SYNTHESIS AND MOLECULAR DOCKING OF *N,N'*-[SUCCINYLBIS(OXY)]DIBENZAMIDES AS INHIBITORS OF CATHEPSIN S AND CATHEPSIN K

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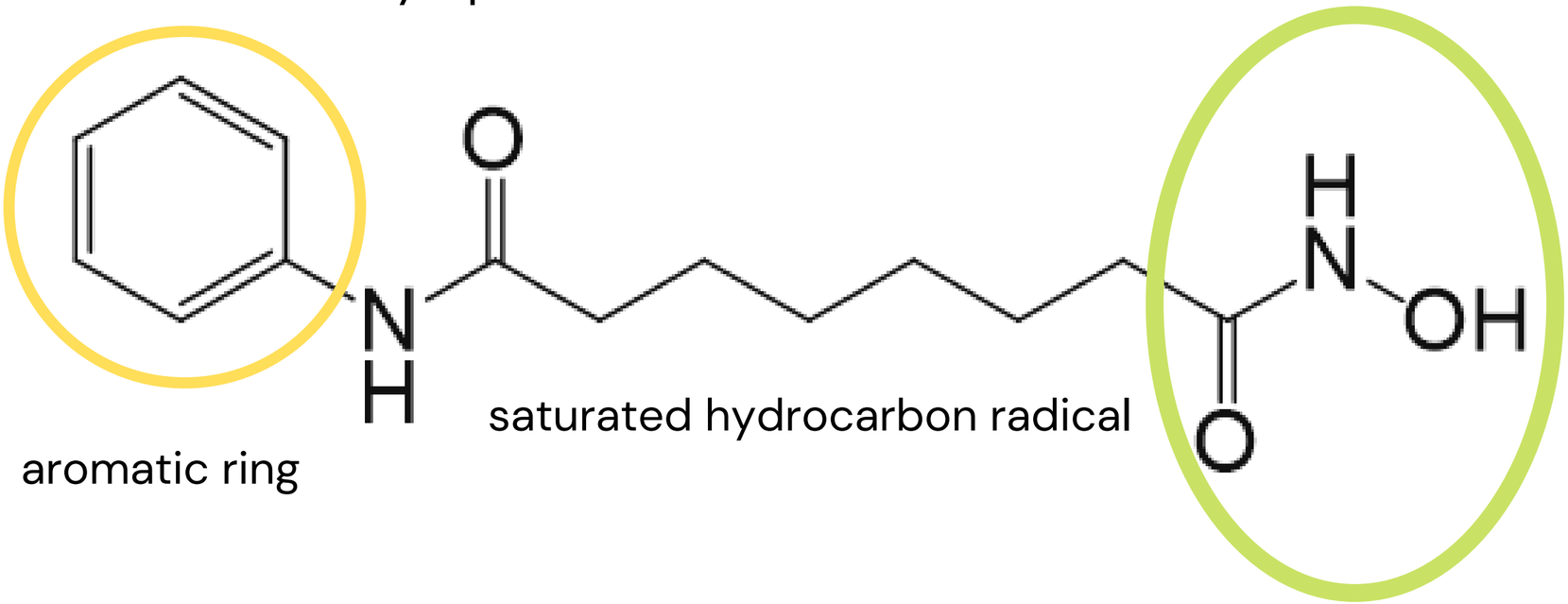
Introduction

Suberoylanilide of hydroxamic acid, available under the trade name Vorinostat, has been used as a drug in the treatment of T-cell lymphoma



