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$Cu(PPh_3)_3Br$-CATALYZED SYNTHESIS OF NEW PARACETAMOL-1,2,3-TRIAZOLE MOLECULAR HYBRIDS FROM EXPIRED COMMERCIAL TABLETS AND THEIR *IN-SILICO* ASSESSMENT TO STUDY THEIR PHARMACOLOGICAL PROPERTIES

Chaired by DR. ALFREDO BERZAL-HERRANZ;
Co-Chaired by PROF. DR. MARIA EMÍLIA SOUSA

pharmaceuticals MDPI

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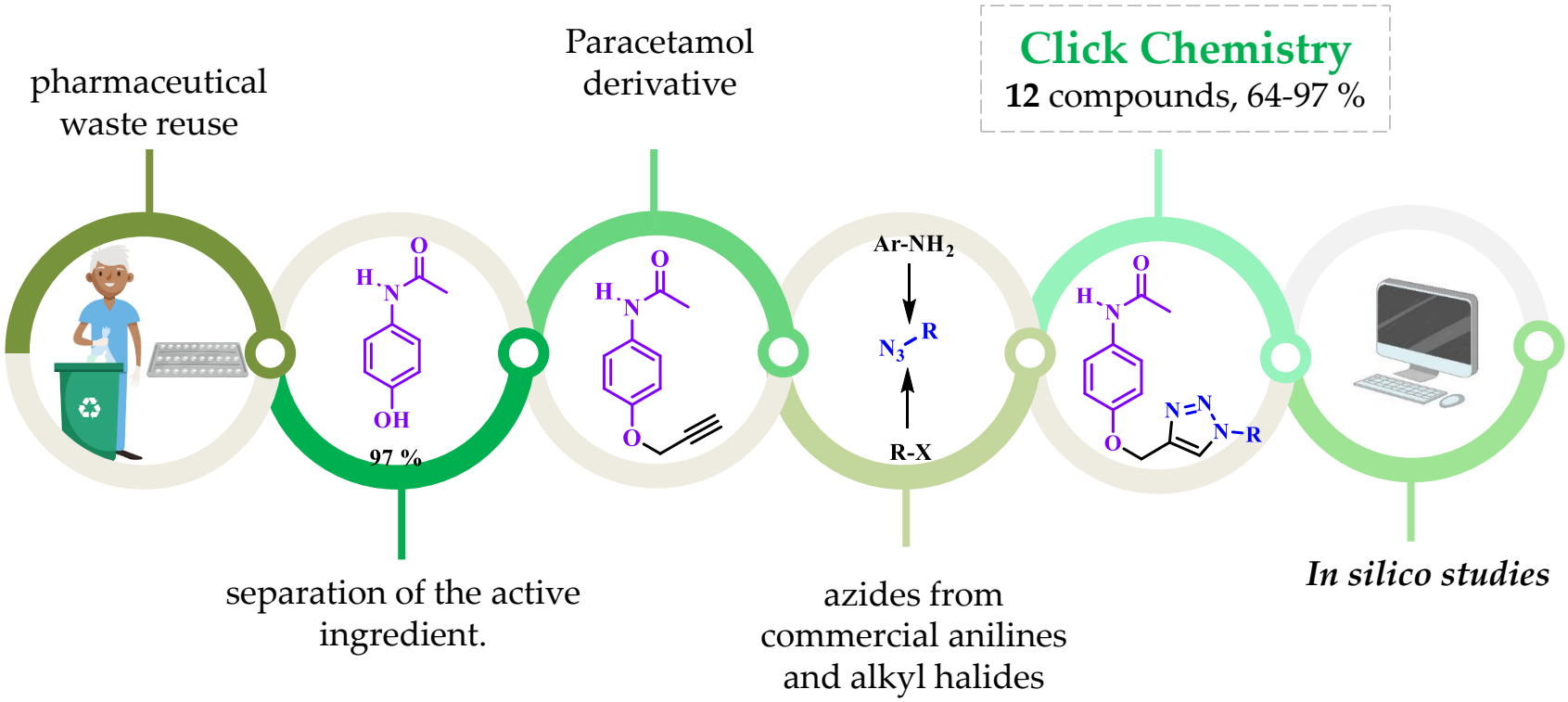


