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Short communication

Design, synthesis and characterization of N_9/N_7-substituted 6-aminopurines as VEGF-R and EGF-R inhibitors

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Abstract

In this study we report on the design, synthesis and biological characterization of novel N_9 or N_7 arylethanone-substituted 6-aminopurines and 6-methoxypurines, respectively, as EGF-R and VEGF-R inhibitors. The compounds were initially profiled in a panel of 24 cancer-relevant protein kinases. Dependent on the regio-substitution of the purine core we found inhibition activity for EGF-R and VEGF-R with IC_{50} values in the μM range. The two novel N_9/N_7 2-(6-amino-purine)-1-(1*H*-indole-3-yl)ethanone derivatives were characterized in an enhanced panel of 78 kinases showing the N_9 derivative to also inhibit MNK1 and IRR while the N_7 isomer was found to be specific for VEGF-R2.

Keywords: VEGF-R; EGF-R; Protein kinase inhibitors; N_7/N_9-Substituted 6-aminopurines

1. Introduction

Small molecule inhibitors of the receptor tyrosine kinases VEGF-R (vascular endothelial growth factor receptor) [1] and EGF-R (epidermal growth factor receptor) [2,3] are in particular of pharmaceutical interest because these protein kinases (PKs) are considered to be validated drug targets in angiogenesis and cancer [4]. In recent publications we presented compounds combining the purine system from the original cosubstrate ATP and phenyl moieties in order to explore possible interactions with the different regions of the ATP binding site in several disease-related protein kinases [5,6].

In this communication we report on the design, synthesis and results of our SAR investigation directed at the N_9/N_7-regiospecific substitution of the 6-aminopurine scaffold (I and II, Scheme 1) as VEGF-R/EGF-R inhibitors and the biological characterization of the compounds in a panel of 24 cancer-relevant PKs. Furthermore, two novel compounds have been tested in a specificity profile over 78 PKs.

2. Results and discussions

We designed the scaffolds I and II on the basis of the modelled binding mode of compound **1** (belonging to scaffold I) in the ATP pocket of VEGF-R2 (Fig. 1). Herein, the pose of **1** involves H-bond interactions of the 6-aminopurine moiety addressing the hinge-region carbonyl of Cys917. In contrast to the situation in ATP where N_1 is accepting an H-bond from the protein, in this binding mode an H-bond is accepted by N_7 of the adenine scaffold (Fig. 1). The N_9 indolylethanone substitution is directed towards the hydrophobic pocket I (HPI) where the indole moiety forms π–π stacking interactions to the Phe1045 residue of the DFG motif [7]. However, in particular this interaction towards HPI was considered to determine activity and selectivity of the inhibitor for VEGF-R2/3 [8]. Furthermore, in this binding mode of **1** the hydrophobic region II (HRII) is not yet addressed and, therefore, leaving chemical space for optimization. To prove the

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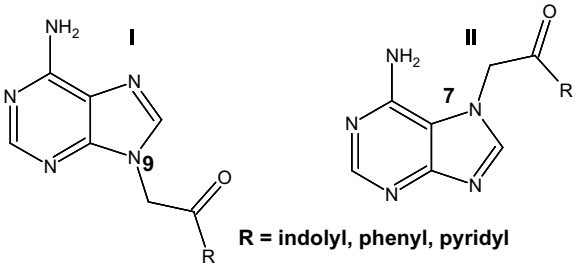

Scheme 1. N_9/N_7 regioselective-substituted 6-aminopurine scaffolds I and II.

concept of the inhibitor design as a lead structure the N_9/N_7-regiospecific-substituted 6-aminopurines **1**, **2** and related analogues were synthesized and evaluated for biological activity.

3. Chemistry

The synthesis for both I and II starts from 6-chloro-9*H*-purine. Due to the tautomeric situation in the purine nucleus, modifications of the purine scaffold in this study by base catalyzed S_N reaction with 2-bromo-1-arylethanone derivatives leads mainly to N_9-substituted purines with only 5–10% of N_7-substituted purines. Vice versa, major regioselective N_7-substitution was conveniently afforded by use of the auxiliary cobaloxime [9] $CH_3Co(DH)_2OH_2$ whereas N_9-substitution occurred only in 5–12% (Fig. 2) [10].