aromatic ring

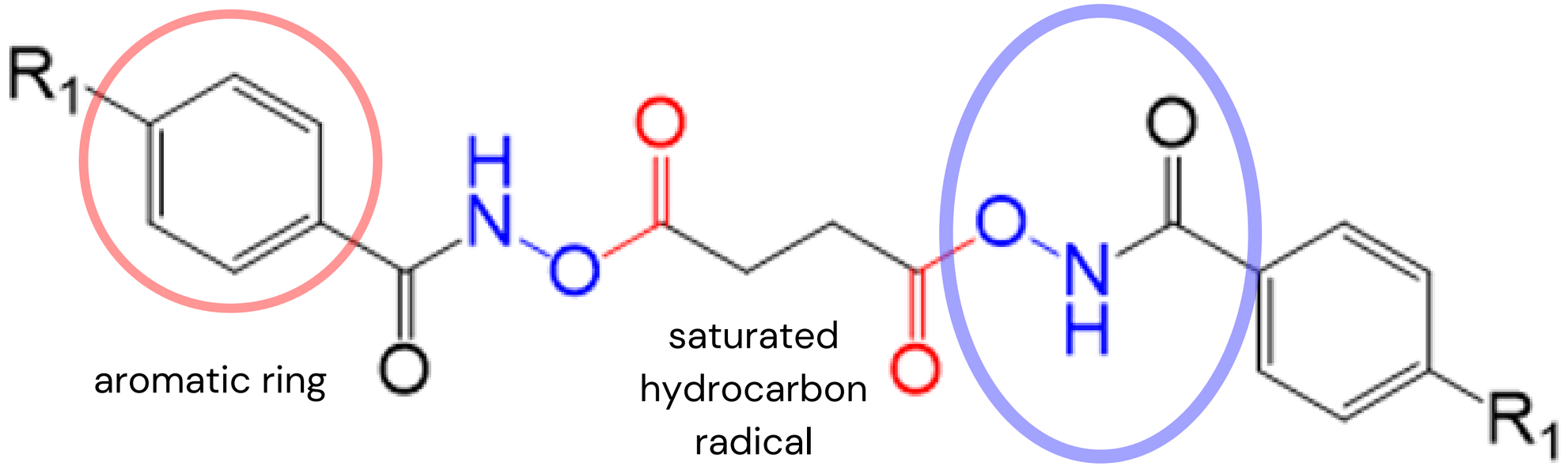
saturated hydrocarbon radical

hydroxamic component

Obtaining compounds of a similar structure, namely, containing in their structure a hydroxamic component, an aromatic ring and a saturated hydrocarbon radical can be a step towards the creation of new drugs.

Results and discussion

We have studied the reaction of interaction of benzhydroxamic acids with succinyl chloride. It was found that during boiling in acetonitrile *N,N'*-[succinylbis(oxy)]dibenzamides **6a,b** are formed



