Universidad del País Vasco
Euskal Herriko Unibertsitatea

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Synthesis of novel Bisarylpyrazoles – a new herbicidal hit class.

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Resumen

En los proyectos de investigación dirigidos a la búsqueda de compuestos con actividad biológica, es una práctica habitual sintetizar análogos donde se mantiene siempre intacto el núcleo estructural (en este caso, un pirazol, heterociclo que ha sido empleados en campos de estudios farmacéuticos) y únicamente se modifican los grupos funcionales de las cadenas laterales de la estructura general.

En este proyecto de grado, se ha trabajado la síntesis orientada a la diversificación. Se han creado, por tanto, múltiples compuestos análogos que posteriormente han sido estudiados en el campo de la actividad herbicida.

Aunque todas las moléculas sean estructuralmente muy similares, al diferir en uno o varios grupos funcionales, sus propiedades biológicas son completamente diferentes e impredecibles.

Todos estos análogos han sido recogidos en rutas sintéticas lineales formadas por reacciones de acoplamiento como Suzuki y Sonogashira y otras reacciones orgánicas como clorinaciones, saponificaciones, esterificaciones, etc.

Abstract

In research projects focused on the search for biologically active compounds (pharmaceuticals, herbicides, pesticides...) it is common practice to synthesize analogs where the structural core remains intact (in this case, a pyrazole, which has been used in pharmaceuticals research fields) while the functional groups from the side chains are modified.

In this bachelor degree project, synthesis orientated to diversification has been worked, creating for that, multiple analogs that later have been studied for their herbicidal properties.

Although all the molecules are structurally very similar, as they differentiate from one or more functional groups, their biological properties are completely different and unpredictable.

All these analogs have been collected in some linear synthetic routes which are formed by coupling reactions such as Suzuki or Sonogashira, and other organic reactions like chlorinations, saponifications, esterifications, etc.

Abbreviations

BAP: Bisarylpyrazole

DMA: Dimethylacetamide

DMAP: 4-(Dimethylamino)pyridine

DMF: Dimethylformamide

EDC: 1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide

HOBt: 1-Hydroxybenzotriazol

LC: Liquid Chromatography

LC-MS: Liquid Chromatography-Mass Spectrometry

MW: Microwave

NBS: N-Bromosuccinimide

NCS: N-Chlorosuccinimide

NIS: N-Iodosuccinimide

NMR: Nuclear Magnetic Resonance

NMR+MS: Nuclear Magnetic Resonance- Mass Spectrometry

RT: Room temperature

T3P: Propanephosphonic acid anhydride

THF: Tetrahydrofuran

TLC: Thin Layer Chromatography

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1- Introduction

WARNING: For confidential purposes, the general structures will be illustrated, but some of the substituents cannot be shown.

1.1- Hit to lead (H2L)

In early drug discovery, it is very common the hit to lead (H2L) process, which is based on, first, finding the hit, which is a molecule with a biological or pharmacological activity that can be improved by doing some modifications to fit better to the target molecule. Then, plenty of analogs of the hit are synthesized and tested to find the lead, which is the molecule with the desired properties and activity.[1,2] These meanings of "hit" and "lead" can change in different situations or among several authors. H2L is usually coupled with computational techniques.[3]

The analogs have different types of modifications, such as introducing a heteroatom (an alkoxy group instead of an alkyl group, or a pyridine instead of benzene) or changing the functional groups (from carboxylic acid to an ester). Sometimes new side chains are introduced or the heteroatom is substituted by another heteroatom (Br or I instead of Cl), among others.

The variability with the different possible combinations is huge, but there are some limitations like the synthetic viability. For example, if the reactive is a carboxylic acid, and the ester is the target, it could be quite easily transformed by the very well-known esterification reaction, which usually affords good yields. But not all the chemical transformations are easy to perform or are efficient, so the synthetic route must be focused on achieving the best yield in each step and also on being viable, avoiding reactions that would need special expensive equipment.

The core and precursor must be quite reactive so that it is easy to introduce side chains or other modifications. But it should not be too reactive because it would be difficult to avoid the formation of mixtures or undesired side products. In those cases, if more than one reaction occurs at the same time, the yield would decrease and a further purification step would be needed.

[1] Cuffari, B.; Hit to Lead (H2L) Process in Drug Discovery; *AzoLifeSciences*; **2022**.

[2] Keserű, G.M.; Makara, G.M.; Hit discovery and hit-to-lead approaches; *Drug Discovery Today*; **2006** , *11*, 741–748.

[3] Hughes, J.P.; Rees, S.; Kalindjian, S.B.; Philpott, K.L.; Principles of early drug discovery; *Br J Pharmacol*; **2011**, *162*, 1239-1249.

1.2- Heterocyclic compounds in agrochemistry

Heterocyclic compounds are a significant part of organic compounds. They are present in a wide selection of products such as pharmaceuticals or dye products.

Besides, they are used as precursor to synthesize other organic compounds with interesting properties, i.e. antibiotics like penicillin (**A**) or analgesics like morphine (**B**) (Figure 1).[4]

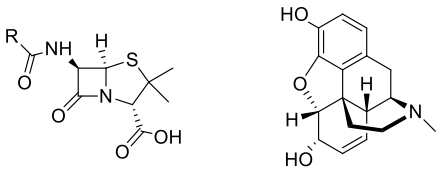


Figure 1: Structures of Penicillin and Morphine respectively

Heterocyclic compounds have also an important role in agrochemistry. More than 60% of all agrochemicals that have been introduced to the market during the last two decades have heterocyclic rings in their structure. An example of this agrochemicals are herbicides, which are selective compounds with the ability of killing not only weeds but also undesired crops. These compounds are strictly regulated by governments to ensure that they are not toxic, that the plant will be edible, that they do not contaminate groundwater, and so on.

The presence of heterocycles has positive and significant effects for agrochemicals, such as the synthetic accessibility (thanks to the high reactivity) or adequate physicochemical properties (like optimal solubility ranges).

An example to illustrate it could be the substitution of a phenyl for a pyridine in the butyl 2-(4-(4-(trifluoromethyl)phenoxy)phenoxy)propanoate (**C**) which results in fluazifop-butyl (**D**) (Figure 2). The herbicidal activity did not improve significantly; however, the ability to translocate into the plant tissue of the target grass weeds did, due to the partition coefficient of the heterocyclic analog.[5]

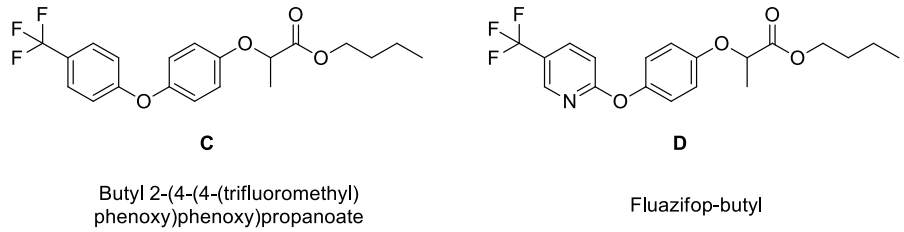


Figure 2: Phenyl and Pyridyl analogs used in agrochemistry

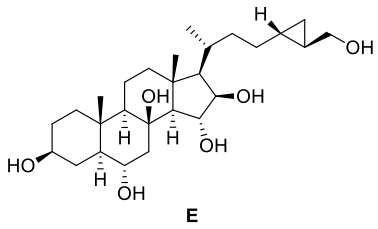
In addition, functional groups like trifluoromethyl are also considered important in medicinal chemistry. Thanks to its stability, lipophilicity and high electronegativity it has interesting

[4] Arora, P.; Arora, V.; Lamba H.S.; Wadhwa D.; Importance of Heterocyclic Chemistry: A Review; *Int J Pharm Res Sci*.; **2012**, *3*, 2947-2955.

[5] Lamberth, C.; Heterocyclic chemistry in crop protection; *Pest Manage Sci*; **2013**, *69*, 1106–1114.

properties for bioorganic chemistry.[6] In fact, it is present in some anesthetic and diuretic agents.[7]

The cyclopropane ring has also uncommon steric and electronic properties that makes it significant for fields like agrochemical, medical and perfume industry. Actually, it has been found in some natural steroids like Phyrgiasterol (**E**), found in the Pacific Starfish known as Hippasteria phrygiana. [8,9]



E

Phyrgiasterol

Figure 3: Structure of a natural steroid cointaining a cyclopropane

1.3- Pyrazoles

In this project, the core structure of all the analogs contains a pyrazole scaffold.

Pyrazoles or 1,2 diazoles are a five-member ring with two nitrogen atoms at adjacent positions, three carbon atoms and two double bonds, which render the molecule aromatic.

They are highly appreciated for their biological potential, bearing anticancer, anti-inflammatory, analgesic, antiviral, and other interesting properties.[10,11]

For example, compound **F** (ethyl 1-(20-hydroxy-30-aroxypropyl)-3-aryl-1H-pyrazole-5-carboxylate derivatives) and compound **G** (1-arylmethyl-3-aryl-1H-pyrazole-5-carbohydrazide derivatives) show interesting properties against A549 lung cancer (Figure 4).[12]

[6] Fei, X.-S.; Tian, W.-S.; Ding, K.; Chen Q.-Y; New, Convenient Route for Trifluoromethylation of Steroidal Molecules; *Org Synth;* **2010**, *87*, 126.
[7] Yale, H. L.; The Trifluoromethyl Group in Medical Chemistry; *J Med Pharm Chem*; **1959**, *1*, 121–133.
[8] Zdenko, C.; Synthetic Approaches to Contemporary Drugs that Contain the Cyclopropyl Moiety; *Synthesis*; **2020**, *52*, 1315-1345.
[9] Stonik, A.V.; Ivanchina, N.V.; Kicha, A.A.; New Polar Steroids from Starfish; *Nat Prod Commun*; **2008**, *3*, 1587-1610.
[10] Kumar, H; Saini, D.; Jain, S.; Jain, N.; Pyrazole scaffold: A remarkable tool in the development of anticancer agents; *Eur J Med Chem*; **2013**, *70*, 248-258.
[11] Ananda, H.; Sharath Kumar, K.S; Nishana, M.; Hedge, M.; Srivastava, M.; Byregowda, R.; Choudhary, B.; Raghavan, S.C.; Rangappa, K.S.; Regioselective synthesis and biological studies of novel 1-aryl-3, 5-bis (het) aryl pyrazole derivatives as potential antiproliferative agents; *Mol Cell Biochem*; **2017**, *426*, 149–160.
[12] Pal, D.; Saha, S.; Singh, S.; Importance of pyrazole moiety in the field of cancer; *Int J Pharm Pharm Sci;* **2012**, *4*, 98-104.

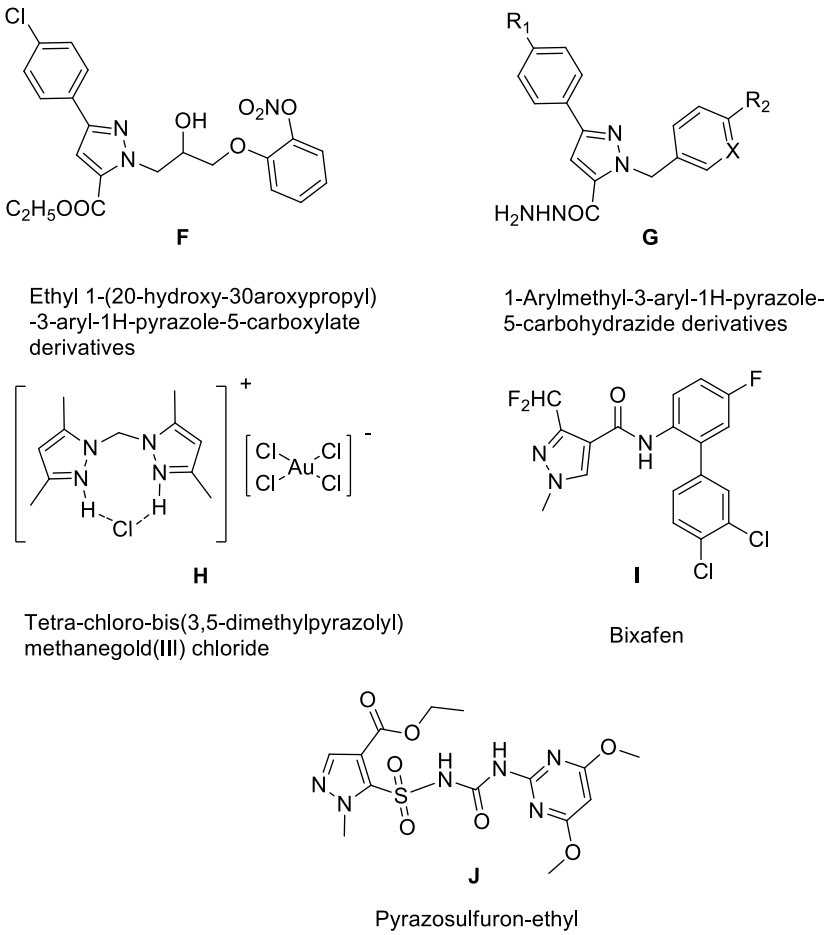


Figure 4: Pyrazole containing bioactive structures

Complexes like compound **H** (tetra-chloro-bis(3,5-dimethylpyrazolyl)methanegold(III) chloride), has been observed that are pyrazolyl metallo-antivirals. This compound, specifically, is an inhibitor for HIV (Human Immunodeficiency Virus)-1 reverse transcriptase and protease which besides, can inhibit at concentrations which are non-toxic for human cells.[13]

Pyrazoles have important roles, not only in the pharmaceutical, but also in the crop science field. In 2010, fungicides based on a difluoromethyl-substituted pyrazole core were introduced to the market (for example, Bixafen (**I**), Figure 4).[14]

Bixafen was developed to control pathogens in cereals. It is an inhibitor of the succinate dehydrogenase of the fungal respiratory chain. Furthermore, plants treated with Bixafen got a better grain yield as a result of its ability to delay the senescence (the process of losing cell power to grow and to divide) of leaves and ears, in addition to the ability to increase the metabolic activity during grain filling.[15]

Another example is formed by the family of 5-sulfonylureaspyrazoles, which are inhibitors of the acetatolactate synthase (ALS). This enzyme is involved in the biosynthesis of the valine,

[13] Fonteh, P.N.; Keter, F.K.; Meyer, D.; Guzei, I.A.; Darkwa, J.; Tetra-chloro-(bis-(3,5-dimethylpyrazolyl)methane) gold(III) chloride: An HIV-1 reverse transcriptase and protease inhibitor; *J Inorg Biochem*; **2009**, *103,* 190-194.
[14] Mykhailiuk, P.K.; Fluorinated Pyrazoles: From Synthesis to Applications; *Chem Rev;* **2021**, *121*, 1670–1715.
[15] Berdugo, C.A.; Steiner, U.; Dehne, H.-W.; Oerke, E.-C; Effect of bixafen on senescence and yield formation of wheat; *Pestic Biochem Physiol;* **2012**, *104*, 171-177.

leucine and isoleucine (three essential amino acids). A commercialized compound of this type is pyrazosulfuron-ethyl, (**J)** (Figure 4).

Other structures with interesting biological activity are some derivatives of the 5-hydroxypyrazole, which are 4-hydroxyphenylpyruvate dioxygenase (HPPD) inhibitors. HPPD is an enzyme involved in the protection of the chloroplasts, which avoids the photooxidation (radical degradation induced by light). The mechanism of action of HPPD is first, to catalyze the biosynthesis of homogentisic acid, which is a precursor of plastoquinone. Plastoquinones are cofactors for the phytoene desaturase, an enzyme that is involved in the biosynthesis of carotenoids, essential compounds for the protection of the chloroplasts. Thus, HPPD inhibitors cause a deprotection of the chloroplasts, boosting the photooxidation.

An example of a commercial compound is pyrazolynate (**K**) which is the pro-drug (a biologically inactive compound which can be metabolized in the body to produce a drug) of the 5-hydroxypyrazole form (**L**) (Figure 5).[16]

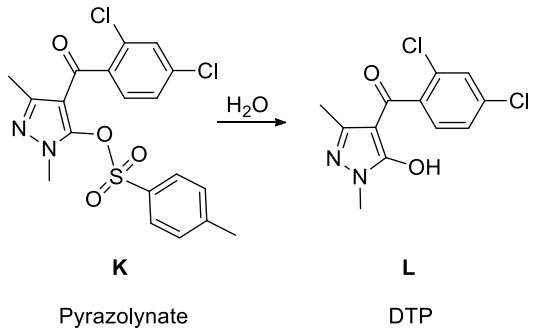


Figure 5: Hydrolysis of the pyrazolynate resulting in DTP

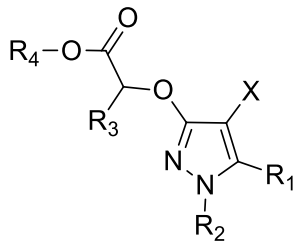
1.4- BAPs- Bisarylpyrazoles

This project is focused on bisarylpyrazoles where the aryl groups are in positions 1 and 5 of the pyrazole ring.

Note: As stated at the beginning of this manuscript, the specific aryl groups used in this work cannot be shown, as their exact structure has been considered confidential by the company Bayer CropScience.

A general overview of the pyrazole structure is shown in the Figure 6, where R_1 and R_2 remain hidden. Each side chain can be formed by different functional groups where synthesis has been focused on the following below:

[16] Lamberth, C.; Pyrazole Chemistry in Crop Protection; *Heterocycles*; **2007**, *71*, 1467-1502.



