

Synthesis of new quinoline analogs of selected neuroleptics

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INTRODUCTION & AIM

Neuroleptics are used as psychotropic medication for treatment of psychosis, schizophrenia, bipolar disorder, apathy and neurosis. The latest research on their biological activity shows their new activities including anticancer against brain, lung, breast, liver and colon cancer, antiviral against SARS-CoV and suppression of infections caused by dengue virus. Neuroleptics such as fluphenazine, trifluoperazine and trifluoperazine were the research subject. In terms of structure they are phenothiazine derivatives (figure 1). Their antagonistic effect on dopamine receptors located in presynaptic and postsynaptic membranes allows them to be used as medication for mental disorders. They can be also used to control vomiting, nausea and severe hiccups. The aim of the study was to synthesize new quinoline analogs of selected neuroleptics as new drugs' candidates with more beneficial ADMET profiles.

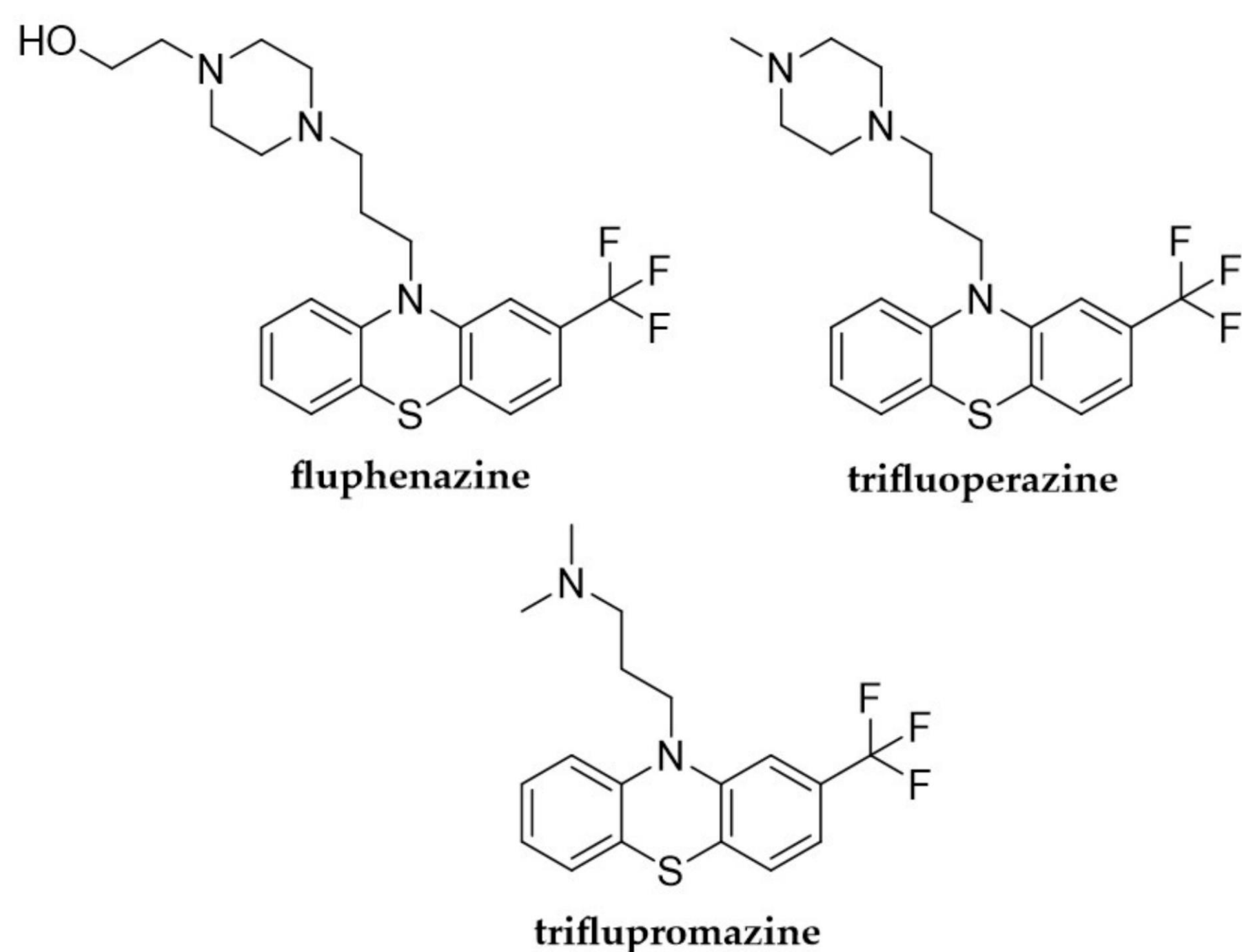


Figure 1. Structure of fluphenazine, trifluoperazine and trifluoperazine.

RESULTS & DISCUSSION