aromatic ring

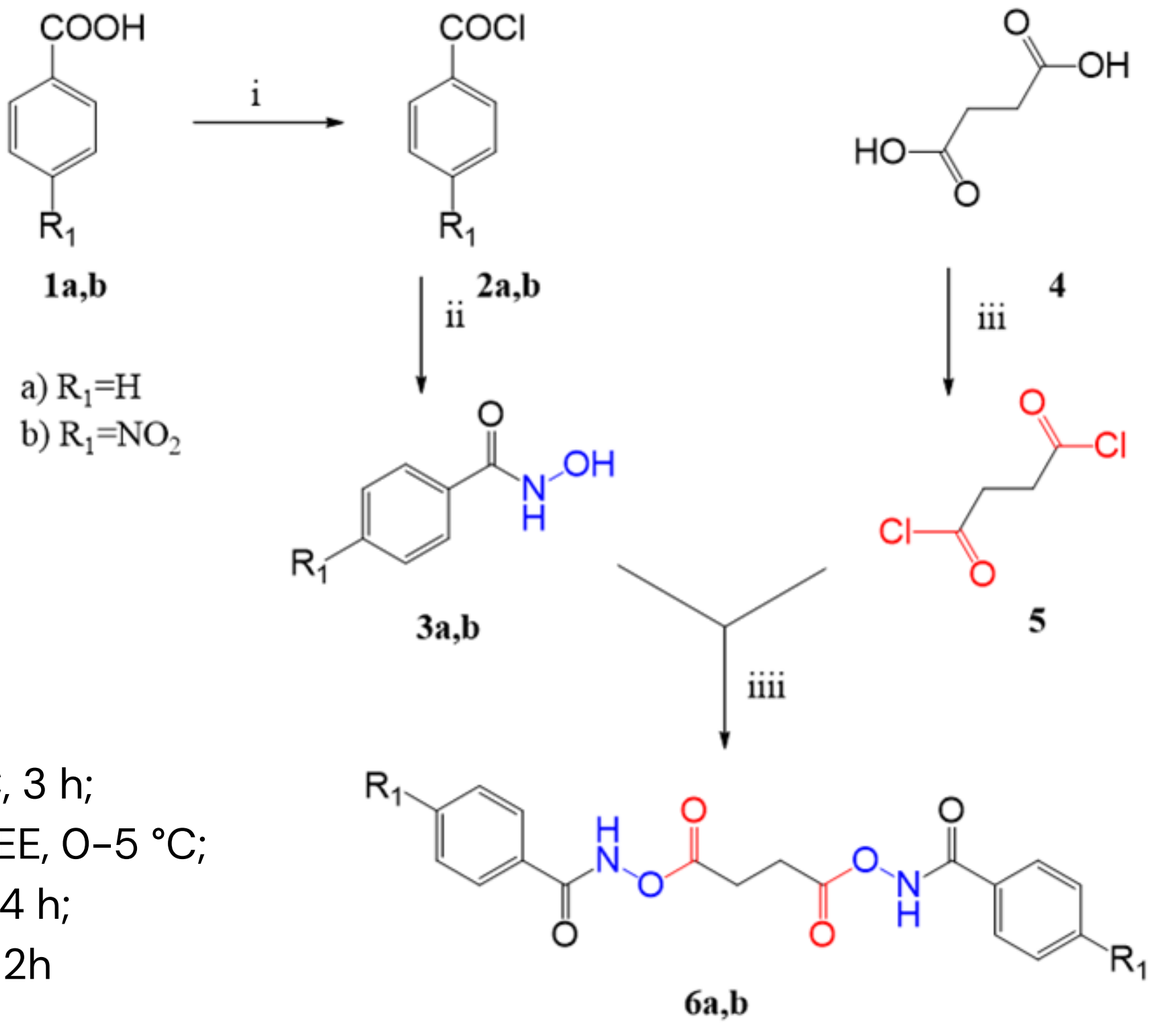
saturated hydrocarbon radical

hydroxamic component

a) R1=H;
b) R1=NO2

Results and discussion

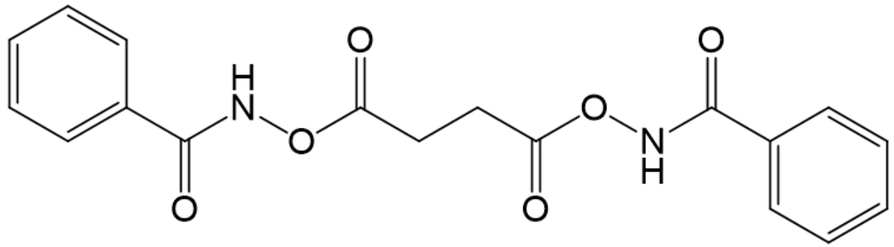
Commercially available benzoic acids **1a,b** were used as starting reagents for the synthesis of **6a,b**. The synthesis was carried out in three stages