X : H, CN, I, Br, Cl, Cyclopropyl, CF_3

R_1 : R_{1A}, R_{1B}

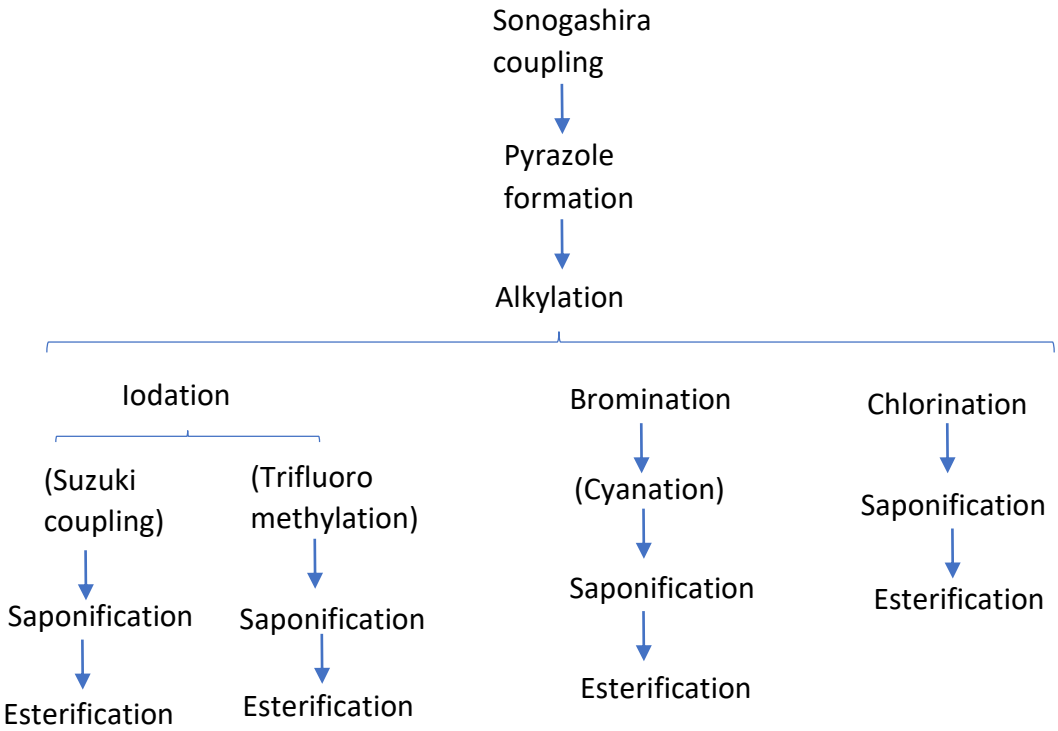
R_2 : R_{2C}, R_{2D}, R_{2E}, R_{2F}

R_3 : CH_3 (R enantiomer), H

R_4 : H, CH_3, CH_2CH_3

Figure 6: Overview of the bisarylpyrazole structure

Initially, the following synthetic routes were proposed, which are based on a common starting point (Scheme 1):



Scheme 1: Overview of the general synthetic routes

The aim is to check the biological activity of all the synthesized analogs. For this purpose, they have been tested in crops such as rice (Oryza), maize (Zea Mays) and soybean (Glycine max), and several weeds like amaranth, where has been worked with a resistant strain.

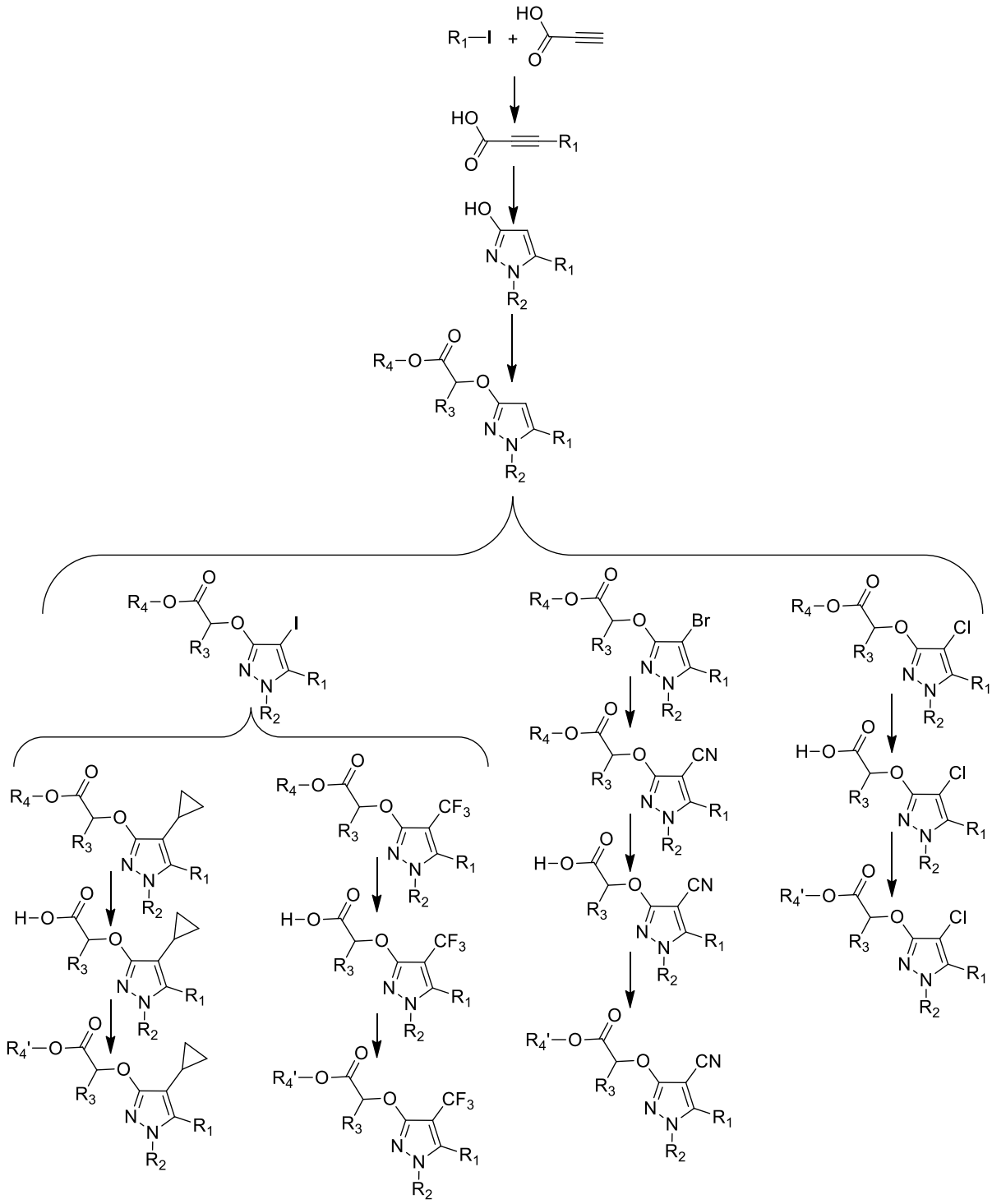
All the compounds, before being tested, have been checked by NMR that they were clean, at least 95% pure. Mixture of products or presence of solvents would alter the outcome.

The ideal results would be that the compound kills not only all the weeds, but also all the crops except the desired one. However, as it is not easy to get it, commercial herbicides normally are a mixture of compounds.

It must also be taken into account that not all lands are equal, depending on their environment their biological properties are different, which leads to a variety of weeds and crops in every

area. Therefore, is impossible to create a general herbicide, each one is specific for a type of land.

Another factor to consider is the resistance developed by plants, which may affect to the effectiveness of the herbicide over time and requires further research into new herbicides.



Scheme 2: Overview of the general synthetic route with structures

2- Objectives

The aim of this project is to synthesize as many analogs as possible, where each analog will be sent to the biochemistry department to be tested and checked its herbicidal properties in different crops and weeds.

Compounds that perform well, will serve as precursors for further research. Functional groups with higher activity will be prioritized for the elaboration of further analogs in a second phase. New combinations will be developed while keeping that functional group intact. On the other hand, those functional groups which have given poor results, will be discarded.

For the synthesis of these analogs, a synthetic route has been designed where reactivity and viability have been studied, in order to get an efficient process. A certain yield is required where pure products must be isolated. Mixtures with impurities will not be accepted for screening as it would be troublesome for the tests, the results would not be trustful.

For the cases where a reaction has a particularly low yield, an alternative will be sought, but not too many resources will be dedicated, since our objective is to obtain the product in synthetically useful amounts, and not to find the optimum reaction conditions.

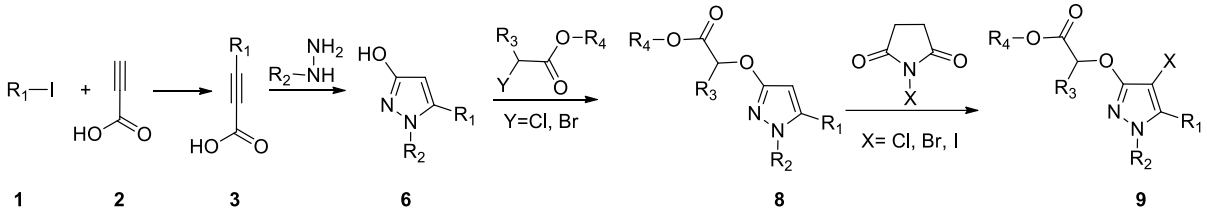
The compounds will be thoroughly purified to assure at least completely clean H-NMR and C-NMR spectra, to ensure that impurities do not interfere with the biological results.

3- Results and discussion

3.1- Introduction

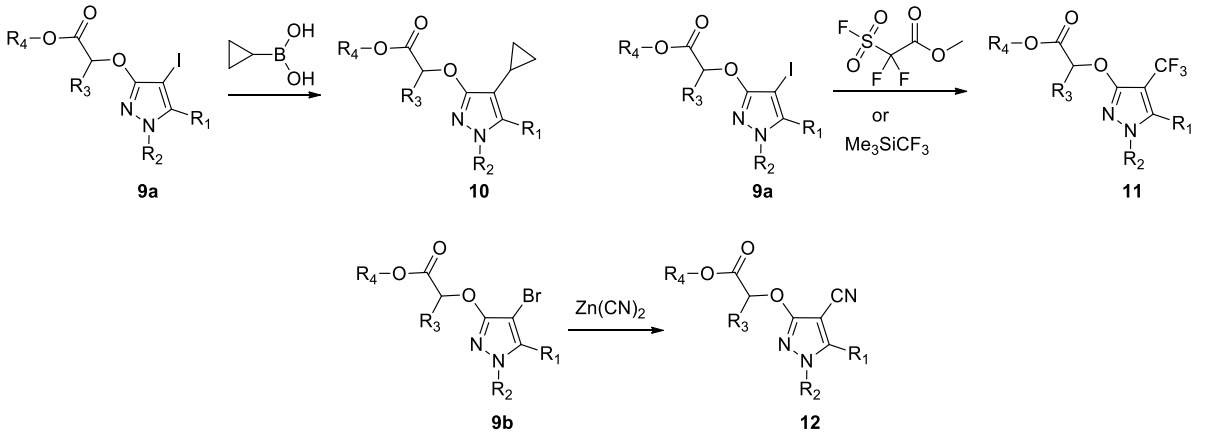
The goal has been to synthesize the largest possible number of analogs following for that, the same strategy but using different starting materials, which leads to multiple diverse parallel paths.

The first part, from Sonogashira coupling to halogenation, has been common in all the routes. Those four reactions have been done in each path as it is shown in Scheme 3.



Scheme 3: First parts of the synthetic route

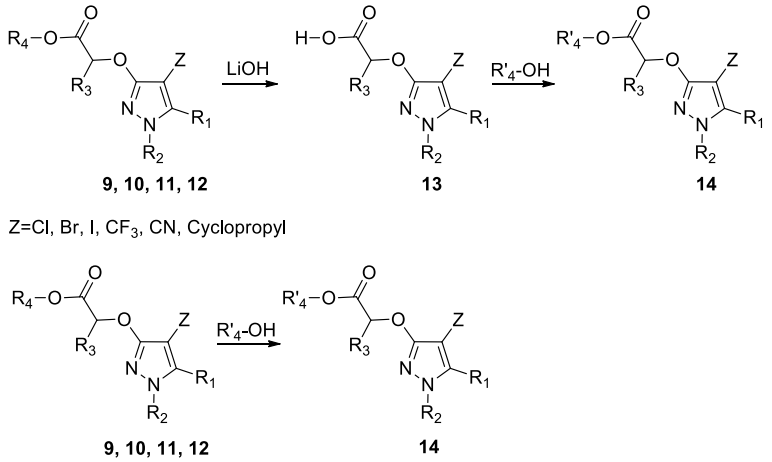
The first reaction has been Sonogashira coupling with aryl iodide (**1**) (where R_1 can be R_{1A} or R_{1B}), propiolic acid (**2**), bis(triphenylphosphin)palladium(II)chloride, copper(I) iodide and diisopropylamine. The product (**3**) will react with a hydrazine derivative (where R_2 can be R_{2C}, R_{2D}, R_{2E} or R_{2F}), with propanephosphonic acid anhydride (T3P) and triethylamine. Heat will be needed to get the cyclization work, leading to the pyrazole ring construction (**6**). For the alkylation, ethyl bromoacetate or methyl (2S)-2-chloropropanoate have been used, in the presence of cesium carbonate as the base. The halogenation is the next step where chloro-/bromo-/iodosuccinimide can be used for the introduction of the chloride, bromide or iodide (Scheme 3).



Scheme 4: Second part of the synthetic route

At this point, different routes have been followed. If the product has an iodide, Suzuki coupling or trifluoromethylation have been performed. For the Suzuki coupling, cyclopropyl boronic acid, copper (I) iodide, cesium fluoride and a palladium complex has been needed. For the trifluoromethylation, two reactions have been used, one with methyl 2,2-difluoro-2-fluorosulfonyl-acetate and the other with trimethyl(trifluoromethyl)silane. In case of having

the brominated product, cyanation has also been performed with zinc cyanide and with a palladium complex in a Microwave (MW) reactor (Scheme 4).



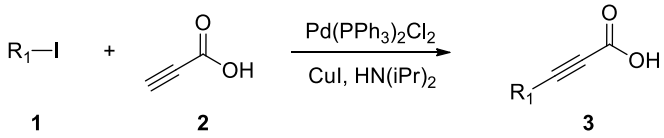
Scheme 5: Third and last part of the synthetic route

The last steps have been a saponification with lithium hydroxide and an esterification with methanol or ethanol, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC), 4-dimethylaminopyridine (DMAP) and hydroxybenzotriazole hydrate (HOBt). In some cases, the esterification has given poor yields, so a transesterification with methanol or ethanol and indium (III) chloride has been done to get the other ester (Scheme 5).

3.2- Sonogashira coupling

The Sonogashira coupling is the first reaction of all our synthetic routes. The aim is to prepare the aryl alkyne (**3**), which is not commercial, from the aryl iodide (**1**) and the propiolic acid (**2**) in presence of bis(triphenylphosphine)palladium(II) dichloride, copper(I) iodide and diisopropylamine.

The Sonogashira coupling reaction was discovered by Sonogashira and Hagihara in 1975 following the work developed by Heck and Cassar. This coupling is a very useful reaction as it forms C_{sp^2}-C_{sp} bonds between alkynes and aryl halides or triflates (Scheme 6).[17]



Scheme 6: Sonogashira coupling of the starting materials

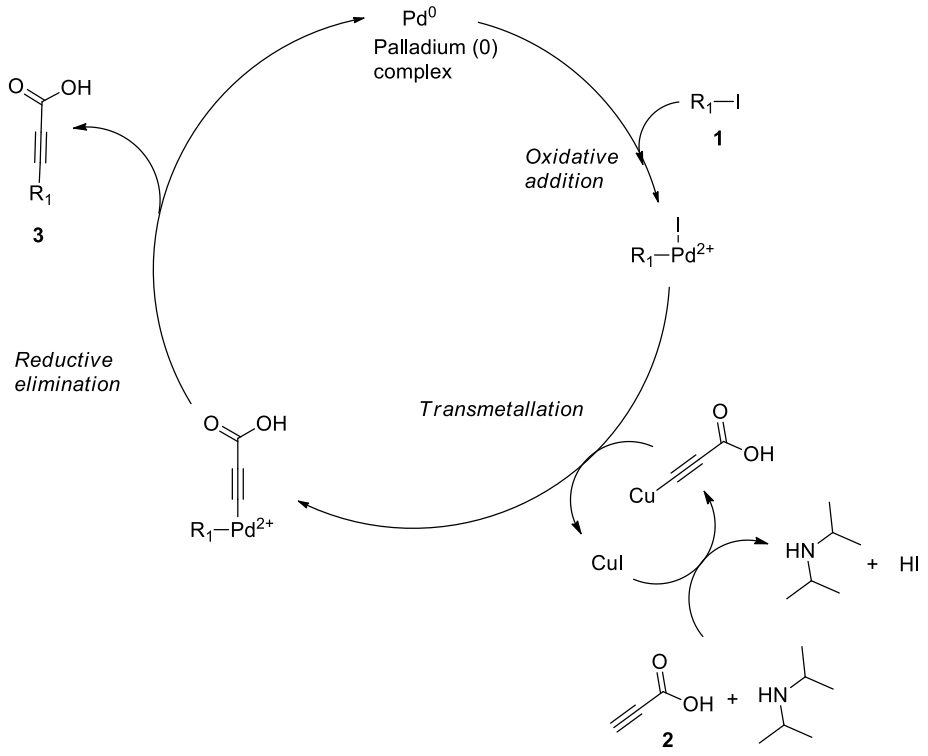
The Sonogashira reaction has been thoroughly studied, and the widely accepted mechanism involves two catalytic cycles, one for each metal catalytic species, palladium and copper.

First, the oxidative addition takes place between the starting material and the palladium(0) complex. In this case, the precatalyst has been $Pd(PPh_3)_2Cl_2$ where the palladium is Pd(II), but

[17] Wang, D.; Gao, S.; Sonogashira coupling in natural product synthesis; *Org Chem Front*; **2014**, *1*, 556-566.

it gets reduced to Pd(0) in the reaction medium. The next step is the transmetallation with the organometallic copper species, which needs one equivalent of diisopropylamine to deprotonate the alkyne so that in presence of copper (I) iodide, the alkyne gets attached to the copper. After the transmetallation, the two organic fragments are bound to palladium. The last step is the reductive elimination, where the final product is obtained and the palladium (0) complex is recovered (Scheme 7).[18]

In the experimental procedure, HCl has been added to form the diisopropylamine chloride salt, which is soluble in water, to facilitate its separation and removal by extraction.