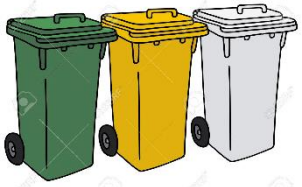
Abstract

The 1,2,3-Triazole ring has remarkable importance in medicinal chemistry due to its unique biological properties such as metabolic stability and ability to form hydrogen bonds. Several biological activities had been reported for this structural nucleus, while paracetamol (acetaminophen, *N*-(4-hydroxyphenyl)acetamide) is one of the most popular and widely used drugs for the treatment of pain and fever. Applying a molecular hybridization strategy, numerous 1,2,3-triazole-based compounds have been designed, prepared, and studied for pharmacological applications in multiple laboratories around the world. Considering this context, we used expired acetaminophen pills as starting material for generating new series of functionalized paracetamol-1,2,3-triazole hybrids. Their synthesis consists of $Cu(PPh_3)_3Br$-catalyzed 1,3-dipolar cycloaddition reaction of *O*-propargyl-acetaminophen and several azides prepared from commercially available anilines, following the protocol reported by Filimonov et al. Performing click chemistry and considering green chemistry principles, interesting paracetamol-1,2,3-triazole derivatives were easily prepared in 53-93 % yields. Obtained hybrids were subjected to *In-Silico* analysis (Molinspiration, OSIRIS, and DRUDIT), evaluating some physicochemical properties and toxicity risks. According to the predicted biological properties, most of the prepared hybrid molecules exhibit adequate parameters as potential pharmacological agents, presenting high inhibitory activity, low risks of toxicity, and good affinity for various biological targets. This work highlights the recycling of expired drugs and the accessibility to new paracetamol-based compounds under green mild reaction conditions (H_2O/*tert*-BuOH mixture, rt) and low catalytic loads (1 mol% $Cu(PPh_3)_3Br$).

Keywords:,1,3-dipolar cycloaddition; *In-Silico* studies; Paracetamol-1,2,3-triazole hybrids

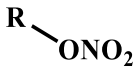
Introduction

144 tons of pharmaceutical drugs waste during 2020

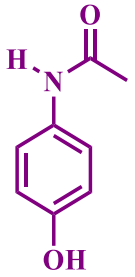


paracetamol concentration up to 50 µg/L in Colombian wastewater

A molecular hybridization strategy

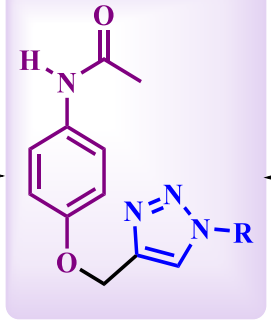


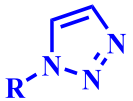
antimicrobial activity.
bactericidal activity.
antiviral activity.
vasodilator activity.
cytoprotective activity.



paracetamol

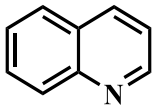
antipyretic activity.
analgesic activity.
anti-inflammatory activity.





triazole ring

anticancer activity.
neuroprotective activity.
antibacterial activity.
antiparasitic activity.



Quinoline

anticancer, antimycobacterial, antimicrobial, anticonvulsant, antiinflamatory and cardiovascular activities.