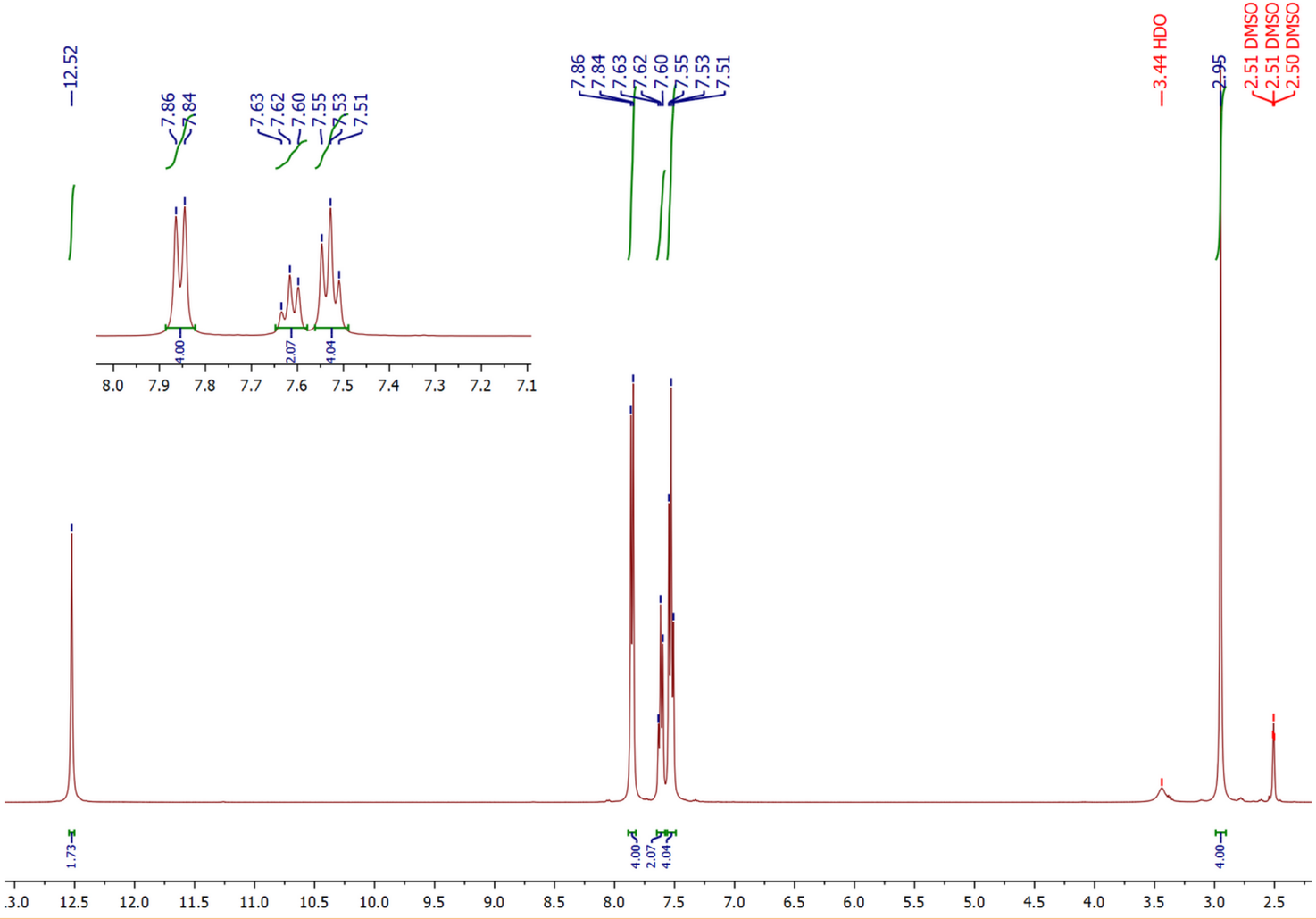
i: SOCl2, DMFA, 40°C, 3 h;
ii: NH2OH*HCl, Na2CO3, DEE, 0–5 °C;
iii: SOCl2, Py, 40°C, 4 h;
iiii: acetonitrile, Δ, 2h

Results and discussion

Typical 1H NMR spectrum for compounds **6a,b** by the example of 1H NMR spectrum for **6a**. The spectrum was recorded in DMSO-d6 (400 MHz) relatively tetramethylsilane as internal standard

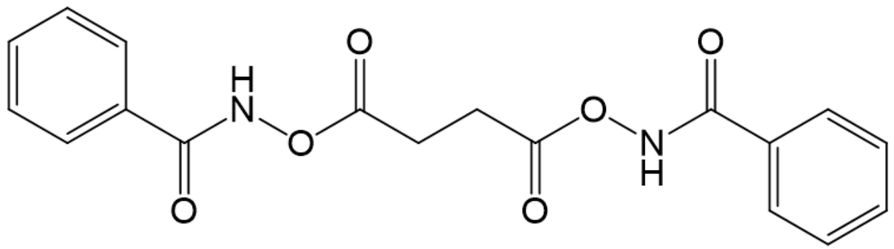


1H NMR (400 MHz, DMSO-d6)
δ 2.96 (s, 4H), 7.52 (t, J = 7.8 Hz, 4H), 7.62 (t, J = 7.8 Hz, 2H), 7.85 (d, J = 7.2 Hz, 4H), 12.52 (s, 2H).



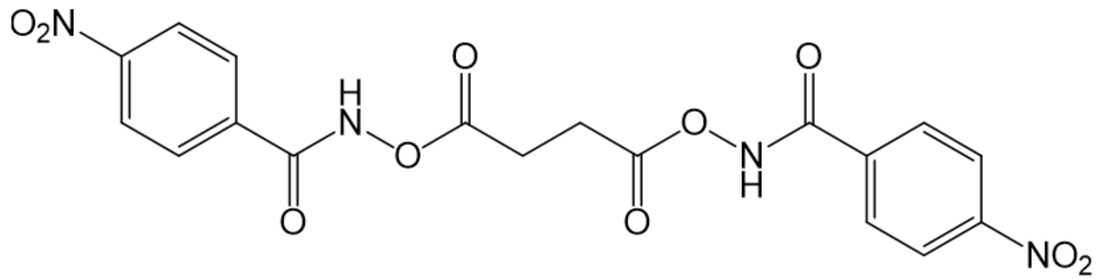
Results and discussion

Biological activity by PASS-online for compounds **6a,b**



6a

Pa	Pi	Activity name
0,929	0,001	Growth hormone agonist
0,529	0,016	GABA aminotransferase inhibitor
0,544	0,039	Antiarthritic
0,550	0,099	Fibrinolytic
0,475	0,070	Cytoprotectant
0,436	0,037	Cathepsin T inhibitor