Scheme 7: Mechanism of the Sonogashira coupling

As the initial point of our multiple sythesis, two different starting material have been used R_{1A} and R_{1B} with an average yield of 77 and 93% respectively. (Table 1)

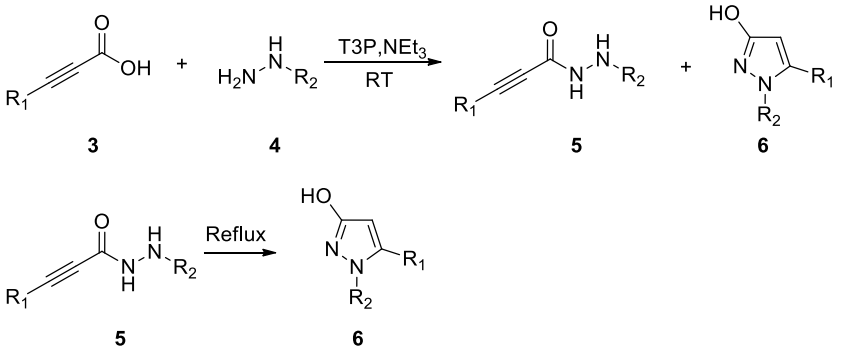
	R_1	Number of reactions done	Average yield (%)
Sonogashira Coupling	A	5	77
	B	5	93

Table 1: Sonogashira coupling reactions

[18] Chinchilla, R.; Nájera, C.; The Sonogashira Reaction: A Booming Methodology in Synthetic Organic Chemistry; *Chem Rev*; **2007**, *107*, 874–922.

3.3- Pyrazole formation

The pyrazole formation is one of the most important reactions of the route, as this heterocyclic ring is the core structure of all the analogs. The non-commercial aryl alkyne (**3**) prepared before, needs T3P and triethylamine to react with the aryl hydrazine (**4**). In this first step, as it occurs at room temperature, the product is mostly the uncycled form (**5**). For this reason, we must heat it to force the cyclization leading to the hydroxy pyrazole (**6**). This is a one-pot reaction even though it is a two steps reaction (Scheme 8).



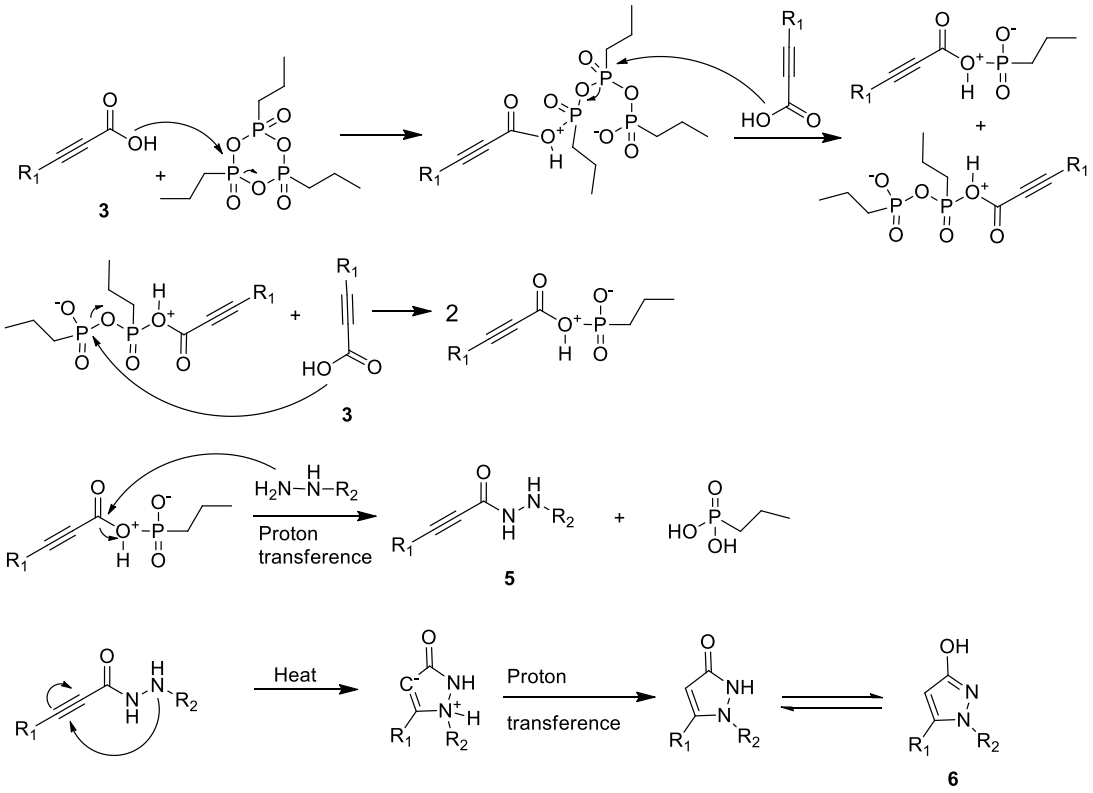
Scheme 8: Pyrazole formation from the aryl iodide and aryl hydrazine

The mechanism of the reaction confirms that the reaction takes place in two main steps:

First, the amide coupling, where T3P is used to activate the carboxylic acid and then a nucleophilic attack from the derivate of the hydrazine takes place. As we can observe in Scheme 9, each T3P molecule can react with three molecules of starting material (**3**).

The second step is the cyclization, which needs heat to take place and leads to the 3-hydroxypyrazole (**6**) (Scheme 9).[19]

[19] Fustero, S.; Sánchez-Roselló, M.; Barrio, P.; Simón-Fuentes, A.; From 2000 to Mid-2010: A Fruitful Decade for the Synthesis of Pyrazoles; *Chem Rev*; **2011**, *111*, 6984–7034.



Scheme 9: Mechanism of the pyrazole formation

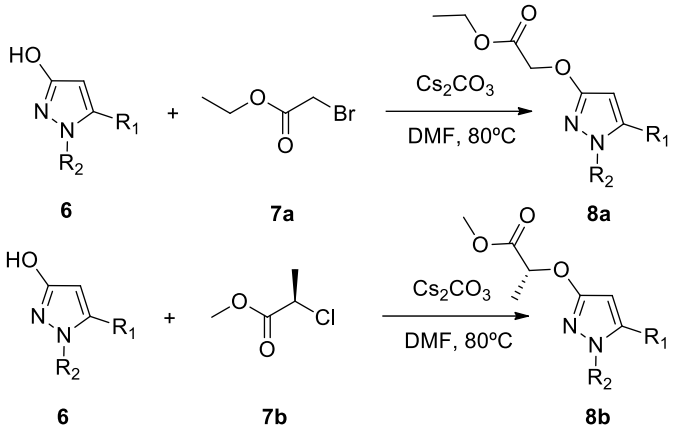
For this reaction four different hydrazine derivatives have been used R_{2C}, R_{2D}, R_{2E}, R_{2F} with overall moderate-good yields, ranging from 56 to 72% (Table 2).

	R_1	R_2	Number of reactions done	Average yield (%)
Pyrazole Formation	A	C	1	57
	A	D	2	62
	A	E	2	60
	B	C	1	56
	B	D	2	59
	B	E	2	61
	B	F	1	72

Table 2: Pyrazole formation reactions

3.4- Alkylation

The alkylation, is the reaction which determines if the product will be chiral (**8b**) or achiral (**8a**) depending if we use methyl (2S)-2-chloropropanoate (**7b**) or ethyl bromoacetate (**7a**) as the reactive (Scheme 10).



Scheme 10: Alkylation of the hydroxypyrazole with ethyl bromoacetate or methyl (2S)-2-chloropropanoate

The alkylation of the OH was carried out through a typical S_N2 reaction. The general strategy initially involves the addition of a base to deprotonate the alcohol and then, the electrophile is added, ethyl bromoacetate, for instance. The order is really important, since the enolate of the ethyl bromoacetate could be formed in case of adding first the base. An interesting aspect of this reaction is that it is stereospecific, since the formation of a single isomer was noted.

Two different electrophiles have been used: ethylbromoacetate (a) and methyl (2S)-2-chloropropanoate (b) with a range of yields of 55 to 87% and 63 to 79% respectively (Table 3).

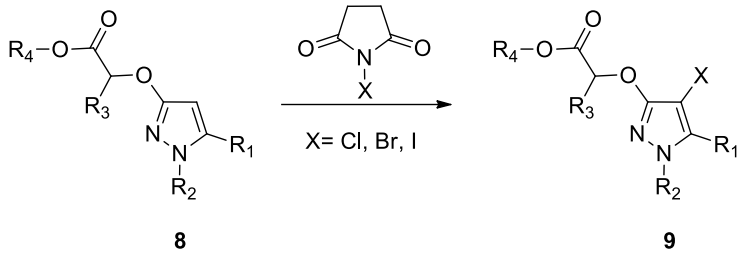
	Reactant	R_1	R_2	Number of reactions done	Average yield (%)
Alkylation	a	B	F	2	66
	a	B	C	1	87
	a	A	D	2	74
	a	B	D	2	55
	a	A	E	2	79
	a	B	E	2	73
	b	A	C	1	68
	b	B	C	1	73
	b	B	F	2	79
	b	A	D	2	76
	b	B	D	2	63
	b	A	E	2	74
	b	B	E	2	67

Table 3: Introduction of substituents at position 3 by alkylation reactions

3.5- Bromination, chlorination and iodination

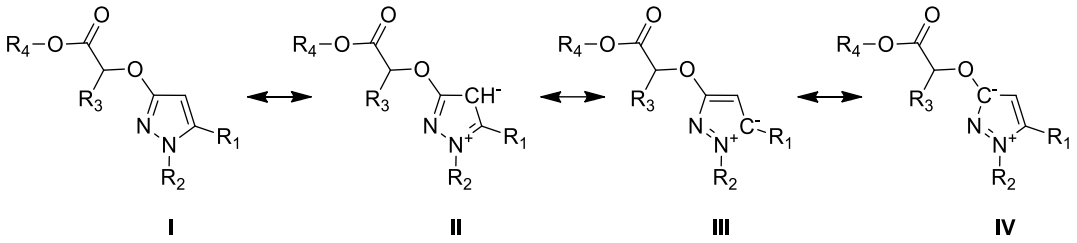
The halogenation is a particularly interesting reaction, not only because of the biological activity of its products, but also because it opens up a wide range of possible reactions like Suzuki coupling, cyanation and trifluoromethylation.

Bromo-, chloro- and iodosuccinimide has been used to halogenate the 4th position of the pyrazole (Scheme 11).



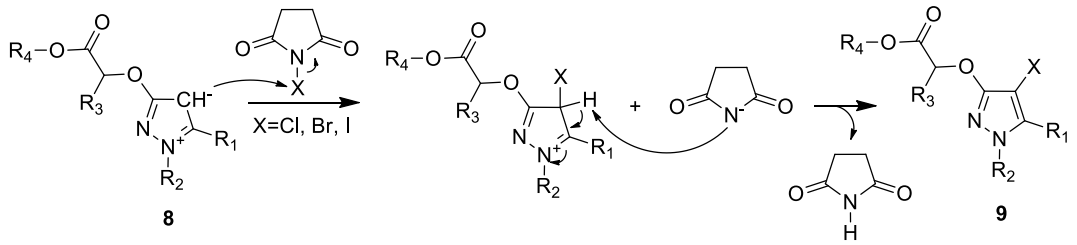
*Scheme 11: Bromination, chlorination and iodination of the alkylated product **8***

The pyrazole ring has a nucleophilic carbon due to resonance[20] which attacks the electrophilic halide from the succinimide (Scheme 13). It is best represented by its non-charged resonance form, but the second on the left (estructure **II**) makes also a large contribution to the final structure, enhancing the negative character of the CH carbon (Scheme 12).



Scheme 12: Resonance estructure for pyrazoles

In this type of reactions, the solvent must be aprotic, otherwise the halide would not be so reactive due to the formation of the bond H-X. Protic solvents tend to solvate the anions, reducing their reactivity. The mechanism of the halogenation is shown in Scheme 13:



Scheme 13: Mechanism of the bromination, chlorination and iodination reactions

[20] Devi, N.; Shankar, R.; Singh, V..; 4-Formyl-Pyrazole-3-Carboxylate: A Useful Aldo-X Bifunctional Precursor for the Syntheses of Pyrazole-fused/Substituted Frameworks; *J Heterocycl Chem;* **2017**; *55*, 373-390.

In each case, the reaction and purification conditions have been optimized to get the best efficiency. For example, in the chlorinations, the chlorinated product has similar retention times to the succinimide (which is a byproduct non-visible by TLC). For this reason, the separation gradient has been changed to 1:3 heptane/acetone as it is capable of isolating the product properly. This optimization process was done by my research team before my arrival.

The optimal conditions have been collected in the following Table 4:

Reaction	Reactive	Temperature	Time	Separation Gradient
Chlorination	NCS	80°C	3h	a
Bromination	NBS	RT	2h	b
Bromination	NBS	60°C	1h	b
Iodination[c]	NIS	95°C	3h	b

Table 4: Optimal conditions for bromination, chlorination and iodination

a) 1:3 Heptane/ Acetone b) 1:1 Heptane/ Ethyl Acetate

c) In the iodination, sodium metabisulfite is added during the work-up to eliminate the excess of iodine. There are two steps of reaction, where the second is a redox process:

1- $Na_2S_2O_5 + H_2O \rightleftharpoons 2\ NaHSO_3$
2- $2\ NaHSO_3 + I_2 \rightleftharpoons 2\ HI + Na_2SO_4 + SO_2$

Most of the chlorinations had great yields between 84 to 99%. Only in three cases the yield has been lower than 75%, and the lowest yield has been 57% (Table 5).

	R_1	R_2	R_3	OR_4	Number of reactions done	Average yield (%)
Chlorination	B	C	CH_3	OMe	1	96
	A	F	H	OMe	2	95
	B	F	H	OEt	1	91
	B	C	H	OEt	1	93
	A	C	H	OMe	1	91
	A	C	CH_3	OMe	1	89
	B	F	CH_3	OMe	1	99
	A	D	H	OEt	1	57
	A	D	CH_3	OMe	1	59
	B	D	H	OEt	1	84
	B	D	CH_3	OMe	1	99
	A	E	H	OEt	1	95
	A	E	CH_3	OMe	1	86
	B	E	H	OEt	1	74
	B	E	CH_3	OMe	1	85

Table 5: Chlorination reactions

All the brominations except one has given satisfactory results from 79 to 95% yield (Table 6).

	R_1	R_2	R_3	OR_4	Number of reactions done	Average yield (%)
Bromination	A	C	H	OEt	1	88
	A	F	H	OMe	1	85
	A	C	CH_3	OMe	1	89
	A	F	CH_3 (S enantiomer)	OMe	1	95
	A	D	H	OEt	1	96
	A	D	CH_3	OMe	1	91
	B	D	H	OEt	1	51
	B	D	CH_3	OMe	1	79
	A	E	H	OEt	1	87
	A	E	CH_3	OMe	1	79
	B	E	H	OEt	1	82
	B	E	CH_3	OMe	1	89

Table 6: Bromination reactions

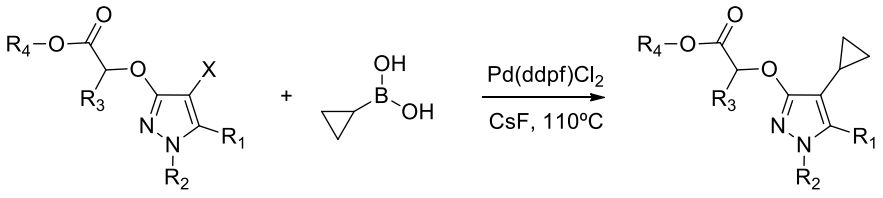
The iodinations (Table 7) worked slightly better than the chlorinations (Table 5) and brominations (Table 6), as the lowest yield has been 79% (Table 7).

