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N-ALKYLATED SULFAMIDES AS NEUTRAL SOLUBILITY IMPROVING GROUPS FOR KINASE INHIBITORS

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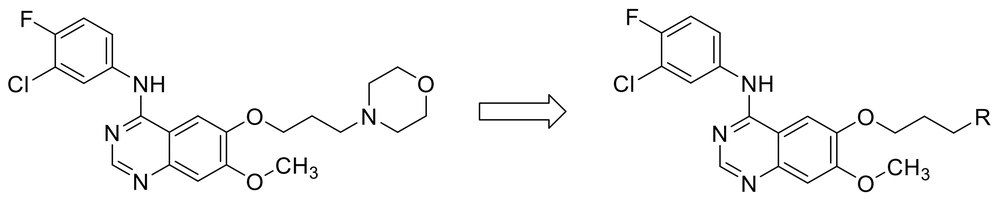
INTRODUCTION

Because hyperactivity of protein kinases is associated with hyperproliferation, various kinase inhibitors are used to treat cancer or inflammatory diseases [1]. One of the problems frequently encountered with protein kinase inhibitors is poor solubility.

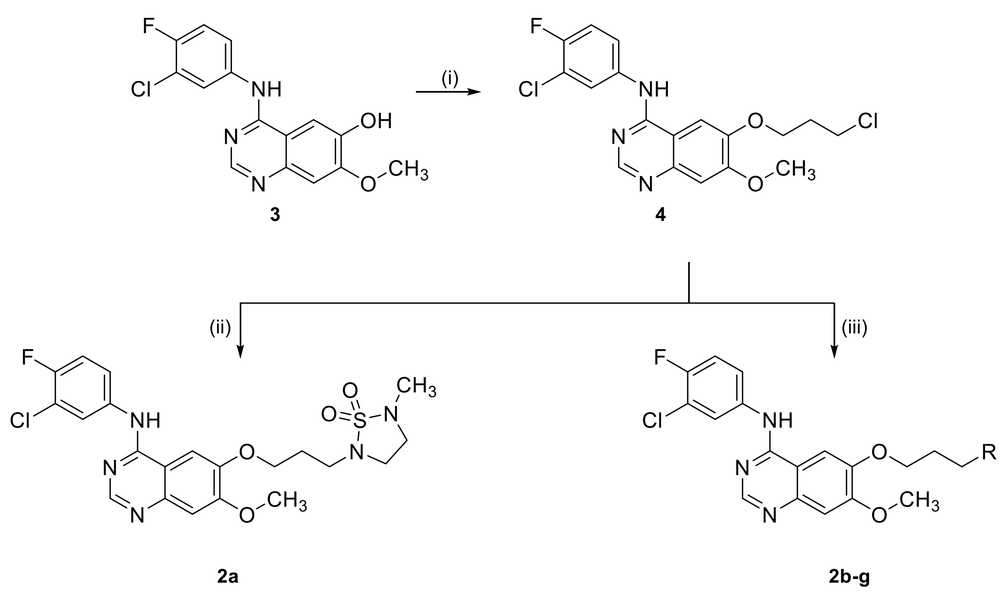
Basic centers in drug molecules not only increase solubility, but also the liability for hERG channel blockade [2]. *N*-Alkylated sulfamides are neutral solubility improving groups (NeuSIGs) which although raising molecular mass and complexity do not increase lipophilicity and thus are feasible alternatives for basic amino groups in drug molecules.

The basic morpholino element of the epidermal growth factor receptor (EGFR) kinase inhibitor gefitinib (**1**) was exchanged for NeuSIGs. The resulting new anilino-quinazolines **2a-g** were evaluated for inhibition of the EGF receptor kinase and three unrelated kinases.



1 **2a-g**

SYNTHESES



Scheme 1. Synthesis of anilinoquinazolines **2a**-**2g**: (i) 1-bromo-3-chloropropane, Cs_2CO_3, ACN, reflux, 3-5 h, 36%; (ii) 2-methyl-1,2,5-thiadiazolidine 1,1-dioxide, NaH, DMF, 0 °C → rt, 48 h, 20%; (iii) sulfamide derivatives, NaH, DMF, 0 °C → 100 °C, 5-12h, 20-45%.

BIOLOGICAL ACTIVITY [a]

	ABL1 wt	CDK8/CycC	EGF-R	VEGF-R2
1	$1.92*10^{-5}$	$>10^{-4}$	$<3*10^{-9}$	$1.58*10^{-5}$
2a	$6.37*10^{-5}$	$>10^{-4}$	$<3*10^{-9}$	$9.68*10^{-6}$
2b	$>10^{-4}$	$>10^{-4}$	$<3*10^{-9}$	$>10^{-4}$
2c	$>10^{-4}$	$>10^{-4}$	$<3*10^{-9}$	$3.94*10^{-5}$
2d	$>10^{-4}$	$8.34*10^{-5}$	$<3*10^{-9}$	$6.84*10^{-5}$
2e	$>10^{-4}$	$>10^{-4}$	$3.29*10^{-9}$	$1.69*10^{-5}$
2f	$>10^{-4}$	$>10^{-4}$	$<3*10^{-9}$	$3.08*10^{-5}$
2g	$6.80*10^{-5}$	$9.46*10^{-5}$	$7.85*10^{-9}$	$1.79*10^{-5}$

Table 2. Protein kinase inhibition profile of gefitinib (**1**) and **2a-g** (IC_{50}, M). [a] Results from a radiometric protein kinase assay (^{33}PanQinase® Activity Assay).