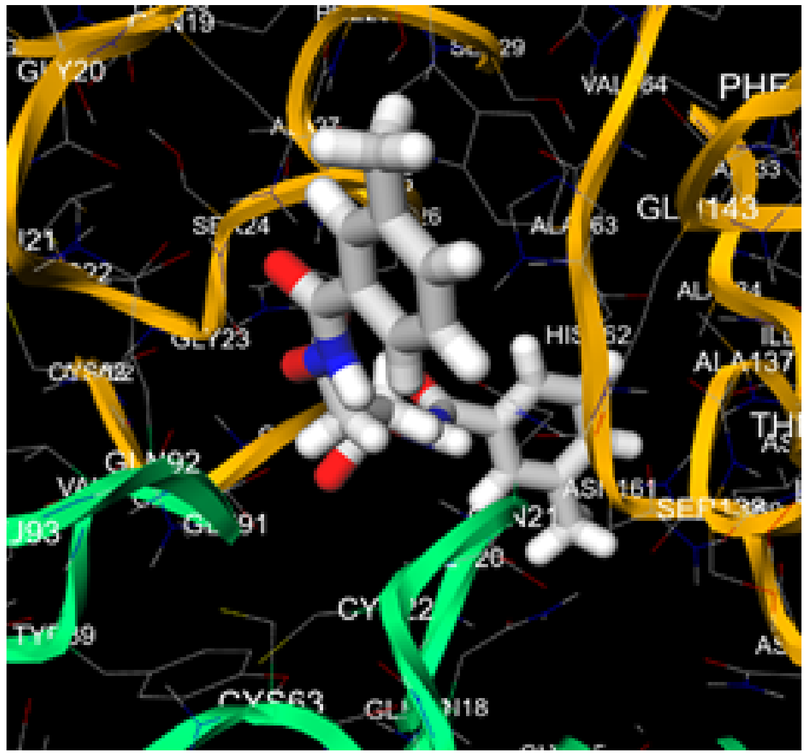
6b

Pa	Pi	Activity name
0,882	0,001	Growth hormone agonist
0,579	0,020	Radiosensitizer
0,465	0,068	Antiviral (Picornavirus)
0,444	0,057	Antihypoxic
0,404	0,051	Chemosensitizer
0,380	0,057	GABA aminotransferase inhibitor
0,329	0,067	Antiviral (Adenovirus)
0,187	0,143	Cathepsin T inhibitor

