Anticancer evaluation of 4-substituted-*N*-(quinolin-8-yl)pyridine-3-sulfonamides

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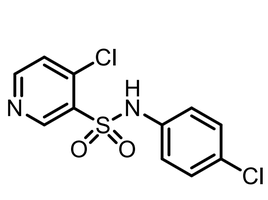
Introduction:

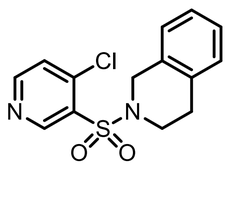
During our research over biological activity of different *N*-aryl-pyridine-3-sulfonamides we have found that only compound bearing *N*-(quinolin-8-yl) substituent possess a significant anti-tumor activity (**Figure 1**).

Mechanisms of anticancer activity of *N*-(quinoline)sulfonamide derivatives and similar shaped molecules (**Figure 2**) was reported to be inhibition of NF-κB pathway [1,2,3]. Nuclear factor NF-κB regulates expression of genes that control cell proliferation and cell survival thus it is consider as potential molecular targets for the prevention and treatment of cancer. Based on this information we decided to synthesize and evaluate series of 4-amino-*N*-(quinolin-8-yl)pyridine-3-sulfonamides **5** - **8**, which contain both 8-aminonoquinolin group and pyridine-3-sulfonamide scaffold.

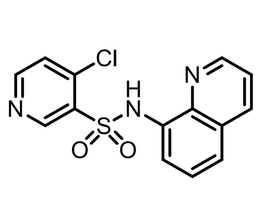
Figure 1



IC_{50}:
HCT-116 >100 μM
HeLa >100 μM
MCF-7 >100 μM



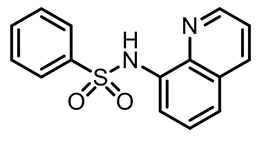
IC_{50}:
HCT-116 = 92μM
HeLa = 100 μM
MCF-7 >100 μM

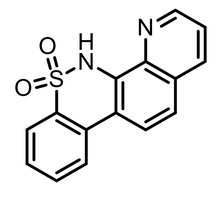


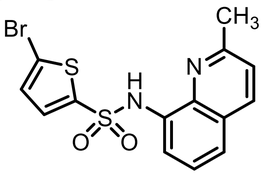
IC_{50}:
HCT-116 = **4.5**μM
HeLa = **9** μM
MCF-7 = **6.5** μM

Figure 2

Some known *N*-quinolin-sulfonamides targeting NF-κB



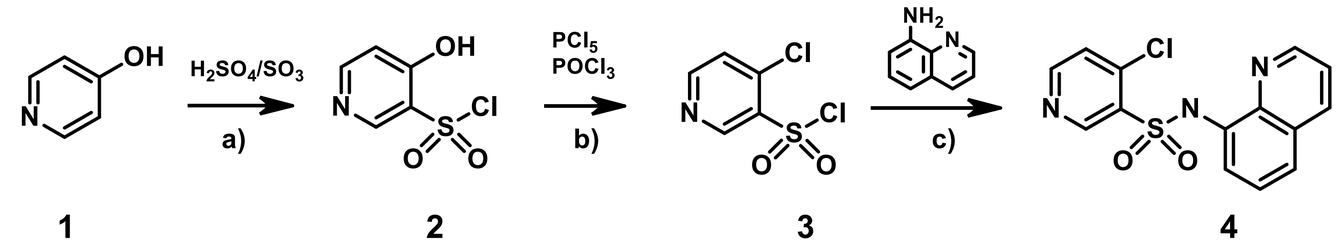


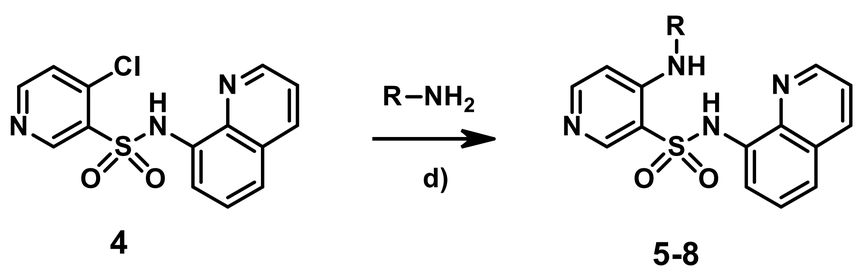


Synthesis:

The necessary substrates used in synthesis were obtained by sulfonation of 4-hyroxypiridne (**1**) and further reaction with PCl_5 and $POCl_3$, giving 4-chloropyridine-3-sulfonyl chloride (**3**), *N*-(quinolin-8-yl)-4-chloropyridine-3-sulfonamide (**4**) was obtained in recation of **3** with 8-Aminoquinoline.

Target compounds **5**-**8** were obteined by aromatic nucleophilic substitution reaction of chlorine atom in position 4 of pyridine ring (**4**) with varius amines. Structures of final compounds was confirmed using the spectroscopic methods: IR, ^{1}H NMR, and elemental analysis (C, H, N).





5 R = H

6 R = n-C_4H_9

7 R = C_6H_5

8 R = $CH_2C_6H_5$

Conditions:

a) H_2SO_4/SO_3 ,$HgSO_4$, 180°C, 24 h;

b) PCl_5 $POCl_3$ reflux 24 h;

c) 8-aminoquinoline, DIPEA, CH_2Cl_2, 0°C 1 h,r.t. 7 h

d) R-NH_2, MeOH, reflux 2-26 h;

Table:

Cytotoxic activity of compounds 4-8

IC_{50} [μM]				
Comp.	**Cell line**			
	HCT-116	**HeLa**	**MCF-7**	**HaCaT**
4	4.5	9	6.5	16
5	14	43	18	54
6	5	11	8	23
7	5	11	6	24
8	5	9	6	24
cisplatin	3.8	2.2	3	-

Biological studies:

Compounds **4** – **8** were submitted to test towards their effect on growth of human cancer cell lines: colon cancer HCT-116, breast cancer MCF-7, cervical cancer HeLa and *non*-tumorigenic human epidermal *HaCaT*. Cell viability was measured using MTT assay after 72 h of incubation with tested compound in concentrations 1 – 100 μM. Cytotoxic evaluation was reported as IC_{50} – the concentration required for 50% inhibition of cell viability (**Table**) .

New compounds were also analyzed with SwissADME Web Tool [4] to predict their bioavailability after oral administration in human organism.

The results of the calculations show that each of the compounds **4** – **8** meet the Lipiński's rules, moreover, the number of rotatable bonds and the polar surface area of the compounds are also within the standards compliant with the Veber's rule. Moreover, the calculated gastrointestinal absorption parameter indicates high absorption of carry from the gastrointestinal tract. Therefore, we can assume that these compounds, as potential drugs, will show adequate bioavailability after oral administration.

Conclusions:

All compounds showed very high cytostatic activity comparable to cisplatin. The presence of aliphatic or aromatic substituents on the amine fragment does not significantly affect the activity (relative to compound 4), thus modification at this position can be efficiently used in optimization of the ADME-related physicochemical parameters such as solubility and lipophilicity, of *N*-(quinolin-8-yl)pyridine-3-sulfonamides derivatives.

Literature:

[1] Xie Y. et al Bioorg. Med. Chem. Lett. 18(1), **2008** 329-335
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[3] Kalac et al., iScience, 23, **2020,** 101884
[4] A. Daina et al. Sci. Rep, 7. **2017**; :42717

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