The 7th International Electronic Conference on Medicinal Chemistry (ECMC 2021)
01–30 NOVEMBER 2021 | ONLINE

Modulation of cannabinoidergic system by a novel pyrazole styrylquinazolinone

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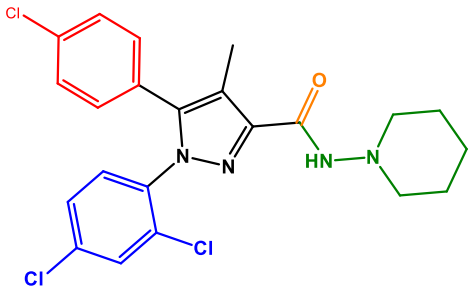
DIPARTIMENTO DI SCIENZE E TECNOLOGIE BIOLOGICHE CHIMICHE E FARMACEUTICHE (STEBICEF)

UNIVERSITÀ DEGLI STUDI DI PALERMO

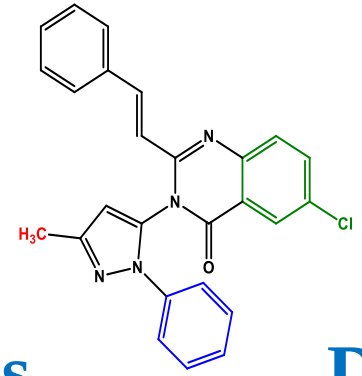
Modulation of cannabinoidergic system by a novel pyrazole styrylquinazolinone

Graphical Abstract



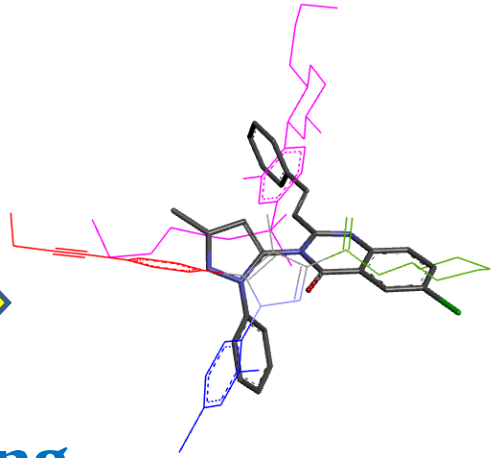
Rimonabant

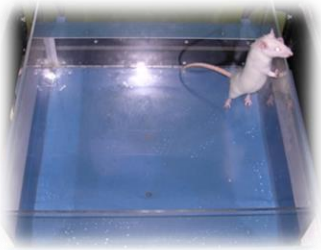
Synthesis



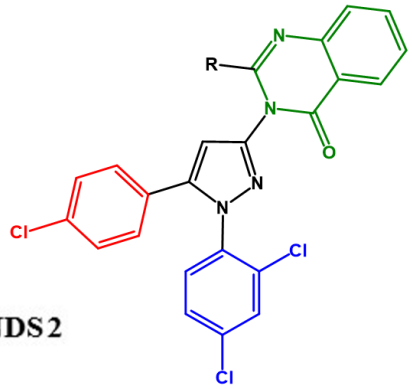
COMPOUND 1

Docking





Tetrad Task



COMPOUNDS 2

Abstract: Endocannabinoid receptors type 1 and 2 can be managed by pharmacological compounds to regulate different neuronal processes. Hyperactivity or dysfunction in the endocannabinoid system might be implicated in disturbance or abnormality of neural processes, evidencing its relevance for several pathologies. The reported study shows that a new structural analogue of rimonabant, (E)-6-chloro-3-(3-methyl-1-phenyl-1H-pyrazol-5-yl)-2-styrylquinazolin-4(3H)-one (1), is able to counteract the behavioral signs of the activation of the endocannabinoidergic system induced by the administration of the agonist CP 55,940.

The analogue of rimonabant (1) is characterized by a quinazolinone structure bearing a heterocyclic pyrazole nucleus. Behavioral assessment was carried out by tetrad task and the novel object recognition tested on rats, to evaluate cannabinoid effects on declarative memory. The endocannabinoidergic system was activated by the administration of the cannabinoid agonist CP 55,940.

Our study shows that compound 1 at the dose of 10 mg/kg, 30 min before CP 55,940 administration, is able to counteract the effects exerted by CP 55,940, as shown by an increase in body temperature, in total distance travelled, in latency to fall down and a decrease in tail flick latency. Furthermore, the memory impairment induced by the cannabinoid agonist is prevented by compound 1 showing that it is able to counteract the cannabinoid activation induced by the agonist CP 55,940. Further investigations are in progress to evaluate the pharmacological profile of compound 1 and consider it as a potential candidate for clinical studies and as pharmacological agent in managing different pathological conditions as motor incoordination, obesity, and brain related disorders.