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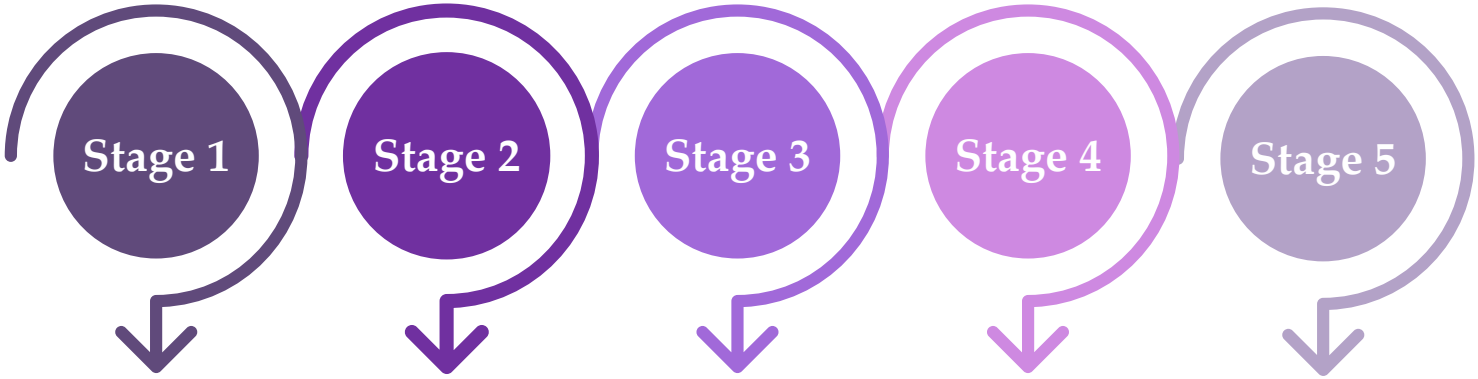
Methodology



Extraction

Of paracetamol from expired commercial tablets though simple protocol.

Primary precursor

Synthesis of an alquine using paracetamol as starting material.

Secondary precursors

Synthesis of aromatic and aliphatic azides.