Accordingly, in this study the reaction performed well for 2-bromo-1*H*-indol-3-ylethanone and 2-bromo-1-phenylethanone to yield compounds **1**–**4** (Fig. 3). Unexpectedly, the cobaloxime strategy was not successful for 2-bromo-1-pyridylethanones **5** and **6** and hence only the N_9-substituted derivatives were obtained. Due to the additional pyridine nitrogen the cobaloxime–purine complex was probably not stable using these reaction conditions. The N_9/N_7-regiospecific-substituted isomers were isolated by flash chromatography and subsequently heated with concentrated ammonium hydroxide solution in a Berghof B25 pressure reactor to yield the corresponding 6-aminopurine derivatives (I/II, Fig. 3). In light of the aminolysis of 6-chloropurine derivatives, catalytic amounts of Cu(I)I decreased the yields and side products occurred [11]. The reaction of adequate N_9/N_7-precursors in a methanolic solution of ammonia gave compounds **7** and **8** [12] as major products besides minor amounts of **3** and **4** [13–16].

Compound **9** was obtained under basic conditions (K_2CO_3) by the reaction of 6-chloropurine and 2-bromo-1*H*-indol-3-ylethanone in non-distilled DMF which contains dimethylamine. Hence, in a one-pot reaction both the alkylation of N_9 according to the general scheme as well as the nucleophilic substitution of purine-C_6 by dimethylamine occurs.

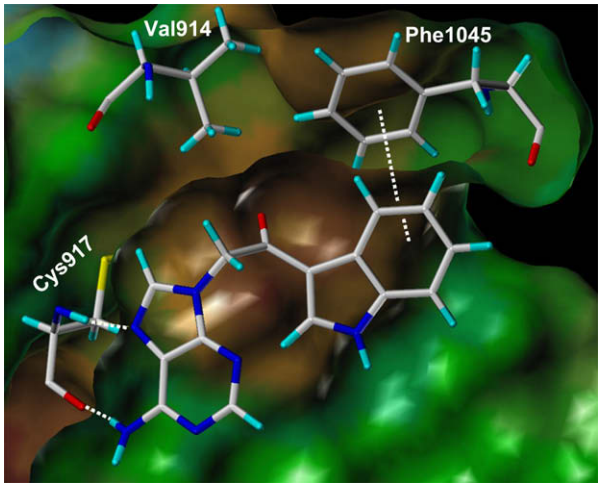

Fig. 1. Modelled binding mode of **1** in the crystallographically determined ATP binding pocket of VEGF-R2 (PDB 1Y6A [7]). Compound **1** forms key H-bonds to Cys917 (hinge-region) and π–π stacking interactions to Phe1045 in the hydrophobic pocket I; Val914 (gatekeeper).

4. Biological evaluation

These nine compounds have been evaluated for their potency against 24 cancer-relevant protein kinases belonging to different families of the kinome (Table 1) [17]. Consistent with the modelling hypothesis, **1** inhibited VEGF-R2 ($IC_{50} = 81$ μM) and slightly more potently blocked the epidermal growth factor receptor (EGF-R, $IC_{50} = 35$ μM; a modelled binding mode of **1** in EGF-R [18] comparable to VEGF-R2 is available in the Supporting information). Concerning SAR, the involvement of the amino-function of **1** in ligand–protein interactions to these PKs is supported by complete loss of the biological activity of aminomethylated derivative **9** in the panel. Inhibition in the μM range for VEGF-R2 was also found for **2**, **6** and **7** whereas EGF-R is inhibited by **2**, **3**, **5** and **6**. Compounds **1** and **2** inhibited VEGF-R2 but not the highly homologous VEGF-R3. In contrast, compound **7** shows an IC_{50} of 25 μM for VEGF-R2 and 45 μM for VEGF-R3 with specificity over the other kinases of this panel. In light of the modelled binding mode of **1** (Fig. 1) this result was unexpected since the amino-function in **1** (H-bond donor) is replaced in **7** by a methoxy group (H-bond acceptor). Furthermore, the corresponding N_7 regioisomer **8** was not inhibiting any of the PKs. However, the inhibition of **7** indicates an alternative binding mode in VEGF-R for this compound which was not predicted by our modelling studies. Interestingly, dependent on the regio-substitution of the 1*H*-indol-3-ylethanone moiety, compound **1** (N_9) inhibited EGF-R more potently than VEGF-R2 whereas the converse situation is true for **2** (N_7, VEGF-R2 over EGF-R).

