EXERCISE V.11

SYNTHESIS, LIPOPHILICITY DETERMINATION, AND QSAR STUDY OF CHALCONES AND ANALOGS WITH ANTITUMORAL ACTIVITY

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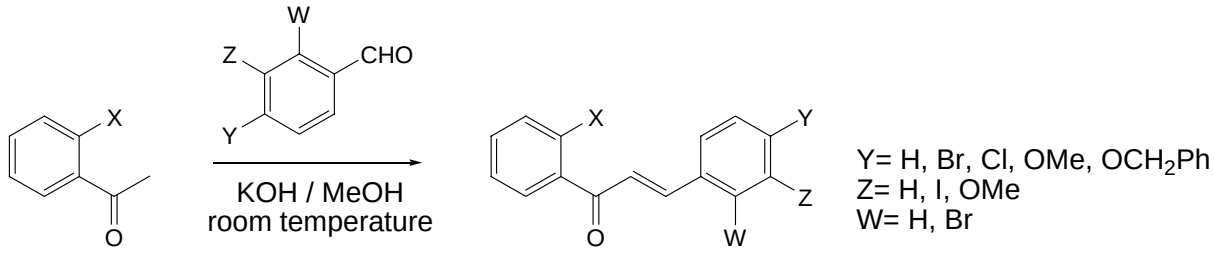
Objectives: 1) To apply a simple and safe synthetic procedure to prepare chalcones and analogs with activity against MCF-7 cells.
2) To determine lipophilicity of these compounds by different methods (experimentally and theoretically).
3) To obtain correlations between lipophilicity and activity.

Synthetic procedures for derivatives 1–11 (see Table)[1,i]



X= H, OH

A mixture of the corresponding ketone (2-hydroxyacetophenone or acetophenone) (1 equiv), the corresponding aldehyde (1 equiv), potassium hydroxide (10 equiv), and ethanol as solvent (50 mL for each gram of ketone) was stirred at room temperature during 24 h. After that, the mixture was acidified with aqueous solution of HCl (10 %). The precipitate was filtered off, washed with cold ethanol, and crystallized from methanol.

Lipophilicity determination

Theoretical calculations[2,3]

The lipophilicity of the chalcone derivatives and analogs will be expressed as LogP. For the theoretical LogP (CLogP, Table) it could be employed using free programs from the Internet[2], or other kind of programs.
In the present proposal, the CLogP was calculated using Villar method, at AM1 semiempirical method, implemented in Spartan'04, 1.0.1 version, suite of programs[3] (Table).

Experimental determinations[4,i]

First, stock solutions of chalcones and analogs were prepared in pure acetone prior to use. The corresponding stock solutions were applied on precoated thin-layer chromatography (TLC) plates SIL RP-18W/UV_{254}. The TLC was eluted with MeOH:physiological serum (80:20, v/v). The plates were developed in a closed chromatographic tank, dried, and the spots were located under UV light. The R_f values were averaged from two to three determinations, and converted into R_M values via the relationship:

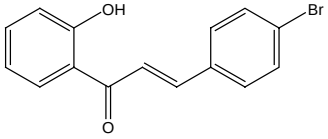
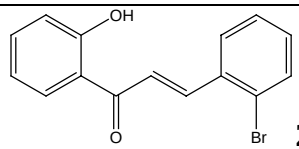
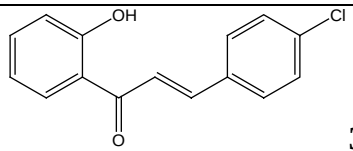
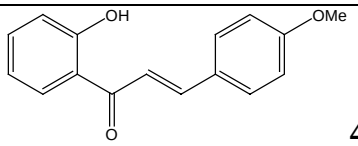
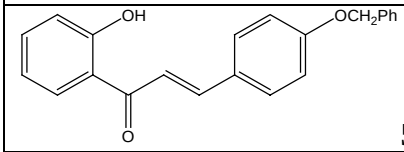
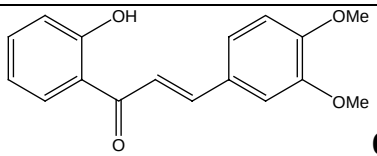
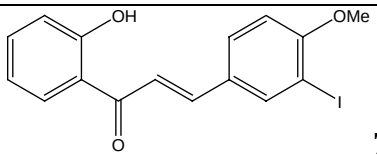
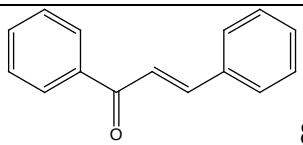
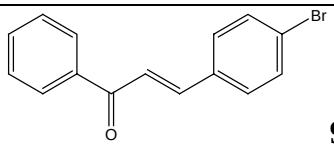
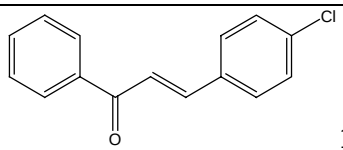
$$R_M = \log [(1/R_f)–1]$$

