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Organoselenium Chemistry: after 200 years the "*Gold Rush*" is still open

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Abstract: This manuscript aims to be a celebrative tribute to the 200th anniversary of "selenium birthday" presenting an overview of the contribute of our group in different fields of this research, ranging from the development of new reagents for green chemistry and catalysis to the design and synthesis of novel molecules as anti-HIV and, as recently reported by others, antimicrobial agents. We are strongly convinced that in the next future important discoveries could emerge as a result of a research that produces thousands of new publications every year. In the form of prospective article here we just collect selected results among those presented by our young students at 6th Workshop of the SeSRedCat Network which was held in Wroclaw, Poland (21th23rdSeptember 2017)

Selenium (Se) was named by J. J. Berzelius exactly 200 years ago after its discovery in the residue of sulfuric acid preparations from a mining operation. At the beginning Berzelius believed to have in his hands a sample of Tellurium (discovered some years before) and only at the beginning of 1818 further investigations on the redox properties demonstrated that it was a new element and the name Selenium (from Selene meaing “moon” in Greek) was chosen for the similarity with Tellurium (“Heart”). Fora long time, the main biological activity of selenium derivatives was supposed to be connected to their toxicity and some exotic theories correlated historical events to the selenium poisoning. In 1285, Marco Polo, crossing the Shanxi Province of Western China, observed an unknown intoxication of the animals on his ships (loss of hair) that later was supposed to be selenosis and in 1860, a US Army surgeon documented the first selenium poisoning in livestock, suggesting a fascinating theory that an intoxication by selenium slowed General Custer's Cavalry relief. [1] In 1560, the first case of human chronic selenosis characterized by loss of hair and nails was described by Father Simon Pedro in Columbia. [2] Even if nowadays several studies have confirmed that some disorders in animals and humans are consequence of selenium bioaccumulation it is also clear that selenium is fundamental for life having the role of essential micronutrient in mammals. As direct consequence of these prejudices the research in the field was particularly slow in the past and relegated to a restricted number of groups in the world. Nowadays

it is known that selenium is an essential micronutrient for mammals and that the reduction of peroxides in living systems is a catalyzed by the selenoenzyme glutathione peroxidase (GPx).[3] GPx has a crucial role in controlling the reactive species of oxygen (ROS) mediated damage of lipid membranes and other cellular structures. More than 25 selenium-containing proteins are expressed by humans and are distributed in a broad range of tissues and cells.[4] Among them the thioredoxin reductase (TrxR), selenoprotein P, selenoproteins K, M, N and H having different roles, in some cases not fully studied and understood.[5]

In 2009 for the first time we proposed that, following a biomimetic approach, selenium catalysts could be considered a good strategy to setup new reactions following the paradigms dictated by the twelve principles of Green Chemistry. [6] Considering the reaction mechanism proposed for GPx, it can be depicted as an oxidation performed in aqueous conditions in which the selenium of the selenoenzyme is the catalyst, hydrogen peroxide is the oxidant (affording as side product a molecules of water) and glutathione acts as a substrate. Removing the sulfur containing cofactor, selenium can be overoxidized affording to a more flexible and versatile protocol for the oxidation of a broad range of substrates. (Figure 1)

