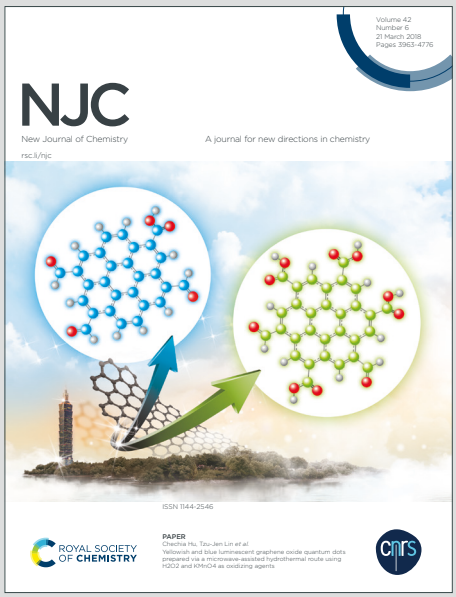
NJC

New Journal of Chemistry

A journal for new directions in chemistry

Accepted Manuscript



NJC

View Article Online
DOI: 10.1039/D0NJ04735J

ARTICLE

Synthesis of 2'-(1,2,3-triazoyl)-acetophenones: molecular docking and *in vitro* monoamine oxidase activity inhibition

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

Gabriel P. Costa,[a] Ítalo F. C. Dias,[a] Mariana G. Fronza,[b] Evelyn M. Besckow,[c] Jenifer Fetter,[b] José Edmilson R. Nascimento,[a] Raquel G. Jacob,[a] Lucielli Savegnago,[b] Cristiani F. Bortolatto,[c] César A. Brüning[c]* and Diego Alves[a]*

We described our results for the synthesis of 2'-(1,2,3-triazoyl)-acetophenones by copper catalyzed azide-alkyne cycloaddition of 2'-azidoacetophenone with alkynes. The corresponding 2'-(1,2,3-triazoyl)-acetophenones were obtained in moderated to excellent yields and according to our experiments, it was observed that ultrasound accelerates the reaction compared to conventional heating. In addition, the obtained compounds were screened by molecular docking for possible inhibitory effect on monoamine oxidase (MAO) activity, an enzyme responsible for degradation of monoamine neurotransmitters. Three compounds were selected and presented inhibitory effect on both MAO-A and B isoforms activities *in vitro*. These new MAO inhibitors may be of interest to treat monoamine deficit related-neuropsychiatric disorders, such as depression and Parkinson's disease.

Introduction

Among the various *N*-heterocycles, triazoles are undeniably important due your different applications in materials chemistry[1] such as corrosion inhibitors,[2] and organic dyes.[3] Meantime, they have occupied a relevant position in the field of medicinal and pharmaceutical chemistry,[4] having a wide variety of biological activities, such as amnesia-ameliorative effect, for treatment of Alzheimer's disease, anticonvulsant, antinociceptive, anti-inflammatory, among others.[5] In addition to countless activities already reported, this nucleus is also found in the structure of some drugs, such as Rufinamide which acts as anticonvulsant agent, as well as, Tazobactam and Cefatrizine which are antibiotics (Figure 1).[6]

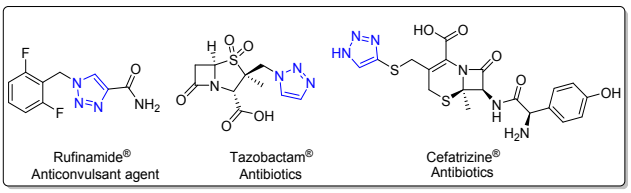


Figure 1 Drugs containing 1,2,3-triazole nucleus.

The 1,4-disubstituted 1,2,3-triazoles can be easily selectively accessed via dipolar cycloaddition using organic azides and alkynes through the copper catalysis (CuAAC reactions).[7] Beyond the above, they can effectively mimic trans-amide bonds that makes triazole a privileged support for the construction of medicinal compounds. This one effect is due to their similar size, planarity, H-bonding capabilities, dipole moment and performing secondary interactions which are able to bind to biological receptors.[4a,4c,8] Analyzing the structure potential of the 1,2,3-triazole nucleus, the presence of N2 and N3 nitrogen with lone electron pairs which may have potential display hydrogen bond acceptor properties. Besides, π-π stacking interactions of the aromatic ring and a weak hydrogen bonding donor (C-H).[4a,4c,8]

In the medicinal chemistry, the ketone group is easily found and shows important structural feature when referring at biological recognition processes. The presence of two lone pairs of electrons and the planarity of ketone group can be interact with a bonding site through hydrogen bonding, in which carbonyl oxygen acts as a hydrogen bond acceptor.[9] Besides, the ketone group may also perform dipole-dipole interaction with the binding site due to its significant dipole moment.[9] Considering the presented potential of the compounds containing ketones and 1,2,3-triazole groups, hybrid compounds with both structures would be an advantageous strategy to search for new bioactive molecules.

In this sense, monoamine oxidases (MAO, E.C. 1.4.3.4.) are flavoenzymes linked to the external mitochondrial membrane of mammals. Since their discovery almost a century ago,[10] these enzymes have been the target of extensive biochemical and pharmacological studies, mainly due to its central role in the metabolism of neurotransmitters.[11] MAO exists in two different isoforms, MAO-A and MAO-B, which exhibit different specificities regarding their substrates, inhibitors, and tissue locations.[12] MAO-A preferentially oxidizes serotonin (5-HT), norepinephrine (NE) and

[a] *Laboratório de Síntese Orgânica Limpa – LASOL, CCQFA, Universidade Federal de Pelotas – UFPel, P. O. Box 354, 96010-900, Pelotas, RS, Brazil* *diego.alves@ufpel.edu.br *(D. Alves)*
[b] *Grupo de Pesquisa em Neurobiotecnologia - GPN, CDTec, Universidade Federal de Pelotas - UFPel, Pelotas, RS, Brazil.*
[c] *Laboratorio de Bioquímica e Neurofarmacologia Molecular - LABIONEM, Universidade Federal de Pelotas - UFPel, Pelotas, RS, Brazil.*
*cabruning@yahoo.com.br *(C. A. Brüning)*
† Footnotes relating to the title and/or authors should appear here.
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

View Article Online
DOI: 10.1039/D0NJ04735J

epinephrine (EN) and is irreversibly inhibited by low doses of clorgyline, while MAO-B uses phenylethylamine as a substrate and is irreversibly blocked by low doses of selegiline .[12] Besides, dopamine (DA) and tyramine are common substrates for both isoforms.[13]

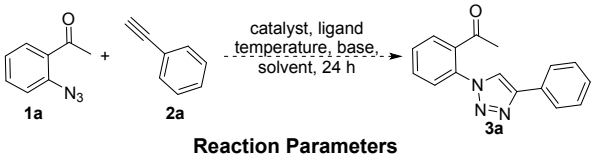
These biogenic amines, such as 5-HT, NE and DA, play a crucial role in modulating mood and emotion, as well as in motor, perceptual and cognitive function control, so abnormal levels of these monoamines have been associated with several neuropsychiatric disorders,[14] such as Parkinson's disease,[15] depression[16] and Alzheimer's disease.[17] In this context, MAO inhibitors have long been developed and are widely used in clinics for the treatment of many neuropsychiatric and neurodegenerative disorders. For example, MAO-A inhibitors have been shown to be effective as antidepressant drugs[18] and MAO-B inhibitors have been used for the treatment of Parkinson's disease.[19] 2'-(1,2,3-Triazoyl)-acetophenones are not structurally related to classical MAO inhibitors, that usually have structure similar to phenylethylamine and most of them with reactive groups, like hydrazine, propargylamine and cyclopropylamine. However, triazol-containing molecules have already demonstrated inhibitory effect on both MAO-A and MAO-B activities.[20]

In view of what was explained above and according to our studies on the development of new functionalized 1,2,3-triazoles, we report herein the results of the synthesis of 2'-(1,2,3-triazoyl)-acetophenones by a CuAAC of 2'-azidoacetophenone with alkynes using thiourea as a ligand. Molecular docking and MAO activity analyses of synthesized compounds were performed to evaluate whether the 2'-(1,2,3-triazoyl)-acetophenones inhibit MAO isoforms.

Results and discussion

Synthesis

Focused on proceed the studies using the thiourea as ligand to form a new class of 1,2,3-triazoles by CuAAC reactions, the initial conditions were based in a previous repot in literature by our research group.[21] Thus, we carried out a long study to obtain the optimized conditions for the synthesis of triazole **3a** through the reaction between 2'-azidobenzophenone **1a** and phenylacetylene **2a** using conventional heating, as well as the use of ultrasound irradiation (US)[22] as an alternative energy source (Scheme 1) (for more details see support information, Tables S1 and S2).



Reaction Parameters

Under conventional heating

Catalyst: **CuI**, CuBr, $CuBr_2$, $Cu(OAc)_2$
Catalyst (mol%): 5, **10**, 15, without
Temperature (°C): 25, 50, **60**, 70, 80, 100, 120
Solvent: **DMSO**, 1,4-dioxane, DMF, Ethanol, H_2O, DMSO:H_2O (3:1)
Ligand: **Thiourea**, Bipy
Ligand (mol%): 10, **20**
Base: **Et_3N**, DBU

Under US irradiation

Solvent: DMSO, **DMSO:H_2O (3:1)**
Amplitude (%): 20, 30, **40**, 50, 60
Time (min): 20, **30**

Scheme 1

In order to explore the generality, the reaction scope was extended using both conventional heating (method A, Table S1, entry 5) and the ultrasound irradiation (method B, Table S2, entry 2). Initially, the reactivity was evaluated using different terminal alkynes. The reaction tolerated arylalkynes containing electron-donating groups, such as *p*-methyl, *p*-ethyl, *p*-^{t}butyl and *p*-methoxy, giving the desired compounds in a good to excellent yields in both methods (Figure 2, method A: 85-98%, method B: 86-97%, compounds **3a**-**e**).

