; N: 16.36.

Methyl 5-chloro-6-fluoroindole-2-carboxylate (10a) and Methyl 7-chloro-6-fluoroindole-2-carboxylate (10b). A mixture of **9** (2.38 g, 10.11 mmol) and xylene (180 mL) was heated under reflux for 45 min. The solvent was removed. There were obtained 1.00 g (47.8 %) of an almost 1:1 mixture of **10a**

and **10b** as white crystals which was used in the next step without further purification. ¹H-NMR: (DMSO-*d*₆) δ 12.37 (s, 1H, NH, **10b**), 12.22 (s, 1H, NH, **10a**), 7.91 (d, J_{H-F}=7.47 Hz, 1H, H4, **10a**), 7.67 (m, 1H, H4, **10b**), 7.35 (d, J_{H-F}=9.87 Hz, 1H, H7, **10a**), 7.29 (s, 1H, H3, **10b**), 7.17 (t, ³J=9.20 Hz, 1H, H5, **10b**), 7.15 (s, 1H, H3, **10a**), 3.89 (s, 3H, OCH₃), 3.88 (s, 3H, OCH₃); MS: *m/z* 227.0 (M⁺).

5-Chloro-6-fluoroindole-2-carboxylic acid (11a) and 7-Chloro-6-fluoroindole-2-carboxylic acid (11b). A suspension of an almost 1:1 mixture of **10a** and **10b** (2.04 g, 8.96 mmol) in ethanol (90 mL) and sodium hydroxide solution (2 *N*, 45 mL) was stirred at ambient temperature for 2 h. The alcohol was evaporated and the residue was treated with hydrochloric acid (2 *N*). The crystals were isolated, washed with water and dried. There were obtained 1.8 g (94.1 %) of an almost 1:1 mixture of **11a** and **11b** as white solid. ¹H-NMR: (DMSO-*d*₆) δ 13.10 (s, 2H, COOH, **11a**, **11b**), 12.18 (s, 1H, NH, **11b**), 12.02 (s, 1H, NH, **11a**), 7.88 (d, J_{H-F}=7.48 Hz, 1H, H4, **11a**), 7.65 (m, 1H, H4, **11b**), 7.33 (d, J_{H-F}=9.94 Hz, 1H, H7, **11a**), 7.21 (s, 1H, H3, **11b**), 7.13 (t, ³J=9.07 Hz, 1H, H5, **11b**), 7.08 (s, 1H, H3, **11a**); MS: *m/z* 212.9 (M⁺).

5-Chloro-6-fluoroindole (12a) and 7-Chloro-6-fluoroindole (12b). A suspension of 1.92 g (8.99 mmol) of an almost 1:1 mixture of **11a** and **11b** in diphenyl ether (45 mL) was stirred at 260 °C for 4 h. The reaction mixture was chromatographed over silica gel with *n*-hexane and *n*-hexane/toluene (3:1). There were obtained 0.70 g (45.9 %) of **12a** as white and 0.40 g (26.3 %) of **12b** as lightbrown crystals. **12a**: mp: 83 °C [Lit. 14: 88-90°C, light brown crystals]; ¹H-NMR (DMSO-*d*₆): δ 11.32 (s, 1H, NH), 7.70 (d, J_{H-F}=7.40 Hz, 1H, H4), 7.41 (t, J=5.70 Hz, 1H, H2), 7.38 (d, J_{H-F}=10.22 Hz, 1H, H7), 6.43 (t, J=5.02 Hz, 1H, H3); MS: *m/z* 169.2 (M⁺). Anal. Calcd. for C₈H₅ClFN: C: 56.66; H: 2.97; N: 8.26. Found: C: 56.67; H: 3.06; N: 8.24. **12b**: mp: 42 °C [Lit. 14: dark brown oil]; ¹H-NMR (DMSO-*d*₆): δ 11.61 (s, 1H, NH), 7.53 (m, 1H, H4), 7.42 (t, J=5.46 Hz, 1H, H2), 7.04 (t, ³J=8.79 Hz, 1H, H5), 6.54 (t, J=4.94 Hz, 1H, H3); MS: *m/z* 169.1 (M⁺). Anal. Calcd. for C₈H₅ClFN: C: 56.66; H: 2.97; N: 8.26. Found: C: 56.63; H: 3.09; N: 8.17.