However, in order to reveal their potential as multikinase inhibitors [19] **1** and **2** were additionally characterized in an enhanced specificity panel of 78 PKs at a concentration of 10 μM [20] (data available in the Supporting information). Herein, **1** inhibited MNK1 [21] (MAP kinase signal-integrating kinase, 73 ± 3% inhibition at 10 μM) and IRR [22] (insulin-receptor related receptor, 51 ± 1% inhibition at

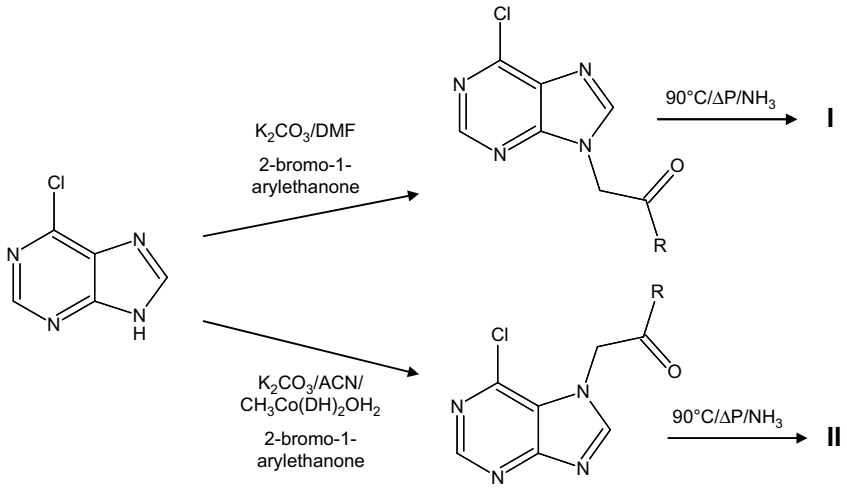

Fig. 2. Synthesis of purine derivatives with regioselective substitution of the scaffold at N_9 (I) and at N_7 (II) by the use of auxiliary cobaloxime−H_2O complex.

10 μM) while **2** not significantly blocked by any of the 78 PKs in this panel.

Thus, compounds **2** and **7** are interesting lead structures for the development of potent and selective VEGF-R2 inhibitors.

5. Experimental section

5.1. General method for N_9 alkylation of 6-chloro-9H-purine

K_2CO_3 (0.21 g; 1.55 mmol) was suspended in a solution of 0.24 g (1.55 mmol) 6-chloro-9*H*-purine in 10 ml DMF and stirred for 30 min. Then 2-bromo-1-arylethanone reagent (1.55 mmol) was slowly added and the progress of the reaction was monitored by TLC (ethylacetate 9/ethanol 1). After completeness of the reaction 20 ml H_2O was dropped in and the mixture extracted by ethylacetate (3×30 ml), the organic phase separated, dried over Na_2SO_4 and evaporated. The product was purified by flash chromatography.