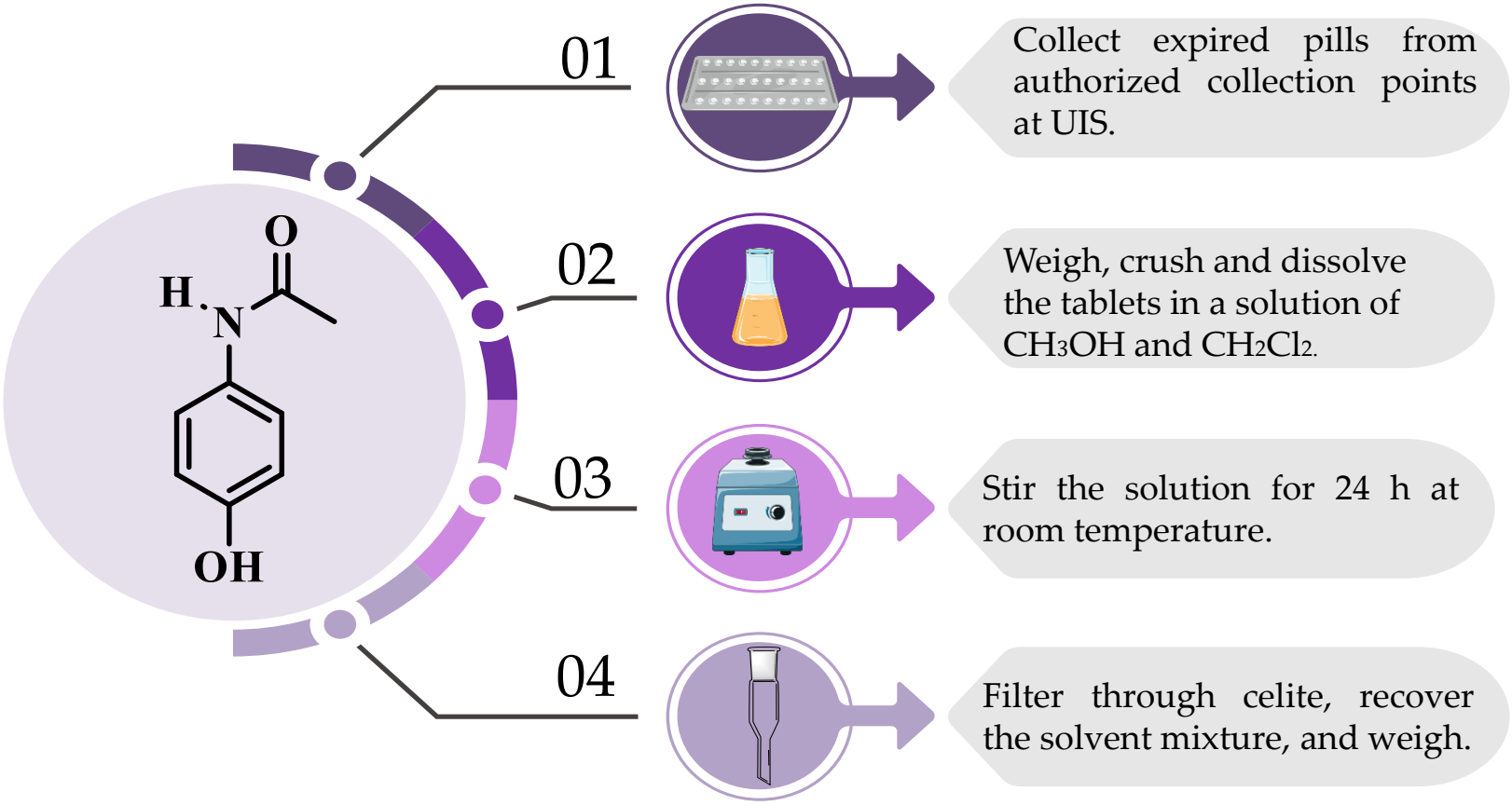
Click Chemistry

Synthesis of new 1,2,3-triazole-paracetamol hybrids using [CuBr(PPh3)3].

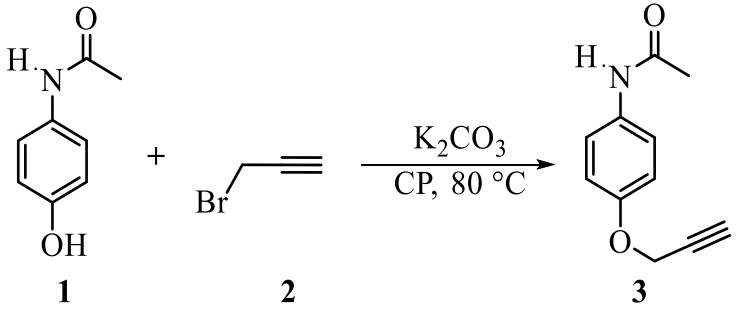
***In-silico* studies**

Assessment of pharmacological properties using online free tools.

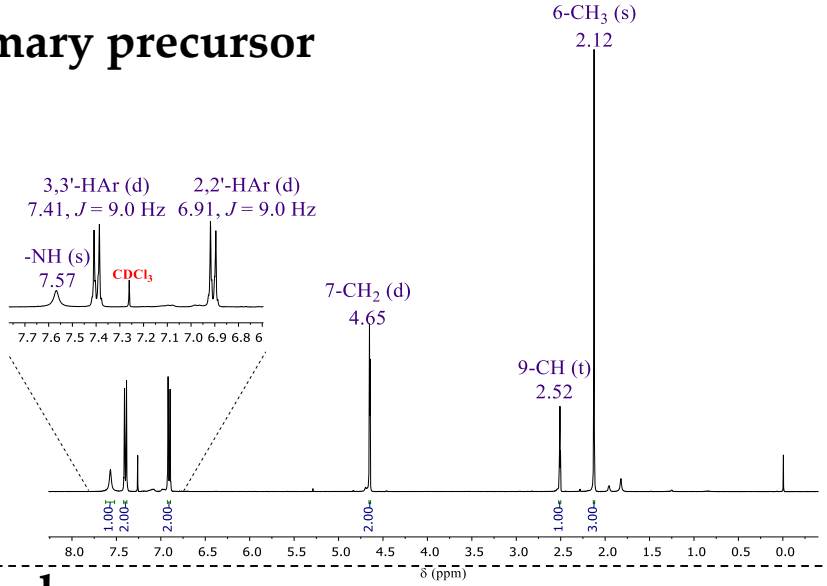
Obtaining paracetamol from expired commercial tablets