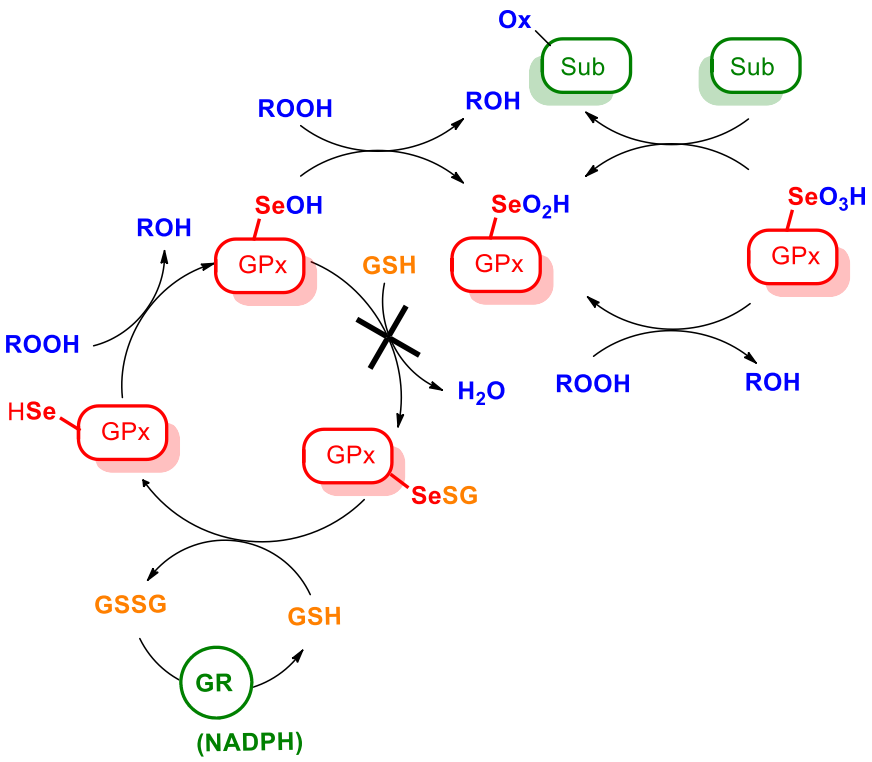

Figure 1: Schematic mechanism of Glutathione Peroxidase (GPx) and biomimetic approach.

Based on this kind of approach several transformations were recently reported by our group and, in some cases, the possibility to recover the catalyst together with the reaction medium (water) represents a considerable improvement in terms of eco-sustainability respect the currently known methods. Carbon-carbon double bonds can be converted into the corresponding diols and the reaction is completely stereospecific due to the intermediate formation of an epoxide.[7] In a similar way when the olefin contains, in a suitable position, an internal nucleophile, like an alcohol or a carboxylic acid the reaction proceeds though the intramolecular ring opening of the epoxide affording the corresponding cyclic ethers or lactones in very good yields.[8] Very recently some of us reported the first example of selenium catalyzed oxidation under flow conditions.[9] A convenient method for the oxidation of aldehydes into the corresponding alcohols (or esters if the reaction is performed in alcohol) has been developed using the hydrogen peroxide mediated oxidation in water of hydrated aldehydes. The reaction is particularly clean, and it was optimized to perform the gram scale synthesis of benzoic acid in pharmaceutical grade purity without the use of chromatographic purification. [10]

The same catalytic oxidative machinery can be used for the chemoselective oxidation of sulphides to sulfoxide or sulphones using one or two equivalents of oxidant, respectively.[11]

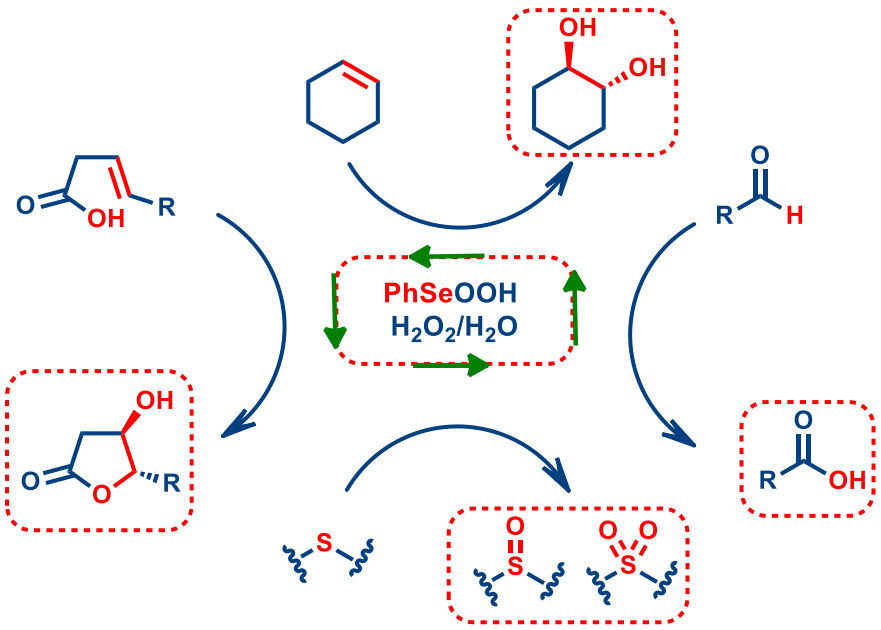

Figure 2: Bioinspired “Green Oxidations”