5.2. General method for N_7 alkylation of 6-chloro-9H-purine

Methylaquacobaloxime (0.5 g; 1.55 mmol) was dissolved in 10 ml absolute acetonitrile and stirred in the dark. To this solution, 6-chloro-9*H*-purine (0.24 g; 1.55 mmol) was added to form the purine−cobaloxime complex which precipitates

Compound	scaffold	R
1	I	3-indolyl
2	II	3-indolyl
3	I	phenyl
4	II	phenyl
5	I	2-pyridinyl
6	I	3-pyridinyl

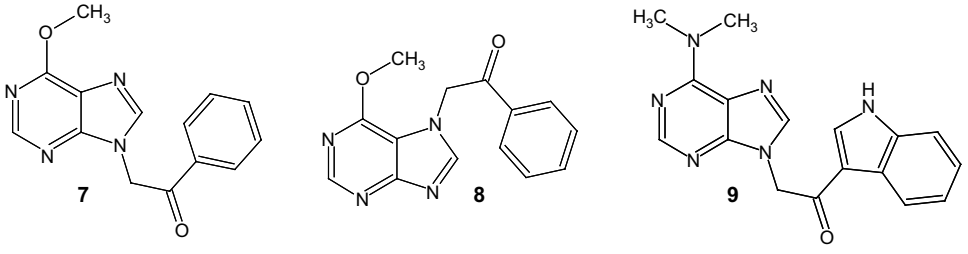

Fig. 3. Set of test compounds **1**–**9**.

Table 1
IC_{50} values (μM) of test compounds in a profiling panel of 24 cancer related PKs

PK	1	2	3	4	5	6	7	8	9
AKT1	–	–	–	–	–	–	–	–	–
ARK5	–	–	–	–	–	–	–	–	–
Aurora-A	–	–	–	–	–	–	–	–	–
Aurora-B	69	–	–	–	–	–	–	–	–
B-RAF-VE	82	–	–	–	–	–	–	–	–
CDK2/CycA	–	–	–	–	–	–	–	–	–
CDK4/CycD1	–	–	–	–	–	–	–	–	–
COT	–	–	–	–	–	–	–	–	–
EGF-R	35	82	75	–	89	93	–	–	–
EPHB4	–	–	–	–	–	–	–	–	–
ERBB2	95	–	–	–	–	–	–	–	–
FAK	–	–	–	–	–	–	–	–	–
IGF1-R	–	–	–	–	–	–	–	–	–
SRC	–	82	–	–	–	75	–	–	–
VEGF-R2	81	30	–	–	–	58	25	–	–
VEGF-R3	–	–	–	–	–	–	45	–	–
FLT3	–	–	–	–	–	–	–	–	–
INS-R	–	–	–	–	–	–	–	–	–
MET	–	–	–	–	–	–	–	–	–
PDGFR-beta	–	–	–	–	–	–	–	–	–
PLK1	–	–	–	–	–	–	–	–	–
SAK	–	–	–	–	–	–	–	–	–
TIE2	85	95	–	–	–	–	–	–	–
CK2alpha1	–	–	–	–	–	–	–	–	–

'–' indicates no significant inhibition up to 100 μM.

as an orange solid. Acetonitril 5 ml and K_2CO_3 (0.21 g; 1.55 mmol) were added and the mixture was stirred at room temperature. After 30 min the 2-bromo-1-arylethanone reagent (1.55 mmol) was added and the progress of the reaction was monitored by TLC (ethylacetate 9/ethanol 1). After completeness of the reaction the solvent was evaporated and 20 ml of 4 M NaOH was dropped in. The mixture was extracted by dichloromethane, the organic phase separated, dried over Na_2SO_4 and evaporated. The product was purified by flash chromatography.

5.3. General method for S_N reaction of N_9N_7-alkylated 6-chloro-purines

A Berghof B25 high pressure reactor was charged with the N_9 or N_7-alkylated 6-chloro-purine derivative and 20 ml of concentrated NH_3. The mixture was heated to 90 °C and the progress of the reaction was monitored by TLC (ethylacetate 9/ethanol 1). After completeness of the reaction 20 ml H_2O was added and the mixture extracted by ethylacetate (3 × 30 ml), the organic phase separated, dried over Na_2SO_4 and evaporated. The product was purified by flash chromatography.

