3rd International Electronic Conference on Medicinal Chemistry
1-30 November 2017
chaired by Dr. Jean Jacques Vanden Eynde
sponsored by pharmaceuticals

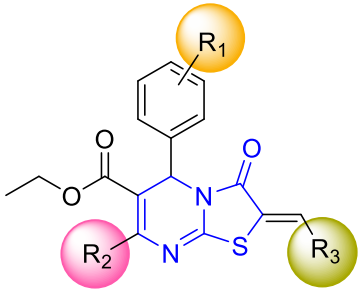
Synthesis, Characterization, Molecular docking and Structure-Activity Relationships of Novel Thiazolo[3,2-*a*]pyrimidines as Prospective Acetylcholinesterase Inhibitors

Mohamed Y. Mahgoub [1,2]*, Awatef M. Elmaghraby [2], Abd-Elfttah A. Harb [2], João L. Ferreira da Silva [1], Gonçalo C. Justino [1], and M. Matilde Marques [1]

[1] Centro de Química Estrutural, Instituto Superior Técnico, Universidade de Lisboa, 1049-001 Lisboa, Portugal;
[2] Chemistry Department, Faculty of Science, South Valley University, Qena 83523, Egypt.

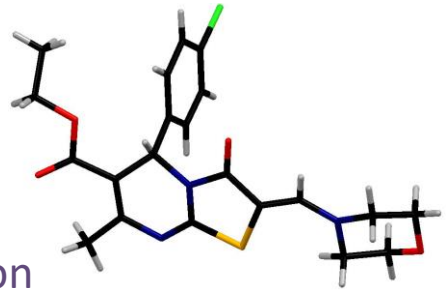
* Corresponding author: m.mahgoub2013@gmail.com

Synthesis, Characterization, Molecular docking and Structure-Activity Relationships of Novel Thiazolo[3,2-*a*]pyrimidines as Prospective Acetylcholinesterase Inhibitors