Several procedures were reported in the past to perform electrophilic selenol addition reactions to carbon-carbon double bonds. Very recently a solvent free approach has been proposed by Braga and coworkers using catalytic amount of iodine in the presence of a stoichiometric amount of dimethyl sulfoxide as stoichiometric oxidant. The methoxyselenylation reaction, depicted in figure 3, was demonstrated to be efficient for a number of substrates and a number of nucleophiles affording, under microwave activation in just ten minutes, the desired products in good or excellent yields. [12]

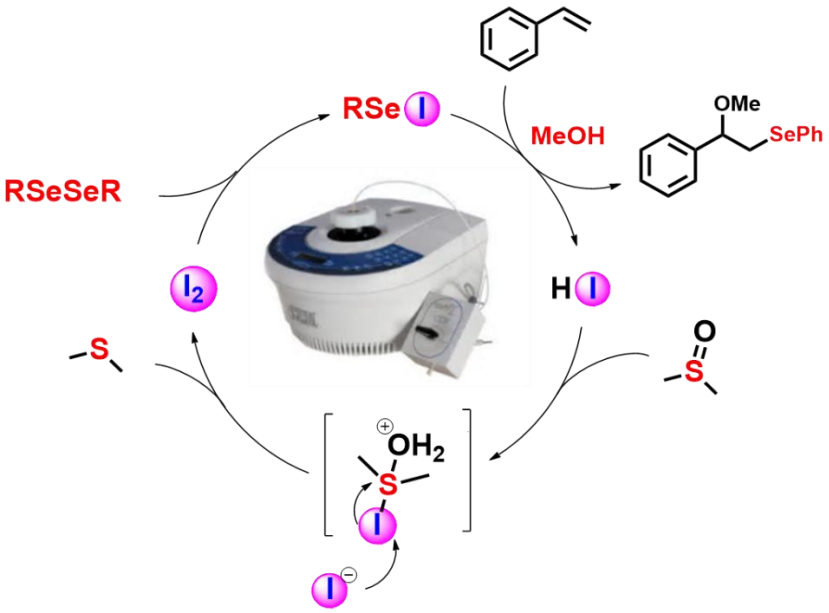

Figure 3: Solvent Free methoxy selenation

Our pioneering idea of selenium-containing compounds as powerful catalysts/ reagents in new green protocols [6] was rapidly developed by many researchers affording many interesting results in different applications. Some of these results were recently collected in a review article entitled “the Green side of the Moon” [13] and in a special issue edited in Current Green Chemistry,[14] demonstrating a growing interest in this field. A large interest has been directed to the reaction that using selenium reagents or catalyst can be efficiently performed “in water” or “on water” even if in several cases the simple use of water is not enough to considered eco-friendly a given protocol. [15]

In this field ten years ago, we synthetized the first class of stable zinc selenates (Fig 4) that, in addition to the exceptional stability, showed a remarkable rate acceleration in all the nucleophilic reaction performed in water suspension probably positively affected by the hydrophobic effect. This reagents, also known as Santi's reagents, are nowadays commercially available even if they can be easily prepared starting from PhSeCl or the corresponding bromide by oxidative insertion of the metal into the Se-halogen bond in refluxing THF.[16]