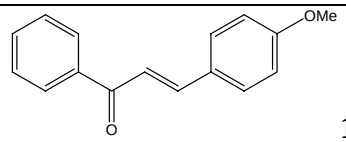
TLC was performed on precoated silica gel 60 F 254 TLC plates, and eluted with petroleum ether:ethyl acetate (80:20, v/v). The plates were developed in a closed chromatography tank, dried, and the spots were located under UV light.

Correlations between lipophilicity and activity

As it is well known, the lipophilicity of a drug plays a significant role in numerous biological responses[5]. So, the relationship between this property and the antitumoral activity (Table) could be studied.

Plot the different forms of expression of the lipophilicity for this family of compounds (CLogP, R_M, and R_f, Table) versus percentage of survival of MCF-7 cells treated with 100 μM of derivatives. Study the relationships.

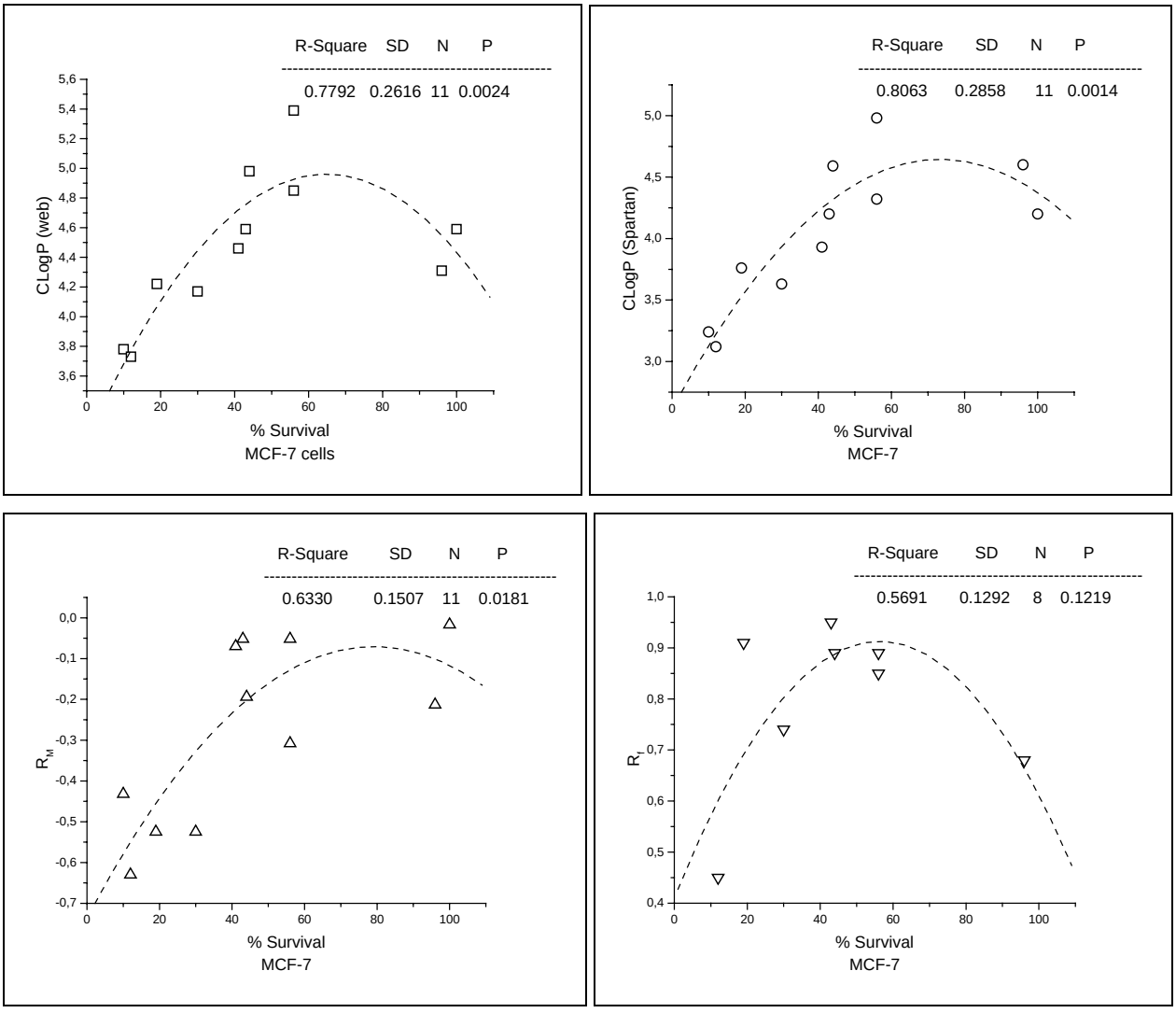
Derivative	Percentage of survival of MCF-7 cells treated with 100 μM of derivatives[a]	CLogP web[b]	CLogP Spartan[c]	R_M C18[d]	R_f SiO_2[e]
 **1**	**43**	**4.59**	**4.20**	**–0.052**	**0.95**
 **2**	**100**	**4.59**	**4.20**	**–0.017**	**nd[f]**
 **3**	**41**	**4.46**	**3.93**	**–0.070**	**nd**
 **4**	**10**	**3.78**	**3.24**	**–0.432**	**nd**
 **5**	**56**	**5.39**	**4.98**	**–0.052**	**0.85**
 **6**	**1.2**	**3.73**	**3.12**	**–0.630**	**0.45**
 **7**	**96**	**4.31**	**4.60**	**–0.213**	**0.68**
 **8**	**19**	**4.22**	**3.76**	**–0.525**	**0.91**
 **9**	**44**	**4.98**	**4.59**	**–0.194**	**0.89**
 **10**	**56**	**4.85**	**4.32**	**–0.308**	**0.89**