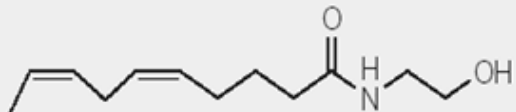
Keywords: Agonist CP 55,940; Endocannabinoid receptors; Quinazolinone derivate; Rimonabant; Tetrad task

Introduction

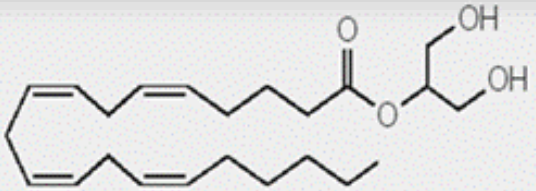
CANNABINOIDS

PHYTOCANNABINOIDS

ENDOCANNABINOIDS

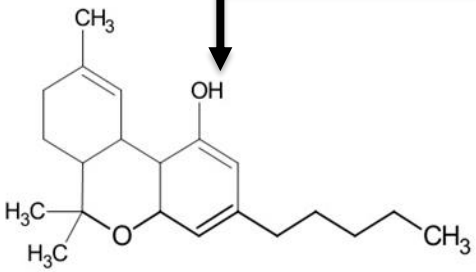


Anandamide (CB_1>CB_2)

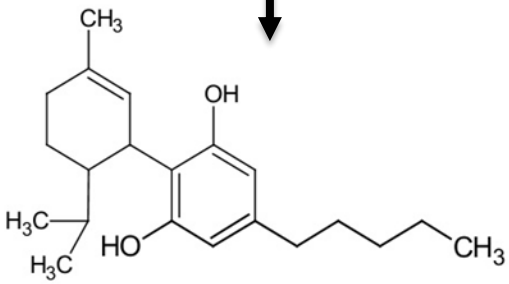


2-Arachidonoylglycerol (CB_1 = CB_2)

CANNABIS



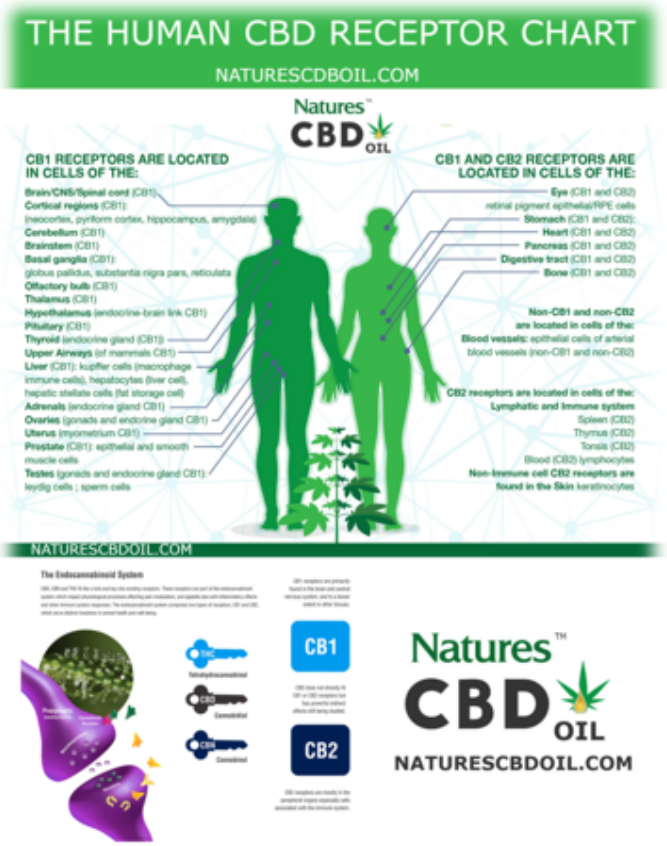
Tetrahydrocannabinol (THC)



Cannabidiol (CBD)

CANNABINOIDS RECEPTOR

CANNABINOID RECEPTOR (CB1 - CB2)



Cannabinoids receptors are widely distributed throughout our body.

In particular, the CB1 receptors are ubiquitous while the CB1 receptors are preferentially expressed in the immune system.

The localization of CB1 receptors in the central nervous system accounts for most of its pharmacological effects.

Koch M. Front Neurosci. 2017 May 24;11:293
Rossi S, et al.Mol Nutr Food Res. 2010 54(4):525-31.

Introduction

Neuropsychopharmacology (2015) 40, 1936–1947
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www.neuropsychopharmacology.org

Hippocampal Cannabinoid Transmission Modulates Dopamine Neuron Activity: Impact on Rewarding Memory Formation and Social Interaction

Michael Loureiro[1], Justine Renard[1], Jordan Zunder[1] and Steven R Laviolette[*,1,2,3]

NIH Public Access
Author Manuscript
Int Rev Psychiatry. Author manuscript; available in PMC 2009 August 25.

Published in final edited form as:
Int Rev Psychiatry. 2009 April ; 21(2): 104–112. doi:10.1080/09540260902782752.

Actions of delta-9-tetrahydrocannabinol in cannabis:

Relation to use, abuse, dependence

ZIVA D. COOPER and MARGARET HANEY

CNS & Neurological Disorders Drug Targets

CNS Neurol Disord Drug Targets. 2015;14(4):502-17.

Individual differences and vulnerability to drug addiction: a focus on the endocannabinoid system.

Sagheddu C, Melis M[1].

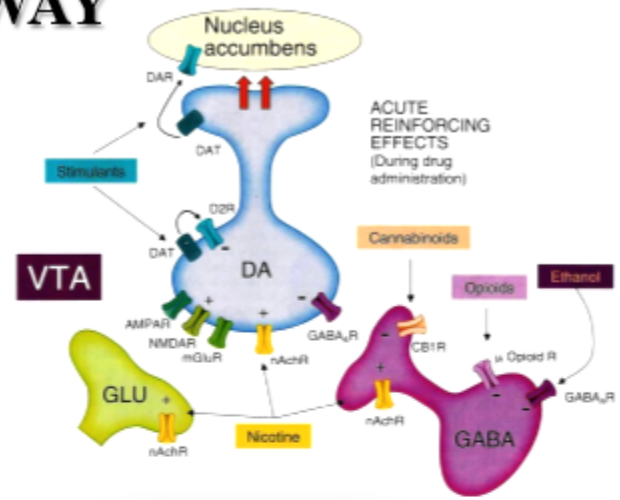
frontiers in PSYCHIATRY

REVIEW ARTICLE
published: 25 March 2015
doi: 10.3389/fpsyt.2015.00041

Role of the endogenous cannabinoid system in nicotine addiction: novel insights

*Islam Hany Gamaleddin[1,2†], Jose M. Trigo[1†], Aliou B. Gueye[1], Alexander Zvonok[3], Alexandros Makriyannis[3], Steven R. Goldberg[4] and Bernard Le Foll[1,5,6,7,8]**