The research carried out allowed to synthesize 6H-8-trifluoromethylquinobenzothiazine and to obtain new quinoline analogs with pharmacophore dialkylaminoalkyl substituents. Currently, eleven new quinoline analogs were synthesized. The reaction of 2-amino-4-trifluoromethylthiophenol **A** with 3-bromo-2-chloroquinoline **B** allowed to selectively obtain 6H-8-trifluoromethylquinobenzothiazine **1** with high efficiency. The study for anticancer activity allowed to determine concentration of new compounds required for 50% inhibition of three human cancer cell lines: breast (MDA-MB-231), pancreatic (Mia-PaCa-2) and lung (A-549) (table 1). Compounds 3, 8 and 12 show the most promising anticancer activity among analysed new quinoline analogs.

Table 1. Cytotoxic activity of compounds 1–13 via MTT assay.

No. of compound	Cell lines			
	MDA-MB-231	Mia-PaCa-2	A-549	HaCaT
1	>100	>100	>100	46.88 ± 4.69
2	>100	>100	>100	>100
3	78.75 ± 5.45	5.32 ± 0.38	4.90 ± 1.48	2.48 ± 0.03
4	>100	>100	>100	55.44 ± 6.58
5	24.42 ± 3.40	19.56 ± 2.25	24.13 ± 5.45	25.51 ± 2.86
6	>100	43.38 ± 3.85	47.75 ± 2.28	>100
7	45.14 ± 4.32	31.28 ± 2.47	49.90 ± 4.11	20.59 ± 2.28
8	9.96 ± 0.05	6.98 ± 2.13	7.52 ± 0.59	13.06 ± 2.51
9	>100	>100	>100	12.22 ± 1.00
10	>100	>100	>100	37.77 ± 6.51
11	17.88 ± 4.67	12.18 ± 4.92	11.31 ± 3.93	11.29 ± 2.65
12	10.76 ± 0.42	5.16 ± 0.53	4.22 ± 0.10	7.21 ± 3.61
13	>100	>100	>100	>100
Doxorubicin	0.50 ± 0.13	24.20 ± 0.50	0.26 ± 0.09	0.30 ± 0.11
Cisplatin	1.90 ± 0.42	3.15 ± 0.09	3.17 ± 1.24	6.30 ± 0.70