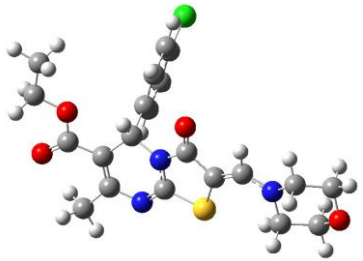


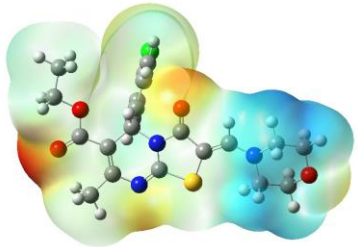
45 Compounds

Full characterization

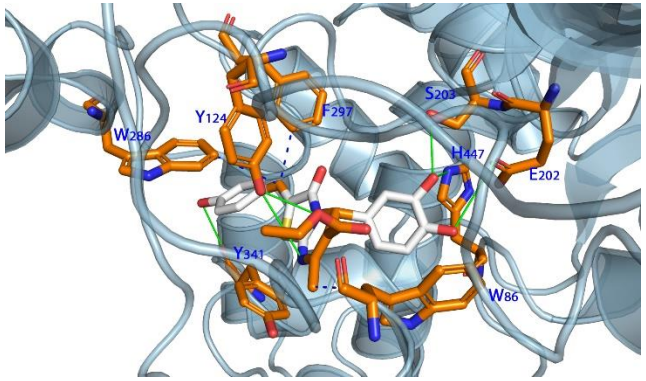


DFT study





Molecular docking



Biological activity

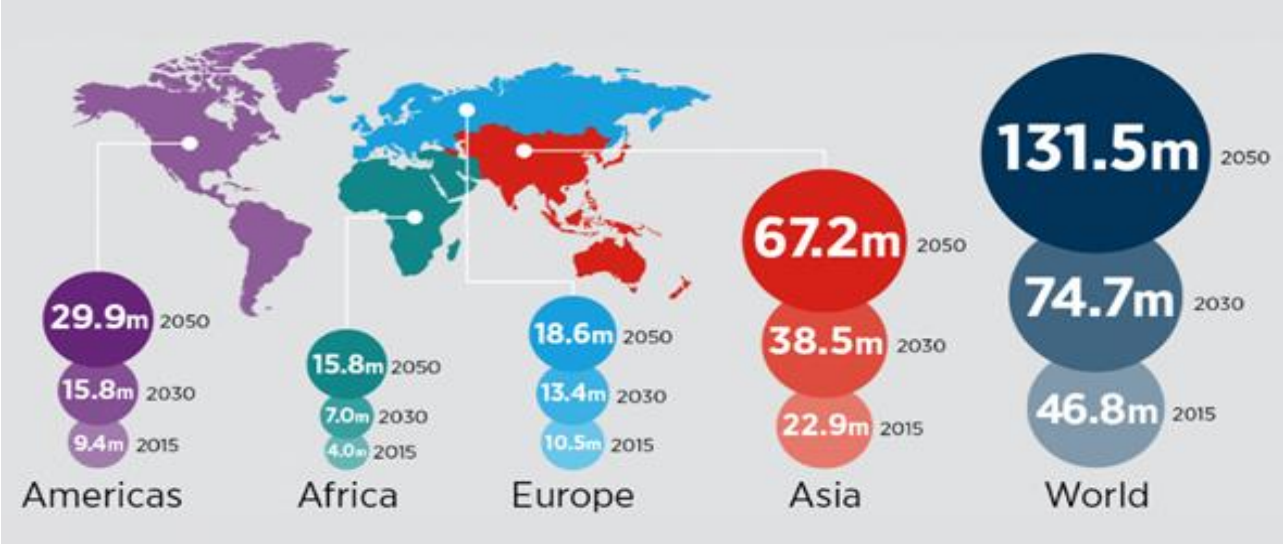
On going

Abstract: Acetylcholinesterase (AChE) is the enzyme that catalyzes the hydrolysis of the neurotransmitter acetylcholine (ACh) into acetic acid and choline, a crucial mechanism for regulation of neurotransmission at synapses in all nervous systems. According to the cholinergic hypothesis, depleted levels of ACh are associated with Alzheimer's disease. As part of a program aimed at preparing new bioactive heterocycles with kinase and AChE inhibition properties, we designed and synthesized a series of (*Z*)-2-arylidene- and 2-aminomethylene derivatives of thiazolo[3,2-*a*]pyrimidine by a convenient multicomponent method. The products were fully characterized by 1D- and 2D-NMR, high resolution ESI-MS/MS and single crystal X-ray diffraction analysis, which indicated a consistent *Z* configuration at the arylidene and aminomethylene double bond. Additionally, molecular docking simulations of the series of 2-arylidene/aminomethylene-thiazolo[3,2-*a*]pyrimidine derivatives to human AChE (PDB ID: 4m0f, chain A) were conducted to investigate the binding mode of those compounds in comparison to Territrem B (TB), used as positive control. The results indicate that some of the test compounds have binding energies to AChE that are comparable, or better, than the positive control, TB. Biological activity studies are underway to assess the activities of the new compounds.

Keywords: Thiazolopyrimidines; acetylcholinesterase; molecular docking; enzyme inhibition

Alzheimer's disease

- Alzheimer's disease (AD) was first identified more than 100 years ago.
- 70 years passed before AD was recognized as the most common cause of dementia, as well as a major cause of death in elderly people.
- Worldwide, **nearly 47 million** people have Alzheimer's or a related dementia (see map).
- The global cost of Alzheimer's and dementia is estimated to be **$605 billion.**

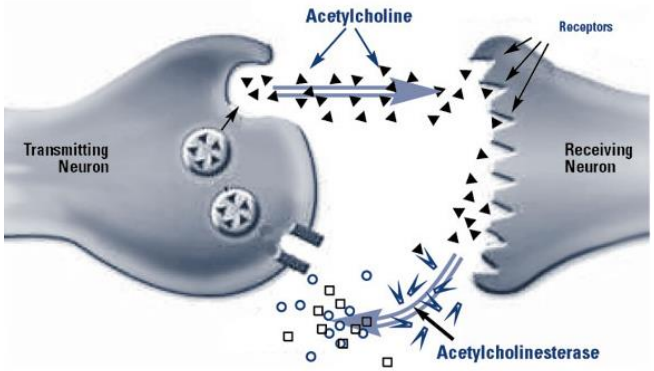


- Alzheimer's Association. 2016 Alzheimer's Disease Facts and Figures. Alzheimer's & Dementia 2016; 12(4).
- Alzheimer's Disease International's World Report (accessed 17 October 2017).

Disease mechanistic hypothesis

Cholinergic hypothesis

- One of the oldest mechanistic theories for the onset of AD is the ***cholinergic hypothesis***.
- Acetylcholinesterase (AChE) is the enzyme that catalyzes the hydrolysis of the neurotransmitter acetylcholine (ACh) into acetic acid and choline.
- According to the cholinergic hypothesis, depleted levels of ACh are associated with Alzheimer's disease.