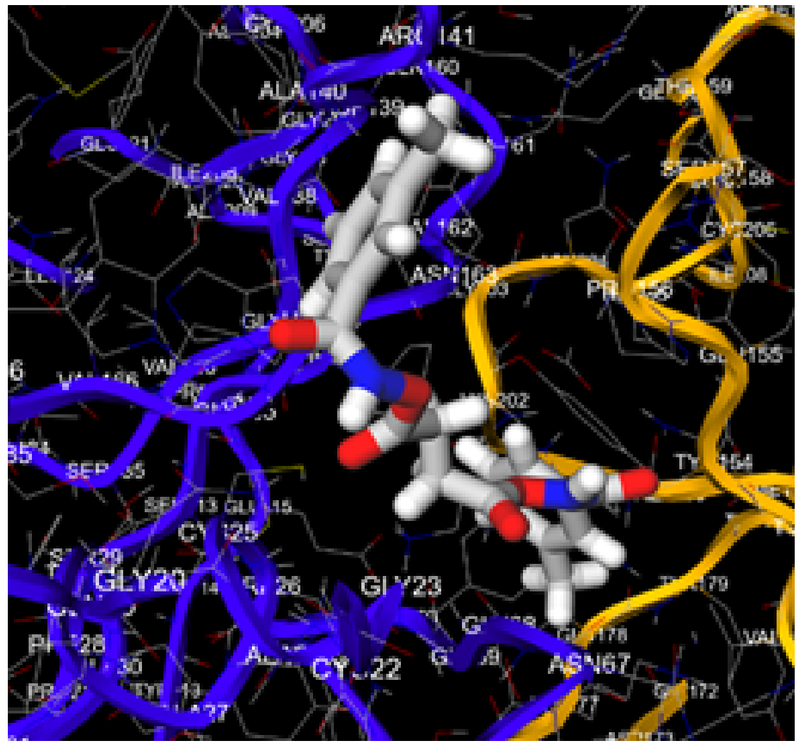
Results and discussion

In order to search for the most active inhibitors of Cathepsin proteases, we studied the molecular docking of the obtained dibenzamides **6a,b** and their analogs. The study was carried out in the online program Mcule, where Cathepsins S (2hxz) and K (1tu6) were selected as a receptor.

Analysis in the Mcule program using the example of *N,N'*-(succinylbis(oxy))bis(3-methylbenzamide).