REWARD PATHWAY



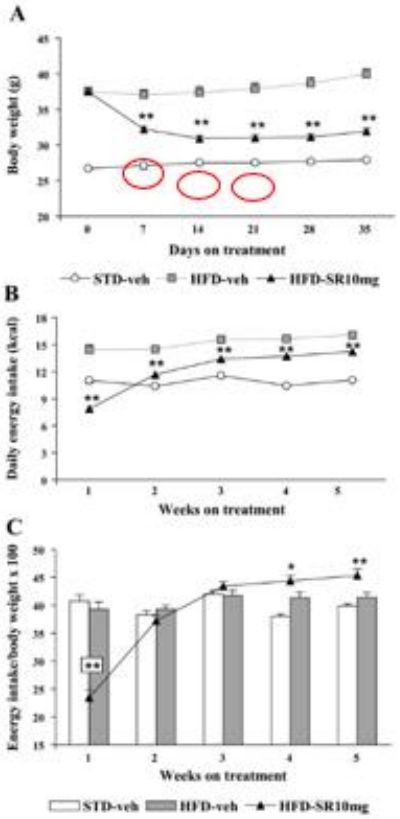
Introduction

THERAPEUTIC APPLICATION OF CANNABINOIDS

nature publishing group
ARTICLES
INTEGRATIVE PHYSIOLOGY

The Central Cannabinoid CB1 Receptor Is Required for Diet-Induced Obesity and Rimonabant's Antiobesity Effects in Mice

Zhen Pang[1], Nancy N. Wu[1], Weignang Zhao[1], David C. Chain[1], Erica Schaffer[1], Xin Zhang[1], Preeti Yamdagni[1], Vaseem A. Palejwala[1], Chunpeng Fan[2], Sarah G. Favara[1], Holly M. Dressler[1], Kyriakos D. Economides[1], Daniel Weinstock[1], Jean S. Cavallo[1], Souad Naimi[1], Anne-Marie Galzin[4], Etienne Guillot[4], Marie-Pierre Pruniaux[4], Michael J. Tocci[1] and H. Greg Polites[1]



frontiers in BEHAVIORAL NEUROSCIENCE
ORIGINAL RESEARCH ARTICLE

Acetaldehyde as a drug of abuse: insight into AM281 administration on operant-conflict paradigm in rats

*Fulvio Plescia, Anna Brancato, Rosa A. M. Marino and Carla Cannizzaro**

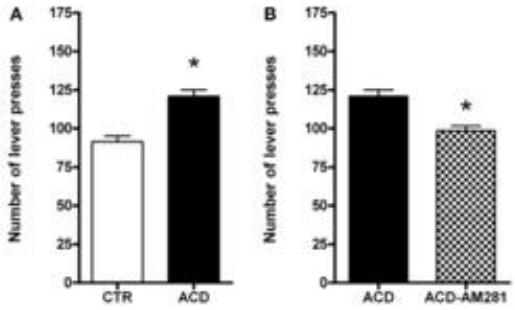
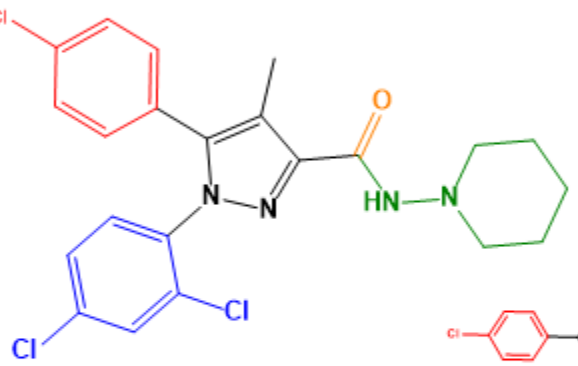


FIGURE 2 | Effects of ACD (A) and AM281 treatment (B) on the number of lever presses during the extinction day. Each value represents the means ± S.D. of 16 rats. *$p < 0.001$ vs. respective control groups.

Introduction

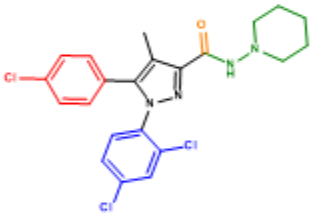
ANALOGUES OF RIMONABANT

A cannabinoid analogue is Rimonabant which has been found to be a potent antagonist of CB1 receptors with notable side effects such as nausea, vomiting, depression, dizziness, anxiety, suicidal idea…….