	R_1	R_2	R_3	OR_4	Number of reactions done	Average yield (%)
Iodination	A	C	CH_3	OMe	1	90
	B	F	H	OEt	2	89
	B	C	H	OEt	1	88
	B	C	CH_3	OMe	1	95
	A	F	H	OMe	1	83
	B	F	CH_3	OMe	1	79
	A	D	H	OEt	1	79
	A	D	CH_3	OMe	1	87
	B	D	H	OEt	1	79
	B	D	CH_3	OMe	1	81
	A	E	H	OEt	2	78
	A	E	CH_3	OMe	2	88
	B	E	CH_3	OMe	2	89
	B	E	H	OEt	2	93

Table 7: Iodination reactions

3.6- Suzuki coupling

The Suzuki coupling is a versatile reaction to introduce interesting functional groups like the cyclopropyl in halogenated compounds. The only required reactives are the boronic acid, a palladium complex and cesium fluoride (Scheme 14).[21]



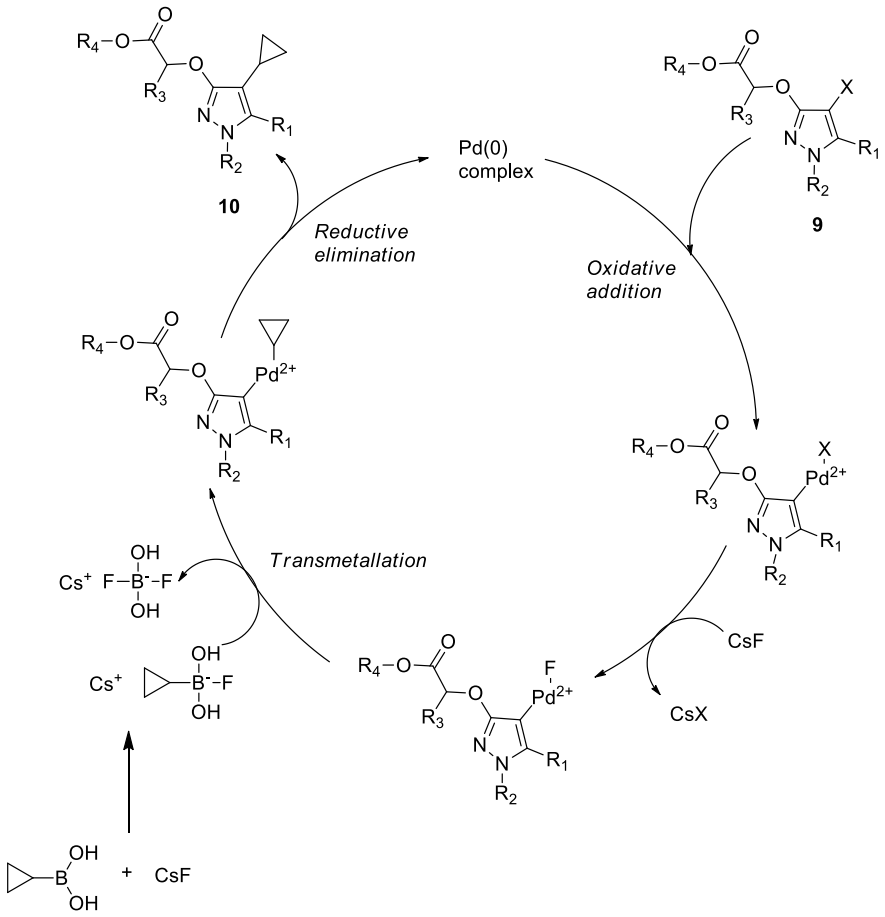
9 **10**

Scheme 14: Suzuki coupling for the cyclopropination of the halogenated product

Regarding the mechanism, the catalytic species is a palladium(0) complex, and the mechanistic cycle starts, as usually, with an oxidative addition between the palladium (0) complex and the aryl halide to give the corresponding palladium (II) species. Next, a substitution between the halide (iodide in this case) and the fluoride takes place. The third step involves a transmetallation with the activated boronic acid, and finally, the reductive elimination occurs, resulting in the formation of the product and the recovery of the palladium (0) species (Scheme 15).[22]

[21] Gujral, S.K.; Smriti, K.; Riyal, P.; Suzuki Cross Coupling Reaction-A Review; *Indo Global Journal of Pharmaceutical Sciences*; **2012**, *2*, 351-367.

[22] Biswas, B.; Kulsi, G.; Solving the Riddle- the Mechanism of Suzuki Cross Coupling: A Review; *Asian Journal Of Advanced Basic Sciences;* **2016**, *4*, 131-140.



Scheme 15: Mechanism of the Suzuki coupling

The unique boronic acid used has been the cyclopropyl boronic acid. There has been a wide range of yields from 55 to 89% (Table 8).

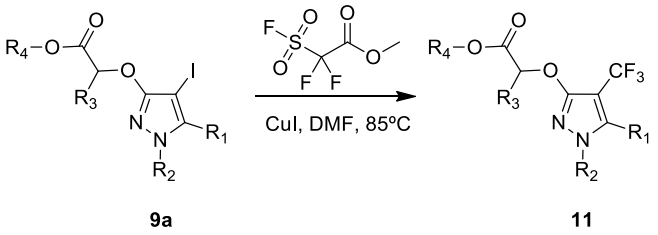
	R_1	R_2	R_3	OR_4	Number of reactions done	Average yield (%)
Suzuki Coupling	A	C	CH_3	OMe	1	74
	B	F	H	OEt	2	55
	B	C	H	OEt	1	81
	A	C	H	OMe	1	63
	B	C	CH_3	OMe	1	87
	A	F	H	OMe	1	74
	B	F	CH_3	OMe	1	67
	A	D	H	OEt	1	66
	A	D	CH_3	OMe	1	86
	B	D	H	OEt	1	57
	B	D	CH_3	OMe	1	88
	A	E	H	OEt	1	85
	A	E	CH_3	OMe	1	81
	B	E	H	OEt	1	87
	B	E	CH_3	OMe	1	89

Table 8: Suzuki coupling reactions

3.7- Trifluoromethylation

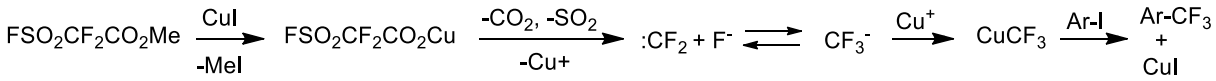
The trifluoromethyl group is an interesting functional group due to its chemical and biological properties.[23] This reaction has been performanced in two different ways, one of the using methyl 2,2-difluoro-2-fluorosulfonyl-acetate (Method A) and the other making use of trimethyl(trifluoromethyl)silane (Method B).

Method A



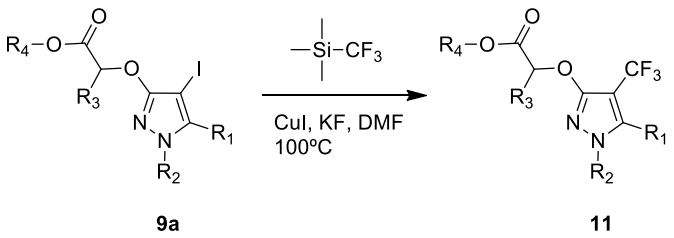
Scheme 16: Trifluoromethylation of a iodinated compound making use of methyl 2,2-difluoro-2-fluorosulfonyl-acetate

First, methyl 2,2-difluoro-2-fluorosulfonyl-acetate reacts with the copper(I) iodide leading to $FSO_2CF_2CO_2Cu$ which suffers a complete fragmentation, resulting in the release of carbon dioxide and sulfur dioxide, and formation of the difluorocarbene intermediate and the fluorine anion. The two latter species recombine to obtain CF_3^-. In the presence of copper(I) cation, trifluoromethyl copper(I) assembles. This last species reacts with the bisarylpyrazole (**9a**) giving the triflouromethylated product (**11**) and recovering copper(I) iodide (Scheme 17).[6,24]



Scheme 17: Mechanim of the trifluoromethylation making use of methyl 2,2-difluoro-2-fluorosulfonyl-acetate

Method B

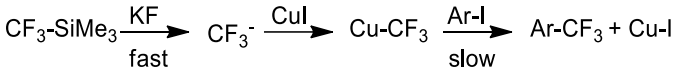


Scheme 18: Trifluoromethylation of an iodinated compound making use of trimethyl(trifluoromethyl)silane

[23] Kiselyov, A.S.; Strekowski, L.; The Trifluoromethyl Group in Organic Synthesis. A Review; *Org Prep Proced Int*; **1996**, *28*, 289–318.

[24] Panja, C.; Puttaramu, J.V.; Methyl-2,2-difluoro-2-(fluorosulfonyl) acetate (MDFA)/copper (I) iodide mediated and tetrabutylammonium iodide promoted trifluoromethylation of 1-aryl-4-iodo-1,2,3-triazoles; *J of Fluorine Chem*; **2020**, *236*.

The trimethyl(trifluoromethyl)silane reacts with potassium fluoride resulting in the trifluoromethyl anion that reacts with the copper(I) iodide, obtaining trifluoromethyl copper(I). Finally, reacts with the bisarylpyrazole (**9a**) giving the triflouromethylated product (**11**) and recovering copper(I) iodide (Scheme 19).[25]



Scheme 19: Mechanism of the trifluoromethylation making use of trimethyl(trifluoromethyl)silane

The yields have not been remarkably good, but at least have been in a range of 56-59% (Table 9).

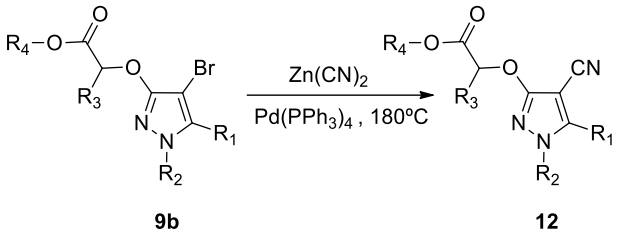
	Reactant	R_1	R_2	R_3	OR_4	Yield (%)
Trifluoromethylation	a	A	E	CH_3	OMe	59
	a	A	E	H	OEt	56
	b	B	E	H	OEt	57

Table 9: Trifluoromethylation reactions

a) methyl 2,2-difluoro-2-fluorosulfonyl-acetate
b) trimethyl(trifluoromethyl)silane

3.8- Cyanation

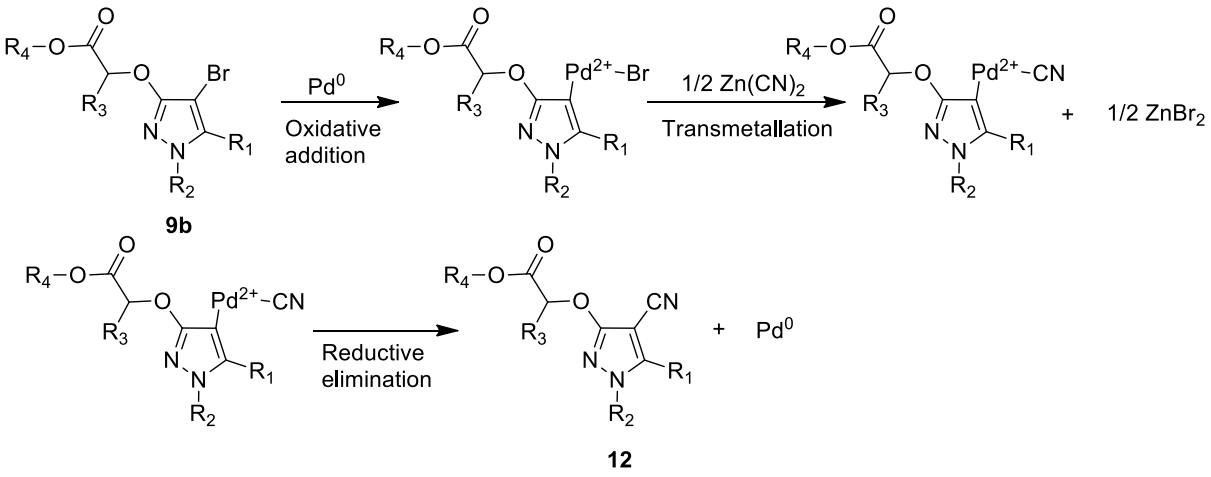
For the cyanation, zinc cyanide and tetrakis(triphenylphosphine) palladium(0) have reacted with the brominated compound (**9b**) in a microwave (MW) reactor (Scheme 20).



Scheme 20: Cyanation of the brominated compound

The mechanism starts with and oxidative addition with a palladium (0) complex which later transmetallates with the zinc cyanide giving rise to zinc bromine as byproduct. The last step takes the reductive elimination where the cyanated product (**12**) is obtained and the palladium (0) complex is recovered (Scheme 21).[26]

[25] Oishi, M.; Kondo, H.; Amii, H.; Aromatic trifluoromethylation catalytic in copper; *Chem Commun*; **2009**, *14*, 1909–1911.
[26] Mark S.; Alexander Z.; Matthias B.; Palladium-Catalyzed Cyanation of Aryl Halides: Recent Developments and Perspectives; *European Journal of Inorganic Chemistry*; **2003**, *19*, 3513-3526.



Scheme 21: Mechanism of the cyanation

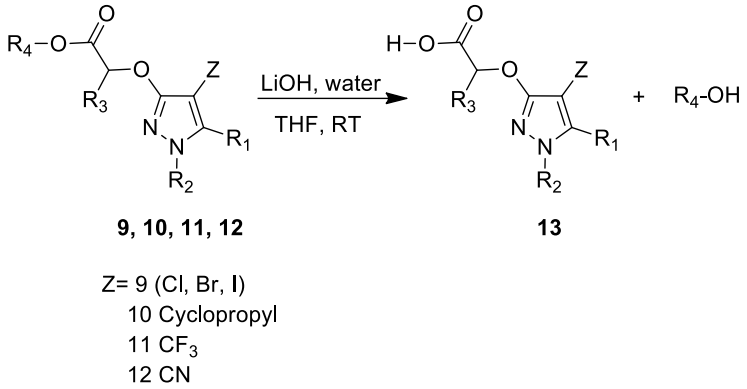
The cyanation have been tried with different halogenated derivatives. The brominated analog worked good giving yields higher than 70% while the iodinated analog yielded as low as 40% (Table 10).

	X	R_1	R_2	R_3	OR_4	Yield (%)
Cyanation	Br	A	C	CH_3	OMe	84
	Br	A	C	H	OEt	71
	I	A	C	H	OEt	40

Table 10: Cyanation reactions

3.9- Saponification

The saponification is one of the last steps of all the synthetic routes (from halogenated, cyanated, cyclopropanated and trifluoromethylated analogs) where the carboxylic acid (**13**) is gotten from one of the esters (**9, 10, 11, 12**) (Scheme 22). This reaction is also interesting as this carboxylic acid can be esterificated to obtain the other ester.



Scheme 22: Saponification of the analogs

All the yields have been very satisfactory, which means that the products are not sensitive to the reaction conditions (Table 11).

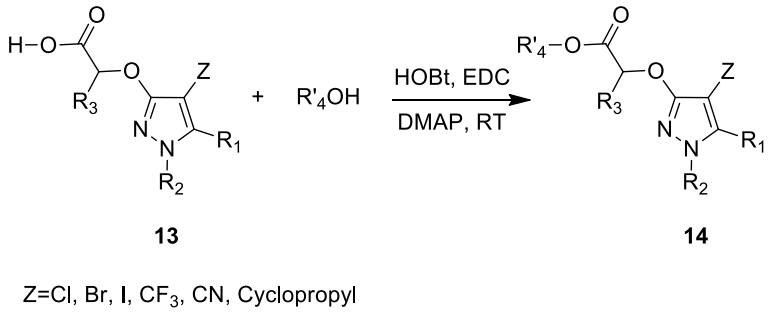
	R_1	R_2	R_3	X	Yield (%)
Saponification	A	C	CH_3	Cyclopropyl	96
	A	C	CH_3	Cl	92
	A	C	CH_3	CN	79
	B	C	CH_3	Cl	89
	B	C	CH_3	I	88
	B	C	CH_3	Cyclopropyl	76
	B	F	CH_3	Cl	95
	B	F	CH_3	I	99
	A	D	CH_3	Br	80
	B	F	CH_3	Cyclopropyl	85
	A	D	CH_3	Cl	71
	A	D	CH_3	I	72
	A	D	CH_3	Cyclopropyl	89
	B	D	CH_3	Br	93
	B	D	CH_3	Cl	97
	B	D	CH_3	I	94
	B	D	CH_3	Cyclopropyl	94
	A	E	CH_3	I	88
	A	E	CH_3	Br	99
	A	E	CH_3	Cyclopropyl	97
	A	E	CH_3	Cl	70
	B	E	CH_3	I	70
	B	E	CH_3	Br	66
	B	E	CH_3	Cyclopropyl	94
	B	E	CH_3	Cl	96
	A	E	CH_3	CF_3	85
	A	C	H	CN	86
	A	F	H	Br	82
	A	F	H	Cl	89
	B	F	H	Cl	80
	B	F	H	I	94
	B	F	H	Cyclopropyl	97
	B	C	H	Cl	89
	B	C	H	I	80
	B	C	H	Cyclopropyl	82
	A	C	H	I	91
	A	C	H	Cyclopropyl	83
	B	F	H	Cl	83
	A	F	H	I	93
	A	D	H	Br	89
	A	F	H	Cyclopropyl	85
	A	D	H	Cl	82
	A	D	H	I	79
	A	D	H	Cyclopropyl	97
	B	D	H	Br	77

	R_1	R_2	R_3	X	Yield (%)
Saponification	B	D	H	Cl	81
	B	D	H	I	82
	B	D	H	Cyclopropyl	96
	A	E	H	Br	96
	A	E	H	I	99
	A	E	H	Cyclopropyl	95
	A	E	H	Cl	93
	B	E	H	Br	86
	B	E	H	I	98
	B	E	H	Cyclopropyl	92
	A	E	H	CF_3	70
	B	E	H	Cl	96
	B	E	H	CF_3	82

Table 11: Saponification reactions

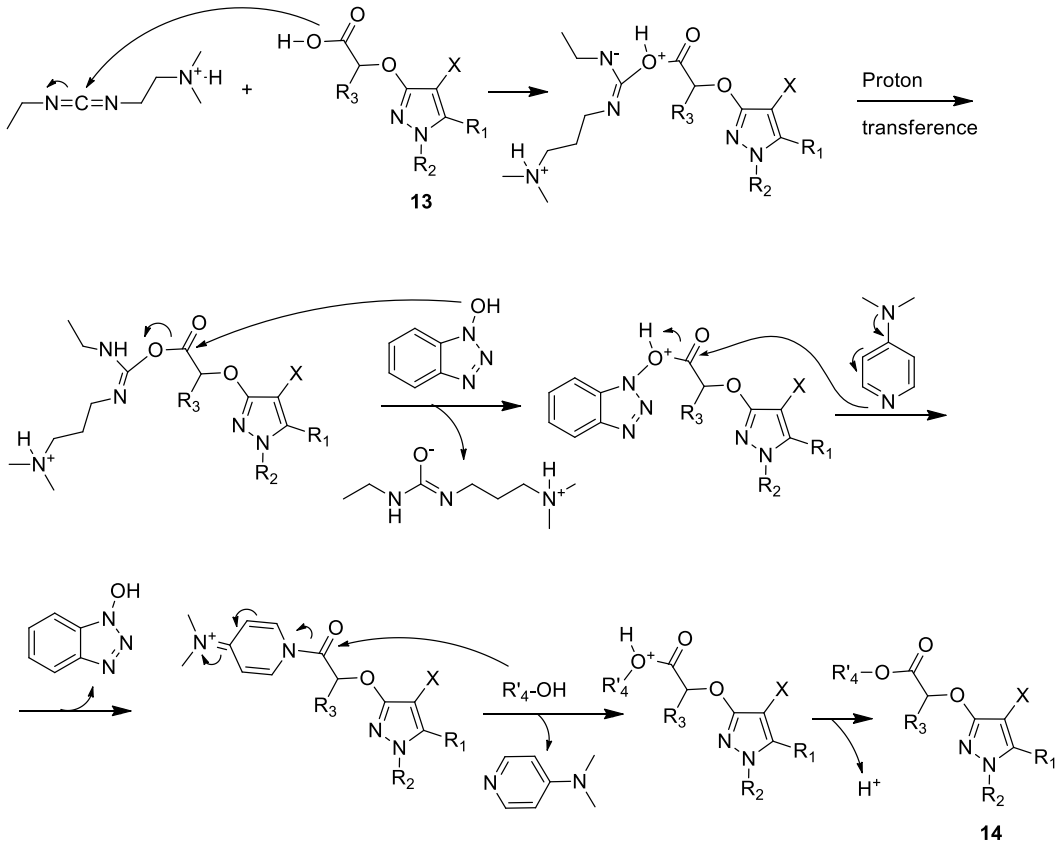
3.10- Esterification

The esterification has been in most of the cases the last reaction of the synthetic route which has been used to get the remaining ester (**14**) from the acid (**13**) (Scheme 23).