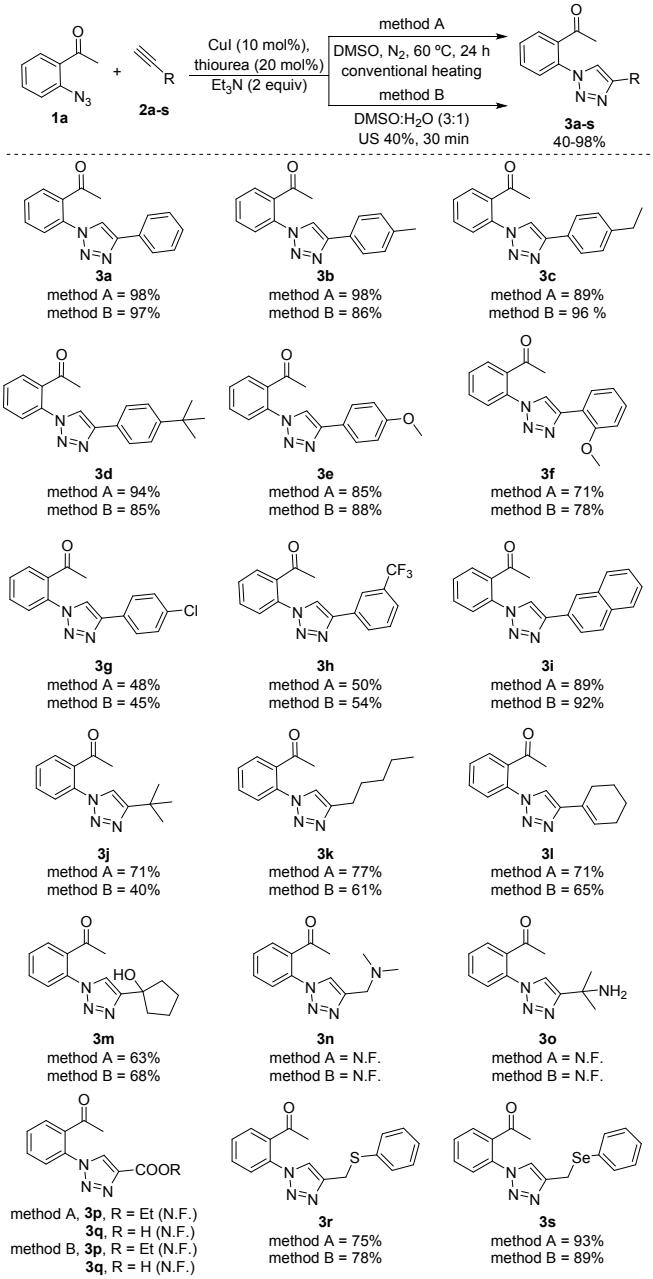


Figure 2: Generality in the synthesis of 2'-(1,2,3-triazoyl)-acetophenone **3**. Method A: the reactions were performed with 2'-azidoacetophenone (**1a**) (0.25 mmol), alkyne (**2a-t**) (0.25 mmol), thiourea (20 mol%), TEA (0.5 mmol), CuI (10 mol%) and DMSO (0.5 mL) at 60 ºC for 24 h under N_2 atmosphere. Method B: the reactions were performed with 2'-azidoacetophenone (**1a**) (0.25 mmol), alkyne (**2a-t**) (0.25 mmol), thiourea (20 mol%), TEA (0.5 mmol), CuI (10 mol%) and DMSO:H_2O (3:1) (0.5 mL) under US irradiation (40% of amplitude) for 30 min.

Indeed, a slight decreasing in the yield was obtained when arylalkyne containing methoxy group in the *orto* position at aromatic ring was used, probably due to steric hindrance (Figure 2, method A: 71%, method B: 78%, compound **3f**).

Unluckily, when arylalkynes having electron-withdrawing groups (*p*-Cl, *m*-CF_3) bonded in aromatic ring were used, a significant decrease in the yield of 1,2,3-triazoles **3g**-**h** were observed (Figure 2, method A: 48-50%, method B: 45-54%, compounds **3g**-**h**, respectively). Interestingly, the 1,2,3-triazole **3i** was obtained in good yield when 2-ethynylnaphthalene **2i** was used as staring material (Figure 2, method A: 89%, method B: 92%, compound **3i**). We extended the reaction scope using alkyl alkynes **2j**-**l** such as 3,3-dimethylbut-1-yne, hept-1-yne, 1-ethynylcyclohex-1-ene, which provided the desired products **3j**-**l** from moderated to good yields (Figure 2, method A: 71-77%, method B: 40-65%, compounds **3j**-**l**). Also, this methodology tolerated the propargyl alcohol derivative **2m** giving the 1,2,3-triazole **3m** in moderated yield (Figure 2, method A: 63%, method B: 68%, compound **3m**).

Unfortunately, when we used as starting materials the corresponding alkynes **2n**-**q**, such as *N*,*N*-dimethylprop-2-yn-1-amine, 2-methylbut-3-yn-2-amine, ethyl propiolate and propionic acid, the desired products **3n**-**q** were not formed in both methods. Finally, aiming to obtain products containing chalcogen atom in their structures, we used propargyl sulfides and selenides as starting materials and the compounds **3r**-**s** were obtained in good to excellent yield (Figure 2, method A: 75-93%, method B: 78-89%, compounds **3r-s**, respectively).

Molecular Docking

With the purpose of select the molecules most probable to have an inhibitory effect in MAO activity, a virtual screening using the molecular docking tool was performed. Our results demonstrated that the 2'-(1,2,3-triazoyl)-acetophenones **3b**, **3c** and **3i** showed the strongest affinity in both isoforms of MAO (Table 1).

Compounds **3b** and **3c** showed an affinity of -9.7 kcal/mol, while the compound **3i**, -11.3 kcal/mol in MAO-A and stayed all in similar position in the catalytic site of the enzyme. More specifically, compound **3b** made hydrophobic interactions with Phe352, Ile335, Tyr407 and a hydrogen bond with Ala68 in MAO-A (Figure 3a and 3d).

Table 1 Molecular docking scores of 2'-(1,2,3-triazoyl)-acetophenones on the isoforms of monoamine oxidase (MAO) -A (PDB ID: 2Z5X) and MAO-B (PDB ID: 5MRL) given by Autodock Vina software.

	Docking Scores (Kcal/mol)	
Compounds	**MAO-A**	**MAO-B**
3a	-7.4	-7.2
3b	-9.7	-8.6
3c	-9.7	-8.5
3d	-7.9	-7.1
3e	-7.6	-6.2
3f	-7.2	-7.0
3g	-7.1	-6.7
3h	-9.2	-7.7
3i	-11.3	-8.4
3j	-6.5	-7.0
3k	-7.2	-5.7
3l	-8.9	-7.3
3m	-8.2	-6.4
3r	-7.0	-6.6
3s	-9.1	-7.4

In the Figures 3b and 3e are shown the interactions made by compound **3c**, such as hydrophobic interactions with Phe352, Ile180, Phe280, Ile335 and Tyr407. Similarly, compound **3i** made multiple hydrophobic interactions with the residues Tyr407, Tyr444, Ile335, Arg51, Cys406 and a hydrogen bond with Ala68 (Figure 3c and 3f).

Noteworthy, it has been described that Tyr407 and Tyr444 are essential residues in MAO-A catalytic activity and may be involved in the non-covalent binding to FAD, forming an aromatic sandwich that stabilizes the substrate binding.[23]

In this sense, these tyrosines have been proposed to orient the substrate for oxidation or to activate the amine by enhancing its nucleophilicity, while the rotation of Phe208 acts like a gatekeeper and allows the two cavities to be fused into one larger site.[24] The Ile335 has also been proposed to have a crucial role in substrate/inhibitor selectivity, accommodating its chemical structure into the catalytic cavity.[25] These reported molecular interactions might suggest **3b**, **3c** and **3i** as MAO-A inhibitors.