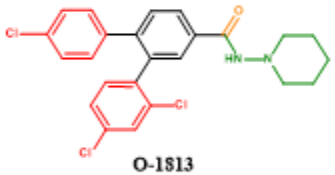


Rimonabant

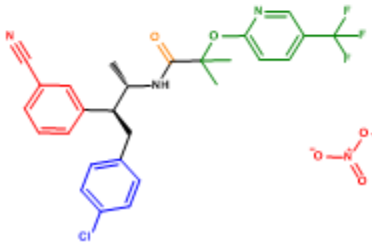
In order to improve the pharmacological effect of rimonabant, new study have been undertaken to modify its structure.
Examples of some molecules are:



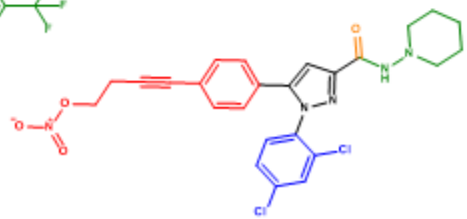
OTENABANT



O-1813



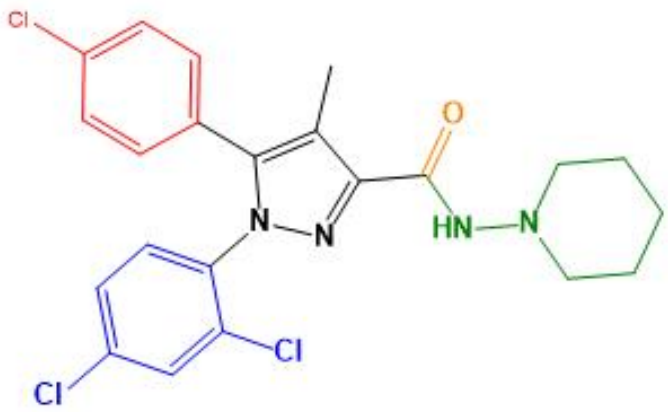
TARANABANT



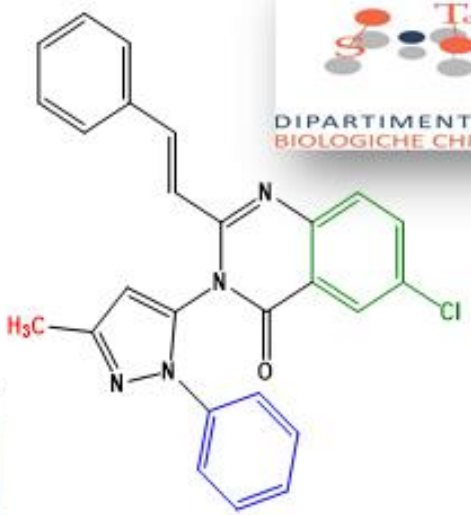
AM-6538

Introduction

Considering the activity reported by these molecules in the laboratory where I carry out my research work, compound 1 with quinazolinones structure has been synthesized, bearing in position 3 a heterocyclic nucleous such as the pyrazole one and which has structural analogies to Rimonabant.



Rimonabant



1

DIPARTIMENTO DI SCIENZE E TECNOLOGIE BIOLOGICHE CHIMICHE E FARMACEUTICHE (STEBICEF)