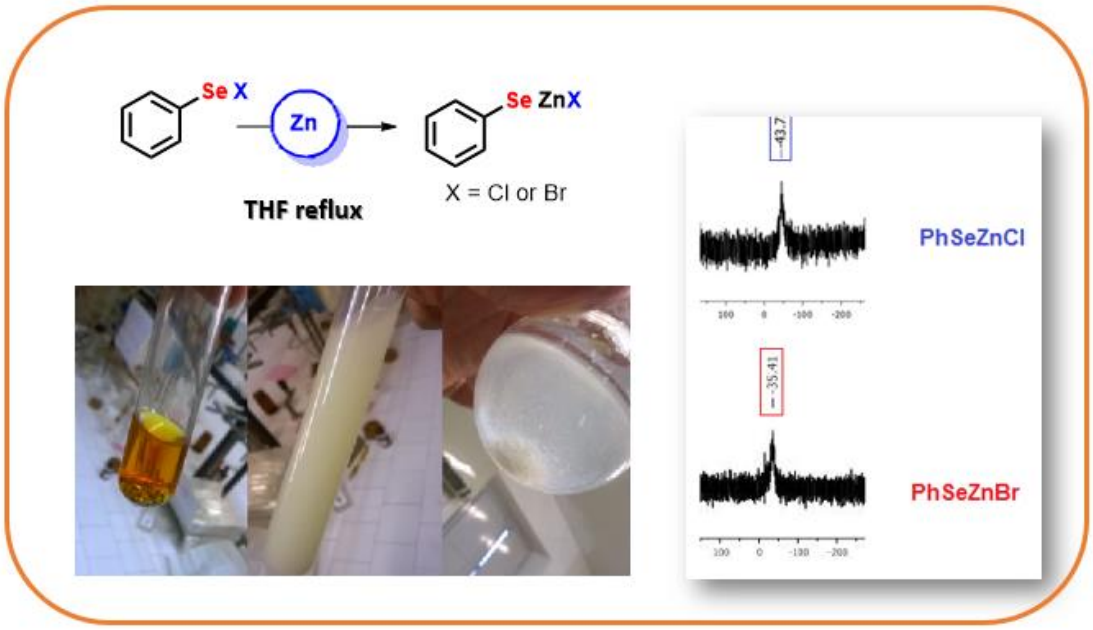

Figure 4: Synthesis of Santi's Reagents

The broad range of applications is depicted in Figure 5 and besides the well-known application of nucleophilic selenium reagents in the ring opening of epoxides [17] several other reactions were optimized. [18-20]

Particularly interesting is the substitution of acyl chlorides that in water showed an unexpected prevalence of the selenation reaction over the most expectable hydrolysis.

This was supposed to be a combination of the hydrophobic effect and the coordination of the zinc with the oxygen of the acyl chloride that force the selenium atom near to the reaction center favoriting the formation of the selenol ester rather than the carboxylic acid.

The role of the zinc as Lewis acid or as coordinating metal is also evident in the ring opening of the stiryl oxide that afforded the product deriving by the attack to the most hindered but positively charged

carbon, and in the vinyl substitution were the observed stereochemical retentions was explained by DFT calculations. [16, 18]