Synthesis of primary precursor

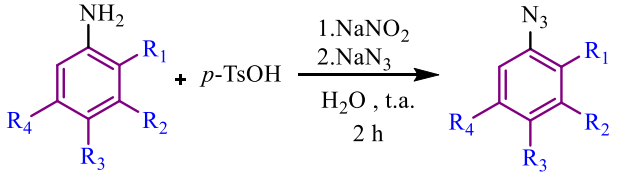


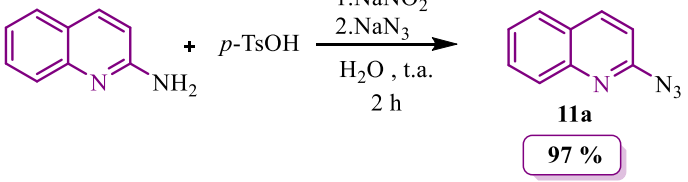
93 %



Synthesis of secondary precursors

Route 1: diazonium salts

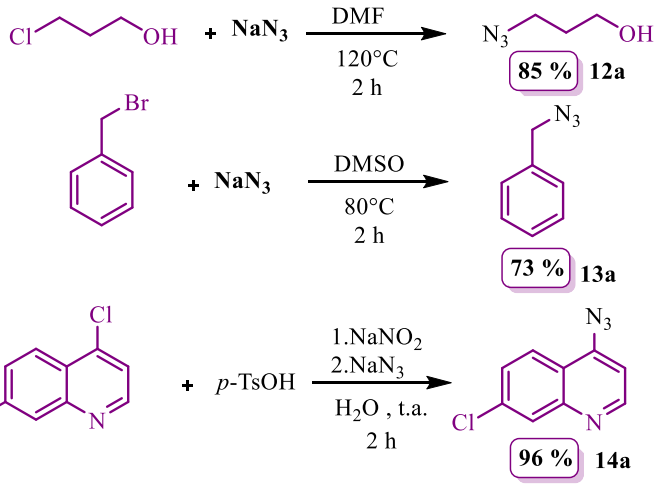




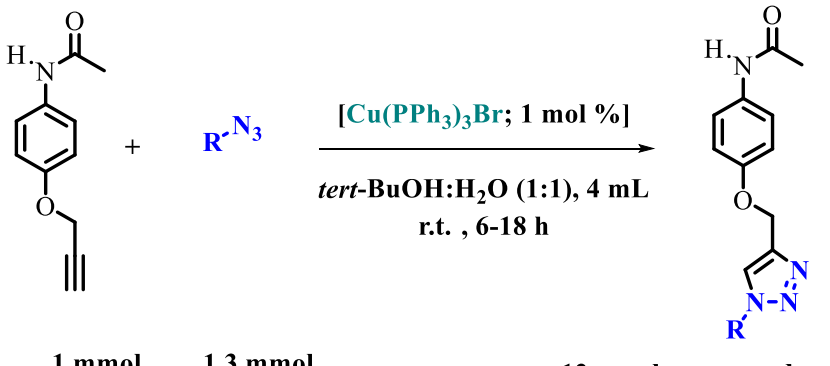
97 %

	R_1	R_2	R_3	R_4	%
4a	H	H	COOH	H	86
5a	H	H	Cl	H	60
6a	H	H	I	H	64
7a	H	H	OH	H	85
8a	Br	H	H	H	86
9a	NO_2	H	CH_3	CH_3	93
10a	H	OCH_3	OCH_3	H	97