Scheme 23: Esterification from the analogs containing the carboxylic acid

First, the acid attacks the EDC, which will be followed by the attack of HOBt to the activated acid where a derived from urea will be the byproduct. Then, the DMAP attacks again the already activated acid, so that HOBt leaves. Finally, the alcohol attacks this last activated acid which leads to the desired ester and the release of DMAP (Scheme 24).[27]



Scheme 24: Mechanism of the esterification

The average yield in esterifications has been around 70%. It is noticeable that in some cases the yields were less than 30% (Table 12). The explanation of those yields is that a second reaction happened with the aryl groups. No more information will be given as it is considered confidential.

[27] Ghosh, A.K.; Shahabi, D.; Synthesis of amide derivatives for electron deficient amines and functionalized carboxylic acids using EDC and DMAP and a catalytic amount of HOBt as the coupling reagents; *Tetrahedron Lett*; **2021**, *63*, 152719 .

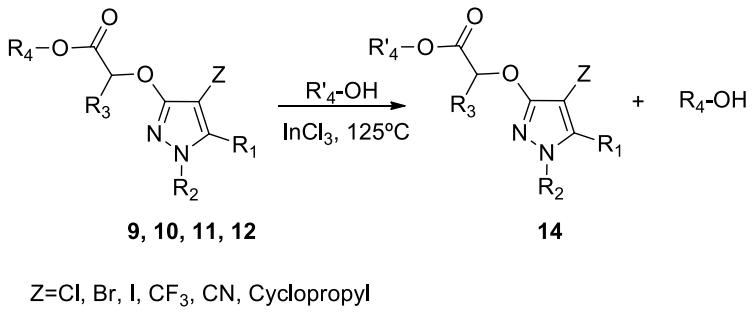
	Reactant	R_1	R_2	R_3	X	Yield (%)
Esterification	MeOH	B	F	H	Cl	70
	MeOH	B	F	H	I	92
	MeOH	B	F	H	Cyclopropyl	72
	MeOH	B	C	H	Cl	87
	MeOH	B	C	H	I	63
	MeOH	B	C	H	Cyclopropyl	81
	MeOH	A	D	H	Br	80
	MeOH	A	D	H	Cl	81
	MeOH	A	D	H	I	73
	MeOH	A	D	H	Cyclopropyl	77
	MeOH	A	F	H	I	80
	MeOH	B	D	H	Br	71
	MeOH	B	D	H	I	82
	MeOH	B	D	H	Cl	86
	MeOH	B	D	H	Cyclopropyl	76
	MeOH	A	E	H	Br	63
	MeOH	A	E	H	I	64
	MeOH	A	E	H	Cyclopropyl	75
	MeOH	A	E	H	Cl	76
	MeOH	B	E	H	Br	74
	MeOH	B	E	H	I	88
	MeOH	B	E	H	Cyclopropyl	70
	MeOH	B	E	H	Cl	90
	MeOH	B	E	H	CF_3	70
	EtOH	A	C	CH_3	Cyclopropyl	70
	EtOH	A	F	H	Br	85
	EtOH	A	F	H	Cl	78
	EtOH	A	C	CH_3	Cl	81
	EtOH	A	C	H	I	80
	EtOH	A	C	H	Cyclopropyl	82
	EtOH	A	C	CH_3	CN	69
	EtOH	B	C	CH_3	Cl	63
	EtOH	B	C	CH_3	I	71
	EtOH	B	C	CH_3	Cyclopropyl	67
	EtOH	A	F	CH_3 (S enantiomer)	Br	51
	EtOH	B	F	CH_3	Cl	83
	EtOH	B	F	CH_3	I	87
	EtOH	A	F	H	I	70
	EtOH	A	D	CH_3	I	73
	EtOH	B	F	CH_3	Cyclopropyl	73
	EtOH	A	F	H	Cyclopropyl	83
	EtOH	A	D	CH_3	Cl	86

	Reactant	R_1	R_2	R_3	X	Yield (%)
Esterification	EtOH	A	F	H	Cl	80
	EtOH	A	D	CH_3	I	89
	EtOH	A	D	CH_3	Cyclopropyl	72
	EtOH	A	C	H	Cl	89
	EtOH	B	D	CH_3	Br	56
	EtOH	B	D	CH_3	Cl	55
	EtOH	B	D	CH_3	I	73
	EtOH	B	D	CH_3	Cyclopropyl	54
	EtOH	A	E	CH_3	I	23
	EtOH	A	E	CH_3	Cyclopropyl	31
	EtOH	A	E	CH_3	Br	21
	EtOH	B	E	CH_3	Br	97
	EtOH	B	E	CH_3	Cyclopropyl	72
	EtOH	B	E	CH_3	Cl	88

Table 12: Esterification reactions

3.11- Transesterification

The transesterification (Scheme 25) was the only reaction which was not planned in the initial synthetic route. It was implemented later because in some specific cases, the yields of the esterification were too low (Table 13), so the transesterification was the alternative which worked better (Table 14).



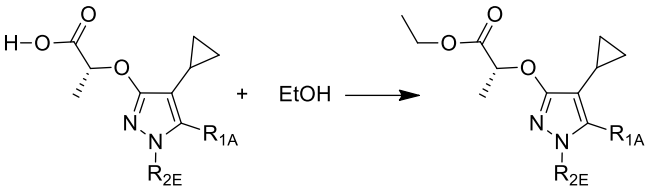
Scheme 25: Transesterification from the methyl/ethyl ester to get the ethyl/methyl ester respectively

	R_1	R_2	R_3	X	Yield (%)
Esterification	A	E	CH_3	Cyclopropyl	31
	A	E	CH_3	I	23
	A	E	CH_3	Br	21

Table 13: Examples of challenging esterifications

EDC, HOBt, DMAP, ethanol and CH_2Cl_2 has been used for the three reactions.

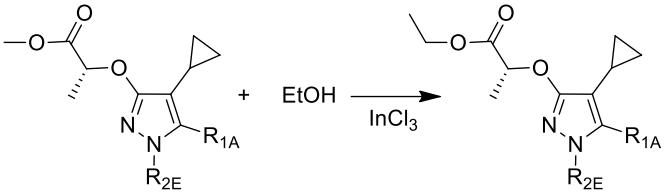
Even though this project was not focused primarily on the optimization of the reaction conditions, in this case, the yields were too low (Scheme 26), and some efforts to increase the efficiency of the reaction were required, as shown:



Scheme 26: Case of a troublesome esterification

Three different conditions were tried to see if the performance could be improved. The first esterification was the one seen previously (Table 13) with EDC, HOBt, DMAP, ethanol and CH_2Cl_2 which gave a 31% yield. The next tried conditions involved with T3P, Et_3N, ethanol and THF, but unfortunately, the yield was as low as 33%. The last try was the Fischer esterification with ethanol as the solvent and sulfuric acid as the catalyst. The performance did not improve significantly, as it was 36%.

Due to that none of the three esterifications worked properly, we sought for other alternative routes. Transesterification was the first pathway tested (Scheme 27):



Scheme 27: Transesterification with a problematic compound

The transesterifications were carried out with ethanol and indium(III) chloride as Lewis acid and catalyst.[28] Thankfully, it worked considerably better yielding 74% (Table 14).

Both methyl and ethyl esters are in equilibrium, and for that reason an excess of ethanol is needed to shift the equilibrium towards the formation of the ethyl ester.

Although this reaction was used as a solution to a specific problem, it has also been used other cases as the yields have been considerably good (Table 14). The advantage of this reaction is the ability of transforming one ester into a different one in just one step, instead of the two step procedure involving saponification and esterification.

[28] Ranu, B. C.; Dutta, P.; Sarkar, A.; A Simple and Efficient Procedure for Transesterification Catalyzed by Indium Triiodide; *J Org Chem*; **1998**, *63*, 6027–6028.

	Reactant	R_1	R_2	R_3	OR_4	X	Yield (%)
Transesterification	EtOH	A	E	CH_3	OMe	Cyclopropyl	74
	EtOH	A	F	H	OMe	Cl	81
	EtOH	A	C	H	OMe	Cl	89
	EtOH	A	E	CH_3	OMe	Cl	68
	EtOH	B	E	CH_3	OMe	Br	92
	EtOH	B	E	CH_3	OMe	I	87
	EtOH	A	E	CH_3	OMe	CF_3	86
	MeOH	B	F	H	OEt	Cyclopropyl	63
	MeOH	A	E	H	OEt	CF_3	71

Table 14: Transesterification reactions

4- Conclusions

In this project, a new family of molecules with potential herbicidal activity has been synthesized. Following previous projects developed in the company Bayer CropScience, our target molecules contained a common heterocyclic pyrazole scaffold, which has been diversified with seven different combinations of substituents at R_1 and R_2 positions. Overall, around one hundred eighty different molecules have been prepared. Each compound has been isolated and checked by NMR to assure a minimum purity of 95%. Then, they have been sent to the biochemistry department for the analysis of their biological properties.

For the synthesis of this large and diverse group of molecules, synthetic strategies including alkylation, bromination, chlorination, cyanation, esterification, formation of the pyrazole, iodination, saponification, Sonogashira coupling, Suzuki coupling, trifluoromethylation and transesterification have been carried out. The main objective of this array of reactions was to get as many different compounds as possible, in enough quantities for the biological tests, without putting too much effort in the optimization of the reaction conditions in each case.

Some of the synthesized molecules have shown good performance in the biological tests, so we resupplied enough amounts of them for further testing. For the same reason, more analogs with similar structures have been prepared to check if their herbicidal properties have been improved, in a diversity oriented type of strategy.

When some of the synthetic routes proved troublesome, other variants were sought. For example, the esterification did not work as expected in a few cases, and transesterification was tried to get the necessary ester. This is an example of how our synthetic routes can be readjusted in order to improve the efficiency. Moreover, transesterification has been used in some other cases as the yields were good.

5- Conclusiones

En este proyecto, se ha sintetizado una nueva familia de moléculas con gran potencial herbicida. Siguiendo el trabajo de otros proyectos desarrollados por Bayer CropScience, nuestras moléculas objetivo contienen un heterociclo pirazol como núcleo estructural, que han sido diversificadas por siete combinaciones diferentes de los sustituyentes R_1 y R_2. En total se han preparado aproximadamente ciento ochenta moléculas distintas. Cada una de ellas ha sido aislada y comprobada a través de RMN para asegurar una pureza mínima del 95%.

Para la síntesis de este amplio y diverso grupo de moléculas, estrategias sintéticas tales como alquilación, bromación, cloración, cianación, esterificación, formación del pirazol, iodación, saponificación, acoplamiento de Sonogashira, acoplamiento de Suzuki, trifluorometilación y transesterificación se han llevado a cabo. El objetivo principal de este conjunto de reacciones ha sido la obtención de la mayor cantidad de compuestos diferentes posibles, en cantidades suficientes para poder realizar los ensayos biológicos, pero sin poner un esfuerzo excesivo en la optimización de las condiciones de reacción en cada caso.

Algunas de las moléculas sintetizadas han dado buenos resultados en los ensayos biológicos, por lo tanto, hemos reabastecido cantidades suficientes para continuar con los ensayos. Por este mismo motivo, se han preparado más análogos con estructuras similares para comprobar si se han mejorado sus propiedades herbicidas, en una estrategia de tipo orientada a la diversidad.

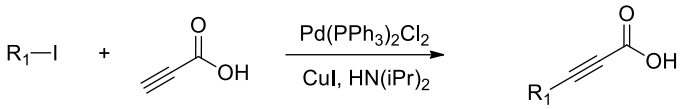
Cuando alguna de las rutas sintéticas da problemas, se buscan otras variantes. Por ejemplo, la esterificación, en algunos casos, no funcionó como se esperaba y se empleó la transesterificación para obtener el éster necesario. Este es un ejemplo de que nuestras rutas sintéticas son reajustables para mejorar la eficiencia. Además, la transesterificación ha sido empleada en otros casos, puesto que sus rendimientos han sido buenos.

6- Experimental

General Instrumentation:

^{1}H NMR spectra were recorded on an Avance Neo (400MHz), Avance III (400MHz) spectrometer δ values are expressed in ppm using TMS as the reference. Mass spectra were recorded on a SQD2 Single Quadrupole Detector. Liquid Chromatography was carried out on SiOH column on a Biotage Isolera One Flash Chromatograph. The reactions were monitored by LC-MS which was carried out on Agilent 6120B Single Quadrupole. The samples selected for biological tests, have been dried at Heraeus ThermoScientific Vacuum oven, at 40 °C.

6.1- Sonogashira coupling



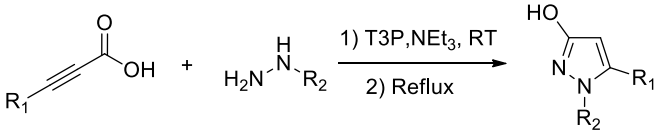
A typical procedure was as follows: aryl iodide (1 equiv) was dissolved in THF (150 mL of THF per 10 g of aryl iodide) in a four-neck round-bottom flask under argon atmosphere. Propyolic acid (1.4 equiv), bis(triphenylphosphin)palladium(II)chloride (0.02 equiv) and copper(I) iodide (0.04 equiv) were added. The mixture was stirred for 15 mins under argon atmosphere to remove the air. The mixture was cooled to 0 °C in an ice-water bath and diisopropylamine (2 equiv) was added dropwise so that the internal temperature raised to a maximum of 10 ° C. (At the beginning a brown solution was formed, and later a precipitate and a fume evolution was observed). The reaction was stirred for 1.5 h at RT. Then, ethyl acetate and water were added, the organic phase was separated, and HCl concentrated was added to the water phase until pH 2-3 had been reached. A brown oily mass formed, to which EtOAc was added. The organic phase was separated and the water phase was extracted three times with EtOAc. Combined organic phases were dried over MgSO4, filtered and the solvent was evaporated. Diethyl ether was added until all the solute dissolved properly, the mixture was stirred for 15 mins and filtered off.

Two phases appeared, a solid and a liquid phase.

When R_1=A, the product is in the liquid phase. In this case, the solution is evaporated.

When R_1=B, the product is in the solid phase.

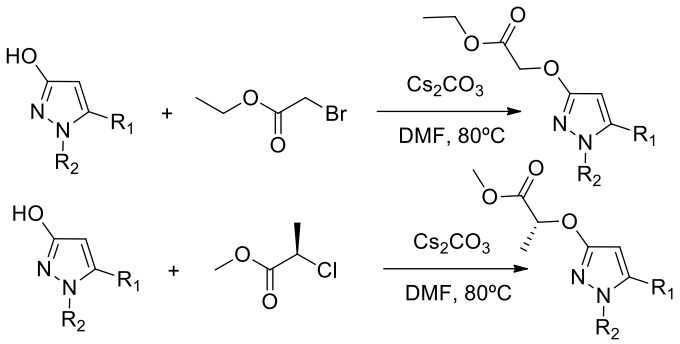
6.2- Formation of the pyrazole



Starting material (1 equiv) and the hydrazine derivative (1.2 equiv) were dissolved in THF in a four-neck round-bottom flask under N_2 atmosphere. Triethylamine (2.5 equiv) was added and the batch was cooled to + 10 °C. Propanephosphonic acid anhydride (2 equiv) was added

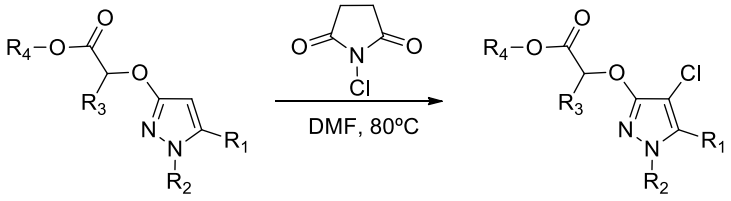
dropwise within 20 mins. The mixture has been stirred at RT for 2.5 h. 150 mL of EtOAc and 80 mL of water were added and was stirred for 20 mins at room temperature. The organic phase was separated and washed twice with NaCl solution/brine. Combined organic phases were dried over $MgSO_4$, filtered and the solvent was evaporated. Acetonitrile was added and heated at reflux temperature for 1.5 h. A mixture 1:1 ethyl acetate / heptane was added and filtered under vacuum. In all the cases (R_1=A and R_1=B), the product has been in the solid phase.