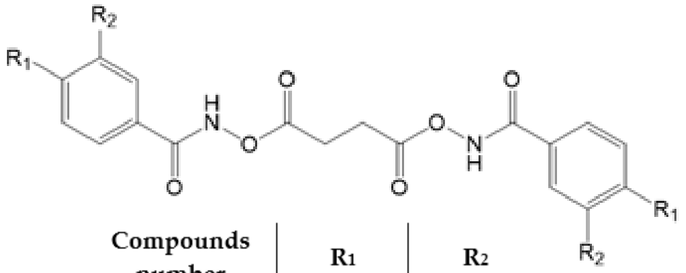
Cathepsin K



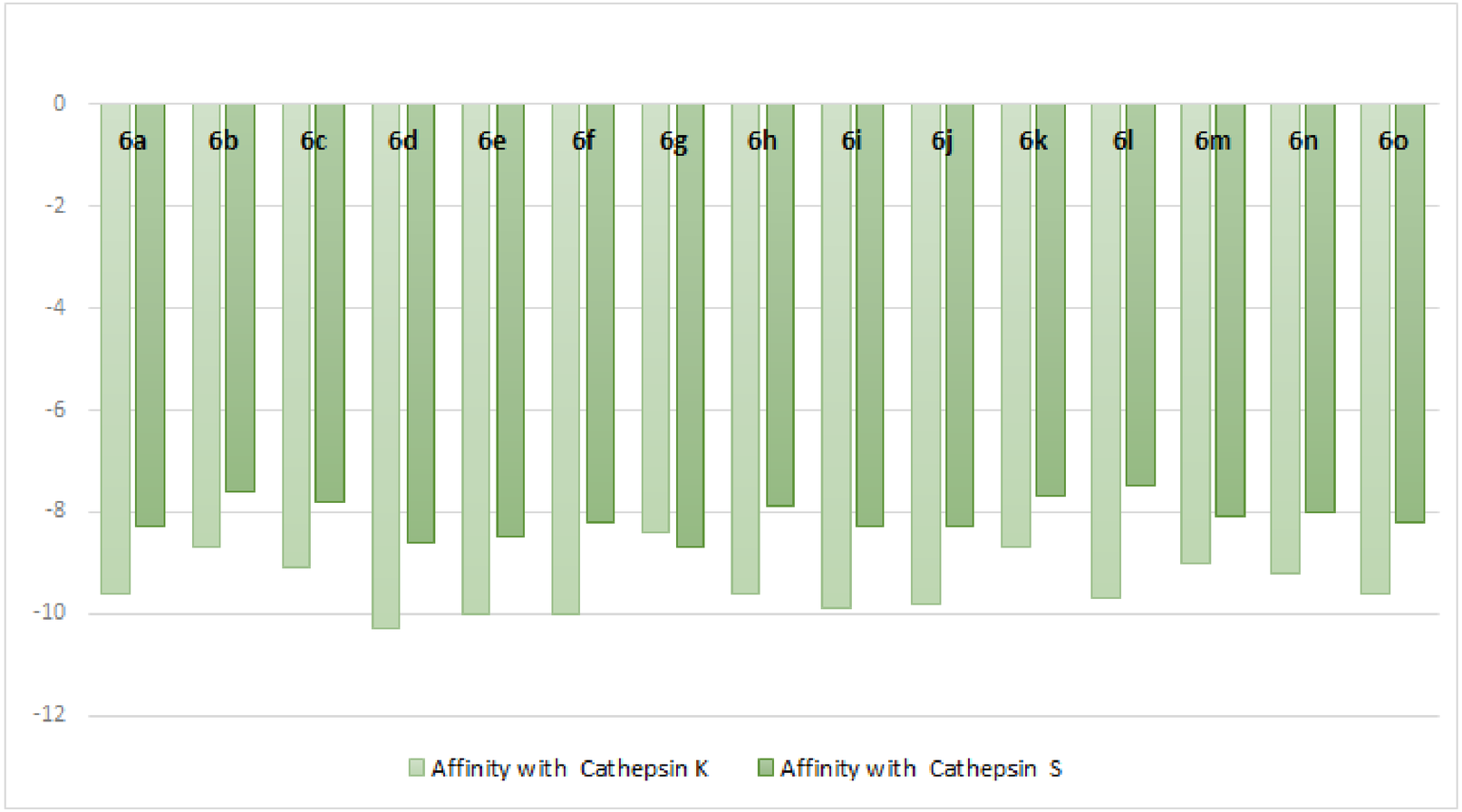
Cathepsin S

Results and discussion

It was found that methyl –, fluoro - and chlorinesubstituted dibenzamides have a higher affinity for binding to Cathepsin. It should be noted that all compounds, with the exception of **6g**, have a higher affinity for Cathepsin K than for Cathepsin S.