 **11**	**30**	**4.17**	**3.63**	**–0.525**	**0.74**

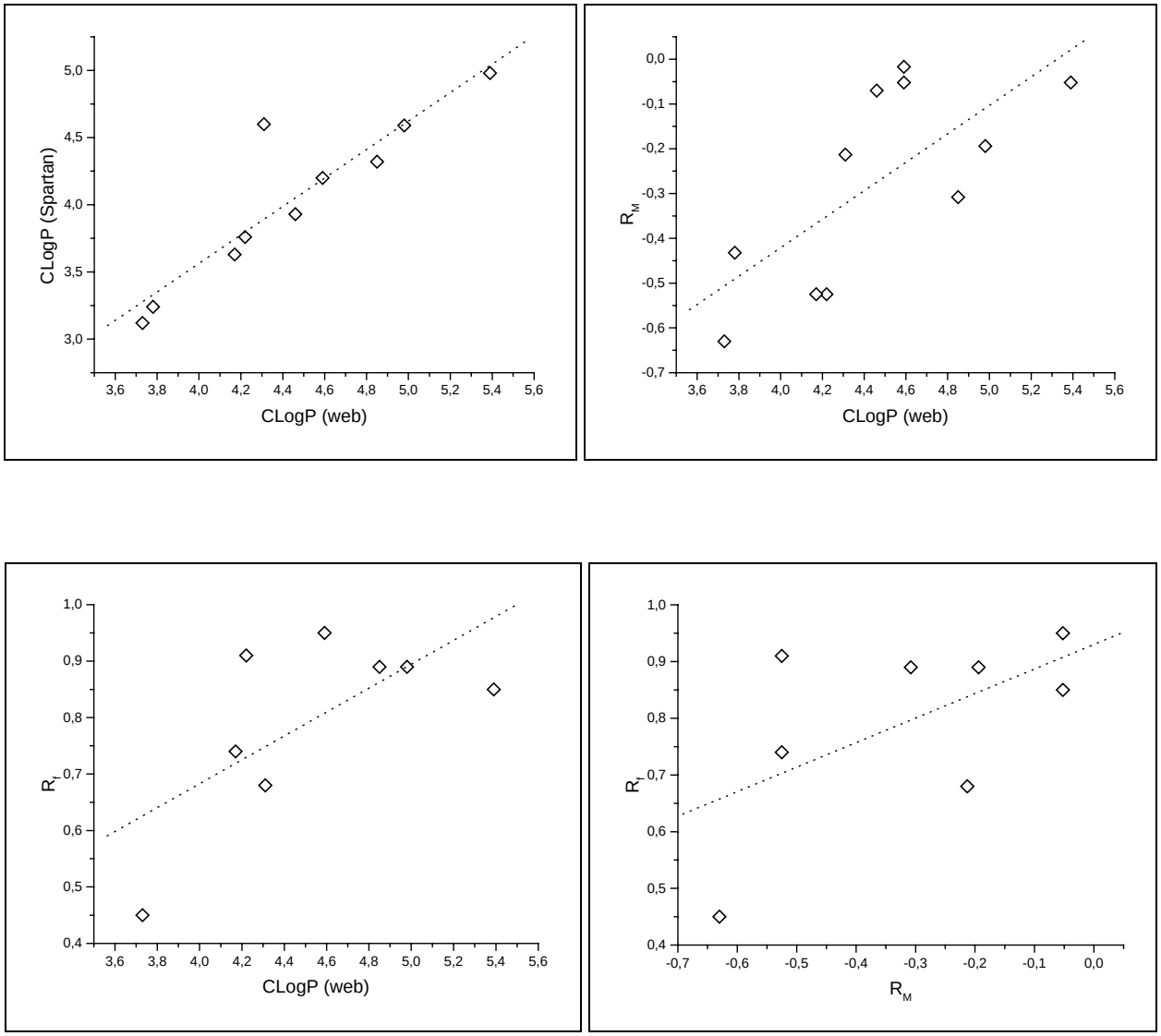
[a]Determined in Centro de Investigaciones en Farmacobiología Aplicada (Pamplona, Spain). Dra. Adela López de Ceráin, Dr. Antonio Monge. [b]http://www.molinspiration.com/cgi-bin/properties. [c]Villar method, reference [3]. [d]SIL RP-18W/UV_{254}, MeOH:physiological serum (80:20, v/v). [e]SiO_2, petroleum ether:ethyl acetate (80:20, v/v). [f]nd: not determined.

Results

In all of cases, like-quadratic correlations were obtained between lipophilicity and antitumoral activity. This is a typical behavior between this property and some kinds of activities[5].



The values that express lipophilicity of the compounds are linearly correlated.



References

1) Song, L.L.; Kosmeder, J.W.; Lee, S.K.; Gerhäuser, C.; Lantvit, D.; Moon, R.C.; Moriarty, R.B.; Pezzuto, J.M. *Cancer Research.* 59 (1999) 578-585.

2) http://www.molinspiration.com/cgi-bin/properties.

3) Spartan'04; Wavefunction, Inc. 18401 Von Karman Avenue, Suite 370. Irvine, California 92612 USA.

4) a) Tsantili-Kakoulidou, A.; Antoniadou-Vyza, A. *Prog. Clin. Biol. Res.* 291 (1989) 71-74. b) Denny, W. A.; Graham, J. A.; Roberts, P. B.; Anderson, R. F.; Boyd, M.; Lock, C. J. L.; Wilson, W. R. *J. Med. Chem.*, 35 (1992) 4832-4841.

5) C. Hansch, A. Leo, The hydrophobic parameter: measurement and calculation, in: Exploring QSAR. Fundamentals and Applications in Chemistry and Biology, American Chemical Society, Washington, 1995, pp 97-124.

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High standards in safety measures should be maintained in all work carried out in Medicinal Chemistry Laboratories.
The handling of electrical instruments, heating elements, glass materials, dissolvents and other inflammable materials does not present a problem if the supervisor's instructions are carefully followed.

This document has been supervised by Prof. Hugo Cerecetto (hcerecet@fq.edu.uy) who has informed that no special risk (regarding toxicity, inflammability, explosions), outside of the standard risks pertaining to a Medicinal Chemistry laboratory exist when performing this exercise.

If your exercise involves any "special" risks, please inform the editor.

Safety aspects
[i] All the procedures must be done in a fume hood.