6.3- Alkylation



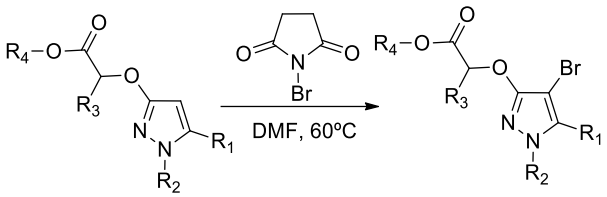
The starting material (1 equiv) was dissolved in DMF in a two-neck round-bottom flask. Cs_2CO_3 (1.5 equiv) and ethyl bromoacetate or methyl (2S)-2-chloropropanoate (1.2 equiv in both cases) was added. The mixture was stirred for 1.5 h at 80 °C. DMF was removed under vacuum. Dichloromethane and water were added and filtered under vacuum with celite. The organic phase was separated, and the water phase was extracted three times with dichloromethane. Combined organic phases were dried over $MgSO_4$, filtered and the solvent was evaporated. The product was isolated by liquid chromatography with a SiOH80 column (starting 5% ethyl acetate, 95% heptane for equilibration of the column to 25% ethyl acetate, 75% heptane within 15 mins).

6.4- Chlorination



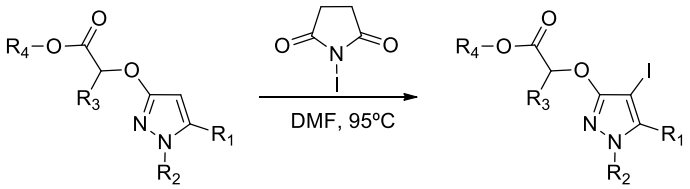
Starting material (1 equiv) was dissolved in DMF in a two-neck round-bottom flask. Then N-chlorosuccinimide (3 equiv) was added and stirred at 80 °C for 3 h. DMF was evaporated in the rotavapor. Water and dichloromethane were added. The water phase was extracted three times with dichloromethane. Combined organic phases were dried over $MgSO_4$, filtered and the solvent was evaporated. The product was isolated by liquid chromatography with a SiOH40 column (starting 5% acetone, 95% heptane for equilibration of the column to 25% acetone, 75% heptane within 15 mins).

6.5- Bromination



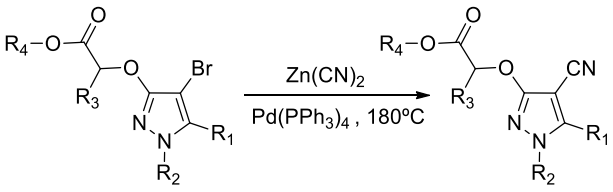
The starting material (1 equiv) was dissolved in DMF in a two-neck round-bottom flask. Then N-bromosuccinimide (3 equiv) was added and stirred at 60 °C for 1 h. DMF was evaporated in the rotavapor. Water and dichloromethane were added. The water phase was extracted three times with dichloromethane. Combined organic phases were dried over $MgSO_4$, filtered and the solvent was evaporated. The product was isolated by liquid chromatography with a SiOH40 column (starting 5% ethyl acetate, 95% heptane for equilibration of the column to 50% ethyl acetate, 50% heptane within 15 mins).

6.6- Iodination



The starting material (1 equiv) was dissolved in DMF in a two-neck round-bottom flask. Then N-iodosuccinimide (3 equiv) was added and stirred at 95 °C for 3 h. DMF was evaporated in the rotavapor. Water and dichloromethane were added. Sodium bisulfite (10% in water) was added until the solution got colourless. The organic and water phase were separated. The water phase was extracted three times with dichloromethane. Combined organic phases were dried over $MgSO_4$, filtered and the solvent was evaporated. The product was isolated by liquid chromatography with a SiOH80 column (starting 5% ethyl acetate, 95% heptane for equilibration of the column to 50% ethyl acetate, 50% heptane within 15 mins).

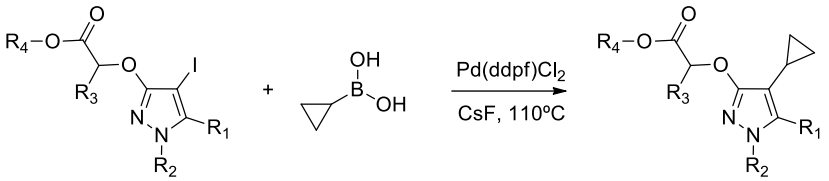
6.7- Cyanation



Under argon atmosphere, zinc cyanide (0.95 equiv) was placed in a MW vial, then tetrakis(triphenylphosphine)palladium (0.1 equiv) was added and stirred. The starting

material (1 equiv) was dissolved in DMA and added to the previous microwave vial. The vial was inserted into the MW reactor and heated at 180 °C for 40 mins. The solution was filtered and water and dichloromethane were added. The water phase was extracted three times with dichloromethane. Combined organic phases were dried over $MgSO_4$, filtered and the solvent was evaporated. The product was isolated by liquid chromatography with a SiOH40 column (starting 5% ethyl acetate, 95% heptane for equilibration of the column to 50% ethyl acetate, 50% heptane within 12 mins).

6.8- Cyclopropanation (Suzuki coupling)

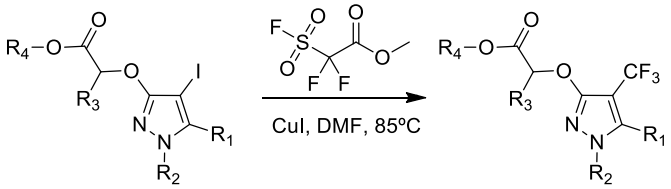


The starting material (1 equiv) was dissolved in 1,4-dioxane in a one-neck round-bottom flask and cesium fluoride (2 equiv), cyclopropyl boronic acid (3 equiv) and [1,1-bis(diphenylphosphino)ferrocene] dichloropalladium (II) complex with dichloromethane (0.1 equiv) were added. The mixture was stirred under nitrogen atmosphere at 110 °C for 3 h. The solution was filtered under vacuum with celite. Water and EtOAc were added. To the organic phase, NaCl saturated solution was added and separated. The water phase was extracted three times with dichloromethane. Combined organic phases were dried over $MgSO_4$, filtered and the solvent was evaporated. The product was isolated by liquid chromatography with a SiOH80 column (starting 5% ethyl acetate, 95% heptane for equilibration of the column to 50% ethyl acetate, 50% heptane within 15 mins).

6.9- Trifluoromethylation

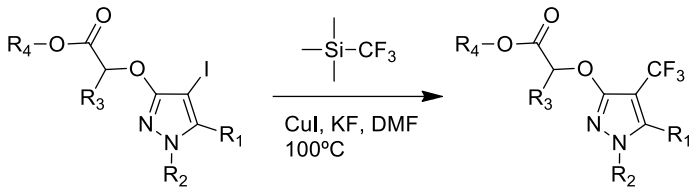
It was carried out in two different ways:

A-



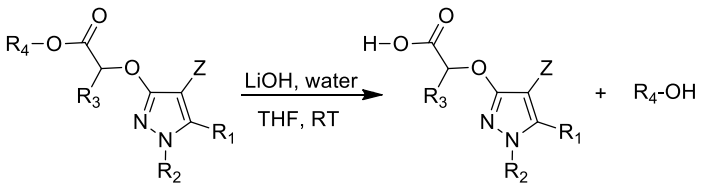
The starting material (1 equiv) was dissolved in DMF in a round-bottom flask. Methyl 2,2-difluoro-2-fluorosulfonyl-acetate (5 equiv) and copper (I) iodide (2 equiv) were added. Then, the mixture was stirred for 5 h at 85 ° C in an oil bath. Dichloromethane was added and filtered under vacuum with celite. Water and dichloromethane were added. The water phase was extracted three times with dichloromethane. Combined organic phases were dried over $MgSO_4$, filtered and the solvent was evaporated. The product was isolated by liquid chromatography with a SiOH80 column (5% Heptane, 95% Dichloromethane for 15 mins).

B-



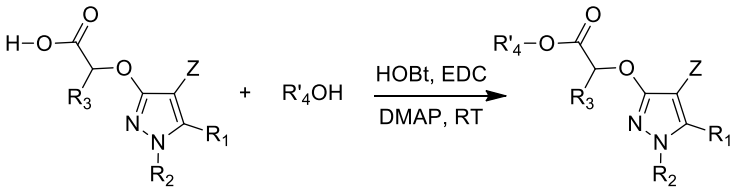
CuI (1.5 equiv) and KF (1.5 equiv) were added to a MW vial. The vial was closed in a flowing argon system. The starting material (1 equiv) was dissolved in DMF and added. Trimethyl(trifluoromethyl)silane (3 equiv) was added and stirred for 2 h at 100 °C. The mixture was evaporated, water and dichloromethane were added and it was filtered under vacuum with celite. The water phase was extracted three times with dichloromethane. Combined organic phases were dried over $MgSO_4$, filtered and the solvent was evaporated. The product was isolated by liquid chromatography with a SiOH80 column (start 5% EE: 95% n-heptane within 18 mins to 25% EE: 75% n-heptane).

6.10- Saponification



The starting material (1 equiv) was dissolved in THF in a one-neck round-bottom flask. Lithium hydroxide (1.5 equiv) and water (ratio 1:4 with respect to THF) were added and stirred for 3 h at RT. THF was evaporated in the rotavapor, water was added and HCl 2M was added until the pH was adjusted to pH=1. The product precipitated so was filtered under vacuum and collected.

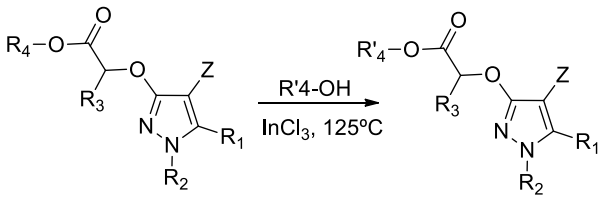
6.11- Esterification



The starting material (1 equiv) was dissolved in dichloromethane and ethanol or methanol (1.4 equiv) was added. 1-Hydroxy-1H-benzotriazol hydrate (HOBT), 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) and 4-(dimethylamino)pyridine (DMAP) were added (all of them 1.3 equiv). The mixture was stirred at RT for 3 h. Water and dichloromethane were added. The water phase was extracted three times with dichloromethane. Combined organic phases were dried over $MgSO_4$, filtered and the solvent was evaporated. The product was isolated by liquid chromatography with a SiOH15 column

(starting 5% ethyl acetate, 95% heptane for equilibration of the column to 50% ethyl acetate, 50% heptane within 15 mins).

6.12- Transesterification



The starting material (1 equiv) was dissolved in dichloromethane to a MW vial. Indium (III) chloride (1.5 equiv), a stirrer and ethanol or methanol (4 mL) were added. It was heated in the MW for 1.5 h at 125 °C. The mixture was evaporated. Water and dichloromethane were added. The water phase was extracted three times with dichloromethane. Combined organic phases were dried over $MgSO_4$, filtered and the solvent was evaporated. The product was isolated by liquid chromatography with a SiOH15 column (starting 5% ethyl acetate, 95% heptane for equilibration of the column to 50% ethyl acetate, 50% heptane within 15 mins).

6.13- Spectra

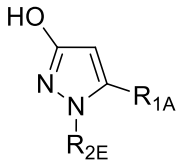
^{1}H NMR spectra were recorded on an Avance Neo (400MHz), Avance III (400MHz) spectrometer δ values are expressed in ppm using TMS as the reference.

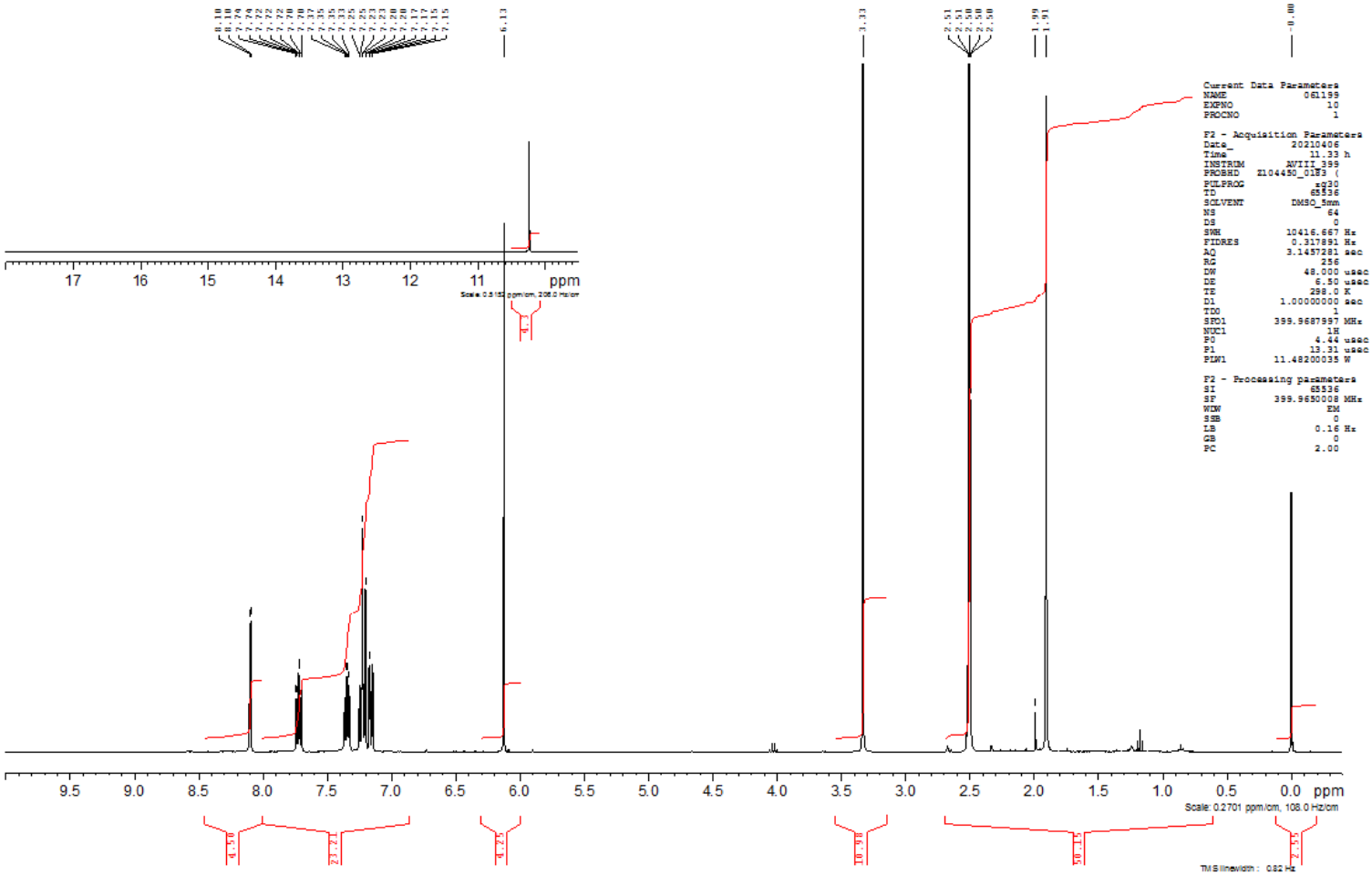
HNMR: chloroform has been used as a solvent in all the compounds, except the ones that had -OH (could be in the 3-hydroxypyrazole or in the carboxylic acid) in which DMSO has been used.

^{1}H NMR ($CDCl_3$): δ= 7.26 ($CDCl_3$ residual peak), 1.56 (water in $CDCl_3$).

^{1}H NMR (DMSO): δ= 3.33 (water in DMSO), 2.5 (DMSO residual peak).

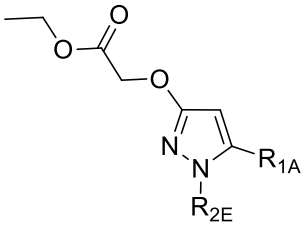
1-.

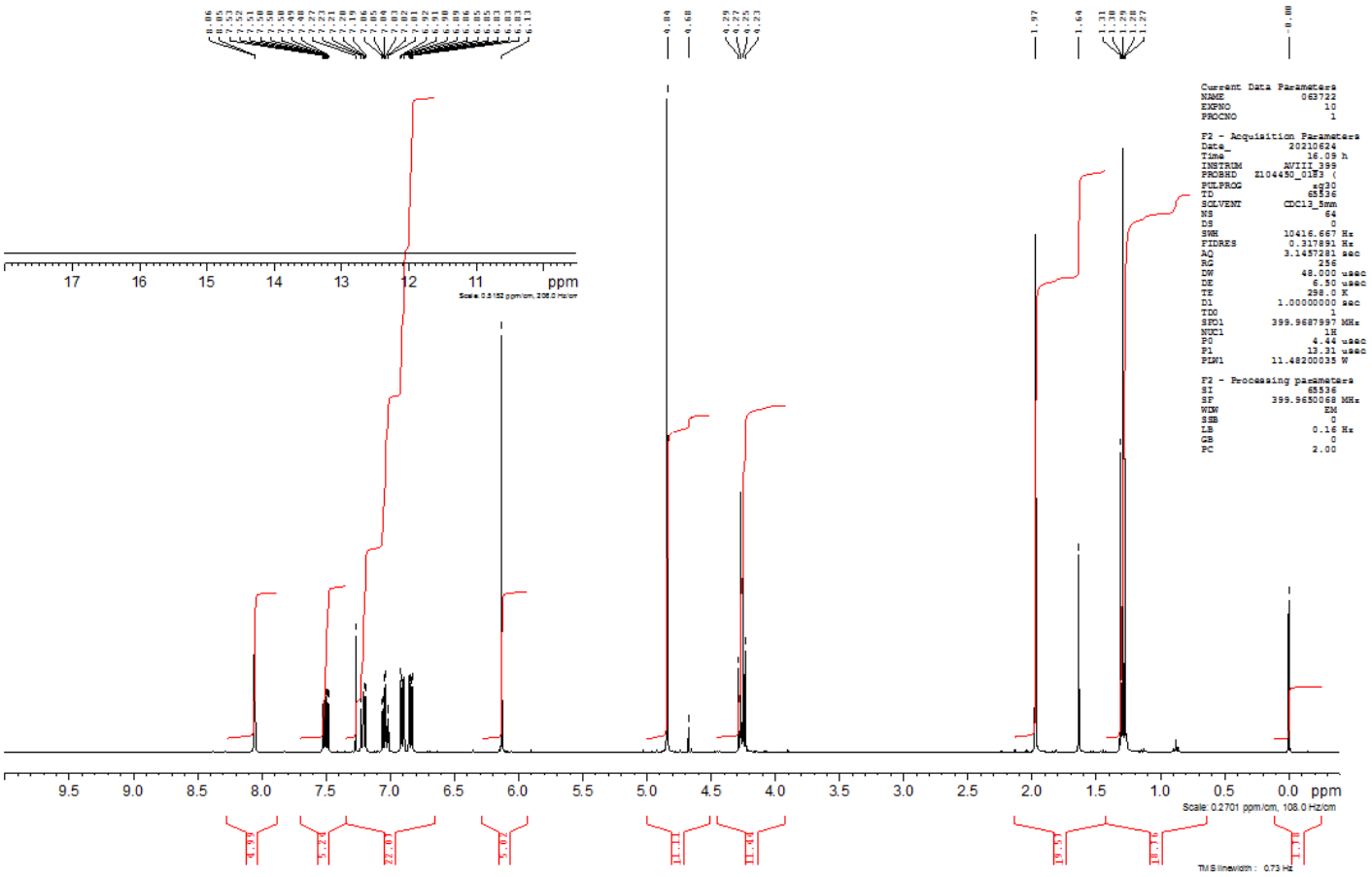




^{1}H NMR (400MHz, $CDCl_3$) δ 10.20 (s, 1H, *H*O-), 8.10-7.15 (m, 6H), 6.13 (s, 1H, *H*-$C_{pyrazole}$), 1.91 (s, 3H).