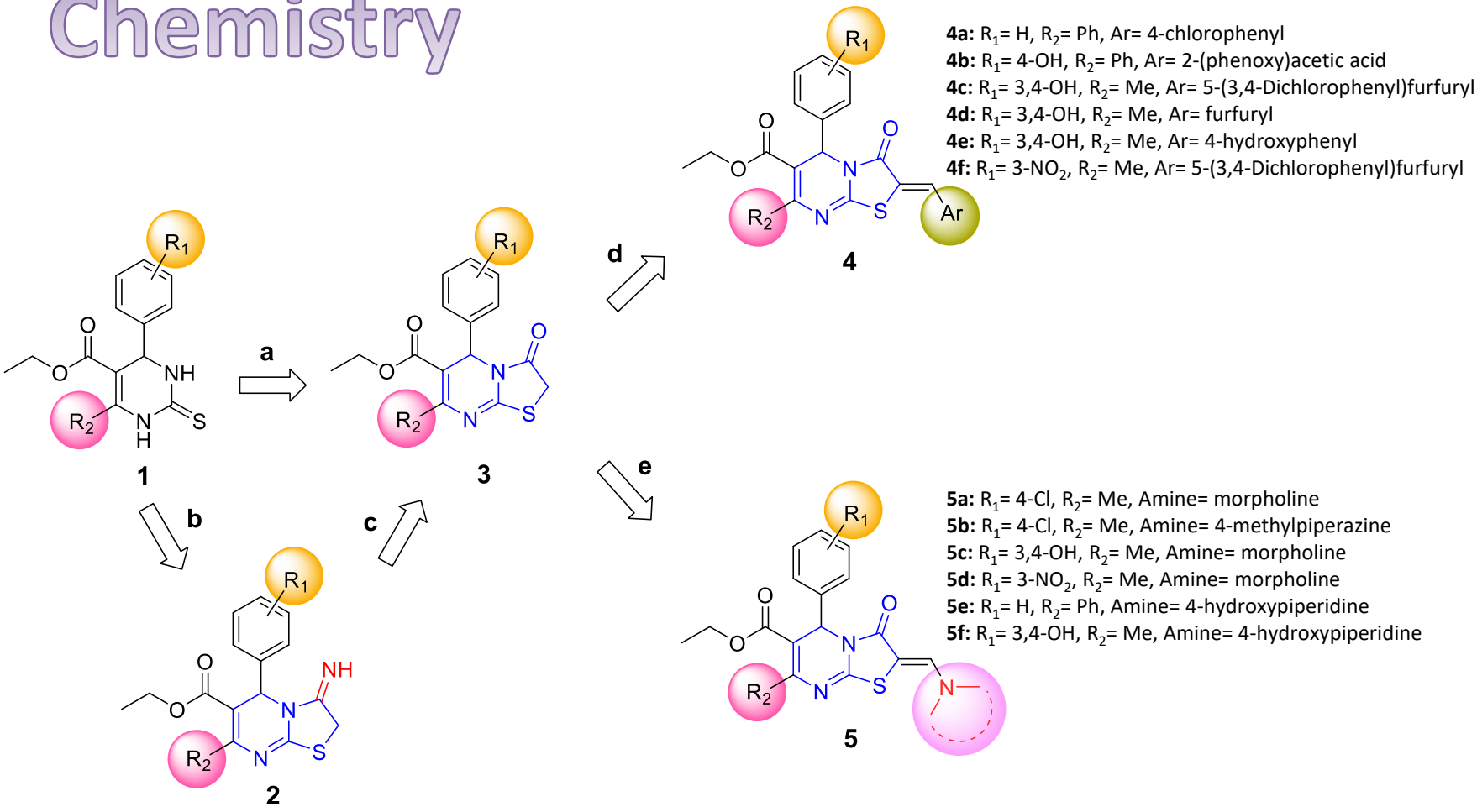


AChE breaks down ACh in the brain.

- ACh hydrolysis is a crucial mechanism for regulation of neurotransmission at synapses in all nervous systems.
- We designed and synthesized a novel series of thiazolo[3,2-*a*]pyrimidine derivatives with prospective AChE inhibition properties.

Francis, P.; Palmer, A.; Snape, M.; Wilcock, G. *J. Neurol. Neurosurg. Psychiatry* **1999,** *66*, 137-147.
http://www.tajaccura.com/natural-galantamine-overcomes-speechlessness-enhances-language-skills-giving-donepezil-a-run-for-its-money/ (downloaded 17 October 2017, 14:09).

Chemistry



4a: R_1= H, R_2= Ph, Ar= 4-chlorophenyl
4b: R_1= 4-OH, R_2= Ph, Ar= 2-(phenoxy)acetic acid
4c: R_1= 3,4-OH, R_2= Me, Ar= 5-(3,4-Dichlorophenyl)furfuryl
4d: R_1= 3,4-OH, R_2= Me, Ar= furfuryl
4e: R_1= 3,4-OH, R_2= Me, Ar= 4-hydroxyphenyl
4f: R_1= 3-NO_2, R_2= Me, Ar= 5-(3,4-Dichlorophenyl)furfuryl

5a: R_1= 4-Cl, R_2= Me, Amine= morpholine
5b: R_1= 4-Cl, R_2= Me, Amine= 4-methylpiperazine
5c: R_1= 3,4-OH, R_2= Me, Amine= morpholine
5d: R_1= 3-NO_2, R_2= Me, Amine= morpholine
5e: R_1= H, R_2= Ph, Amine= 4-hydroxypiperidine
5f: R_1= 3,4-OH, R_2= Me, Amine= 4-hydroxypiperidine

Scheme 1: Reaction conditions: **a)** $ClCH_2COOEt$, $AcONa.3H_2O$, EtOH, Reflux; **b)** $ClCH_2CN$, EtOH, 50°C; **c)** EtOH, HCl/H_2O; **d)** Ar-CHO, piperidine, EtOH, Reflux (10 min-3h); **e)** One pot: amine, DMF-DMA, dry 1,4-dioxane, Reflux, 5-60 min.