Contents lists available at ScienceDirect

Pharmacological Reports

journal homepage: www.elsevier.com/locate/pharep

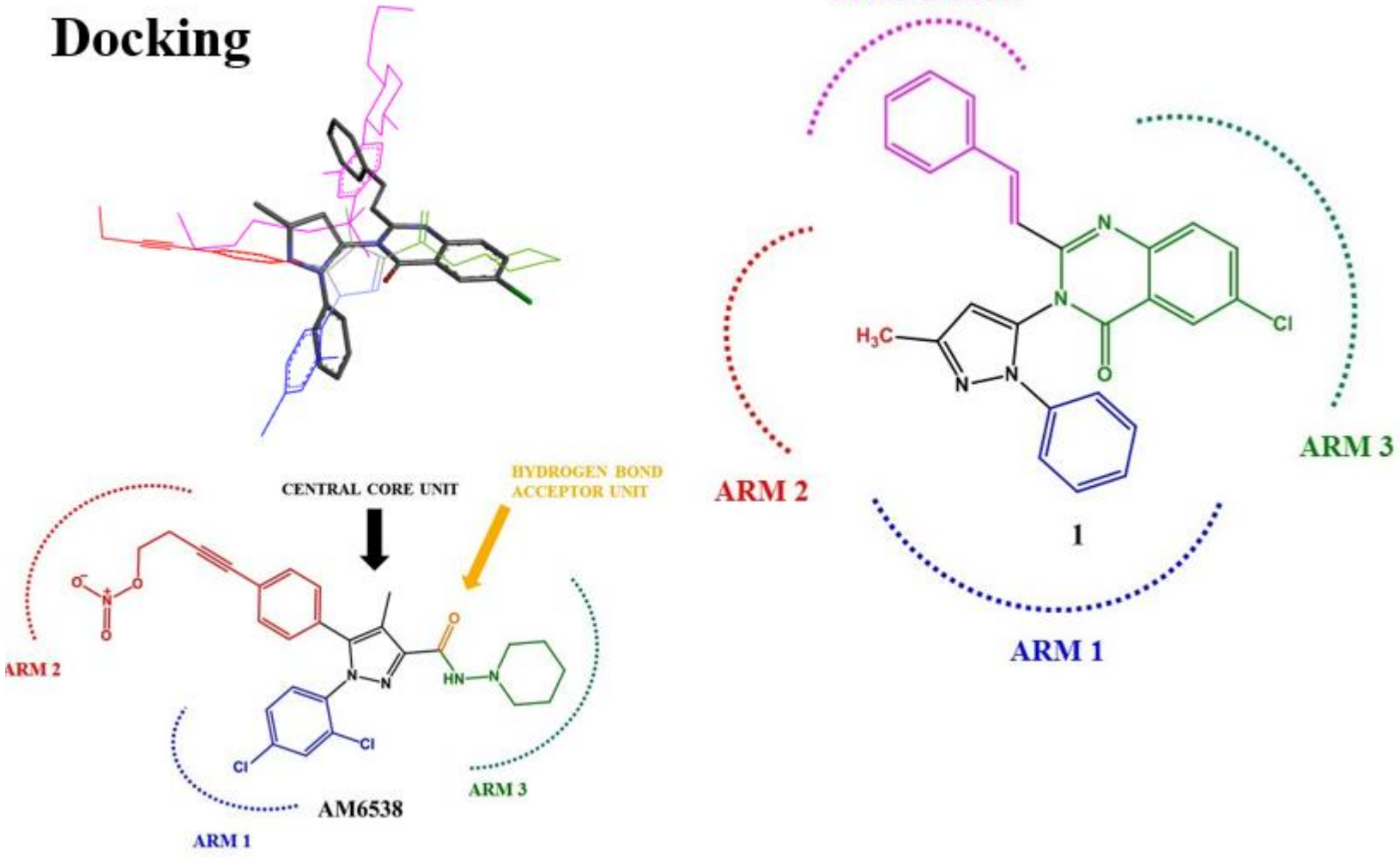
ELSEVIER

Original article

The role of (E)-6-chloro-3-(3-methyl-1-phenyl-1H-pyrazol-5-yl)-2-styrylquinazolin-4(3H)-one in the modulation of cannabinoidergic system. A pilot study

Fabiana Plescia[a,1], Fulvio Plescia[b,*,1], Demetrio Raffa[a], Angela Cavallaro[b], Gianluca Lavanco[c], Benedetta Maggio[a], Maria Valeria Raimondi[a], Giuseppe Daidone[a], Anna Brancato[b], Carla Cannizzaro[b]

Introduction



Introduction

ANIMAL EXPERIMENTAL MODEL

We wanted to evaluate in rats the ability to compound 1 to control the effects induced by the administration of CP 55.940 a known synthetic agonist on the CB1 receptor.

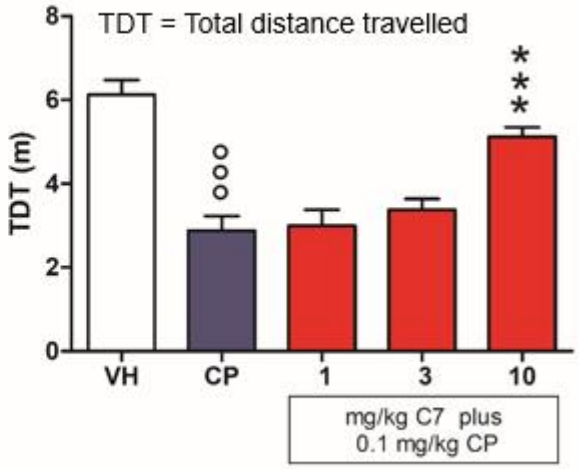
For this purpose, the animals were tested, by our pharmacological collogue, through the «TETRAD TASK», which allows to evaluate the pharmacological activity of compound with a cannabinomimetic action on the CB1 receptor.

- *Hypomobility*–***Open field test***
- Motor coordination–***Rotarod test***
- *Hypothermia* – ***Body temperature***
- *Pain resistance* - ***Hot-water immersion tail-flick test***

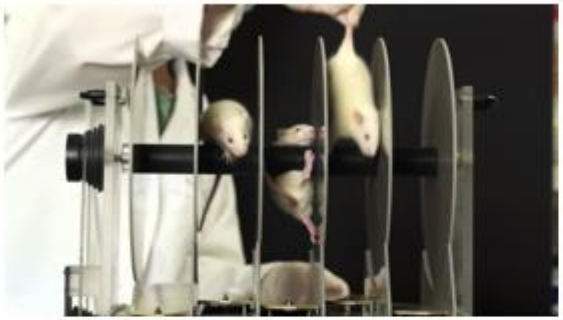
The study was carried out in accordance with the Italian legislation D.L. 116/1992 and the EU Directive 2010/63/UE, and approved by Committee on the Ethics of Animal Experiments. All efforts were made to minimize animal suffering

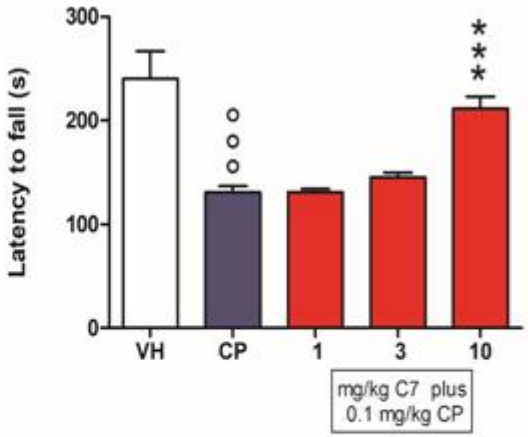
Results

Open field test
Assessment of mobility and behavioral



Rotarod test
Motor Coordination





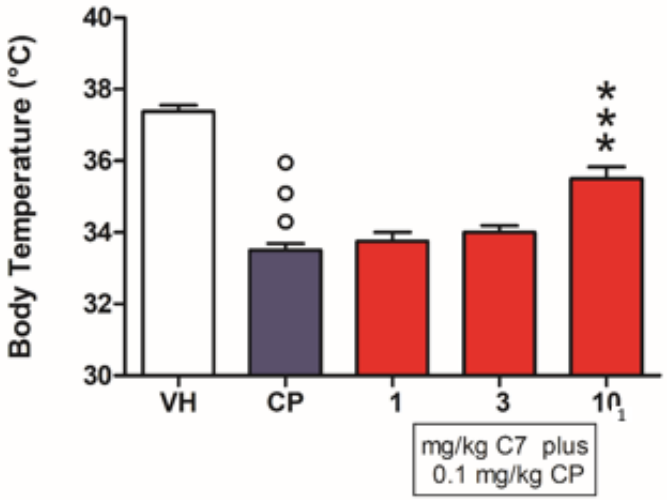
Evaluation of C1 activity on Open Field Test. C1 was able to counteract the effects of CP administration on locomotor activity and motor coordination. Each value represents the mean ± SEM of eight rats.