5.3.1. 2-(6-Amino-9H-purine-9-yl)-1-(1H-indole-3-yl) ethanone (**1**)

The compound was synthesized following general procedures for N_9 alkylation of 6-chloro-9*H*-purine and S_N reaction (yield 80.0%). ^{1}H NMR DMSO-d_6; 200 MHz, δ [ppm] = 5.63 (s, 2H); 7.09–7.38 (m, 4H), 7.39–7.62 (m, 1H); 7.98–8.27 (m, 3H); 8.62 (s, 1H). ^{13}C NMR DMSO-d_6; 50 MHz, δ [ppm] = 49.16, 112.71, 113.80, 118.73, 121.37, 122.50, 123.51, 125.61, 134.79, 136.88, 142.38, 150.31, 152.74, 156.30, 187.50. MS: $m/z = 293$ $(M + H^+)$ HRMS $C_{15}H_{12}N_6O$: 292.10651 calc. 292.10723. Melting point: 362.3 °C.

5.3.2. 2-(6-Amino-7H-purine-7-yl)-1-(1H-indole-3-yl) ethanone (**2**)

The compound was synthesized following general procedures for N_7 alkylation of 6-chloro-9*H*-purine and S_N reaction (yield 81.7%). ^{1}H NMR DMSO-d_6; 200 MHz, δ [ppm] = 5.93 (s, 2H), 6.76 (s, 2H), 7.09–7.36 (m, 2H), 7.52 (s, 1H), 7.96–8.39 (m, 3H), 8.55 (1H). ^{13}C NMR DMSO-d_6; 50 MHz, δ [ppm] = 52.54, 112.48, 112.73, 113.56, 121.42, 122.52, 123.53, 125.66, 135.08, 136.86, 147.42, 151.97, 152.43, 160.09, 187.95. MS: $m/z = 293$ $(M + H^+)$. HRMS $C_{15}H_{12}N_6O$: 292.10467 calc. 292.10723. Melting point: 288.3 °C.

5.3.3. 2-(6-Amino-9H-purine-9-yl)-1-phenylethanone (**3**)

The compound was synthesized following general procedures for N_9 alkylation of 6-chloro-9*H*-purine and S_N reaction (yield 63.6%). ^{1}H NMR DMSO-d_6; 200 MHz, δ [ppm] = 5.86 (s, 2H), 7.25 (s, 2H), 7.56–7.66 (m, 2H, C3), 7.70–7.78 (m, 1H), 8.07–8.0 (m, 3H), 8.12 (s, 1H). ^{13}C NMR DMSO-d_6; 50 MHz, δ [ppm] = 49.4, 118.70, 128.46, 129.40, 134.51, 134.58, 142.00, 150.30, 152.84, 156.31, 193.20. MS: $m/z =$ 253 (M^+). HRMS $C_{13}H_{11}N_5O$: 253.09748 calc. 253.096335. Melting point: 292.4 °C (decomposition).

5.3.4. 2-(6-Amino-7H-purine-7-yl)-1-phenylethanone (**4**) [16]

The compound was synthesized following general procedures for N_7 alkylation of 6-chloro-9*H*-purine and S_N reaction (yield 35%). ^{1}H NMR DMSO-d_6; 200 MHz, δ [ppm] = 6.16 (s, 2H), 6.79 (s, 2H), 7.56–7.66 (m, 2H), 7.68–7.78 (m, 1H), 8.01–8.08 (m, 2H), 8.18 (s, 1H), 8.19 (s). ^{13}C NMR DMSO-d_6; 50 MHz, δ [ppm] = 53.21, 112.45, 128.63, 129.17, 134.38, 134.56, 147.14, 151.84, 152.48, 160.05, 193.77. MS: $m/z = 254$ $(M + H^+)$. HRMS $C_{13}H_{11}N_5O$: 253.09697 calc. 253.096335. Melting point: 244.6 °C.