Results and discussion - Representative Experimental Data

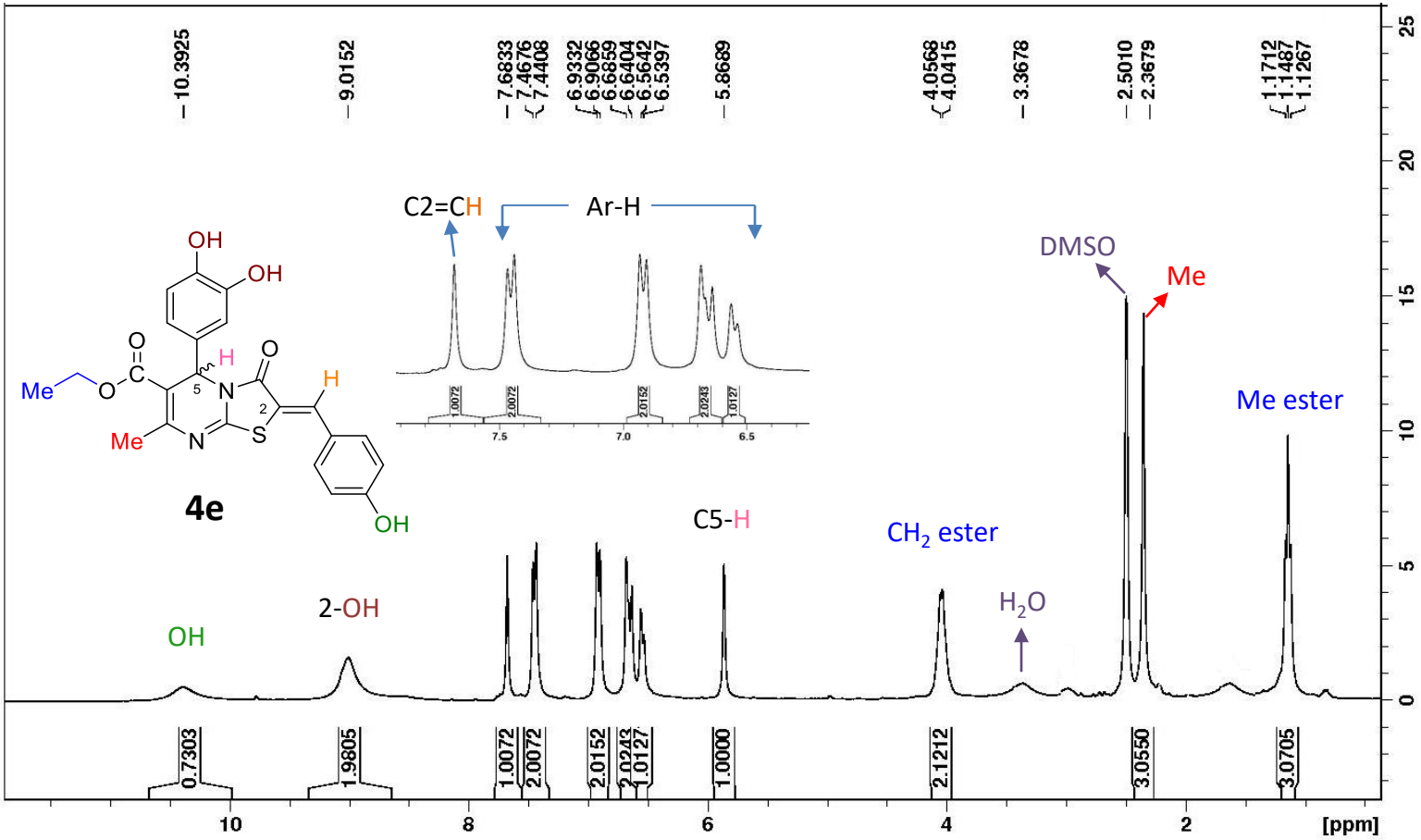


Figure 1. ^{1}H. NMR spectrum of compound **4e**.

Results and discussion - Representative Experimental Data

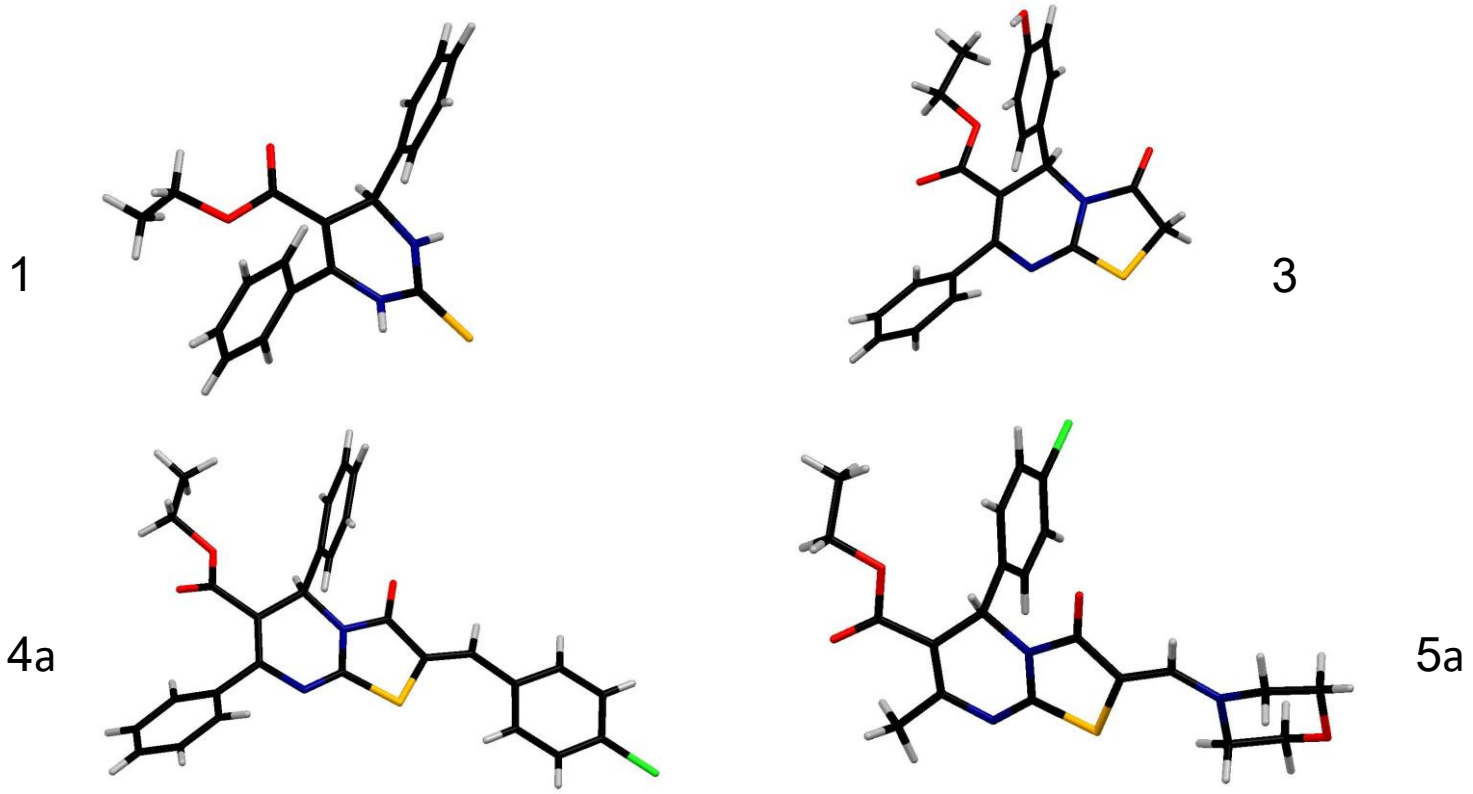


Figure 2. Diagrams of the molecular structure of compounds **1** (R_1= H, R_2= Ph), **3** (R_1= 4-OH, R_2=Ph), **4a** and **5a** obtained by single crystal X-ray diffraction, showing a *Z* configuration at the methylene double bond for **4a** and **5a**.