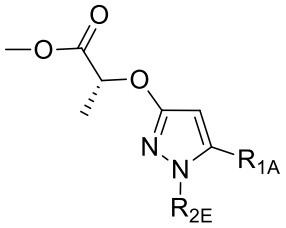
2-

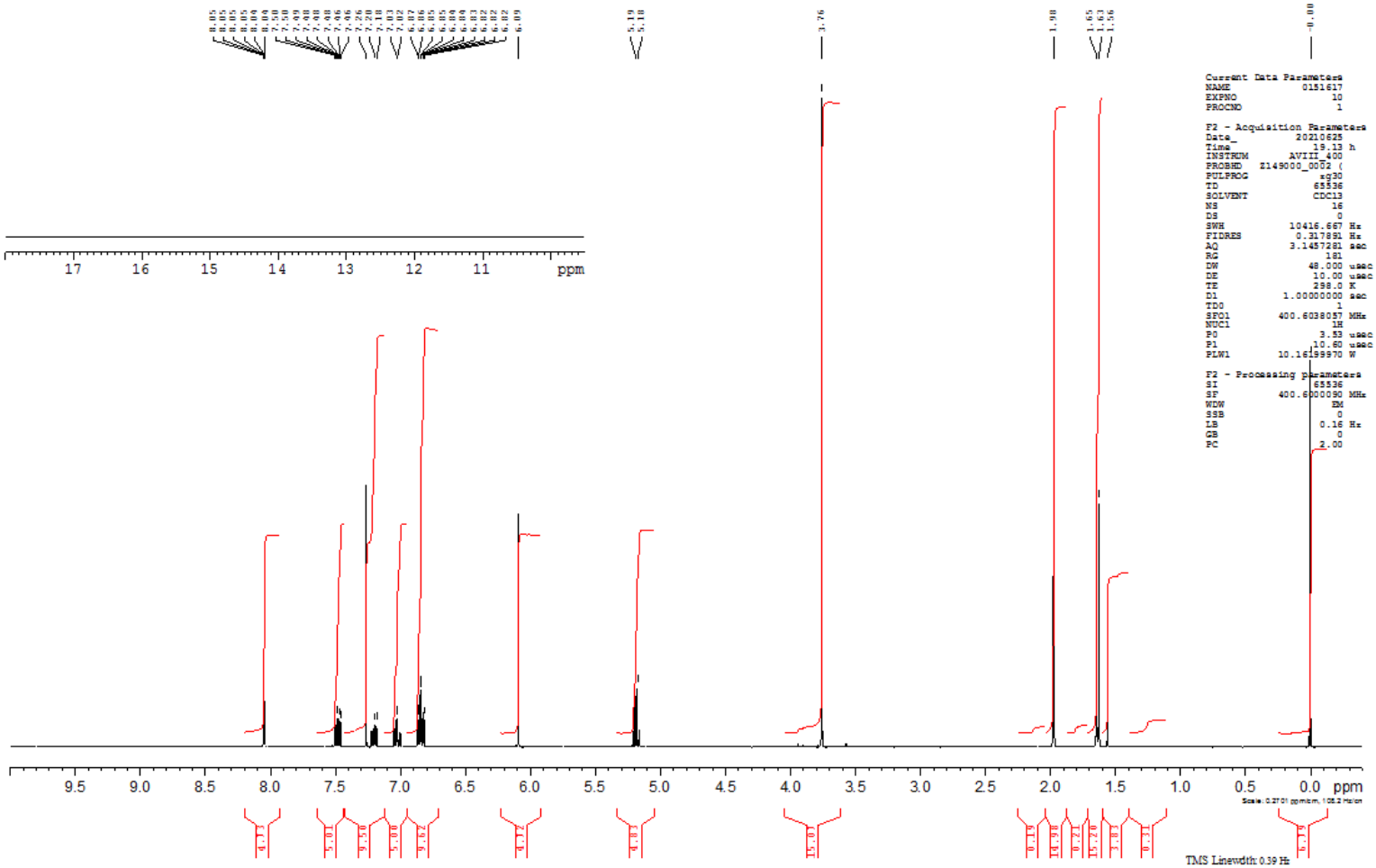




^{1}H NMR (400MHz, $CDCl_3$) δ 8.06-6.83 (m, 6H), 6.13 (s, 1H, *H*-$C_{pyrazole}$), 4.89 (s, 2H, -CO-C*H*$_2$-O-), 4.27 (m, 2H, CH_3-C*H*$_2$-O-), 1.97 (s, 3H), 1.29 (t, 3H, C*H*$_3$-CH_2-O-)

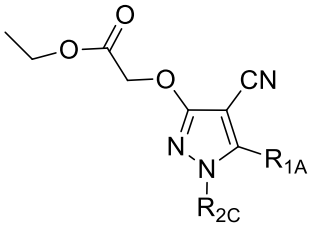
3-.

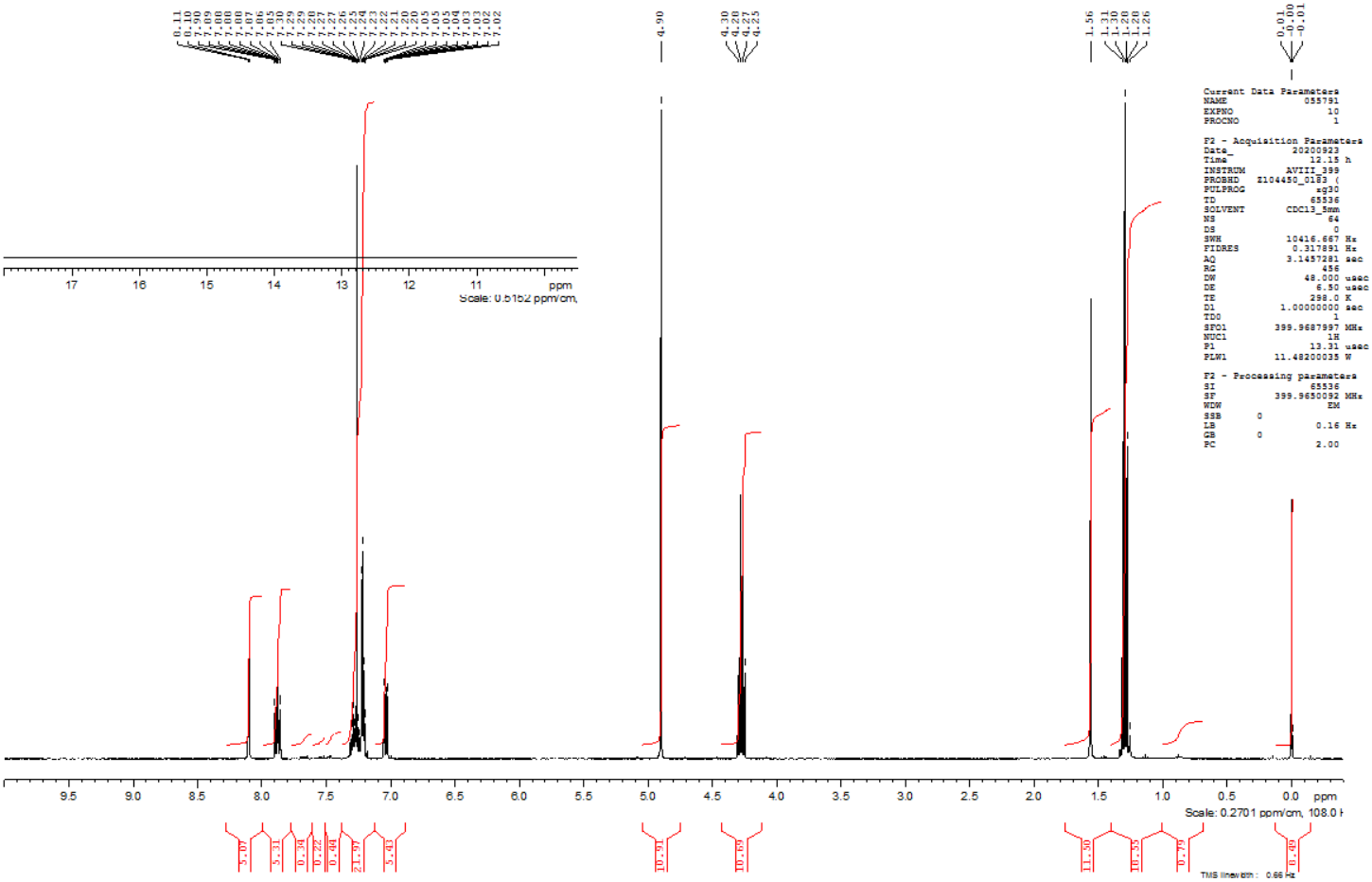




^{1}H NMR (400MHz, $CDCl_3$) δ 8.05-6.82 (m, 6H), 6.13 (s, 1H, *H*-$C_{pyrazole}$), 5.19 (m, 1H, -CO-C*H*(CH_3)-O-), 3.76 (s, 3H, C*H*$_3$-O-CO-), 1.98 (s, 3H), 1.63 (d, 3H, -CO-CH(C*H*$_3$)-O-), 1.29 (t, 3H).

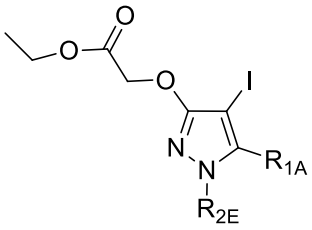
4-.

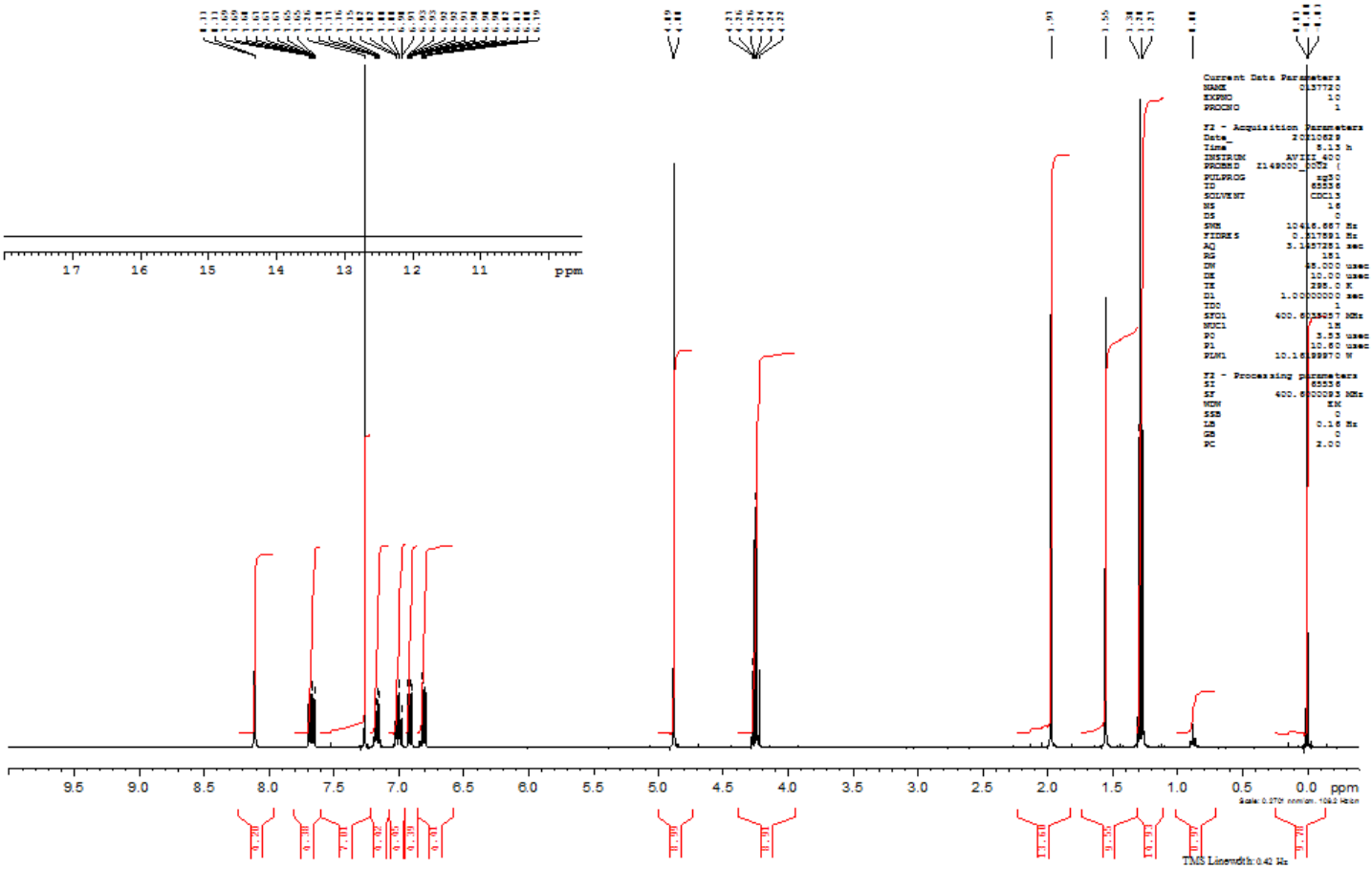




^{1}H NMR (400MHz, $CDCl_3$) δ 8.11-7.02 (m, 6H), 4.90 (s, 2H, -CO-C*H*$_2$-O-), 4.27 (m, 2H, CH_3-C*H*$_2$-O-), 1.29 (t, 3H, C*H*$_3$-CH_2-O-).

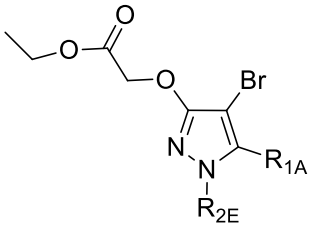
5-.

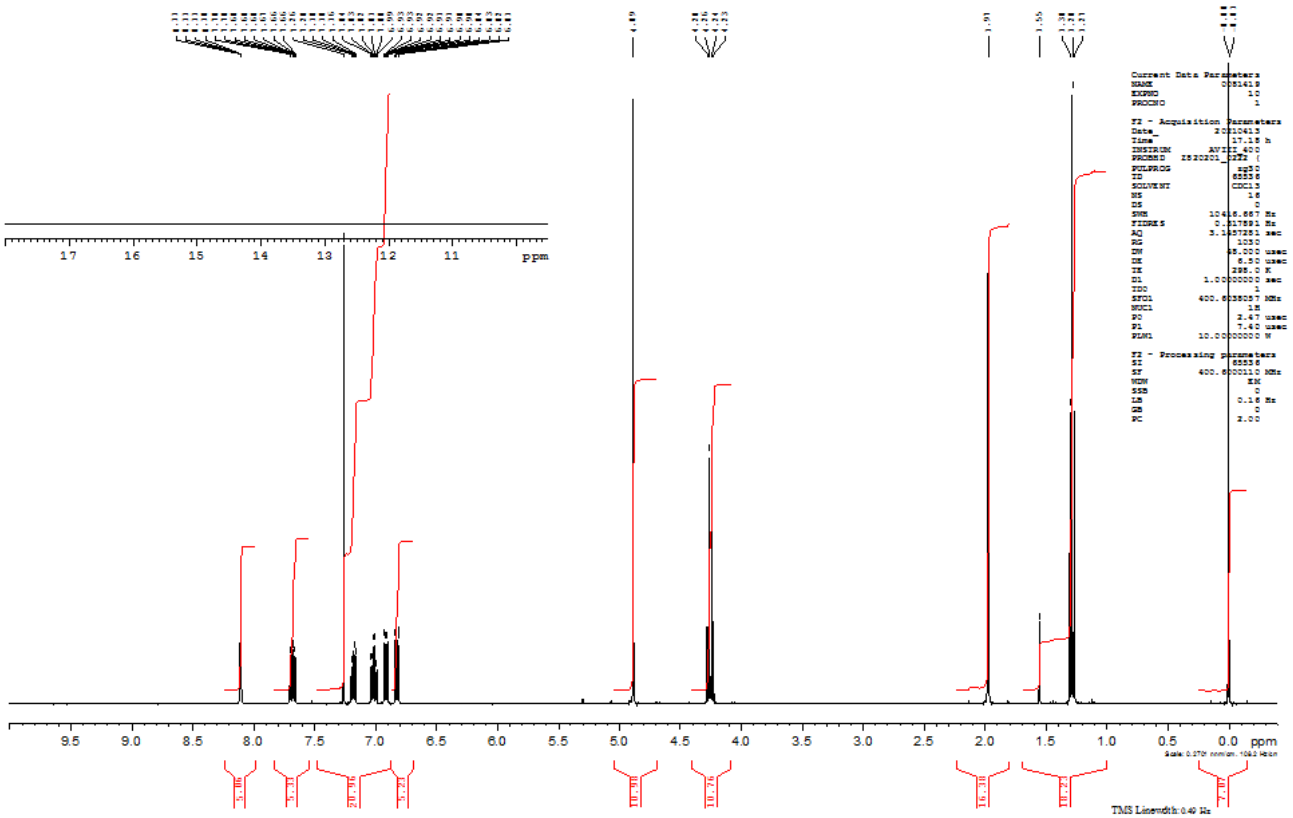




^{1}H NMR (400MHz, $CDCl_3$) δ 8.11-6.79 (m, 6H), 4.89 (s, 2H, -CO-C*H*$_2$-O-), 4.34 (m, 2H, CH_3-C*H*$_2$-O-), 1.98 (s, 3H), 1.32 (t, 3H, C*H*$_3$-CH_2-O-).