View Article Online
DOI: 10.1039/D0NJ04735J

NJC

ARTICLE

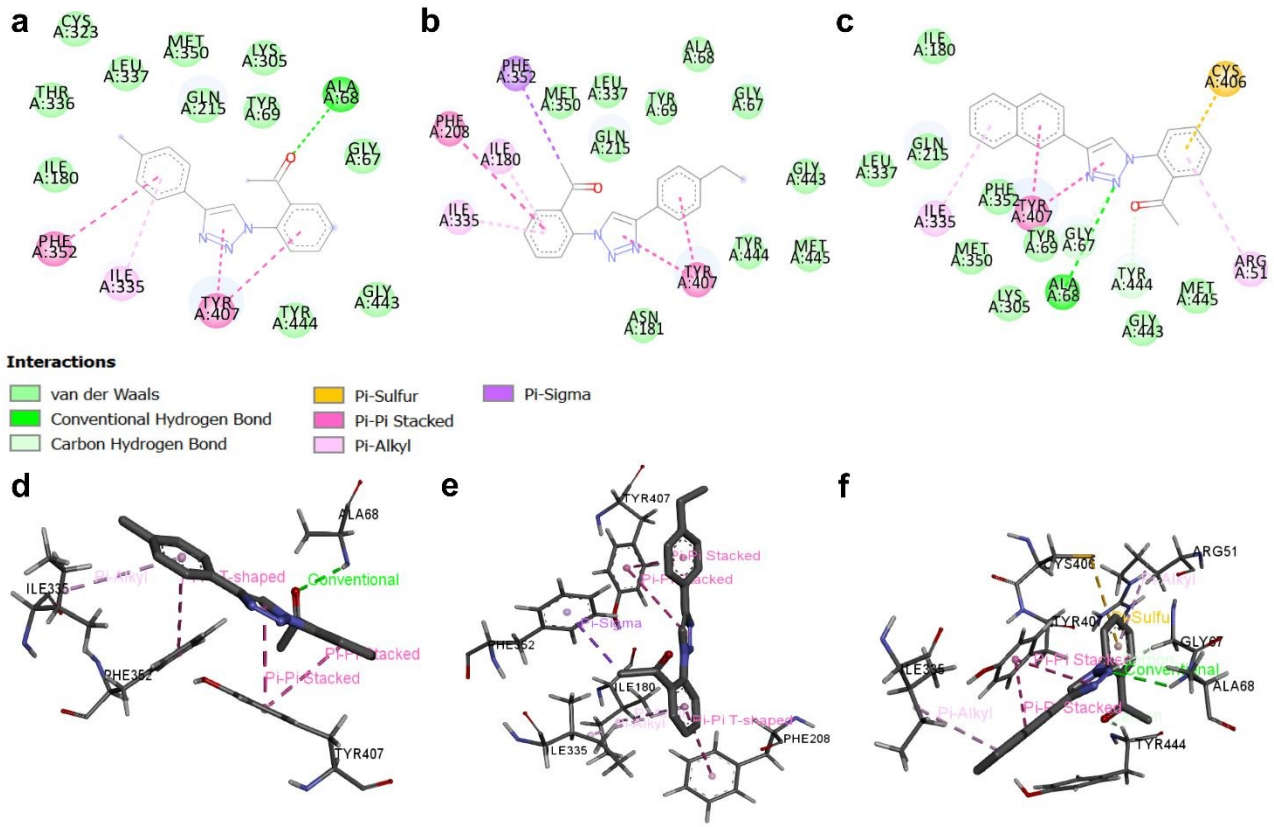


Figure 3. Molecular docking results expressed by protein ligand interactions in (a) compound **3b**, (b) compound **3c,** and (c) compound **3i** and the tridimensional binding position in (d) compound **3b**, (e) compound **3c** and (f) compound **3i** in MAO-A isoform (PDB ID: 2Z5X).

The compounds **3b**, **3c** and **3i** also showed strong affinity with the isoform MAO-B, with docking scores of -8.6, -8.5 and -8.4 kcal/mol, respectively (Table 1). In protein-ligand interactions, **3b** made hydrogen bonds with Tyr112 and Asn116 surrounded by hydrophobic interactions with Phe103, Arg120 and Glu483 (Figure 4a and 4d). Despite the similar docking scores, compound **3c** stay in different position in MAO-B, stabilized through hydrophobic interactions with residues Arg36, Pro277, Glu391, Tyr393 and Pro234 (Figure 4b and 4e). As is shown in Figure 4c and 4f, the compound **3i** stay in a similar position of **3c**, making predominantly hydrophobic interactions, such as Pro277, Tyr393, Pro234 and Leu250. This data can be visualized in Figure 5b, where all the ligands are superimposed to show the differences in the the binding mode between compound **3b** in comparison with the others.

View Article Online
DOI: 10.1039/D0NJ04735J

NJC

ARTICLE

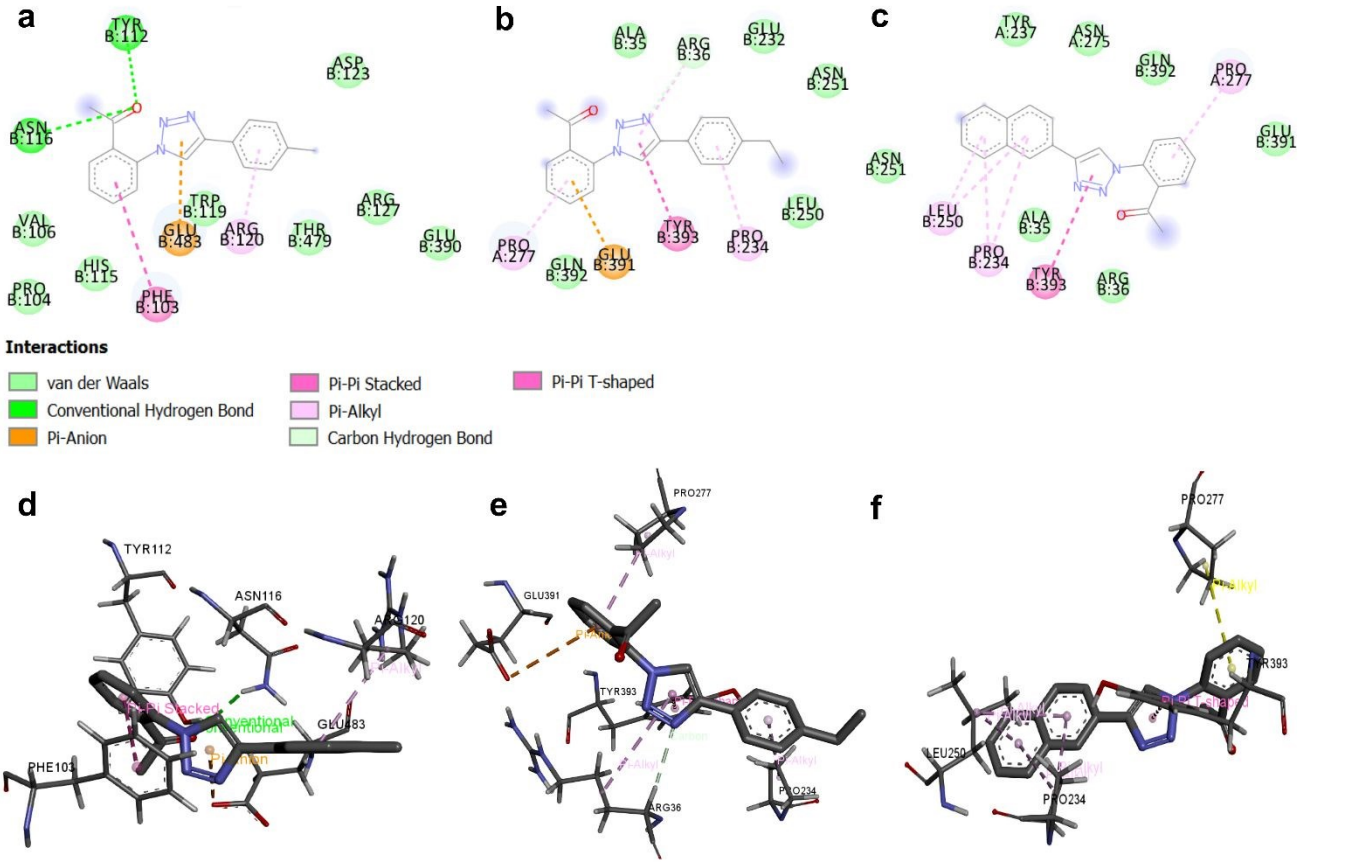


Figure 4. Molecular docking results expressed by protein ligand interactions in (a) compound **3b**, (b) compound **3c** and (c) compound **3i** and the tridimensional binding position in (d) compound **3b**, (e) compound **3c** and (f) compound **3i** in MAO-B isoform (PDB ID: 5MRL).

New proposed MAO-B inhibitors stay in similar position of compound **3b**, as Diels-Alder type adducts[26] through interactions with Tyr112, Phe103, Arg120 and Glu483, which might suggest a different inhibitory mechanism of action, not necessarily related to active site. Besides, it is known that Phe103 is located in the loop guarding the active site cavity and is shown to be one of the targets of MAO-B inhibitors such as pioglitazone and safinamide.[27] Regarding to the interactions performed by **3c** and **3i**, they presented similar binding mode to coumarin derivates with inhibitory MAO-B effect.[28] Interesting, Tyr393 is shown to be crucial for MAO-B inhibition, since participate in covalent binding of FAD directly affecting the catalytic activity of the enzyme.[23]

In vitro results

Monoamine oxidase activity in vitro

Considering the molecular docking results, the compounds **3b**, **3c** and **3i** were selected to test their effect on MAO-A and MAO-B activities *in vitro,* using mice brain homogenates. The results demonstrated that compounds **3b**, **3c** and **3i** inhibited both isoforms of MAO (Figure 6 and 7), confirming the molecular docking prediction. Table 2 shows the calculated IC_{50} values of the compounds **3b**, **3c**, **3i** and the positive controls clorgyline and pargyline on MAO-A and MAO-B activities. In relation to MAO-A activity, the lowest IC_{50} value was obtained with the compound **3c** (2.64 µM), which has the ethyl radical. Regarding the MAO-B isoform, the compound **3i**, which has an aromatic ring as substituent, showed the lowest IC_{50} value (41.47 µM). The IC_{50} values obtained for 2'-(1,2,3-triazoyl)-acetophenones were higher than those obtained for the positive controls clorgyline (0.0015 µM) and pargyline (0.0668 µM), inhibitors of MAO-A and MAO-B, respectively. However, pargyline and clorgyline and the available MAO inhibitors presented many side effects, resulting in poor compliance and hence therapeutic failures.[29] In this way, the discover of new MAO inhibitors is noteworthy.