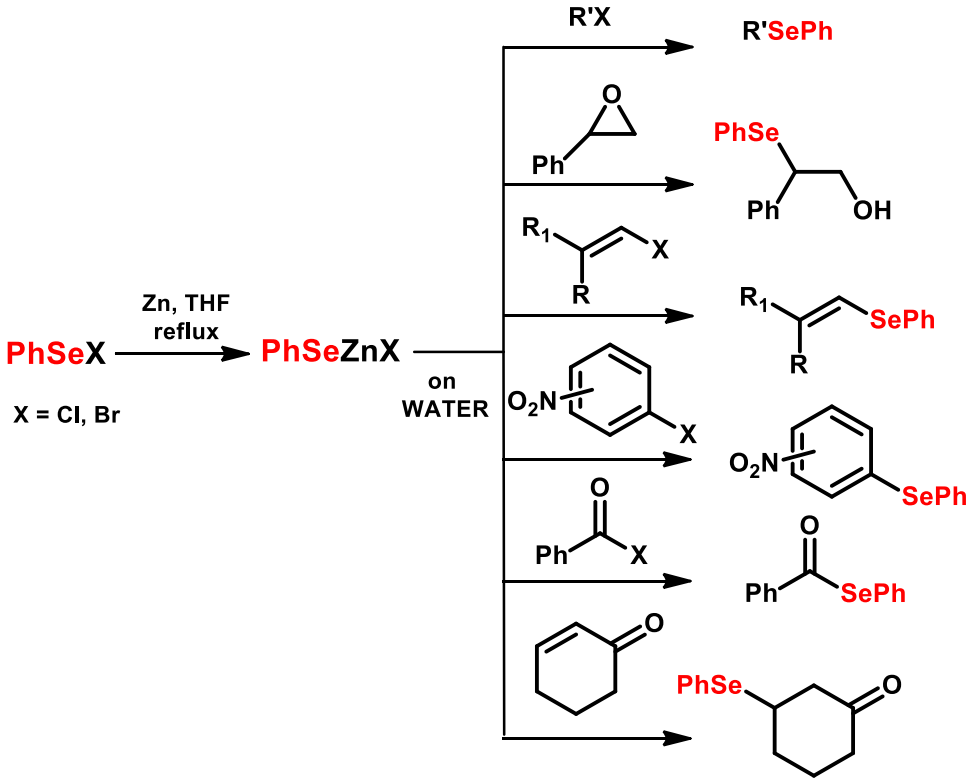

Figure 5: Synthetic applications of Santi's Reagents

Furthermore, one of the most intriguing aspect of the Santi's reagents were the ability of the zinc to stabilize the selenium in the negative (-1) oxidation state, mimicking the catalytic triad of the glutathione peroxidase. This prompted us to fully investigate this molecule as Glutathione Peroxidase mimics. By using NMR based assays, we effectively demonstrated that PhSeZnCl promotes the reduction of peroxides in the presence of glutathione or other thiols.[21] Extensive investigations confirmed that PhSeZnCl promotes the reduction of peroxides in the presence of GSH better than Ebselen and diphenyl diselenide, but the biological applicability appeared to be strongly limited by the higher catalytic affinity for glutathione and other biologically relevant thiols respect to hydrogen peroxide. This is a classical situation in which organoselenium compounds can be considered both: antioxidant or pro-oxidant gaining the term of Janus element. [22] (Fig 6)

Following these consideration, is now our opinion to change the paradigm that for a long time described organoselenium compounds simply as antioxidants and we need to answer to a different question: "is it possible to use prooxidant activity as specific bullet against new therapeutically relevant targets?

Figure 5: "the *Janus* Element"

As an example, PhSeZnCl was demonstrated to be cytotoxic toward various cancer line increasing the ROS generation and inducing apoptosis by the non-reversible inhibition of GSTP-transferase. The selectivity for this specific target suggest a potential use in chemotherapy of drug-resistant cancer. Furthermore, we also demonstrated that mild electrophilic diselenides with their moderate prooxidant activity are able to stimulate a hormetic response Nrf2-mediated that reinforce the self-antioxidant defense of cells. [23] Free thiol of a cysteine can be also the target of Ebselen in the inhibition of bacterial Urease, as recently reported in a research of Wroclaw University and depicted in Fig 6.[24]

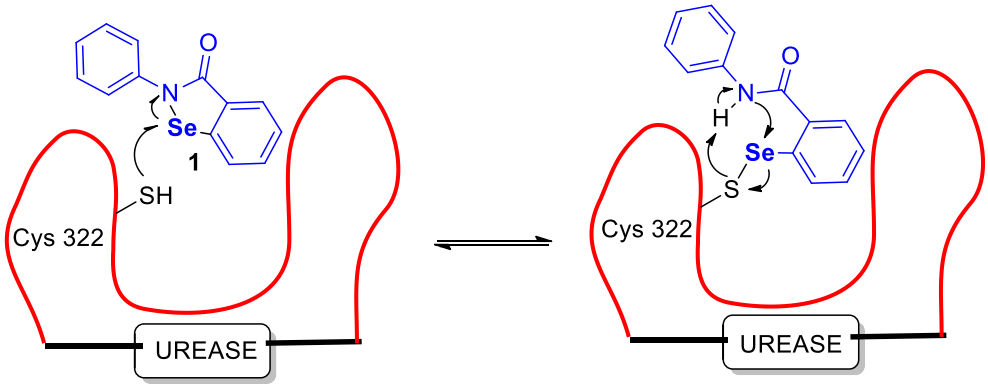

Figure 6: Reversible urease inhibition by Ebselen

Considering the redox modulation in the biological systems an attractive target is represented by the zinc finger domains of proteins having crucial role in the survival process of bacterial and viruses. As an

example, we recently described that some diselenides can specifically interact with the zinc-finger domain of NCp7 protein exploiting an interesting anti-HIV activity. The most active compounds are reported in Figure 7. [25]