5.3.5. 2-(6-Amino-9H-purine-9-yl)-1-(pyridine-2-yl) ethanone (**5**)

The compound was synthesized following general procedures for N_9 alkylation of 6-chloro-9*H*-purine and S_N reaction (yield 88.9%). ^{1}H NMR DMSO-d_6; 200 MHz, δ [ppm] = 5.93 (s, 2H), 7.25 (s, 2H), 7.74–7.83 (m, 1H), 7.97–8.14 (m, 4H), 8.81–8.87 (m, 1H). ^{13}C NMR DMSO-d_6; 50 MHz, δ [ppm] = 49.44, 118.73, 122.20, 129.12, 138.36, 142.05, 149.88, 150.29, 151.37, 152.84, 156.30, 194.12. MS: $m/z =$ 254 (M^+). HRMS $C_{12}H_{10}N_6O$: 254.09411 calc. 254.09158. Melting point: 268.3 °C.

5.3.6. 2-(6-Amino-9H-purine-9-yl)-1-(pyridine-3-yl) ethanone (**6**)

The compound was synthesized following general procedures for N_9 alkylation of 6-chloro-9*H*-purine and S_N reaction (yield 62.8%). ^{1}H NMR DMSO-d_6; 200 MHz, δ [ppm] = 5.92 (s, 2H), 7.25 (s, 2H), 7.8 (m, 1H), 7.9–8.1 (m, 4H); 8.8 (s, 1H). MS: $m/z = 254$ (M^+). HRMS $C_{12}H_{10}N_6O$: 254.09232 calc. 254.09158.

5.3.7. 2-(6-Methoxy-9H-purine-9-yl)-1-phenylethanone (**7**)

The compound was synthesized following general procedures for N_9 alkylation of 6-chloro-9*H*-purine. The S_N reaction was performed with methanolic ammonia to yield 21% of **1** and 57.6% of **7**. ^{1}H NMR Aceton-d_6; 200 MHz, δ [ppm] = 4.15 (s, 3H), 6.02 (s, 2H), 7.58–7.68 (m, 2H), 7.71–7.80 (m, 1H), 8.13–8.20 (m, 2H), 8.25 (s, 1H), 8.44 (s, 1H). ^{13}C NMR Aceton-d_6; 50 MHz, δ [ppm] = 49.35, 53.36, 120.76, 127.99, 128.88, 133.98, 134.46, 143.96, 151.54, 152.84, 160.80, 191.80. MS: $m/z = 268$ (M^+). HRMS $C_{14}H_{12}N_4O_2$: 268.09713 calc. 268.0960. Melting point: 156.5 °C.

5.3.8. 2-(6-Methoxy-7H-purine-7-yl)-1-phenylethanone (**8**) [12]

The compound was synthesized following general procedures for N_7 alkylation of 6-chloro-9*H*-purine. The S_N reaction was performed with methanolic ammonia to yield 35% of **2** and 49.5% of **8**. ^{1}H NMR methanol-d_4; 200 MHz, δ [ppm] = 3.35 (s, 2H), 4.00 (s, 3H), 7.56–7.65 (m, 2H), 7.69–7.78 (m, 1H), 8.08–8.14 (m, 2H), 8.37 (s, 1H), 8.56 (s, 1H). ^{13}C NMR methanol-d_4; 50 MHz, δ [ppm] = 48.33, 53.32, 127.71, 128.67, 128.67, 133.92, 134.13, 147.20, 151.62, 157.51, 160.30, 192.41. MS: $m/z = 268$ (M^+). HRMS $C_{14}H_{12}N_4O_2$: 268.09647 calc. 268.0960. Melting point: 165.7 °C.