These results combined with molecular docking analyses show that indeed compound **3b**, **3c** and **3i** have inhibitory

View Article Online
DOI: 10.1039/D0NJ04775H

activity of MAO-A and B. However, compound **3b** and **3c** demonstrated same affnity with MAO-A, compound **3b** presented a higher potency in *in vitro* evaluation. The same occurs in MAO-B activity, since compound **3i** demonstrated similar docking scores when compared to compound **3b** and **3c**, but showed a lower efficiency. Although, is worth to be highlighted that all the tested compounds demonstrated similar efficacy. This could be explained for several reasons, since there is a high discrepancy between the two adopted methods for evaluation, not making them strictly comparable themselves. In molecular docking approach is used a crystalographic isoform of the enzyme to predict the affinity of the compound through computational calculations, excluding several physicochemical parameters that are involved in *in vitro* evaluation utilizing tissue as substrate, such as solubility and lipophilicity. In this sense, although molecular docking is a great aproach to predict the affinity of compounds with the target protein and to better undestand the interactions and ligand binding mode, the in vitro evaluation might generate data with closer aproximation of reality.

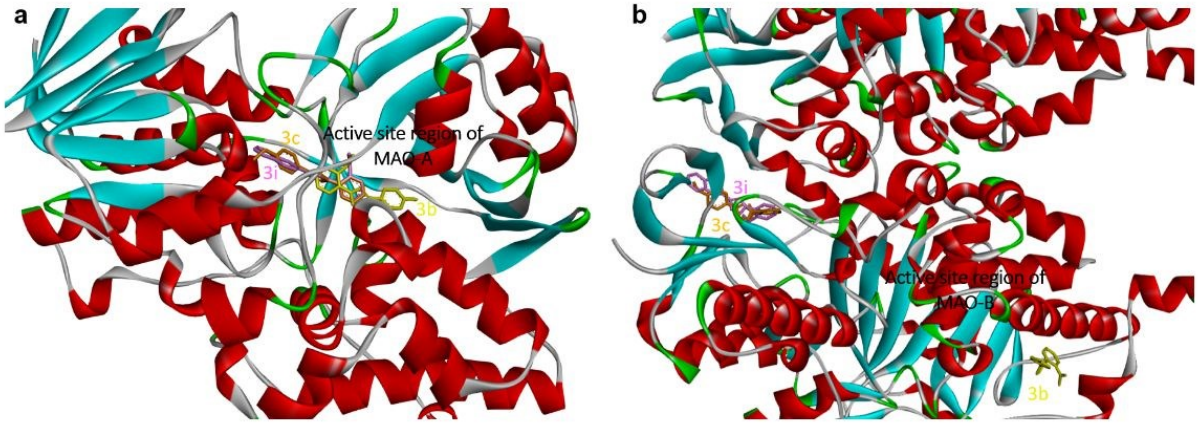


Figure 5. Superimposed binding modes of compounds **3b** (yellow), **3c** (orange) and **3i** (pink) in (a) MAO-A (PDB ID: 2Z5X) and (b) MAO-B (PDB ID: 5MRL).

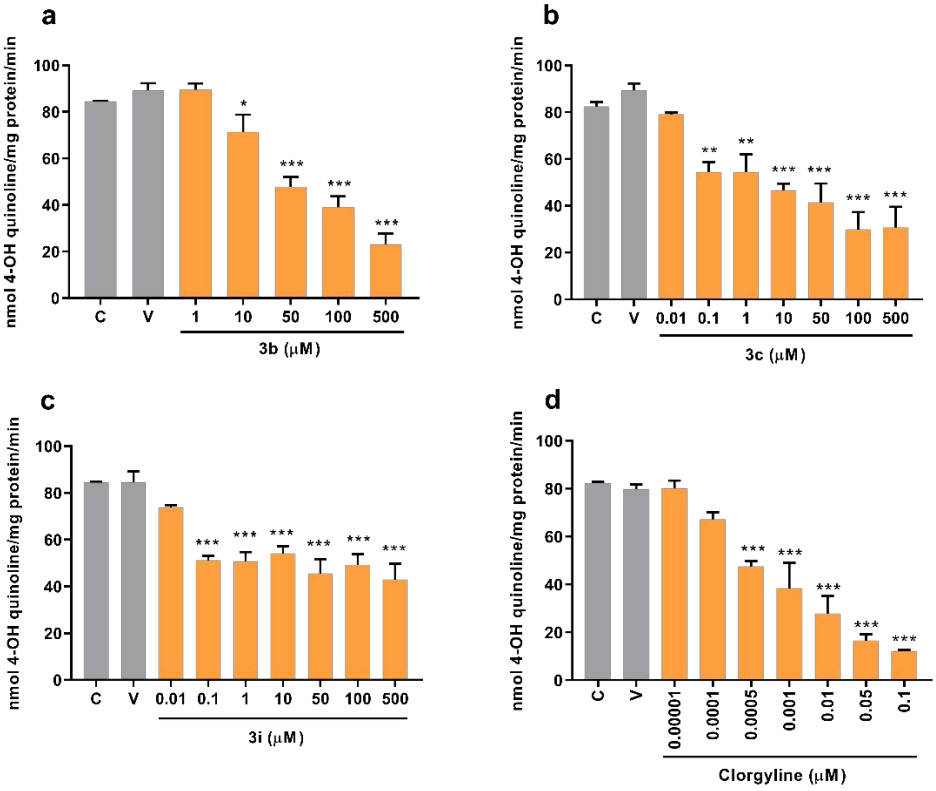


Figure 6. Effect of compounds (a) **3b**, (b) **3c**, (c) **3i** and (d) clorgyline on cerebral MAO-A activity *in vitro*. Data were expressed as means ± S.E.M. of four to six individual experiments. MAO-A activity was expressed as nanomole of 4-hydroxyquinoline per milligram of protein per minute. The values found were considered statistically significant when $p<0.05$. *$p < 0.05$, **$p < 0.01$ and ***$p < 0.001$ when compared with control group (One-way ANOVA followed of the Newman–Keul's test). C: control; V: vehicle.

View Article Online
DOI: 10.1039/D0NJ04735J

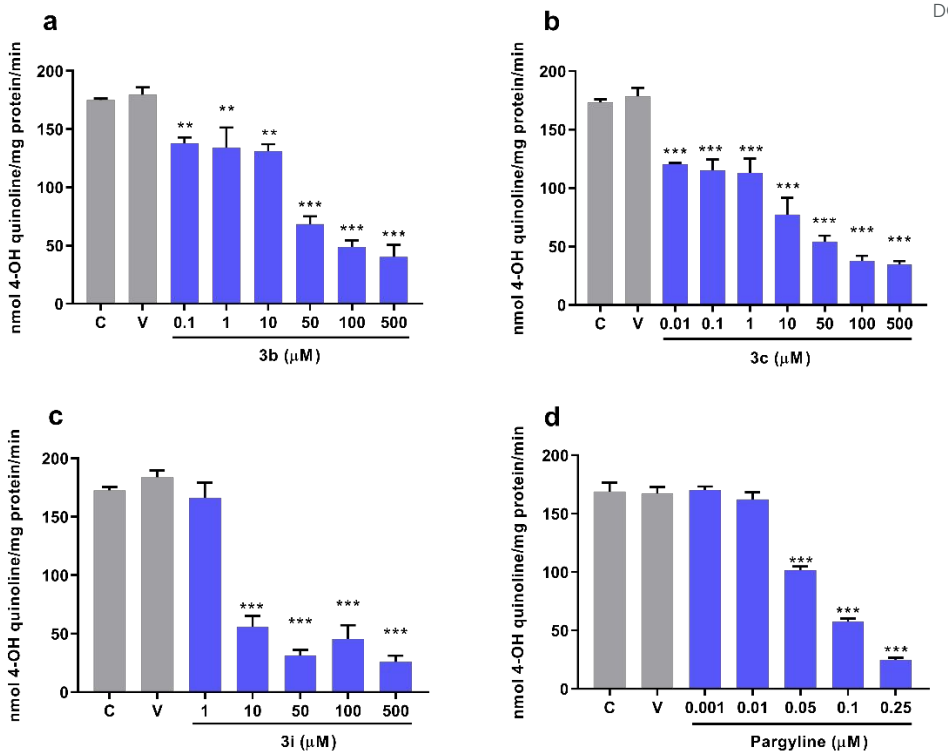


Figure 7. Effect of compounds (a) **3b**, (b) **3c**, (c) **3i** and (d) pargyline on cerebral MAO-B activity *in vitro*. Data were expressed as means ± S.E.M. of four to six individual experiments. MAO-B activity was expressed as nanomole of 4-hydroxyquinoline per milligram of protein per minute. The values found were considered statistically significant when $p<0.05$. **$p < 0.01$ and ***$p < 0.001$ when compared with control group (one-way ANOVA followed of the Newman–Keul's test). C: control; V: vehicle.

Table 2 Half-maximal inhibitory concentration (IC_{50}) values of 2'-(1,2,3-triazoyl)-acetophenones on MAO-A and MAO-B activities

	IC_{50} (μM)	
Compounds	**MAO-A**	**MAO-B**
3b	47.29	173.5
3c	02.64	77.18
3i	ND	41.47
Clorgyline	0.0015	-
Pargyline	-	0.0668

ND: not determined

MAO inhibitors have contributed to the improvement of several pathologies such as depression, Parkinson's disease, Alzheimer's disease, prostate cancer, and heart disease,[30] pointed the therapeutic relevance of these compounds. Despite, their clinical use also showed some limitation due to adverse effects, as well as interactions with food and medicines.[31] In this way, the search for more suitable compounds is particularly important. The 2'-(1,2,3-triazoyl)-acetophenones through molecular docking and *in vitro* studies demonstrated to inhibit both isoforms of MAO, MAO-A and B, and could be explored as new MAO inhibitors.