Route 2: bimolecular substitution

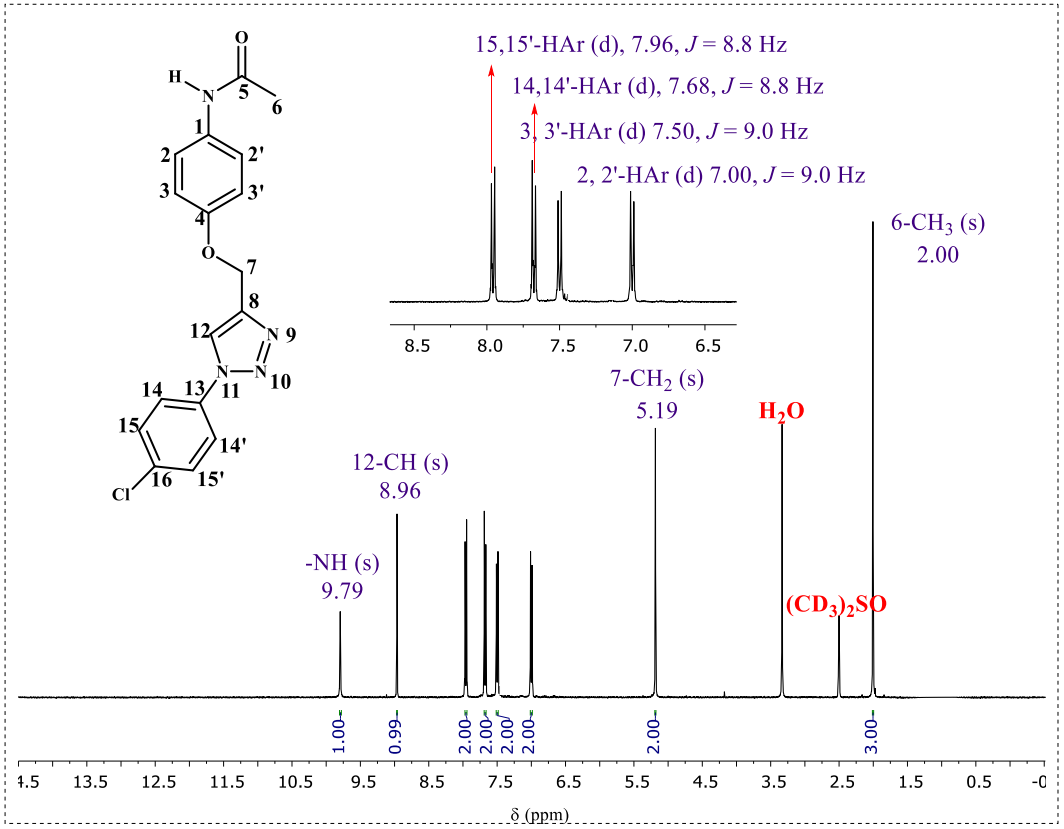


Synthesis of novel paracetamol-1,2,3-triazole hybrids



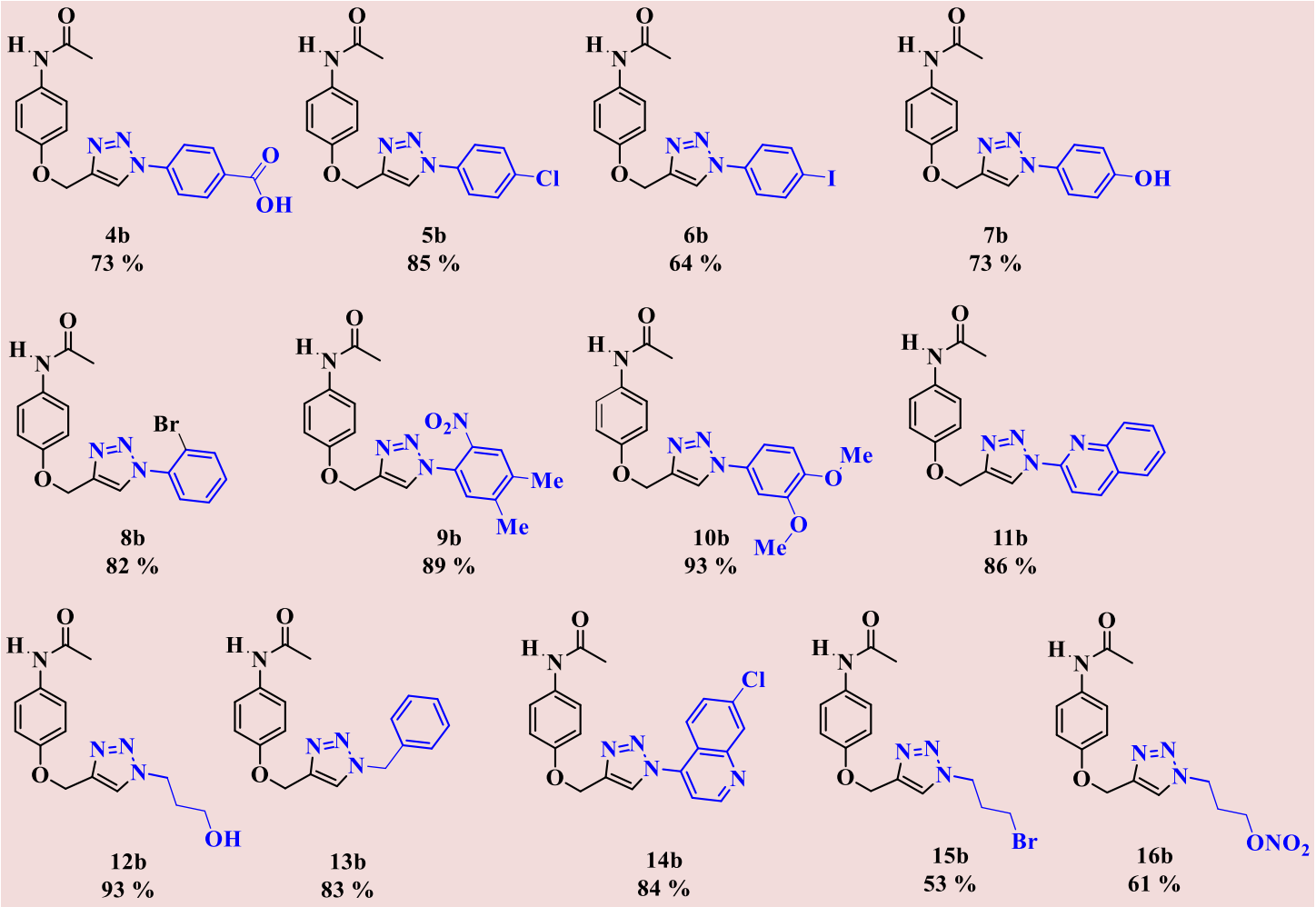
1 mmol 1.3 mmol

12 novel compounds
64 - 93 % yields
several funtional groups



- ✓ Optimization of reaction conditions, evaluating catalyst and catalytic load.
- ✓ Structural characterization using IR and NMR analysis.

Results and discussion



Physicochemical properties using Molinspiration

Comp.	miLogP	MW	nON	nOHNH	N rot. bonds	TPSA	N atoms	volume
4b	2.15	352.35	8	2	6	106.35	26	304.65
5b	2.92	342.79	6	1	5	69.05	24	291.18
6b	3.32	434.24	6	1	5	69.05	24	301.64
7b	1.76	324.34	7	2	5	89.28	24	285.67
8b	3.21	387.24	6	1	5	69.05	24	295.53
9b	3.27	381.39	9	1	7	107.72	28	334.58
10b	2.10	368.74	8	1	7	87.52	27	328.74
11b	3.01	359.39	7	1	5	81.94	27	317.48
12b	0.60	290.32	7	2	7	89.28	21	264.66
13b	2.56	322.37	6	1	6	69.05	24	294.45
14b	3.55	393.83	7	1	5	81.94	28	331.02
15b	1.97	353.22	6	1	7	69.05	21	274.53
16b	1.86	335.32	10	1	9	124.11	24	288.96