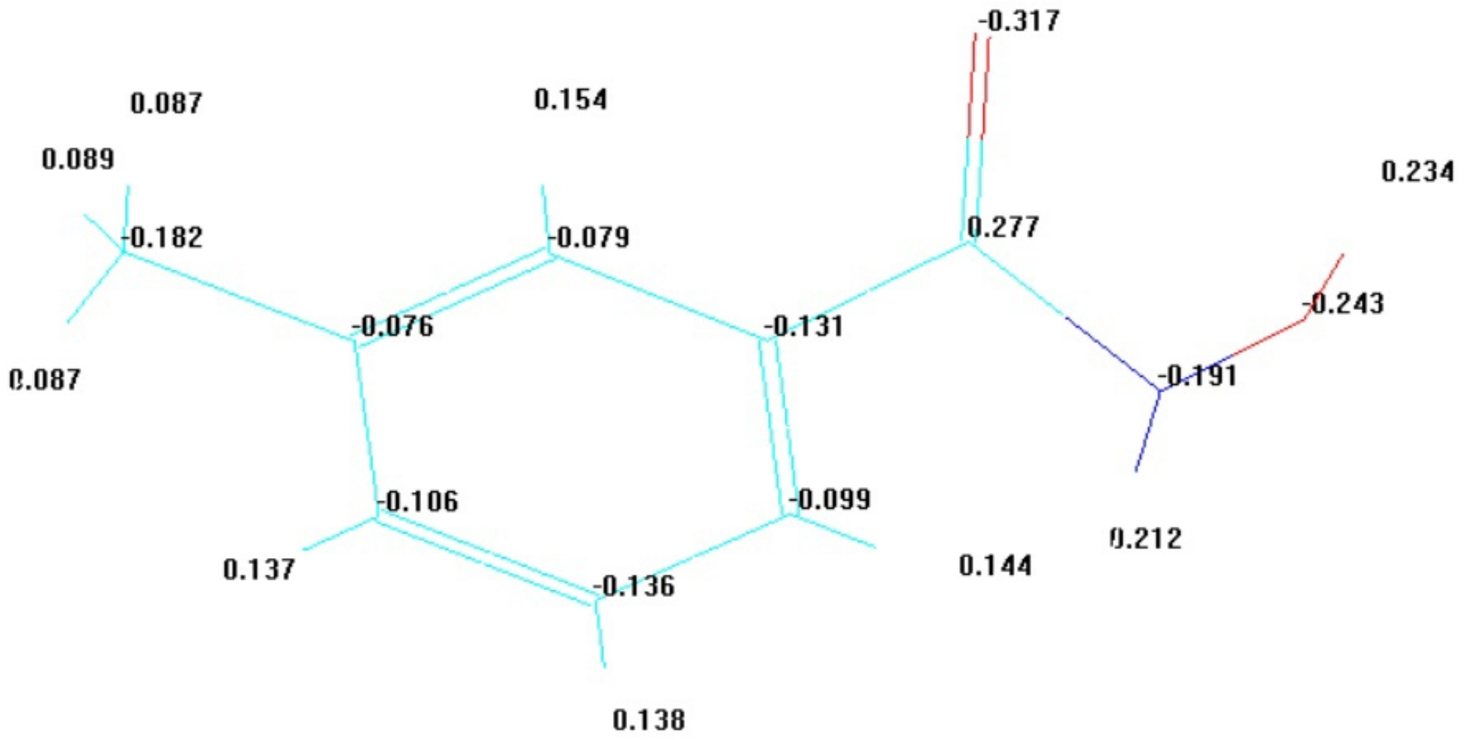


Compounds number	R1	R2
6a	-H	-H
6b	-NO_2	-H
6c	-H	-NO_2
6d	-Me	-H
6e	-H	-Me
6f	-F	-H
6g	-H	-F
6h	-Cl	-H
6i	-H	-Cl
6j	-Br	-H
6k	-H	-Br
6l	-I	-H
6m	-H	-I
6n	-CN	-H
6o	-H	-CN



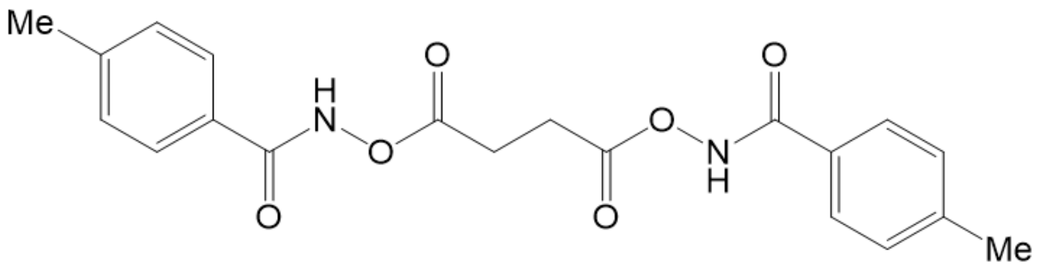
Results and discussion

In order to carry out further synthesis of the most promising molecules, a semi-empirical calculation of charges on oxygen and nitrogen atoms in the corresponding initial benzhydroxamic acids was performed. The calculation was performed using the HyperChem software package using the AM1 method

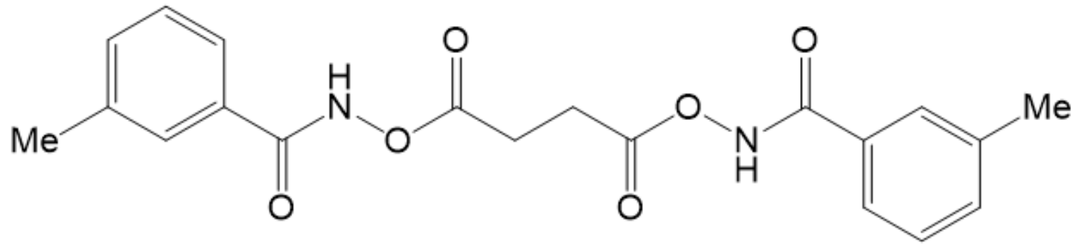


Results and discussion

Based on the above, it is more expedient to obtain methyl-substituted dibenzamides for further *in vivo* biological activity research



6d



6e

Compounds number	R_1	R_2	Charge on the nitrogen atom	Charge on the oxygen atom
6d	-Me	-H	-0,187	-0,244
6e	-H	-Me	-0,191	-0,243
6f	-F	-H	-0,317	-0,171
6g	-H	-F	-0,315	-0,170
6i	-H	-Cl	-0,316	-0,171

Conclusion

- As a result of the reaction of acylation of benzhydroxamic acids with succinyl chloride in acetonitrile medium, *N,N'*-[succinylbis(oxy)]dibenzamides were obtained.
- Their structure was proved by 1H and 13C NMR.
- Using the PASS program, information on the biological activity of new molecules was obtained, in particular, the property of inhibition of Cathepsin proteases was found.
- Using the Mcule program, the values of the affinity of the synthesized dibenzamides and their analogs with Cathepsins S and K were obtained. It was revealed that fluoro-, methyl-, and chlorine-substituted dibenzamides have the highest affinity for Cathepsins S and K.
- Using the HyperChem program, the possibility of obtaining the dibenzamides of interest was analyzed and a conclusion was made about the feasibility of obtaining methyl-substituted dibenzamides in order to further study the biological activity *in vivo*.

Thank you for your attention!

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