Conclusions

In summary we developed two general methods for accessing a series of new 2'-(1,2,3-triazoyl)-acetophenones by a copper catalyzed azide-alkyne cycloaddition of 2'-azidoacetophenone with alkynes. Overall, reactions were performed under mild conditions and the reactions worked well in the presence of catalytic amount of copper iodide as catalyst and thiourea as ligand. When we employed the ultrasound irradiation as alternative source of energy a significant decrease in the time reactional was observed, noting that there were no large differences in yields when compared to those obtained when using conventional heating. In addition, three compounds presented inhibitory effect on MAO-A and MAO-B activities and may be of interest to develop new therapeutic strategies for monoamine deficit related-neuropsychiatric disorders, such as depression and Parkinson's disease.

Experimental

General Information: The reactions were monitored by TLC carried out on Merck silica gel (60 F_{254}) by using UV light as visualizant agent and 5% vanillin in 10% H_2SO_4 and heat as developing agents. Baker silica gel (particle size 0.040-0.063 mm) was used for flash chromatography. The ultrasound-promoted reactions were performed using a Cole Parmer-ultrasonic processor Model CPX 130, with a maxim power of 130 W, operating at amplitude of 40% and a frequency of 20 kHz. Hydrogen nuclear magnetic resonance (^{1}H NMR) spectra were obtained on a Bruker Avance III HD 400 spectrometer at 400 MHz. The spectra were recorded in $CDCl_3$ solutions. The chemical shifts are reported in ppm, referenced to

tetramethylsilane as the internal reference. Coupling constants (*J*) are reported in hertz. Abbreviations to denote the multiplicity of a particular signal are s (singlet), d (doublet), t (triplet), quint (quintet), sext (sextet), and m (multiplet). ^{13}C NMR spectra were obtained on a Bruker Avance III HD 400 spectrometer at 100 MHz. The chemical shifts are reported in ppm, referenced to the solvent peak of $CDCl_3$ Low-resolution mass spectra were obtained with a Shimadzu GC-MS-QP2010 mass spectrometer. High resolution mass spectra (HRMS) were recorded on a Bruker Micro TOF-QII spectrometer 10416.

General procedure for the synthesis of 2'-(1*H*-1,2,3-triazol-1-yl) acetophenone 3a-s (Method A)

In a glass vial was added 0.25 mmol (0.040 g) of 2'-azidoacetophenone 1, 0.25 mmol of alkyne 2a-s, 20 mol% thiourea, DMSO (0.5 mL), TEA (2 equiv.) and CuI (10 mol%). The glass vial was placed under heating in an oil bath at 60 ºC on a magnetic stirrer and under a nitrogen atmosphere. The reaction medium was maintained under stirring for 24 hours. After this time, the mixture was washed with saturated aqueous NaCl solution (3x50 mL) and dichloromethane (DCM) (50 mL). The organic phase was separated and dried by the addition of anhydrous $MgSO_4$. Subsequently, the solvent was evaporated under low pressure. The products were purified through a silica gel chromatographic column with a Hex / AcOEt mixture as the eluent.

General procedure for the synthesis of 2'-(1*H*-1,2,3-triazol-1-yl) acetophenone 3a-s (Method B)

In glass vial was added 0.25 mmol (0.040 g) of 2'-azidoacetophenone **1**, 0.25 mmol of alkyne **2a-s**, 20 mol% thiourea, DMSO:H_2O (3:1) (0.5 mL), TEA (2 equiv.) and CuI (10 mol%). An ultrasound probe was placed in the glass vial containing the reaction mixture. The amplitude of the ultrasound waves was fixed at 40%. Then, the reaction mixture was sonicated for min. After this time, the mixture was washed with saturated aqueous NaCl solution (3x50 mL) and dichloromethane (DCM) (50 mL). The organic phase was separated and dried by the addition of anhydrous $MgSO_4$. Subsequently, the solvent was evaporated under low pressure. The products were purified through a silica gel chromatographic column with a Hex / AcOEt mixture as the eluent.

1-(2-(4-phenyl-1*H*-1,2,3-triazoyl)phenyl)ethan-1-one 3a: method A: yield: 0.064 g (98%), method B: yield: 0.063 g (97%); white solid; mp 106-108 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ= 8.11 (s, 1H), 7.90 (d, *J* = 7.1 Hz, 2H), 7.71 (dd, *J* = 7.4, 1.7 Hz, 1H), 7.66 – 7.57 (m, 2H), 7.51 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.47 – 7.43 (m, 2H), 7.39 – 7.34 (m, 1H), 2.22 (s, 3H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ= 199.8, 148.5, 136.5, 134.5, 132.0, 130.0, 130.0, 129.1, 129.0 (2C), 128.6, 126.0 (2C), 125.6, 121.1, 29.4. MS (relative intensity) *m*/*z*: 263(2.9) 235(99.2), 220(100.0), 206(62.2), 193(56.2), 165(47.1), 130(19.1), 116(56.8), 105(99.5) HRMS (APCI-QTOF) calculated mass for $C_{16}H_{14}N_3O$ [M+H]$^+$: 264.1131, found: 264.1142.

1-(2-(4-(*p*-tolyl)-1*H*-1,2,3-triazoyl)phenyl)ethan-1-one 3b: method A: yield: 0.068 g (98%), method B: yield: 0.059 g (86%); white solid; mp 104-106 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ= 8.06 (s, 1H), 7.79 (d, *J* = 8.1 Hz, 2H), 7.71 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.66 – 7.59 (m, 2H), 7.51 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.26 (d, *J* = 8.1 Hz, 2H), 2.40 (s, 3H), 2.20 (s, 3H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ= 199.9, 148.6, 138.6, 136.6, 134.6, 132.0, 130.0, 129.7, 129.1, 127.2, 125.9, 125.6, 120.7, 29.4, 21.4. MS (relative intensity) *m*/*z*: 277(3.8), 249(86.5), 234(87.0), 220(30.6), 207(46.9), 167(20.3), 149(61.9), 130(68.2), 119(100.0). HRMS (APCI-QTOF) calculated mass for $C_{17}H_{16}N_3O$ [M+H]$^+$: 278.1288, found: 278.1297.

1-(2-(4-(4-ethylphenyl)-1*H*-1,2,3-triazoyl)phenyl)ethan-1-one 3c: method A: yield: 0.064 g (89%), method B: yield: 0.069 g (96%); white solid; mp 101-103 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ= 8.08 (s, 1H), 7.82 (d, *J* = 8.2 Hz, 2H), 7.70 (dd, *J* = 7.5, 1.6 Hz, 1H), 7.64 – 7.55 (m, 2H), 7.50 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.28 (d, *J* = 8.2 Hz, 2H), 2.69 (q, *J* = 7.6 Hz, 2H), 2.18 (s, 3H), 1.26 (t, *J* = 7.6 Hz, 3H).^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ= 199.8, 148.6, 144.9, 136.5, 134.5, 132.0, 129.9, 129.0, 128.5, 127.4, 125.8, 125.5, 120.7, 29.3, 28.8, 15.6. MS (relative intensity) *m*/*z*: 291(2.0), 263(42.3), 248(100.0), 234(28.7), 206(28.8), 133(60.5). HRMS (APCI-QTOF) calculated mass for $C_{18}H_{18}N_3O$ [M+H]$^+$: 292.1444, found: 292.1443.

1-(2-(4-(4-(t-butyl)phenyl)-1*H*-1,2,3-triazoyl)phenyl)ethan-1-one 3d: method A: yield: 0.075 g (94%), method B: yield: 0.068 g (85%); yellowish solid; mp 135-137 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ= 8.30 (s, 1H), 7.85 (d, *J* = 8.3 Hz, 2H), 7.72 – 7.54 (m, 4H), 7.47 (d, *J* = 8.4 Hz, 2H), 2.17 (s, 3H), 1.35 (s, 9H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ= 199.0, 151.1, 147.8, 135.7, 133.8, 131.5, 129.3, 128.5, 126.7, 125.3, 125.1, 124.7, 120.3, 34.2, 30.8, 28.7. MS (relative intensity) *m*/*z*: 319(1.4), 291(33.9), 276(100.0), 261(9.0), 248(10.2), 234(44.3), 161(54.7), 131(34.2). HRMS (APCI-QTOF) calculated mass for $C_{20}H_{22}N_3O$ [M+H]$^+$: 320.1757, found: 320.1757.

1-(2-(4-(4-methoxyphenyl)-1*H*-1,2,3-triazoyl)phenyl)ethan-1-one 3e: method A: yield: 0.062 g (85%), method B: yield: 0.064 g (88%); white solid; mp 122-124 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ= 8.02 (s, 1H), 7.83 (d, *J* = 8.8 Hz, 2H), 7.71 (dd, *J* = 7.5, 1.6 Hz, 1H), 7.66-7.62 (m, 1H), 7.61-7.57 (m, 1H), 7.51 (dd, *J* = 7.7, 1.2 Hz, 1H), 6.99 (d, *J* = 8.8 Hz, 2H), 3.86 (s, 3H), 2.21 (s, 3H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ= 199.9, 160.0, 148.4, 136.5, 134.6, 132.0, 129.9, 129.1, 127.3, 125.5, 122.7, 120.2, 114.5, 55.5, 29.4. MS (relative intensity) *m*/*z*: 293(5.9), 265(33.2), 250(83.6), 208(24.8), 180(5.8), 135(100.0), 91(70.7). HRMS (APCI-QTOF) calculated mass for $C_{17}H_{16}N_3O_2$ [M+H]$^+$: 294.1243, found: 294.1237.