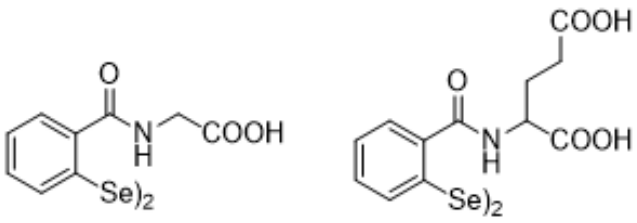

Figure 7: diselenides having anti-HIV activity

Similarly Ebselen has been demonstrated to interact with the zinc finger domains of New Delhi metallo-beta-lactamase (NDM-1) for the potential treatment of multidrug resistant bacterial infections.[26] Ebselen interacts with the thiol of Cys221 displacing the zinc and changing the protein folding and consequently its function. (Figure 8)

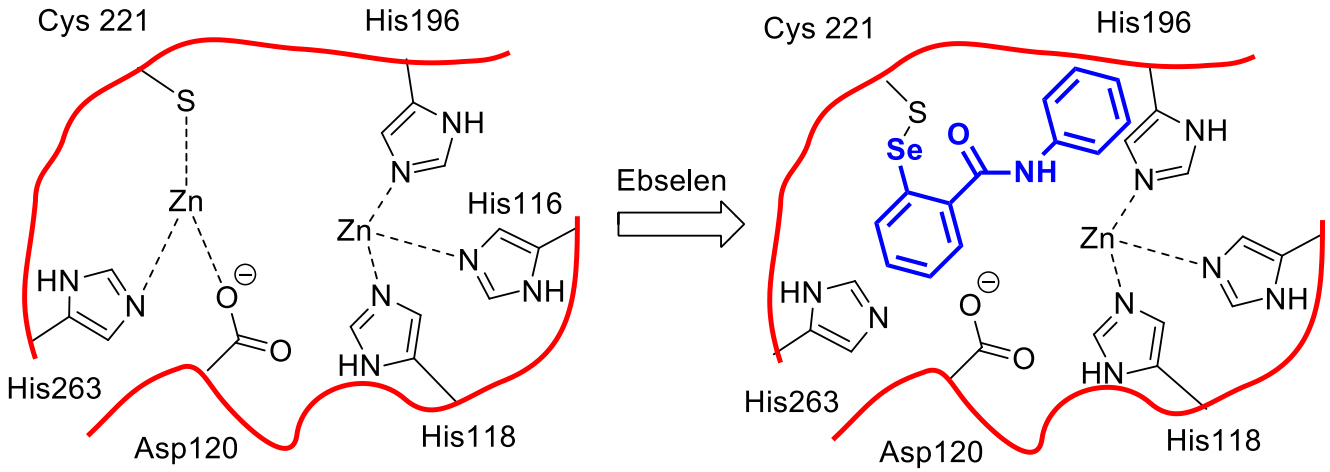

Figure 8: Ebselen and NDM-1

In conclusion, after 200 years from the discovery of selenium the research around organoselenium compounds is still productive and attractive for several research group all around the world. In this prospective article we presented our vision for the future of these field of research that starting from

bio inspiration aims the development of new eco-friendly catalytic applications to the discovery of new selenium containing therapeutic agent considering that selenium derivatives can be sometime much more complicated and potentially powerful than a simple antioxidant agent. This open new field of research demonstrating that “the Gold Rush” is probably just begun.