DOCKING

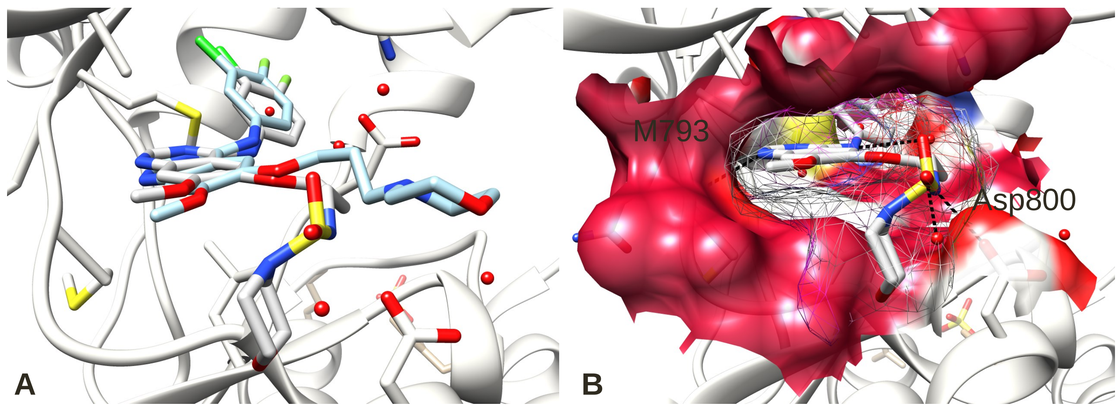


Figure 1. Docking studies of **2f** (grey) in the ATP binding pocket of EGFR (PDB: 4I22) [3] verify that the introduction of an *N*-alkylated sulfamide maintains the general orientation of the anilinoquinazoline scaffold of **1** (cyan). The propylmorpholino group of **1** and the propylmorpholino-4-sulfonamide group of **2f** point towards the solvent exposed entrance of the binding pocket (**A**). **2f** displays an additional H-bond between the sulfamide oxygen and Asp800 (**B**). [4-6]

PHYSICOCHEMICAL PROPERTIES

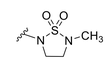
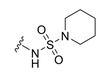
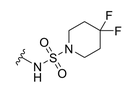
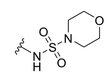
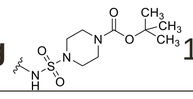
	R	m.p. [°C]	log P [a]	log S [b]	log S (ESOL) [8]	$S_{0,\ exp.,\ kinetic}$ [µM] [c]	log $S_{0,\ exp.,\ kinetic}$
1	-	178	4.31	-5.34	-5.05	56.2-61.1 (58.6)	-4.23
2a		203	2.38	-3.66	-4.89	25.1-28.3 (26.7)	-4.57
2b		221	2.56	-4.02	-4.88	46.1-49.1 (47.6)	-4.32
2c		209	2.79	-4.13	-5.18	39.9-44.9 (42.4)	-4.37
2d		222	3.03	-4.50	-5.48	23.7-25.3 (24.5)	-4.61
2e		199	3.46	-4.70	-5.88	18.0-21.3 (19.6)	-4.71
2f		222	2.40	-3.87	-4.72	40.2-47.9 (44.1)	-4.36
2g		190	2.44	-3.59	-5.74	16.3-23.9 (19.4)	-4.71

Table 1. Experimentally determined and predicted physicochemical properties.
[a] calculated with SILICOS-IT.
[b] calculated according to the general solubility equation: log S = 0.5–log P–0.01*(m.p.–25).[7]
[c] determined by nephelometry in phosphate buffer pH 7.4.

CONCLUSION

Exchange of the morpholino partial structure of gefitinib for sulfamide groups as NeuSIGs produced derivatives **2a-g** which exhibited similar EGFR inhibitory activity and maintained selectivity versus other protein kinases. The kinetic aqueous solubility of **2a-g** was comparable to gefitinib.

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[1] Neul, C., et al.: *Trends Pharmacol. Sci.* **2016**, *37*, 904–932. [2] Gleeson, M.P.: *J. Med. Chem*. **2008**, *51*, 817–837. [3] Gajiwala, K. S., et al.: *Structure* **2013**, *21*, 209–219. [4] Jones, G., et al.: *J. Mol. Biol.* **1997**, *267*, 727–748. [5] *Molecular Operating Environment (MOE)*, 2013.08; Chemical Computing Group Inc., **2015**. [6] Pettersen, E. F., et al.: *J. Comput. Chem.* **2004**, *25*, 1605–1612. [7] Jain, N.; Yalkowsky, S. H.: *J. Pharm. Sci.* **2001**, 90, 234–252. [8] Delaney, J. S.: *J. Chem. Inf. Model.* **2004**, *44*, 1000–1005.