5.3.9. 2-[6-(Dimethylamine)-9H-purine-9-yl]-1-(1H-indole-3-yl)ethanone (**9**)

The compound was obtained following general procedures for N_9 alkylation of 6-chloro-9*H*-purine in DMF to yield 10% of 2-(6-Chloro-9*H*-purine-9-yl)-1-(1*H*-indole-3-yl)ethanone and 42.3% of **3**. ^{1}H NMR DMSO-d_6; 200 MHz, δ [ppm] = 3.37 (s, 6H), 5.68 (s, 2H), 7.14–7.28 (m, 2H), 7.49–7.56 (d, 1H), 8.05–8.12 (d, 1H), 8.13–8.18 (2H), 8.65 (s, 1H), 12.12 (s, 1H). ^{13}C NMR DMSO-d_6; 50 MHz. δ [ppm] = 30.87, 50.10, 112.70, 113.55, 118.89, 121.29, 122.78, 123.81, 125.29, 134.44, 136.58, 141.29, 150.60, 152.05, 154.49, 187.52. MS: $m/z = 321$ ($M + H^+$). HRMS $C_{17}H_{16}N_6O$: 320.13728 calc. 320.13853.

The HPLC retention times and purity data of all compounds are available in the Supporting information.

5.4. Selectivity profiling of compounds by IC_{50} values using 24 protein kinases

A proprietary protein kinase assay (^{33}PanQinase® Activity Assay) was used for measuring the kinase activity of the 24 protein kinases. All kinase assays were performed in 96-well FlashPlatesTM from Perkin Elmer/NEN (Boston, MA, USA) in a 50 µl reaction volume.

The assay for all enzymes contained 60 mM HEPES–NaOH, pH 7.5, 3 mM $MgCl_2$, 3 mM $MnCl_2$, 3 µM Na-orthovanadate, 1.2 mM DTT, 50 µg/ml PEG20000, 1 µM [γ-^{33}P]-ATP (approx. 5×10^5 cpm/well), recombinant protein kinase (50–400 ng). Depending on the kinase, the following substrate proteins were used: AKT1 (GSK3/14-27), ARK5 (autophosphorylation), Aurora-A, Aurora-B (Tetra(LRRWSLG)), B-Raf-VE (MEK1 KM), CDK2/CycA (histone H1), CDK4/CycD1 (Rb-CTF), CK2-A1 (casein), EGF-R, EPHB4, ERBB2, FAK, IGF1-R, SRC, VEGF-R2, VEGF-R3 (poly (Glu,Tyr) 4:1), FLT3, INS-R, MET, PDGFRbeta (poly (Ala,Glu,Lys,Tyr) 6:2:5:1), PLK1 (Casein), SAK (autophosphorylation), TIE2 (poly(Glu,Tyr) 4:1), COT (autophosphorylation). The IC_{50} values were measured by testing 10 concentrations of compounds in singlicate. As a parameter for assay quality, the Z′-factor for the low and high controls of each assay plate ($n = 8$) was used (see Supporting information). The final DMSO concentration in the assay was 1%. The reaction cocktails were incubated at 30 °C for 80 min. The reaction was stopped with 50 µl of 2% (v/v) H_3PO_4, plates were aspirated and washed two times with 200 µl of 0.9% (w/v) NaCl. Incorporation of ^{33}Pi was determined with a microplate scintillation counter (Microbeta Trilux, Wallac). All assays were performed with a BeckmanCoulter/Sagian robotic system.

The specificity testing of compounds **1** and **2** was performed by the Division of Signal Transduction Therapy, University of Dundee, Scotland. Details of the kinase assay panel are available in the Supporting information.

5.5. Molecular modelling

All modellings were performed on a RedHat Linux system. For visualization and building the structures SYBYL 7.2 was used. The Connolly surface was calculated using the MOLCAD module in Sybyl and coloured according to the lipophilicity (from very hydrophobic to hydrophilic corresponds to brown over green to blue). Compound **1** was docked into the active site of VEGFR-2 and EGF-R using the FlexX docking program [23]. The FlexX scoring function was applied during the placement and construction phase of the ligands and DrugScore for the final ranking [24]. The 3D coordinates of the VEGFR-2 catalytic core in complex with a 2-anilino-5-aryl-oxazole inhibitor were taken from the Brookhaven Protein Databank PDB code 1Y6A [7] and of the EGF-R catalytic domain from PDB 1XKK [18].

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Appendix. Supporting information

Supporting information associated with this article can be found in the online version, at doi: 10.1016/j.ejmech.2008.04.012.

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