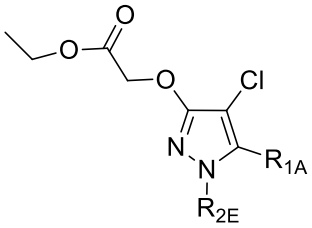
6-.

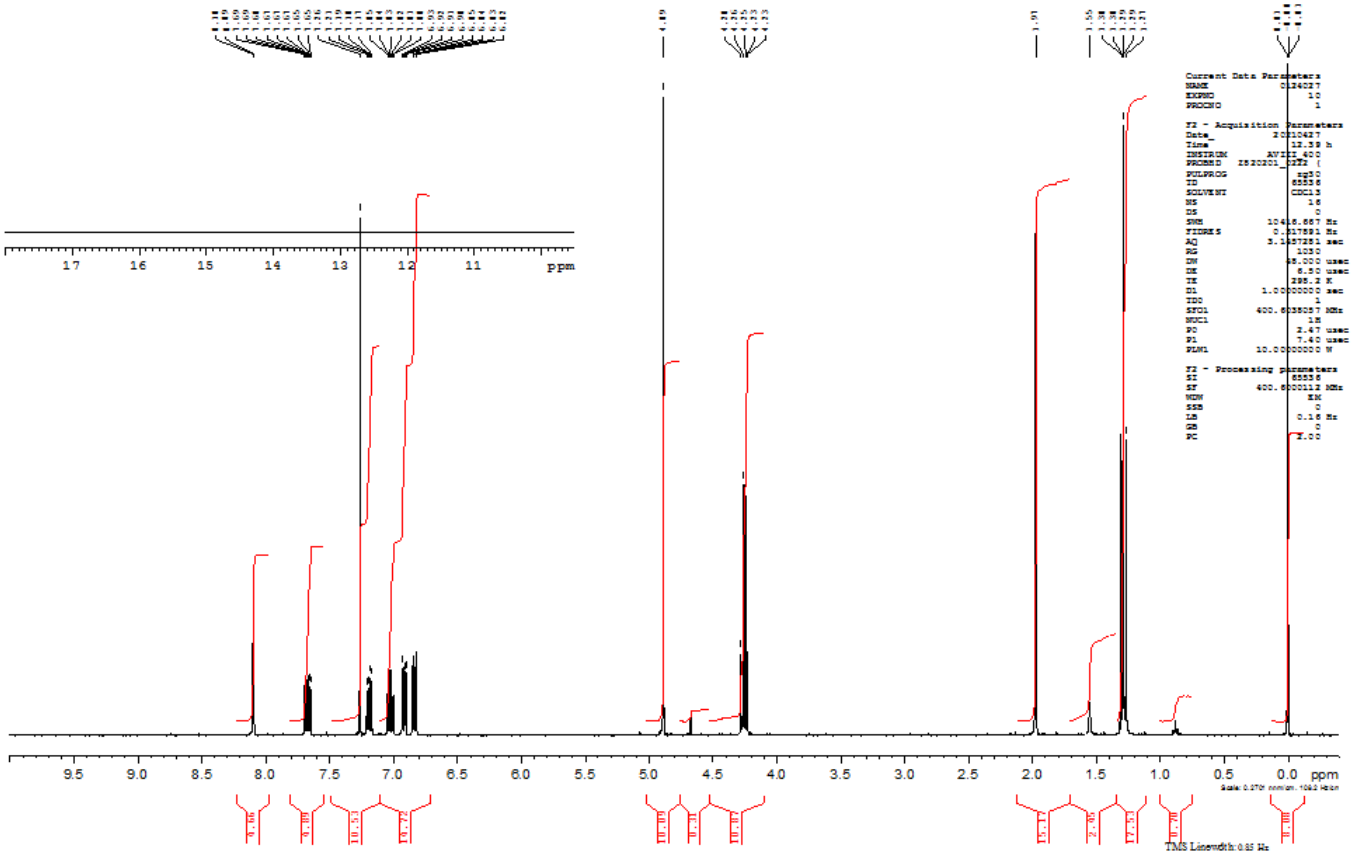




^{1}H NMR (400MHz, $CDCl_3$) δ 8.11-7.02 (m, 6H), 4.90 (s, 2H, -CO-C*H*$_2$-O-), 4.27 (m, 2H, CH_3-C*H*$_2$-O-), 1.91 (s, 3H), 1.29 (t, 3H, C*H*$_3$-CH_2-O-).

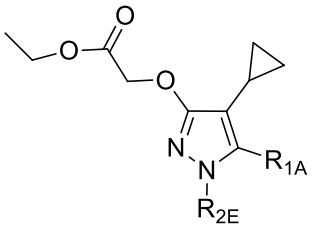
7-.

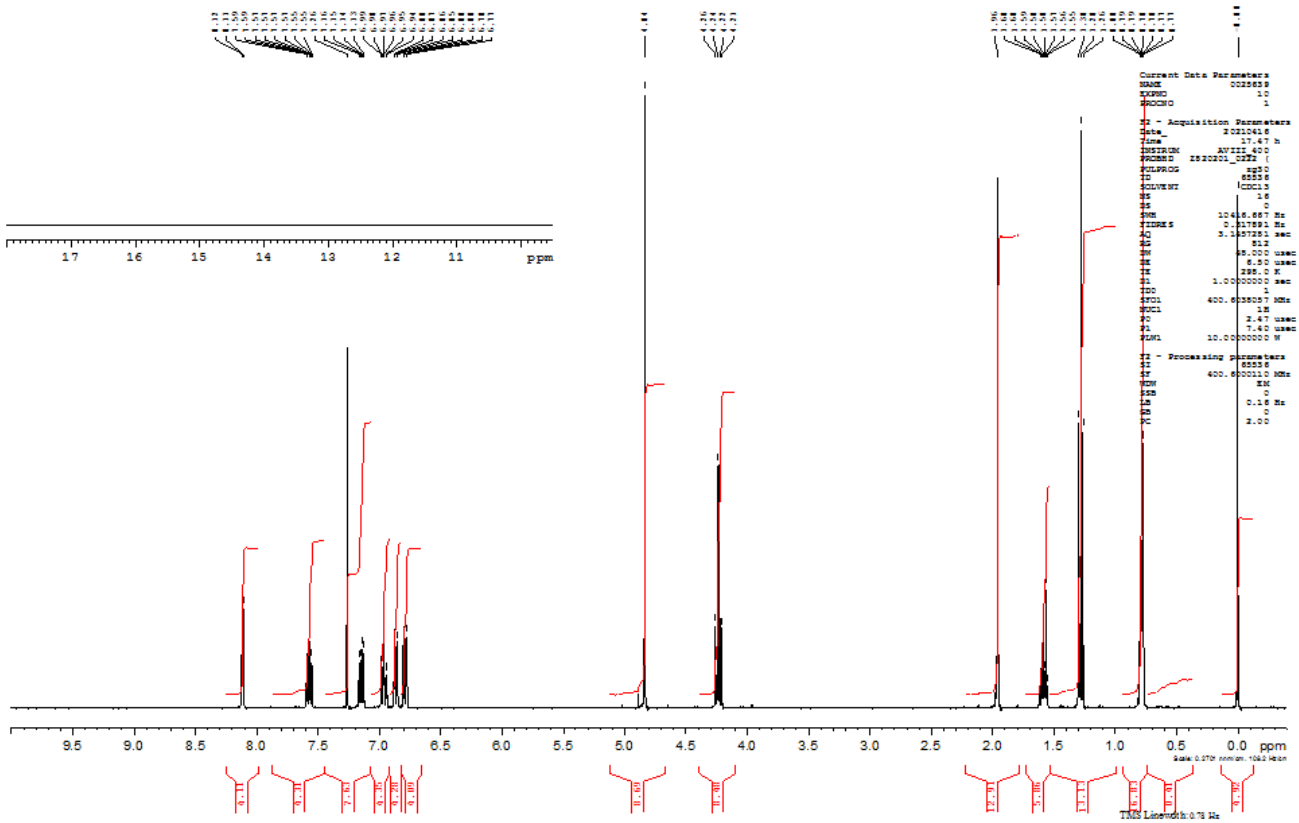




^{1}H NMR (400MHz, $CDCl_3$) δ 8.16-6.82 (m, 6H), 4.89 (s, 2H, -CO-C*H*$_2$-O-), 4.27 (m, 2H, CH_3-C*H*$_2$-O-), 1.91 (s, 3H) 1.29 (t, 3H, C*H*$_3$-CH_2-O-).

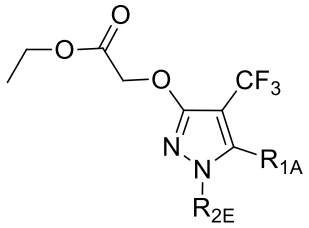
8-.

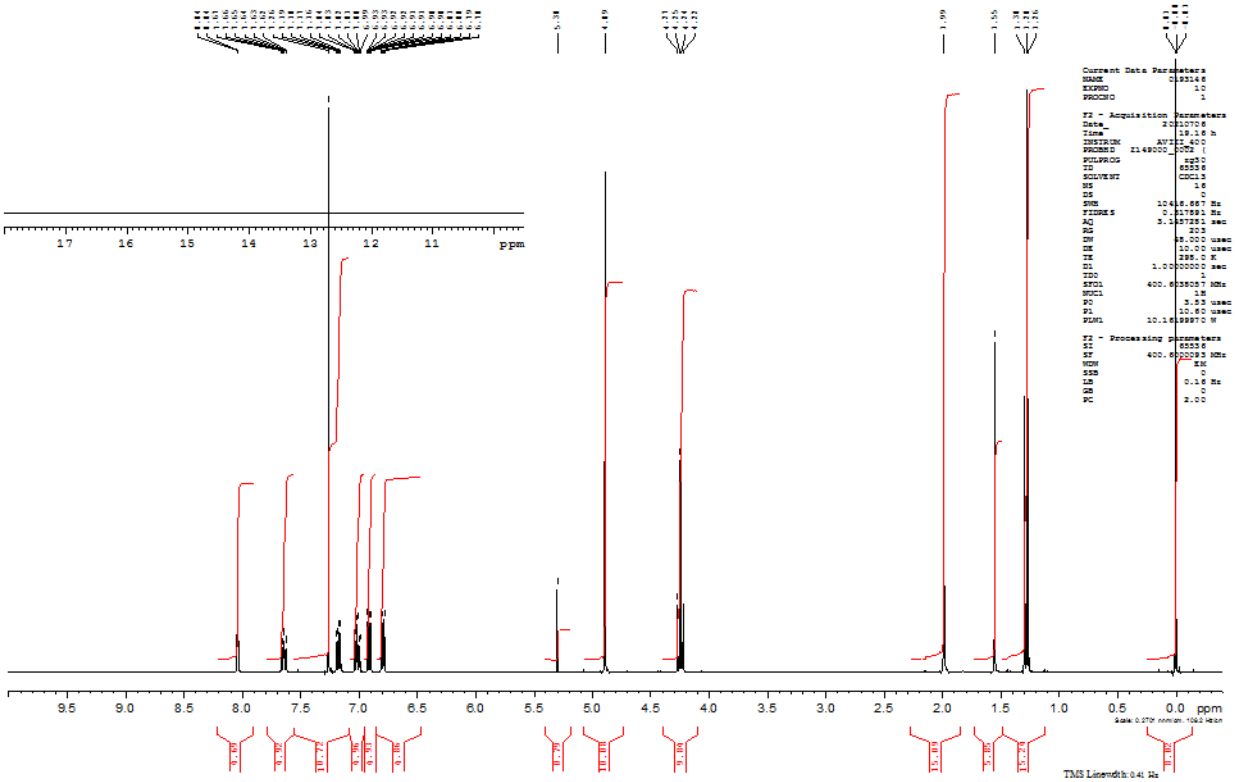




^{1}H NMR (400MHz, $CDCl_3$) δ 8.12-6.71 (m, 6H), 4.84 (s, 2H, -CO-C*H*$_2$-O-), 4.25 (m, 2H, CH_3-C*H*$_2$-O-), 1.96 (s, 3H), 1.58 (m, 1H, $C_{pyrazole}$-C*H*$(CH_2)_2$), 1.29 (t, 3H, C*H*$_3$-CH_2-O-), 1.19 (d, 4H, $C_{pyrazole}$-CH(C*H*$_2)_2$).

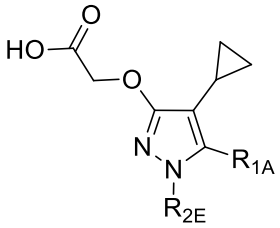
9-.

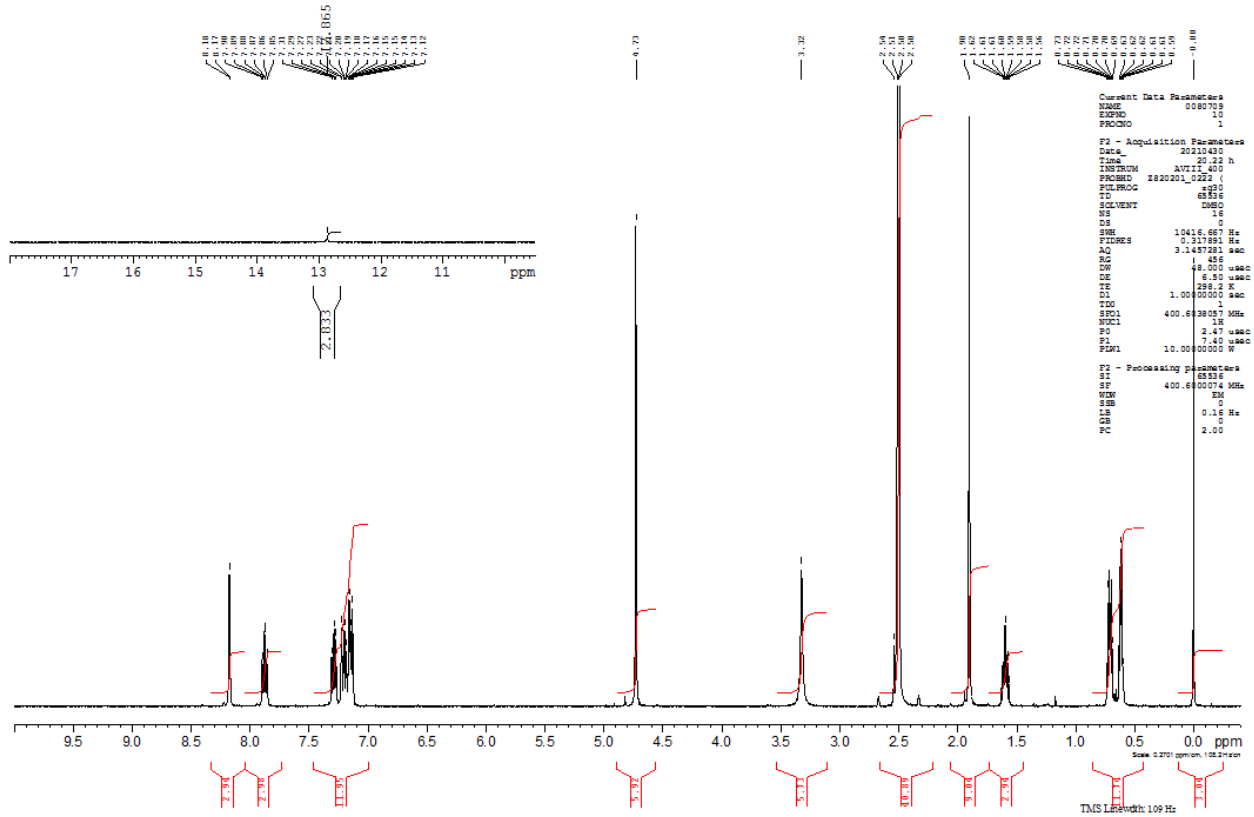




^{1}H NMR (400MHz, $CDCl_3$) δ 8.14-6.78 (m, 6H), 4.89 (s, 2H, -CO-C*H*$_2$-O-), 4.25 (m, 2H, CH_3-C*H*$_2$-O-), 1.99 (s, 3H), 1.29 (t, 3H, C*H*$_3$-CH_2-O-)

10-





^{1}H NMR (400MHz, $CDCl_3$) δ 12.86 (s, 1H, *H*OOC-), 8.12-6.71 (m, 6H), 4.73 (s, 2H, -CO-C*H*$_2$-O-), 1.90 (s, 3H), 1.58 (m, 1H, $C_{pyrazole}$-C*H*$(CH_2)_2$), 1.19 (d, 4H, $C_{pyrazole}$-CH(C*H*$_2)_2$).