∗∗∗ $p < 0.001$ *vs.* CP. ooo $p < 0.001$ *vs.* VH.

Results

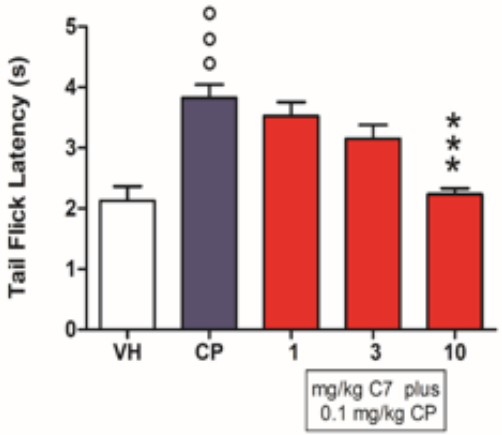
Body temperature

Decrease in temperature



Hot-water immersion tail-flick test

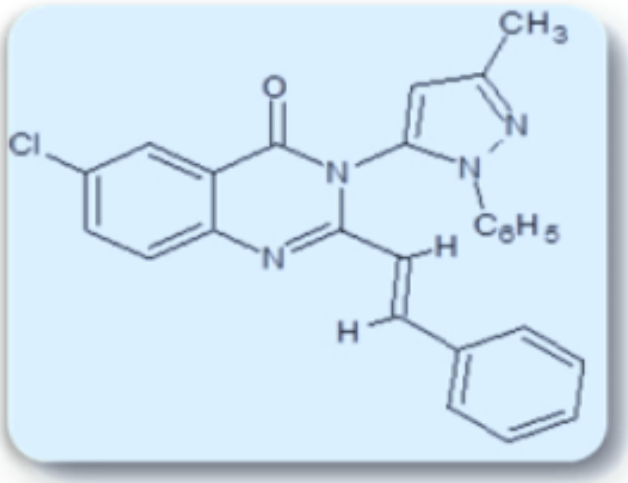
Pain resistance



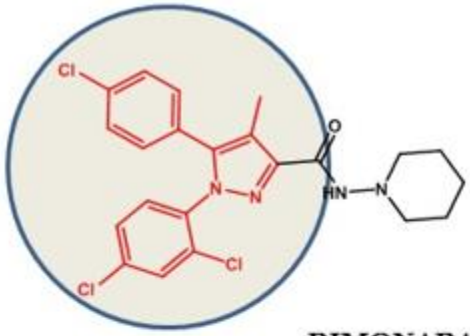
Evaluation of C1 activity on Body temperature and tail-flick test. C7 was able to counteract the effects of CP administration on locomotor activity.
Each value represents the mean ± SEM of eight rats.

∗∗∗ $p < 0.001$ *vs.* CP. ooo $p < 0.001$ *vs.* VH.

On the basis of these results, the second goal of my research was to modify the chemical structure of compound 1 in order to obtain new molecules that have a potentially greater binding affinity to the CB1 receptors site.

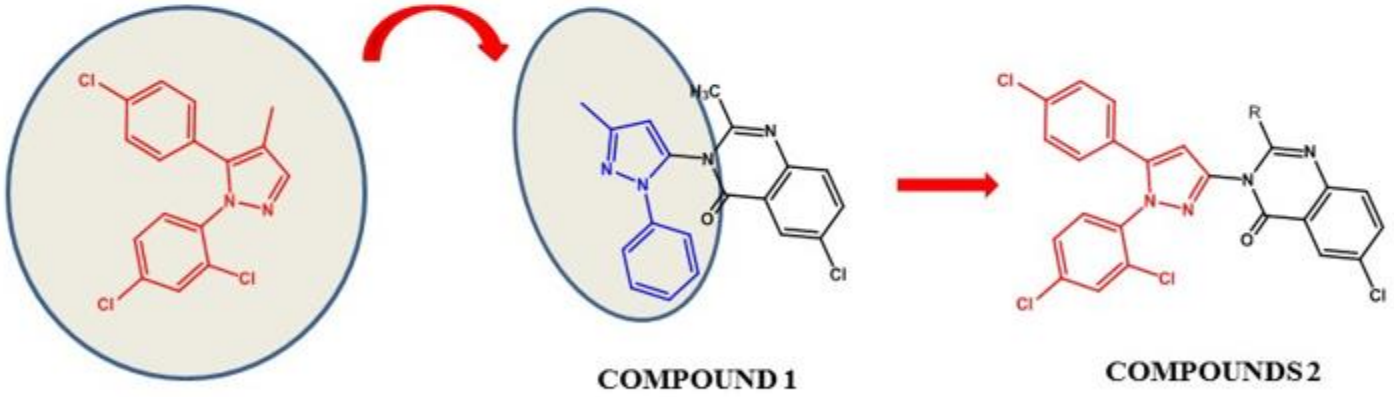


Results



RIMONABANT

New quinazolinones able to occupy the CB1 receptor in a manner more similar to Rimonabant.