1-(2-(4-(2-methoxyphenyl)-1*H*-1,2,3-triazoyl)phenyl)ethan-1-one 3f: method A: yield: 0.052 g (71%), method B: yield: 0.057 g (78%); yellowish solid; mp 109-111 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ= 8.43 (dd, *J* = 7.7, 1.7 Hz, 1H), 8.38 (s, 1H), 7.72 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.67-7.63 (m, 1H), 7.60 – 7.54 (m, 2H), 7.38 – 7.33 (m, 1H), 7.13-7.09 (m, 1H), 7.01 (d, *J* = 8.4, 1H), 3.95 (s, 3H), 2.15 (s, 3H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ= 200.0, 155.9, 144.0, 136.6, 134.8, 132.0, 129.8, 129.5, 129.1, 127.9, 125.5, 124.3, 121.2, 118.8, 110.9, 55.5, 29.3. MS

(relative intensity) *m/z*: 293(2.8), 264(12.1), 250(65.4), 222(43.8), 208(51.7), 180(37.2), 135(100), 91(88.0). HRMS (APCI-QTOF) calculated mass for $C_{17}H_{16}N_3O_2$ $[M+H]^+$: 294.1243, found: 294.1239.

1-(2-(4-(4-chlorophenyl)-1*H*-1,2,3-triazoyl)phenyl)ethan-1-one 3g: method A: yield: 0.035 g (48%), method B: yield: 0.033 g (45%); yellowish solid; mp 115-117 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ= 8.09 (s, 1H), 7.84 (d, *J* = 8.5 Hz, 2H), 7.74 (dd, *J* = 7.4, 1.6 Hz, 1H), 7.68 – 7.60 (m, 2H), 7.52 (d, *J* = 7.6 Hz, 1H), 7.43 (d, *J* = 8.5 Hz, 2H), 2.27 (s, 3H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ= 199.7, 147.4, 136.5, 134.5, 134.4, 132.1, 130.2, 129.3, 129.1, 128.6, 127.3, 125.8, 121.3, 29.5. MS (relative intensity) *m/z*: 297(4.9), 269(99.3), 254(29.7), 240(33.0), 234(72.0), 227(50.1), 219(57.4), 150(52.9), 139(100.0). HRMS (APCI-QTOF) calculated mass for $C_{16}H_{13}ClN_3O$ $[M+H]^+$: 298.0742, found: 298.0746.

1-(2-(4-(3-(trifluoromethyl)phenyl)-1*H*-1,2,3-triazoyl)phenyl)ethan-1-one 3h: method A: yield: 0.041 g (50%), method B: yield: 0.045 g (54%); brown solid; mp 67-69 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ= 8.12 (s, 1H), 8.08 (s, 1H), 8.00 (d, *J* = 7.5 Hz, 1H), 7.65 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.59 – 7.46 (m, 4H), 7.43 (dd, *J* = 7.6, 1.3 Hz, 1H), 2.20 (s, 3H). ^{13}C NMR {^{1}H} (100 MHz, $CDCl_3$) δ= 199.5, 147.0, 136.3, 134.3, 132.1, 131.4 (q, *J* = 32.5 Hz) , 130.9, 130.2, 129.6, 129.1, 128.1, 125.8, 125.4, 125.2, 125.2, 125.12, 125.14 (q, *J* = 3.7 Hz), 124.1 (q, *J* = 273.7 Hz), 122.8 (q, *J* = 3.8 Hz), 121.8, 120.0, 29.4. MS (relative intensity) *m/z*: 331(1.1), 303(100.0), 288(28.6), 274(48.3), 261(36.9), 234(25.5), 173(55.5), 120(24.7), 91(74.7). HRMS (APCI-QTOF) calculated mass for $C_{17}H_{13}F_3N_3O$ $[M+H]^+$: 332.1005, found: 332.1015.

1-(2-(4-(naphthalen-2-yl)-1*H*-1,2,3-triazoyl)phenyl)ethan-1-one 3i: method A: yield: 0.069 g (89%), method B: yield: 0.072 g (92%); white solid; mp 158-160 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ= 8.33 (s, 1H), 8.12 (s, 1H), 7.89 (dd, *J* = 8.5, 1.6 Hz, 1H), 7.83 – 7.74 (m, 3H), 7.63 (dd, *J* = 7.5, 1.6 Hz, 1H), 7.56 – 7.38 (m, 5H), 2.16 (s, 3H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ= 199.8, 148.5, 136.4, 134.5, 133.6, 133.4, 132.0, 130.0, 129.1, 128.8, 128.4, 127.9, 127.3, 126.7, 126.5, 125.6, 124.9, 123.9, 121.4, 29.4. MS (relative intensity) *m/z*: 313(12.5), 285(100.0), 270(36.5),243(55.7), 215(18.1), 166(70.3), 155(82.1), 139(46.8), 127(23.6). HRMS (APCI-QTOF) calculated mass for $C_{20}H_{16}N_3O$ $[M+H]^+$: 314.1288, found: 314.1287.

1-(2-(4-(^{t}butyl)-1*H*-1,2,3-triazoyl)phenyl)ethan-1-one 3j: method A: yield: 0.043 g (71%), method B: yield: 0.024 g (40%); white solid; mp 93-95 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ= 7.67 (dd, *J* = 7.5, 1.6 Hz, 1H), 7.63 – 7.53 (m, 3H), 7.47 (dd, *J* = 7.7, 1.1 Hz, 1H), 2.10 (s, 3H), 1.42 (s, 9H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ= 200.0, 158.6, 136.5, 134.8, 131.8, 129.6, 128.9, 125.4, 120.2, 31.0, 30.4, 29.1. MS (relative intensity) *m/z*: 214(2.6), 200(100.0), 182(15.9), 157(8.1), 146(16.1), 105(12.0), 91(24.9). HRMS (APCI-QTOF) calculated mass for $C_{14}H_{18}N_3O$ $[M+H]^+$: 244.1444, found: 244.1447.

1-(2-(4-pentyl-1*H*-1,2,3-triazoyl)phenyl)ethan-1-one 3k: method A: yield: 0.049 g (77%), method B: yield: 0.039 g (61%); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ= 7.68 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.64 – 7.54 (m, 3H), 7.46 (dd, *J* = 7.7, 1.2 Hz, 1H), 2.80 (t, *J* = 7.8 Hz, 2H), 2.12 (s, 3H), 1.75 (q, *J* = 7.4 Hz, 2H), 1.40 – 1.37 (m, 4H), 0.93 – 0.90 (m, 3H). ^{13}C NMR {^{1}H} (100 MHz, $CDCl_3$) δ= 199.9, 149.3, 136.5, 134.8, 131.9, 129.7, 128.9, 125.4, 122.2, 31.5, 29.2, 29.1, 25.6, 22.5, 14.1. MS (relative intensity) *m/z*: 229(1.1), 214(5.6), 186(20.5), 172(100.0), 146(12.0), 130(13.8), 91(58.8). HRMS (APCI-QTOF) calculated mass for $C_{15}H_{20}N_3O$ $[M+H]^+$: 258.1601, found: 258.1608.

1-(2-(4-(cyclohex-1-en-1-yl)-1*H*-1,2,3-triazoyl)phenyl)ethan-1-one 3l: method A: yield: 0.047 g (71%), method B: yield: 0.043 g (65%); yellow solid; mp 64-66 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ= 7.74 (s, 1H), 7.68 (dd, *J* = 7.5, 1.3 Hz, 1H), 7.63 – 7.54 (m, 2H), 7.45 (d, *J* = 7.8 Hz, 1H), 6.64 (s, 1H), 2.43-2.41 (m, 2H), 2.24 – 2.22 (m, 2H), 2.15 (s, 3H), 1.83-1.77 (m, 2H), 1.72-1.67 (m, 2H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ= 199.9, 150.2, 136.4, 134.6, 131.9, 129.7, 129.0, 126.8, 126.2, 125.3, 119.6, 29.3, 26.4, 25.4, 22.5, 22.2. MS (relative intensity) *m/z*: 267(1.5), 238(38.1), 224(33.4), 210(61.0),196(61.8), 168(64.4), 146(29.3), 120(33.9), 109(62.0), 91(100.0). HRMS (APCI-QTOF) calculated mass for $C_{16}H_{18}N_3O$ $[M+H]^+$: 268.1444, found: 268.1447.

1-(2-(4-(1-hydroxycyclopentyl)-1*H*-1,2,3-triazoyl)phenyl)ethan-1-one 3m: method A: yield: 0.043 g (63%), method B: yield: 0.046 g (68%); white solid; mp 59-61 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ= 7.77 (s, 1H), 7.61 (dd, *J* = 7.3, 1.9 Hz, 1H), 7.56 – 7.47 (m, 2H), 7.39 (dd, *J* = 7.6, 1.6 Hz, 1H), 2.93 (s, 1H), 2.16 – 1.75 (m, 11H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ= 199.8, 155.1, 136.3, 134.55, 132.0, 129.9, 129.0, 125.6, 121.7, 79.0, 41.4, 29.2, 23.7. MS (relative intensity) *m/z*: 242(12.0), 224(24.9), 214(37.7), 200(32.4), 196(18.6), 186(40.2), 172(50.8), 146(100.0), 120(53.7). HRMS (APCI-QTOF) calculated mass for $C_{15}H_{18}N_3O_2$ $[M+H]^+$: 272.1394, found: 272.1382.

1-(2-(4-((phenylthio)methyl)-1*H*-1,2,3-triazoyl)phenyl)ethan-1-one 3r: method A: yield: 0.058 g (75%), method B: yield: 0.060 g (78%); redish solid; mp 54-56 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ= 7.60 – 7.57 (m, 2H), 7.53 – 7.45 (m, 2H), 7.29-7.27 (m, 3H), 7.21-7.17 (m, 2H), 7.13 – 7.08 (m, 1H), 4.23 (s, 2H), 1.93 (s, 3H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ= 199.5, 145.9, 136.3, 135.1, 134.4, 132.0, 130.0, 129.9, 129.11, 129.08, 126.8, 125.6, 123.7, 29.0, 28.8. MS (relative intensity) *m/z*: 309(19.1), 238(55.6), 172(77.5), 154(16.9), 146(16.0), 130(65.3), 109(21.1), 91(100.0). HRMS (APCI-QTOF) calculated mass for $C_{17}H_{16}N_3OS$ $[M+H]^+$: 310.1009, found: 310.1019.