4-(5-Chloro-6-fluoroindole-3-yl)-7-methoxy-6-(3-morpholin-4-ylpropoxy)quinazoline (15). Under cooling magnesium (0.25 g) and iodine were stirred with a mixture from methyl iodide (1.2 mL) and diethyl ether (5 mL) for 15 min. Afterwards a solution of **12a** (0.50 g, 2.99 mmol) in diethyl ether (15 mL) was given to the reaction mixture and was stirred for 15 min. Subsequently **7** (0.75 g, 2.22 mmol) was added in portions. The mixture was heated under reflux for 1 h and then was added to ice-water. After extraction with ethyl acetate and diethylether the organic layer was dried over molecular sieve and the ethyl acetate was evaporated. The crude product was chromatographed over silica gel with diethylether/ethyl acetate/methanol (3:1:1) and was recrystallised from ethyl acetate/*n*-hexane. There were obtained 0.10 g (9.6 %) of yellow crystals. mp: 186-188 °C; ¹H-NMR (DMSO-*d*₆): δ 12.10 (s, 1H, NH), 9.09 (s, 1H, H2), 8.37 (d, J=2.74 Hz, 1H, H2'), 8.33 (d, 1H, J_{H-F}=7.59 Hz, H4'), 7.65 (s, 1H, H5), 7.54 (d, 1H, J_{H-F}=10.00 Hz, H7'), 7.39 (s, 1H, H8), 4.19 (t, 2H, J=6.65 Hz, H1''), 4.01 (s, 3H, OCH₃), 3.54 (t, 4H, J=7.22 Hz, H2'', H6''), 2.43 (t, 2H, J=7.06 Hz, H3''), 2.34 (t, 4H, J=7.21 Hz, H3'', H5''), 1.96 (m, 2H, J=7.03 Hz, H2''); MS: *m/z* 470.7 (M⁺). Anal. Calcd. for C₂₄H₂₄ClFN₄O₃: C: 61.21; H: 5.14; N: 11.90. Found: C: 61.31; H: 5.28; N: 12.10.

4-(5-Bromoindole-3-yl)-7-methoxy-6-(3-morpholin-4-yl-propoxy)quinazoline (16). Under cooling magnesium (0.25 g) and iodine were stirred with a mixture from methyl iodide (1.2 mL) and diethyl ether (5 mL) for 15 min. Afterwards a solution of 5-bromoindole (0.50 g, 2.55 mmol) in diethyl ether (15 mL) was given to the reaction mixture and was stirred for 15 min. Subsequently **7** (0.75 g, 2.22 mmol) was added in portions. The mixture was heated under reflux for 1 h and then was added to ice-water. After extraction with ethyl acetate and diethylether the organic layer was dried over molecular sieve and the ethyl acetate was evaporated. The crude product was chromatographed over silica gel with diethylether/ethyl acetate/methanol (3:1:1) and was recrystallised from ethyl acetate/n-hexane. There were obtained 0.11 g (10,0 %) of yellow crystals. mp: 204-206 °C; ¹H-NMR (DMSO-*d*₆): δ 12.14 (s, 1H, NH), 9.14 (s, 1H, H2), 8.39 (d, ⁴J=1.97 Hz, 1H, H4'), 7.71 (s, 1H, H5), 7.57 (d, 1H, ³J=8.61 Hz, H7'), 7.44 (s, 1H, H8), 7.41 (dd, 1H, ³J=8.68 Hz, ⁴J=1.94 Hz, H6'), 4.23 (t, 2H, J=6.67 Hz, H1''), 4.07 (s, 3H, OCH₃), 3.60 (t, 4H, J=7.18 Hz, H2'', H6''), 2.49 (t, 2H, J=7.04 Hz, H3''), 2.40 (t, 4H, J=7.19 Hz, H3'', H5''), 2.02 (m, 2H, J=6.99 Hz, H2''); MS: *m/z* 496.2 (M⁺). Anal. Calcd. for C₂₄H₂₆BrN₄O_{3,5}: C: 56.91; H: 5.17; N: 11.06. Found: C: 57.03; H: 5.41; N: 10.78.

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