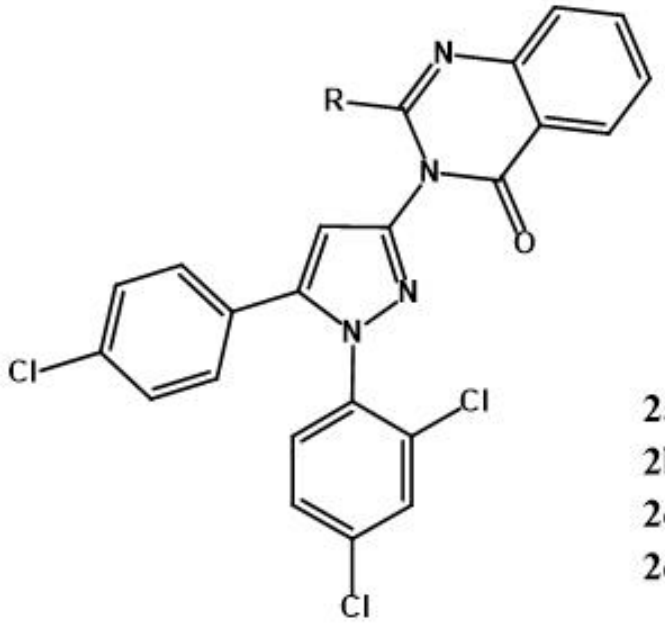


COMPOUND 1

COMPOUNDS 2

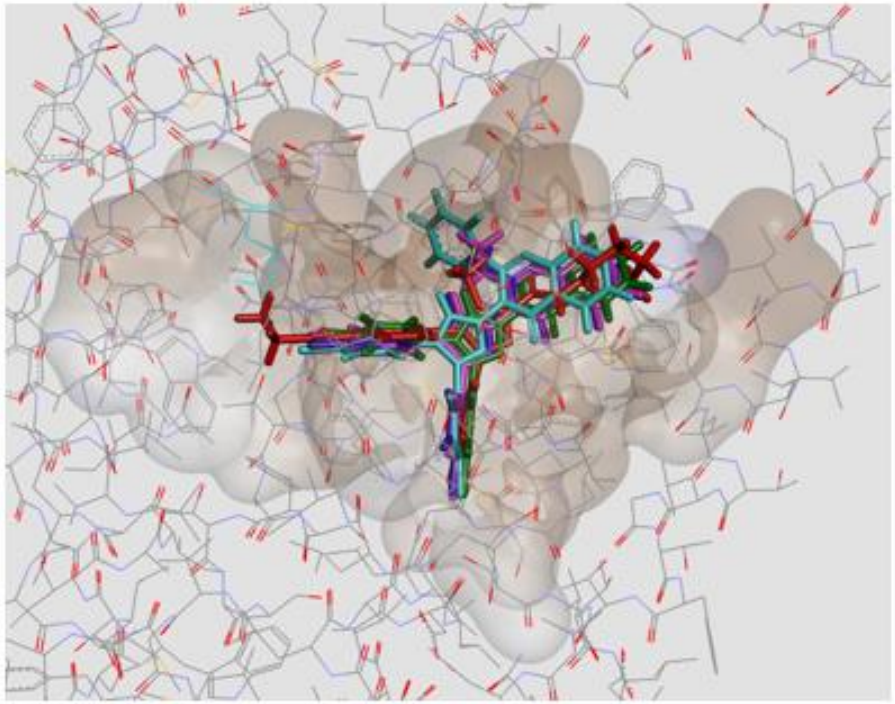
REPLACEMENT OF THE 1-FENIL-1H-PYRAZOL-5-YL NUCLEUS TO THE 1-FENIL-1H-PYRAZOL-3-YL NUCLEUS PRESENT IN THE RIMONABANT