1-(2-(4-((phenylselanyl)methyl)-1*H*-1,2,3-triazoyl)phenyl)ethan-1-one 3s: method A: yield: 0.083 g (93%), method B: yield: 0.079 g (89%); yellowish solid; mp 62-64 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ= 7.60 (dd, *J* = 7.4, 1.8 Hz, 1H), 7.54 – 7.42 (m, 5H), 7.27 (dd, *J* = 7.3, 1.7 Hz, 1H), 7.20 – 7.17 (m, 3H), 4.17 (s, 2H), 1.97 (s, 3H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ= 199.5, 146.5, 136.4, 134.5, 133.6, 132.0, 130.0, 129.5, 129.3, 129.1, 127.7, 125.6, 123.4, 29.1, 20.4. ^{77}Se {^{1}H} NMR (76 MHz, $CDCl_3$) δ= 368.1. MS (relative intensity) *m/z*: 357(8.1), 286(4.9), 172(47.4), 154(26.5), 149(35.1), 130(100.0), 105(13.9), 91(78.8). HRMS (APCI-QTOF) calculated mass for $C_{17}H_{16}N_3OSe$ $[M+H]^+$: 358.0454, found: 358.0463.

Molecular docking

The 2D structures of chemical compounds were draw with Chemdraw, converted to 3D using the software Avogadro 0.9.4 and their geometry was optimized following GAFF method.[32] Auto Dock Tools 1.5.4 program was used to set all rotatable bonds of ligands rotate freely and the protein receptors were considered rigid.[33]

The 3D X-ray crystal structures of MAO isoforms were retrieved from Protein Data Bank (MAO-A PDB ID: 2Z5X; MAO-B PDB ID: 5MRL) and prepared using the software Auto Dock Tools 1.5.4. The protein preparation consisted of fixing structures, deleting molecules, ions, and water, fixing hetero groups and finally optimize the structure using Gasteiger charges with 500 steps of minimization. CHIMERA 1.5.3 software was used previously to remove ligands in 3D structure.[34] The molecular docking using the software autodock vina (version 1.1.1) was conducted with a grid box centered in all atom structure, allowing the program to search for additional places of probable interactions.[35] The protein–ligand interactions were analyzed by Discovery studio visualizer 2016.

Monoamine oxidase (MAO) activity

MAO was obtained from brain mice homogenate. Male adult Swiss mice (25–30 g), from the Central Biotery of the Federal University of Pelotas, were kept in a separate animal room at 22 ± 2 °C under a 12-h light/ dark cycle, lights turning on at 7:00 a.m. Commercial diet and tap water were supplied ad libitum. All animal procedures were performed in accordance with the Guidelines for Care and Use of Laboratory Animals of Federal University of Pelotas and experiments were approved by the Animal Ethics Committee of Federal University of Pelotas (CEEA – number of approval 50890-2019), affiliated to the Council for Control of Animal Experiments (CONCEA) and the animal care was according to the National Institutes of Health Guide for the care and use of laboratory animals (NIH Publications No. 8023, revised 1978). All efforts were made to minimize animals suffering and to reduce the number of animals used in the experiments.

Mice were euthanized and the whole brains were quickly removed and washed in ice cold isolation medium (Na_2HPO_4 0.0168 M/KH_2PO_4 0.0106 M isotonized with sucrose 0.32 M, pH 7.4). Preparations of cerebral mitochondria were used for MAO assay as described by Sampaio *et al.* and Soto-Otero *et al.*.[36] Briefly, after removing blood vessels and pial membranes, brains were manually homogenized with four volumes (w/v) of the isolation medium. Then, the homogenate was centrifuged at 900×g at 4 °C for 5 min. The supernatant was centrifuged at 12,500×g at 4 °C for 15 min. The mitochondria pellet was then washed once with isolation medium and recentrifuged under the same conditions. Finally, the mitochondrial pellet was reconstituted in a buffer solution (Na_2HPO_4 0.0168 M/KH_2PO_4 0.0106 M isotonized with KCl 0.0036 M, pH 7.4) and stored in aliquots at −20 °C for up to 48 h before enzyme assay.

The protein concentration of brain homogenates was measured by the method of Bradford,[37] using bovine serum albumin as the standard, and fixed at 1 mg/mL. MAO activity was determined as described by Sampaio *et al.* and Soto-Otero *et al.* with some modifications.[36] Aliquots of samples were incubated at 37 °C for 5 min in a medium containing buffer solution (Na_2HPO_4 0.0168 M/KH_2PO_4 0.0106 M isotonized with KCl 0.0036 M, pH 7.4) the specific inhibitors pargyline (a MAO-B inhibitor, 250 nM) or clorgyline (a MAO-A inhibitor, 250 nM) to differentiate MAO isoforms, and 2'-(1,2,3-triazoyl)-acetophenones, dissolved in DMSO (final concentrations of 0.01 to 500 µM). The inhibitory effect of the positive controls clorgyline (final concentrations of 0.00001 to 0.1 µM) and pargyline (final concentrations of 0.001 to 0.25 µM) on MAO-A and MAO-B activities, respectively, was evaluated simultaneously. Then submaximal concentrations of kynuramine dihydrobromide (90 µM to MAO-A and 60 µM to MAO-B assay) were added to the reaction mixture as a nonselective substrate. Samples were then incubated at 37 °C for 30 min. After incubation, the reaction was terminated by adding trichloroacetic acid (TCA) 10%.

After cooling and centrifugation at 16,000×g for 5 min, an aliquot of supernatant was added to NaOH 1 M. The fluorescence intensity was measured spectrofluorimetrically with excitation at 315 nm and emission at 380 nm. The concentration of 4-hydroxyquinoline was estimated from its corresponding standard fluorescence curve. MAO activity was expressed as nanomole of 4-hydroxyquinoline per milligram of protein per minute. All the chemical reagents were of analytical grade and obtained from standard commercial suppliers.

Statistical analysis

Statistical analysis of data was performed using a one-way analysis of variance (ANOVA), followed by the Newman-Keul's test. Half-maximal inhibitory concentration (IC_{50}) was determined by nonlinear regression from individual experiments using ''GraphPad Software'' (GraphPad software, San Diego, CA, USA). Data of MAO assay *in vitro* were expressed as means ± S.E.M. Values of $p<0.05$ were considered statistically significant.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

The authors are grateful for the financial support and scholarships from the Brazilian agencies CNPq and FAPERGS (PRONEM 16/2551-0000240-1). CNPq is also acknowledged for the fellowship for R.G.J., L.S. and D.A. This study was partially financed by the Coordenação de Aperfeiçoamento de Pessoal de Nivel Superior-Brasil (CAPES)-Finance Code 001. We are grateful to Prof. Thiago Barcellos from University of Caxias do Sul (UCS) for providing the HRMS analysis.

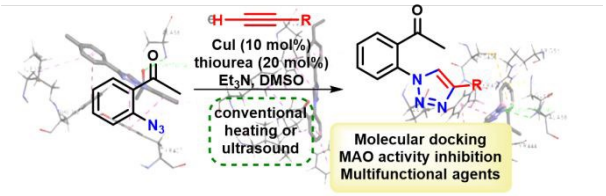
Notes and references

1 a) J.E. Hein, V.V. Fokin, *Chem. Soc. Rev.* 2010, **29**, 1302-1315; b). M. Jurıcek, P.H.J. Kouwer, A. E. Rowan, *Chem. Commun.* 2011, **47**, 8740-8749; c) V. Ganesh, V.S. Sudhir, T. Kundu, S. Chandrasekaran, *Chem. Asian J.* 2011, **6**, 2670-2694; d) J. Lai, F. Yang, H. Guo, Z. Jiao, *Iran. Polym. J.* 2014, **23**, 899-906; e) J. Huo, H. Hu, M. Zhang, X. Hu, M. Chen, D. Chen, J. Liu, G. Xiao, Y. Wang, Z. Wen, *RSC Adv.* 2017, **7**, 2281-2287.