Mahgoub, M. *et al. In Proceedings of the 20th Int. Electron. Conf. Synth. Org. Chem.*, 1–30 November 2016; Sciforum Electronic Conference Series, Vol. 20, 2016 , b008.

Results and discussion - Representative Experimental Data

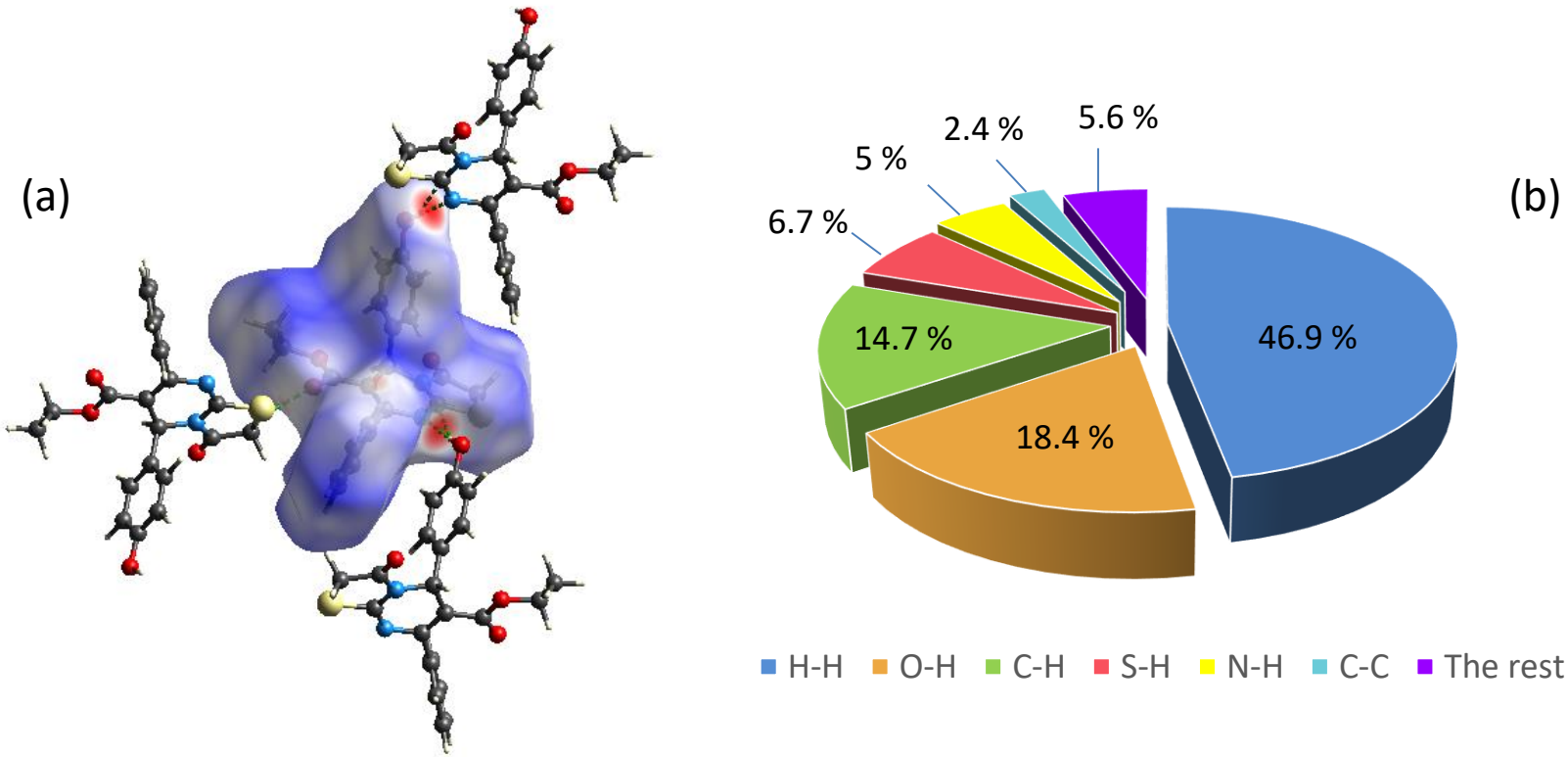


Figure 3. **(a)** The 3D Hirshfeld surface mapped with d_{norm}, with red colored regions showing the main shorter contacts with neighboring molecules; **(b)** Summary of 2D fingerprint plots showing the relative contributions of specific intermolecular contacts in the crystal of compound **3** (R_1= 4-OH, R_2=Ph).