References

[1] J.L. Martin (**1973**) Selenium compounds in nature and medicine. In Organic Selenium Compounds: Their Chemistry and Biology, Klayman DL, Gunther WHH (eds). John Wiley & Sons, New York, pp. 663–91.
[2] S.T. Benavides,F.S. Mojica (**1965**) Selenosis, 2nd edn. Instituto Geografico Augustin Codazzi, Bogota, Columbia.
[3] L. Flohe, W. A. Gu¨nzler and H. H. Schock, FEBS Lett., 1973, 32, 132.
[4] U. Schweizer and N. Fradejas-Villar, *FASEB J.*, 2016, **30**, 3669.
[5] V. M. Labunskyy, D. L. Hatfield and V. N. Gladyshev, *Physiol. Rev*., 2014,**94**, 739.
[6] D. M. Freudendahl, S. Santoro, S. A. Shahzad, C. Santi and T. Wirth, *Angewandte Chemie International Edition*, 2009, **48**, 8409–8411.
[7] C. Santi, R. Di Lorenzo, C. Tidei, L. Bagnoli and T. Wirth, *Tetrahedron*, 2012, **68**, 10530.
[8] L. Sancineto, F. Mangiavacchi, C. Tidei, L. Bagnoli, F. Marini, A. Gioiello, J. Scianowski and C. Santi, *Asian Journal of Organic Chemistry*, 2017, **6**, 988.
[9] B. Cerra, F. Mangiavacchi, C. Santi, A. M. Lozza and A. Gioiello, *React. Chem. Eng*., 2017, **2**, 467.
[10] L. Sancineto, C. Tidei, L. Bagnoli, F. Marini, E. Lenardão and C. Santi, *Molecules*, 2015, **20**, 10496.
[11] C Santi et al, unpublished results
[12] A. A. Vieira, J. B. Azeredo, M. Godoi, C. Santi, E. N. da Silva Júnior and A. L. Braga, *The Journal of Organic Chemistry*, 2015, **80**, 2120.
[13] S. Santoro, J. B. Azeredo, V. Nascimento, L. Sancineto, A. L. Braga and C. Santi, *RSC Advances*, 2014, **4**, 31521.
[14] C. Santi and L. Sancineto*, Current Green Chemistry*, 2016, **3**, 3.
[15] C. Santi, R. Jacob, B. Monti, L. Bagnoli, L. Sancineto and E. Lenardão, *Molecules*, 2016, **21**, 1482.
[16] C. Santi, S. Santoro, B. Battistelli, L. Testaferri and M. Tiecco, *European Journal of Organic Chemistry*, 2008, **2008**, 5387.
[17] M. Tiecco, L. Testaferri, F. Marini, S. Sternativo, F. Del Verme, C. Santi, L. Bagnoli and A. Temperini, *Tetrahedron*, 2008, **64**, 3337.
[18] B. Battistelli, T. Lorenzo, M. Tiecco and C. Santi, *European Journal of Organic Chemistry*, 2011, **2011**, 1848.
[19] S. Santoro, B. Battistelli, L. Testaferri, M. Tiecco and C. Santi, *European Journal of Organic Chemistry,* 2009, **2009**, 4921.
[20] C. Santi, B. Battistelli, L. Testaferri and M. Tiecco, *Green Chemistry*, 2012, **14**, 1277.
[21] C. Tidei, M. Piroddi, F. Galli and C. Santi, *Tetrahedron Letters*, 2012, **53**, 232.
[22] D. Bartolini, M. Piroddi, C. Tidei, S. Giovagnoli, D. Pietrella, Y. Manevich, K. D. Tew, D. Giustarini, R. Rossi, D. M. Townsend, C. Santi and F. Galli, *Free Radical Biology and Medicine*, 2015, **78**, 56–65.
[23] D. Bartolini, J. Commodi, M. Piroddi, L. Incipini, L. Sancineto, C. Santi and F. Galli, *Free Radical Biology and Medicine*, 2015, **88**, 466.
[24] K. Macegoniuk, E. Grela, J. Palus, E. Rudzińska-Szostak, A. Grabowiecka, M. Biernat and Ł. Berlicki, *Journal of Medicinal Chemistry*, 2016, **59**, 8125.
[25] L. Sancineto, A. Mariotti, L. Bagnoli, F. Marini, J. Desantis, N. Iraci, C. Santi, C. Pannecouque and O. Tabarrini, *Journal of Medicinal Chemistry*, 2015, **58**, 9601.
[26] J. Chiou, S. Wan, K.-F. Chan, P.-K. So, D. He, E. W. Chan, T. Chan, K. Wong, J. Tao and S. Chen, *Chem. Commun*., 2015, **51**, 9543.