METHOD

To synthesize new quinoline analogs, 6H-8-trifluoromethylquinobenzothiazine was synthesized by the reaction of 2-amino-4-trifluoromethylthiophenol **A** with 3-bromo-2-chloroquinoline **B** (figure 2). As a result of that reaction the sulfide **C** was obtained as an intermediate. The sulfide can undergo Smiles rearrangement or cyclization to quinobenzothiazine **1b**. The performed synthesis involved reactions that proceed by the Smiles rearrangement which means that sulphur in sulfide transferred its place with nitrogen creating amine **C'** that underwent cyclization. After synthesizing 6H-8-trifluoromethylquinobenzothiazine **1** it was transformed into methyl derivative **2** and then its structure was confirmed by spectroscopic methods. Afterwards 6H-8-trifluoromethylquinobenzothiazine **1** was used as a substrate to obtain new quinoline analogs with pharmacophore dialkylaminoalkyl substituents **3–13**. The structure of each one of newly synthesized compounds was confirmed by the use of spectroscopic methods such as ¹H NMR, ¹³C NMR and ESI HR MS. All synthesized compounds were studied for anticancer activity against three human cancer cell lines: breast (MDA-MB-231), pancreatic (Mia-PaCa-2) and lung (A-549). Doxorubicin and cisplatin were used as reference drug. Human keratinocyte cell line (HaCaT) was used as healthy cells.

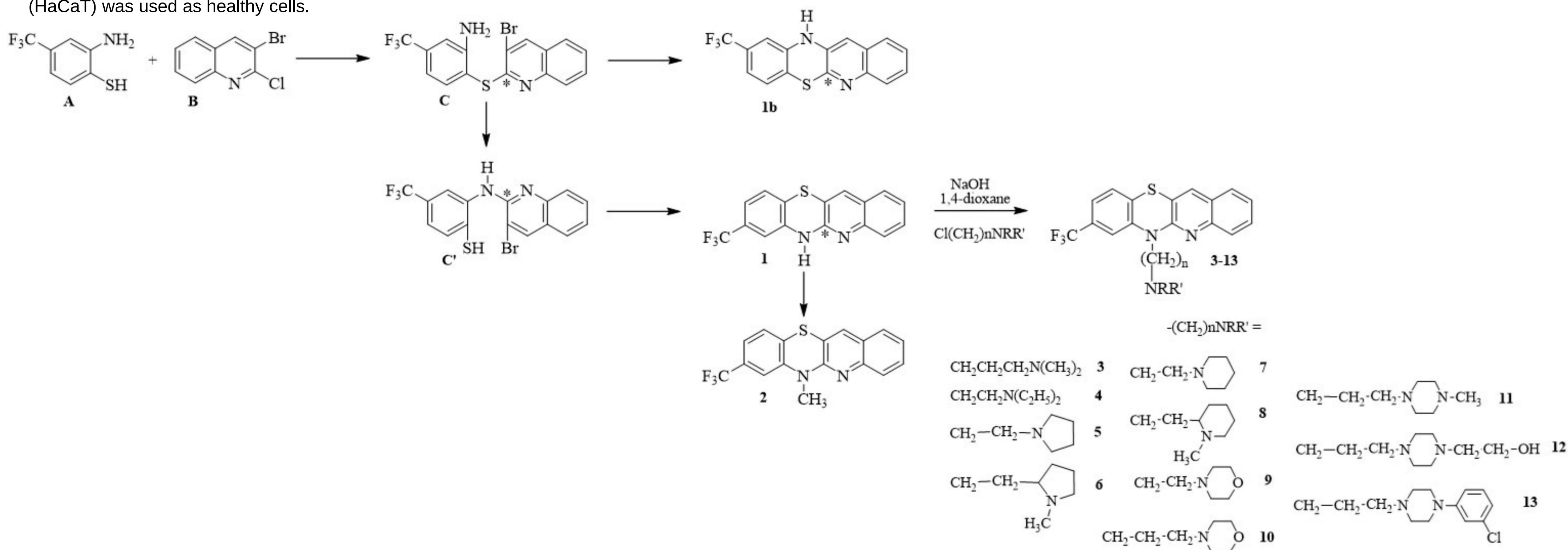


Figure 2. Synthesis of new quinoline analogs.

CONCLUSION

The method chosen to synthesize new quinoline analogs was effective and allowed eleven new compounds to be obtained. The study for anticancer activity against three human cancer cell lines concludes that there are three compounds that show the most promising anticancer activity (IC₅₀ < 5.5 µM).

FUTURE WORK / REFERENCES

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