2 Q. Ma, S. Qi, X. He, Y. Tang, G. Lu, *Corros. Sci.* 2017, **129**, 91-101.

3 T. Duan, K. Fan, Y. Fu, C. Zhong, X. Chen, T. Peng, J. Qin, *Dyes Pigments* 2012, **94**, 28-33.
4 a) A. Massarotti, S. Aprile, V. Mercalli, E. Del Grosso, G. Grosa, G. Sorba, G.C. Tron, *ChemMedChem*. 2014, **9**, 2497-2508; b) E. Bonandi, M.S. Christodoulou, G. Fumagalli, D. Perdicchia, G. Rastelli, D. Passarella, *Drug Discov. Today* 2017, **22**, 1572-1581; c) S.P. Mantoani, P. de Andrade, T.P.C. Chierrito, A.S. Figueredo, I. Carvalho, *Curr. Med. Chem.* 2019, **26**, 4403-4434; d) A. Rani, G. Singh, A. Singh, U. Maqbool, G. Kaur, J. Singh, *RSC Adv.* 2020, **10**, 5610-5635.
5 a) B. Zhang, *Eur. J. Med. Chem*. 2019**, 168**, 357-372; b) Z. Xu, S.-J. Zhao, Y. Liu, *Eur. J. Med. Chem.* 2019, **183**, 111700; c) R. Csuk, H.-P. Deigner, *Bioorg. Med. Chem. Lett*. 2019, **29**, 949-958.
6 M. Xu, Y. Peng, L. Zhu, S. Wang, J. Ji, K.P. Rakesh, *Eur. J. Med. Chem*. 2019, **180**, 656-672.
7 a) V.V. Rostovtsev, L.G. Green, V.V. Fokin, K.B. Sharpless, *Angew. Chem. Int. Ed.* 2002, **41**, 2596-2599; b) C.W. Tornøe, C. Christensen, M. Meldal, *J. Org. Chem.* 2002, **67**, 3057-3064.
8 a) V.D. Bock, D. Speijer, H. Hiemstr, J.H. Van Maarseveen, *Org. Biomol. Chem*. 2007, **5**, 971-975; b) W.S. Horne, C.A. Olsen, J.M. Beierle, A. Montero, M.R. Ghadiri, *Angew. Chem. Int. Ed.* 2009, **48**, 4718-4724; c) M. Tischler, D. Nasu, M. Empting, S. Schmelz, D.W. Heinz, P. Rottmann, H. Kolmar, G. Buntkowsky, D. Tietze, O. Avrutina, *Angew. Chem*. 2012, **124**, 3768-3772; d) I.E. Valverde, A. Bauman, C.A. Kluba, S. Vomstein, M.A. Walter, T.L. Mindt, *Angew. Chem. Int. Ed*. 2013, **53**, 1-5.
9 a) G.L. Patrick, An Introduction to Medicinal Chemistry, Fifth Edition, Oxford, 2013; b) C. Bissantz, B. Kuhn, M. Stahl, *J. Med. Chem*. 2010, **53**, 5061-5084.
10 M.L. Hare, *Biochem. J.* 1928, **22**, 968-979.
11 D. E. Edmondson, C. Binda, *Subcell. Biochem*. 2018, **87**, 117-139.
12 K. F. Tipton, *J. Neural. Transm* (Vienna). 2018, **125**, 1519-1551.
13 C.C. Wang, E. Billett, A. Borchert, H. Kuhn, C. Ufer, *Cell. Mol. Life Sci*. 2013**, 70**, 599-630.
14 C. Singh, M. Bortolato, N. Bali, S.C. Godar, A.L. Scott, K. Chen, R.F. Thompson, J.C. Shih, *Proc. Natl. Acad. Sci. U. S. A*. 2013, **110**, 12816-12821.
15 D. Tao, Y. Wang, X.Q. Bao, B.B. Yang, F. Gao, L. Wang, D. Zhang, L. Li, *Eur. J. Med. Chem*. 2019, **173**, 203-212.
16 S.J. Thomas, M. Shin, M.G. Mcinnis, J.R. Bostwick, *Pharmacotherapy* 2015, **35**, 433-449.
17 D. Knez, M. Sova, U. Kosak, S. Gobec, *Future Med. Chem*. 2017, **9**, 811-832.
18 M. Bortolato, K. Chen, J.C. Shih, *Adv. Drug Deliv. Rev.* 2008, **60**, 1527–1533.
19 S. Mandel, E. Grunblatt, P. Riederer, M. Gerlach, Y. Levites, M.B. Youdim, *CNS Drugs* 2003*,* **17**, 729–762.
20 a) O. Di Pietro, N. Alencar, G. Esteban, E. Viayna, N. Szalaj, J. Vazquez, J. Juarez-Jimenez, I. Sola, B. Perez, M. Sole, M. Unzeta, D. Munoz-Torrero, F.J. Luque, *Bioorg. Med. Chem.* 2016, **24**, 4835-4854; b) S. Haider, M. Alhusban, N.D. Chaurasiya, B. Tekwani, A.G. Chittiboyina, I.A. Khan, *Future Med. Chem.* 2018, **10**, 1435-1448.
21 G.P. Costa, R. Baldinotti, M.G. Fronza, J.E. Nascimento, Í. Dias, M.S. Sonego, F.K. Seixas, T. Collares, G. Perin, R.G.Jacob, L. Savegnago, D. Alves, *ChemMedChem* 2020, **15**, 610-622.
22 a) G. Cravotto, P. Cintas, *Chem. Soc. Rev*. 2006, **35**, 180-196; b) T.J. Mason, *Ultrason. Sonochem.* 2007, **14**, 476-483; c) M. Nüchter, B. Ondruschka, A. Jungnickel, U. Müller, *J. Phys. Org. Chem*. 2000, **13**, 579–586; d) T.J. Mason, *Chem. Soc. Rev*. 1997, **26**, 443-451; e) L. Abenante, F. Penteado, M.M. Vieira, G. Perin, D. Alves, E.J. Lenardão, *Ultrason. Sonochem*. 2018, **49**, 41-46; f) G. Perin, D.R. Araujo, P.C. Nobre, E.J. Lenardão, R.G. Jacob, M.S. Silva, J.A. Roehrs, *PeerJ* 2018, **6**, e4706; g) D.M. Xavier, B.S. Goldani, N. Seus, R.G. Jacob, T. Barcellos, M.W. Paixão, R. Luque, D. Alves, *Ultrason. Sonochem*. 2017, **34**, 107-114.
23 R.M. Geha, K. Chen, J. Wouters, F. Ooms, J.C. Shih, *J. Biol. Chem*. 2002, **277**, 17209–17216.
24 S.-Y. Son, J. Ma, Y. Kondou, M. Yoshimura, E. Yamashita, T. Tsukihara, *Proc. Natl. Acad. Sci. U. S. A*. 2008, **105**, 5739–5744.
25 L. De Colibus, M. Li, C. Binda, A. Lustig, D.E. Edmondson, A. Mattevi, *Proc. Natl. Acad. Sci. U. S. A*. 2005, **102**, 12684–12689.
26 P. Paudel, S.E. Park, S.H. Seong, H.A. Jung, J.S. Choi, *Int. J. Mol. Sci.* 2019, **20**, 6232-6258; b) H.W. Lee, H.W. Ryu, M.-G. Kang, D. Park, H. Lee, H.M. Shin, S.-R. Oh, H. Kim, *Int. J. Biol. Macromol*. 2017, **97**, 598–605; c) S.H. Seong, P. Paudel, J.-W. Choi, D.H. Ahn, T.-J. Nam, H.A. Jung, J.S. Choi, *Mar. Drugs* 2019, **17**, 377-393.
27 C. Binda, M. Aldeco, W.J. Geldenhuys, M. Tortorici, A. Mattevi, D.E. Edmondson, *ACS Med. Chem. Lett*. 2011, **1**, 39–42.
28 S.K. Yusufzai, M.S. Khan, O. Sulaiman, H. Osman, D.N. Lamjin, *Chem. Cent. J*. 2018, **12**, 128-185.
29 a) S. Lipper, D. L. Murphy, S. Slater, M. S. Buchbaum, *Psychopharmacology* 1979, **62**, 123-128; b) D. J. David, D. Gourion, *Encephale* 2016, **42**, 553-561.
30 W. Bernheimer, W. Birkmayer, O. Hornykiewicz, *Klin Wochenschr*. 1961, **39**, 1056-1059; b) W. Birkmayer, P. Riederer, MB. Youdim, W. Linauer, *J. Neural. Transm*. 1975, **36**, 303-326; c) M. Rabey, I. Jsagi, M. Huberman, E. Melamed, A. Korczyn, N. Giladi, R. Inzelberg, R. Djaldetti, C. Klein, G. Berecz, R. S. Group, *Clin. Neuropharmacol*. 2000, **23**, 324-330; d) M.B. Youdim, D. Edmondson, K.F., *Nat. Rev. Neurosci*. 2006, **7**, 295-309; e) S. Corbineau, M. Breton, J. Mialet-Perez, J.F. Costemale-Lacoste, *Int. J. Cardiol.* 2017, **247**, 1-6; f) W. Shao, S. Shu, R. Liu, Y. Jiang, W. Zhang, H. Men, *J. Pharm. Sci*. 2019, **32**, 371-375.
31 C. Huang, J. Xiong, H.D. Guan, C.H. Wang, X. Lei, J.F. Hu, *Bioorg. Med. Chem*. 2019, **27**, 2027-2040.
32 M.D. Hanwell, D.E. Curtis, D.C. Lonie, T. Vandermeersch, E. Zurek, G.R. Hutchison, *J. Cheminform*. 2012, **4**, 17.
33 G.M. Morris, R. Huey, W. Lindstrom, M.F. Sanner, R.K. Belew, D.S. Goodsell, A.J. Olson, *J. Comput. Chem*. 2009, **30**, 2785–2791.
34 E.F. Pettersen, T.D. Goddard, C.C. Huang, G.S. Couch, D.M. Greenblatt, E.C. Meng, T.E. Ferrin, *J. Comput. Chem.* 2004, **25**, 1605–1612.
35 O. Trott, A.J. Olson, *J. Comput. Chem*. 2010, **31**, 455–461.
36 a) T.B. Sampaio, J.T. Da Rocha, M. Prigol, R.A. Saraiva, P.F. Nogara, A.L. Stein, J.B. Da Rocha, G. Zeni, C.W. Nogueira, *J. Mol. Neurosci*. 2016, **59**, 135-145; b) R. Soto-Otero, E. Mendez-Alvarez, A. Hermida-Ameijeiras, I. Sanchez-Sellero, A. Cruz-Landeira, M.L. Lamas, *Life Sci*. 2001, **69**, 879-889.
37 M.M. Bradford, *Anal. Biochem*. 1976, **72**, 248-254.

Table of contents



The synthesis of 2'-(1,2,3-triazoyl)-acetophenones by a CuAAC using thiourea as a ligand, molecular docking and MAO activity analyses were performed.