Results and discussion - Representative Experimental Data

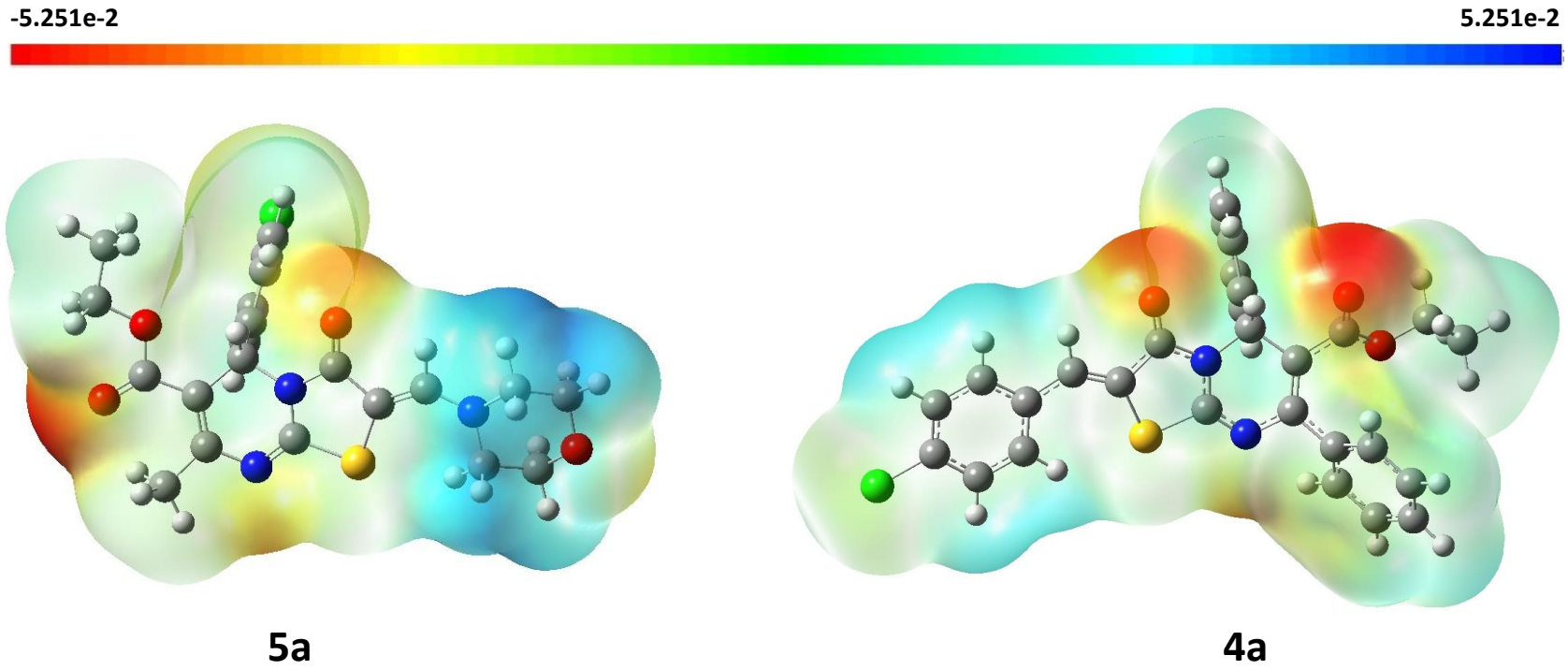


Figure 4. Electrostatic potential surface (EPS) maps of compounds **4a** and **5a** optimized with B3LYP/6-31+G(d) level of theory in the gas phase. EPS was used to visualize the reactive sites for electrophilic (red regions) and nucleophilic (blue regions) attack in the molecules.