*No compound has violations of RO5

Bioactivity scores using Molinspiration

compound	GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Proteasa inhibitor	Enzyme inhibitor
4b	0.04	-0.11	-0.09	-0.13	-0.12	0.06
5b	0.02	-0.11	-0.07	-0.32	-0.21	-0.04
6b	0.03	-0.11	-0.04	-0.27	-0.24	-0.06
7b	0.07	-0.05	0.00	-0.17	-0.14	0.06
8b	0.06	-0.24	-0.17	-0.48	-0.35	-0.03
9b	-0.09	-0.29	-0.14	-0.34	-0.26	-0.06
10b	-0.01	-0.18	-0.06	-0.33	-0.23	-0.05
11b	**0.12**	-0.14	**0.11**	-0.34	-0.24	**0.18**
12b	-0.06	-0.28	-0.02	-0.41	-0.15	0.08
13b	-0.01	-0.16	-0.08	-0.36	-0.14	-0.01
14b	**0.17**	-0.13	0.03	-0.40	-0.21	0.09
15b	-0.12	-0.35	-0.15	-0.50	-0.30	0.09
16b	**0.13**	-0.40	-0.16	-0.45	-0.20	**0.27**

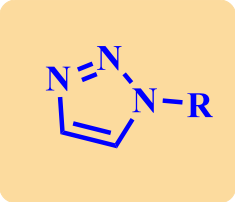
* Parameters marked in bold indicated a strong interaction between the molecule and the biological target.

Toxicity risks using OSIRIS property explorer

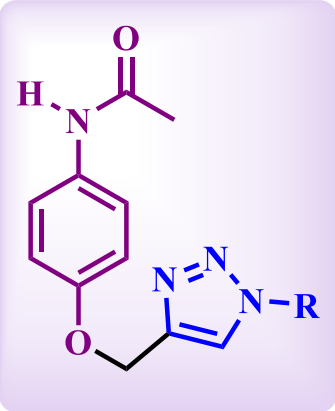
No risk Moderate risk High risk

compound	Mutagenic	Tumorigenic	Irritant	Reproductive effective	*druglikeness*	*drugscore*
4b					-0.52	0.59
5b					1.06	**0.70**
6b					0.65	0.59
7b					0.46	**0.72**
8b					-2.76	-0.4
9b					-0.66	0.17
10b					-1.82	0.48
11b					0.37	0.64
12b					-0.75	0.62
13b					1.72	**0.78**
14b					1.32	0.37
15b					-8.16	0.12
16b					-0.71	0.59

What is next?



Several reports have shown the wide range of biological properties of triazole ring, including antifungal, antibacterial and anticancer activity.



Given that our *in-silico* resulting data showed that some of the synthesized compounds can alter crucial proteins and enzymes for the normal functioning of prokaryotic and eukaryotic cells, we are currently doing *in vitro* bioassays to evaluate antibacterial and antitumor activity.

Conclusions

- ✓ We achieved the extraction of paracetamol from expired commercial tablets recovered from drug collection points with an extraction efficiency of 97 %.
- ✓ Twelve new molecular hybrids containing acetaminophen and 1,2,3-triazole fragments were synthesized in 53-93 % yields and their structures were confirmed using IR and NMR.
- ✓ Overall, the synthetic protocol developed is considered a sustainable protocol since it involves several principles of green chemistry (reuse, effective catalysis, economy of atoms, alternative solvents, etc.).
- ✓ According to *in-silico* studies, most of the compounds do not present risks of toxicity and have a moderate affinity for some biological targets.
- ✓ Biological activity, such as antitumor and antibacterial activity of the obtained compounds are in progress and will be the subject of another report.

Acknowledgments

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Publications

This work was partially published at the Latin American Chemistry Congress (CLAQ 2020).