Results and discussion - Representative Experimental Data

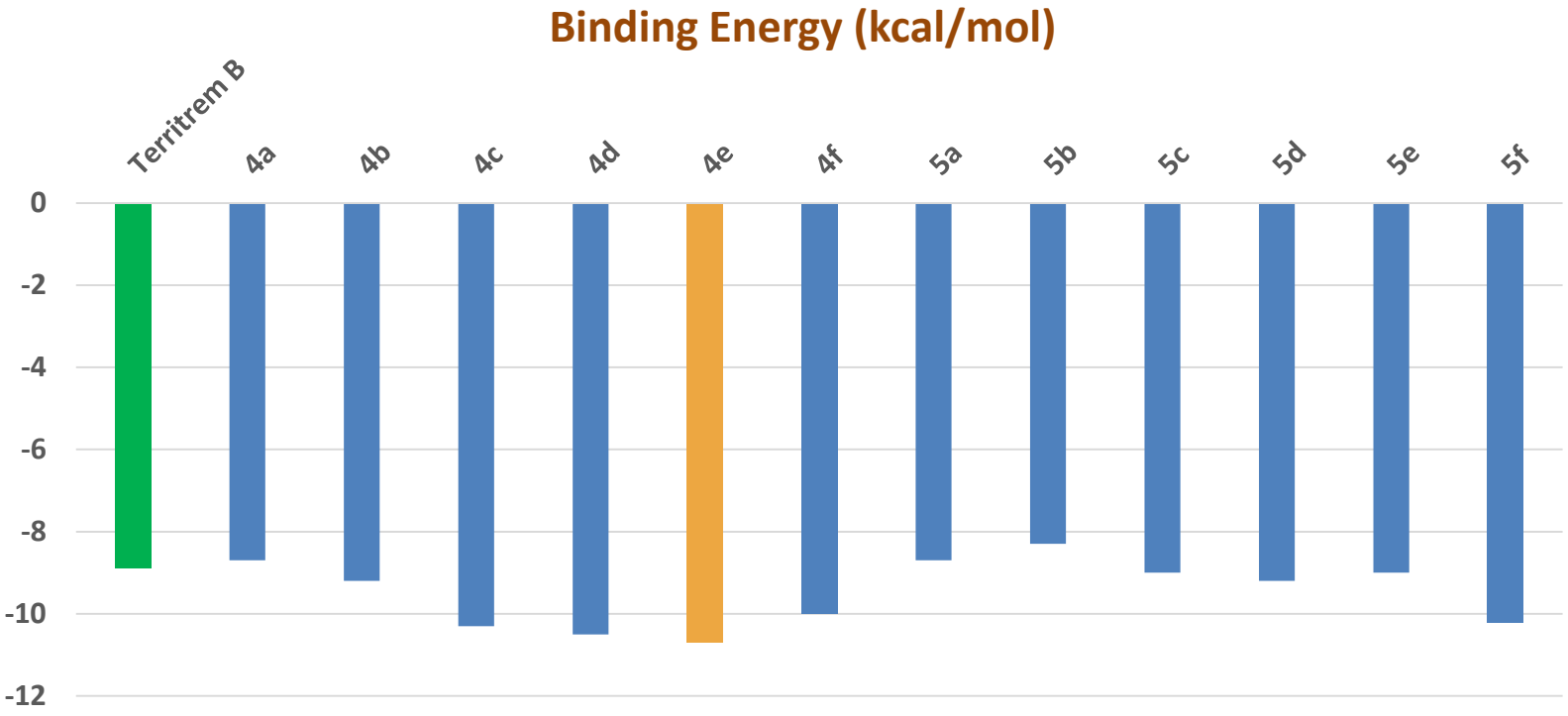


Figure 5. Comparison of the binding free energies of compounds **4a-f**, **5a-f** and the control, Territrem B *, to human AChE. Compound **4e** shows the best binding energy (-10.7 kcal/mol) to AChE. Several of the test compounds bound better than the positive control, Territrem B (-8.9 kcal/mol).

* Cheung, J. *et al*., *ACS Med. Chem. Letters* **2013**, 4, 1091- 1096.

Results and discussion - Representative Experimental Data

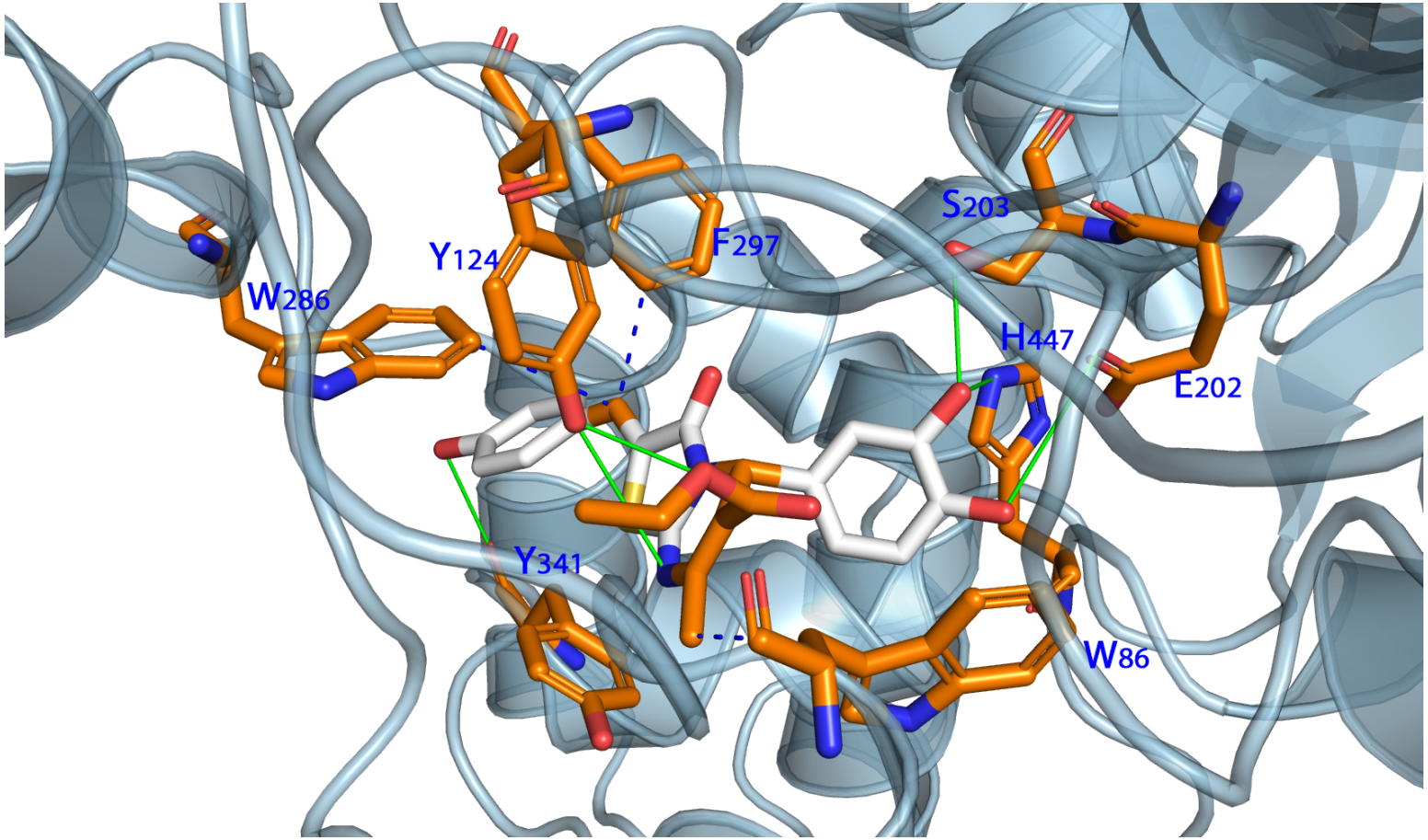


Figure 6. Molecular docking of **4e** to human AChE, showing the relevant interactions with nearby amino acid residues.

Results and discussion - Representative Experimental Data

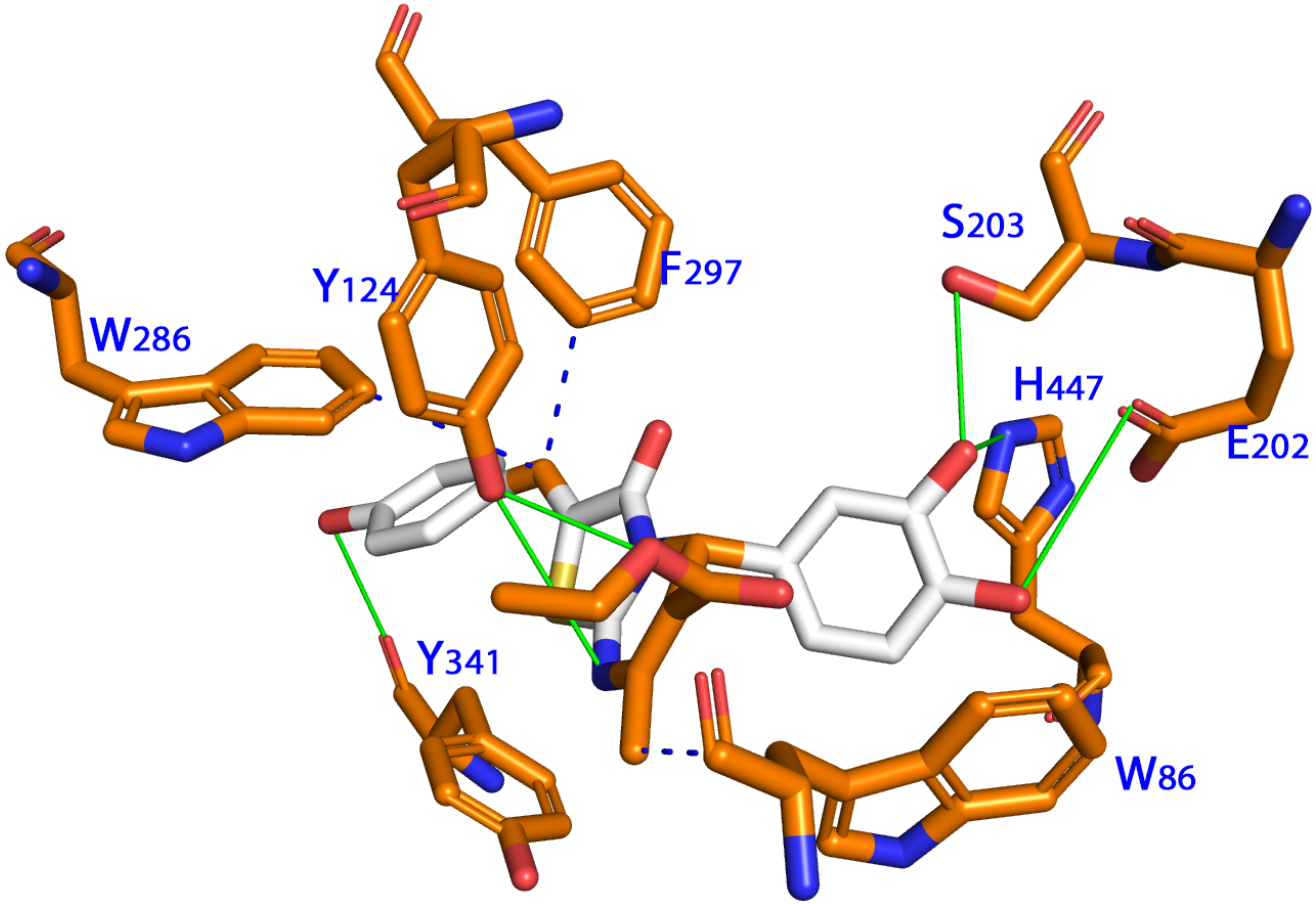


Figure 7. A more clear view of **4e** docked to human AChE, showing the H-bond (green line) and hydrophobic (blue dashed line) interactions with catalytic (**S**203, **H**447 and **E**202) and peripheral sites.

Conclusions

- We have characterized a set of selected racemic 2-arylidene/aminomethylene thiazolo[3,2-*a*]pyrimidines of potential interest for therapeutic uses (**Scheme 1**).

- By using X-ray diffraction studies, we were able to establish that formation of the 2-arylidene/aminomethylene double bond was stereoselective for the *Z* configuration (**Figure 2**).

- The 3D *d*norm Hirshfeld surface map was generated in order to investigate the intermolecular interactions in the crystal for compound **3** (R_1= 4-OH, R_2= Ph) (**Figure 3**).

- EPS maps have been calculated for the optimized structures by DFT at B3LYP/6-31+G(d) level of theory to visualize the reactive sites of representative molecules (**Figure 4**).

Conclusions

- Molecular docking to human AChE indicated that compounds **4e, 4d, 4c, 4f,** and **5f** have the best binding energies (-10.7, -10.5, -10.3, -10 and -10.2 kcal/mol, respectively) and compare favourably with the positive control, Territrem B (-8.9 kcal/mol) (**Figure 5**).

- Molecular docking of **4e** to human AChE, showed the establishment of H-bond and hydrophobic interactions with catalytic (**S**203, **H**447 and **E**202) and peripheral triads (**W**286, **Y**341 and **Y**124) (**Figure 7**).

- The compounds reported herein are currently undergoing biological testing.

Acknowledgments

This work was supported in part by Fundação para a Ciência e a Tecnologia (FCT, Portugal), through grants RECI/QEQ-MED/0330/2012, RECI/QEQ-QIN/0189/2012, UID/QUI/00100/2013 and SAICTPAC/0019/2015. MYM also thanks the Egyptian Higher Education Ministry, Cultural Affairs and Missions sector for financial support. Thanks are also due to Ana Dias and Dr. Conceição Oliveira for obtaining the MS data.