Results



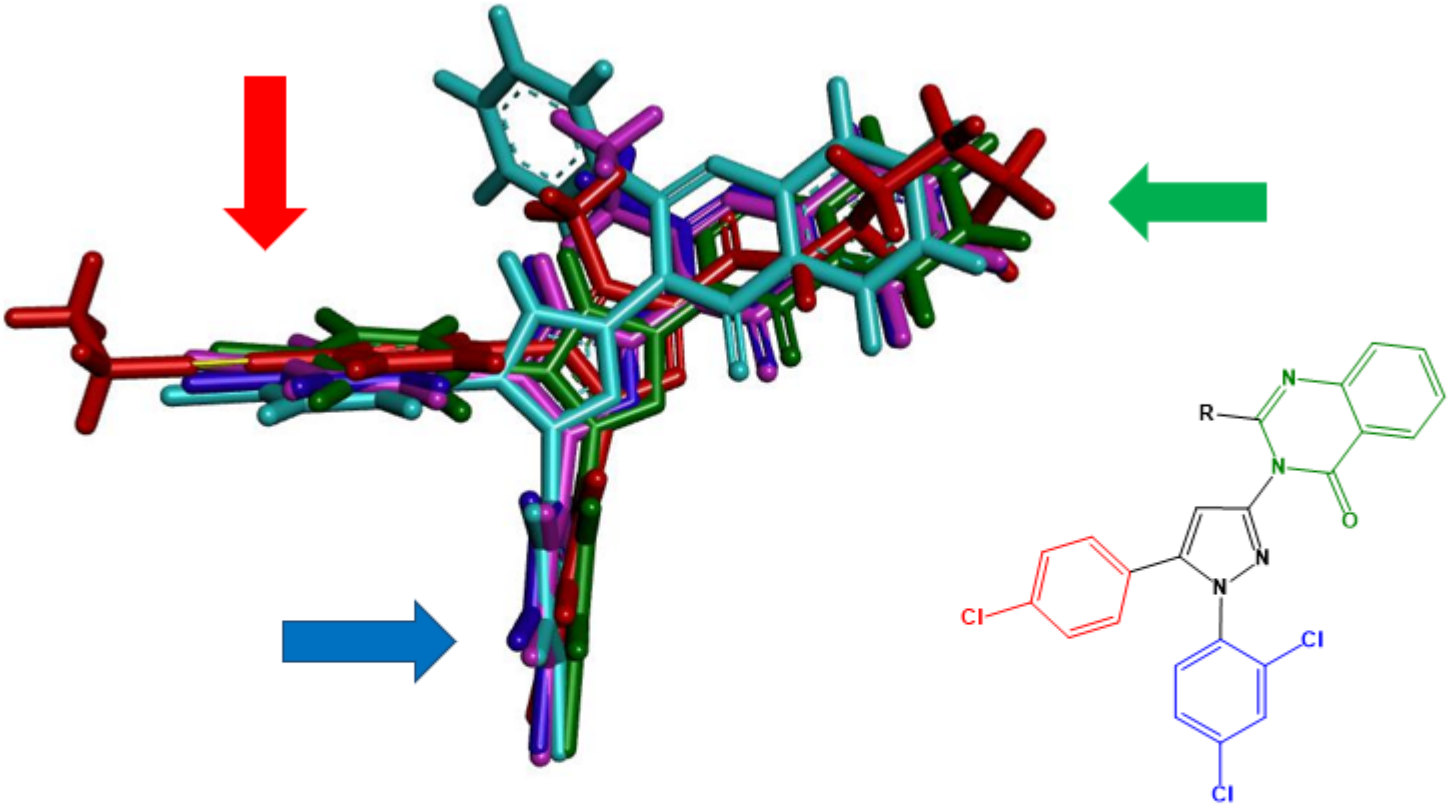
2a R=H
2b R=CH_3
2c R =C_2H_5
2d R=C_6H_5

Quinazolinones 2a-d Threedimensional structures were then built through the discovery studio program, optimizing their geometry



The results obtained from the docking analysis of the 2 a-d structures and of the AM 6538 (in red)how the compound 2 a-d occupy the same space in the binding site of the reference compound AM6538

Results

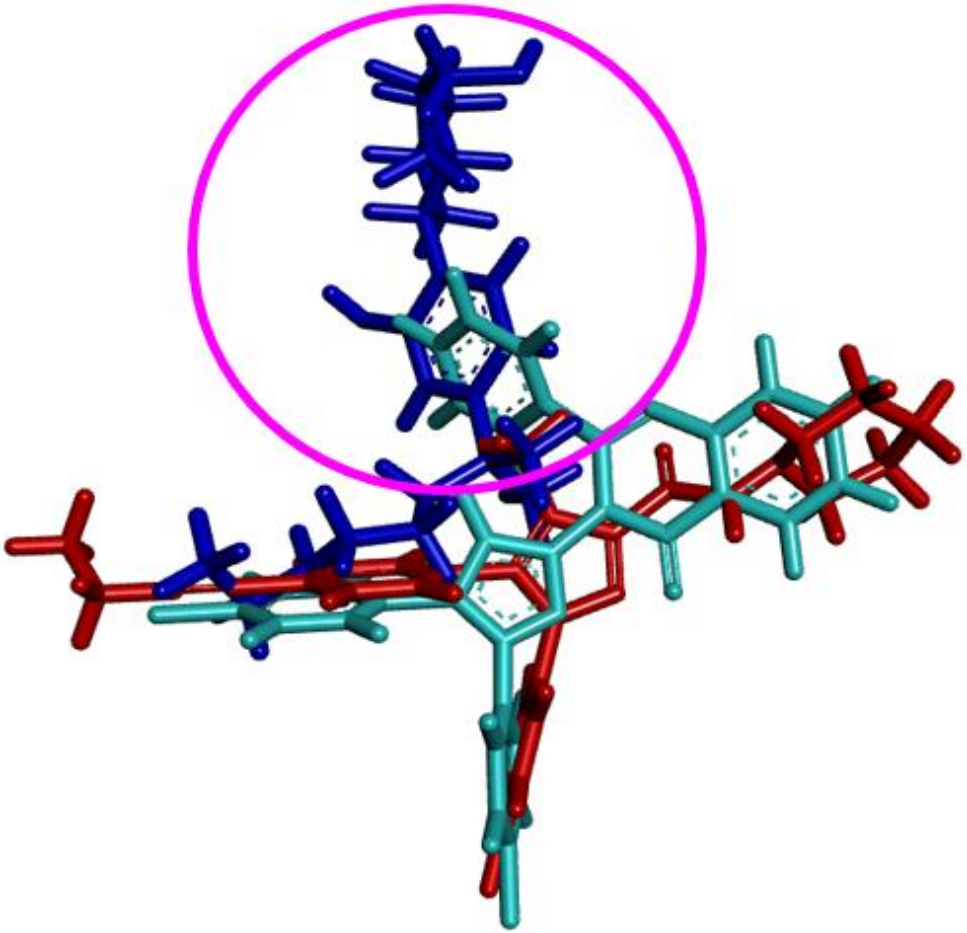


ARM 1: group N-pirazole-2,4-dichlorobenzene

ARM 2: group 4-chlorobenzene

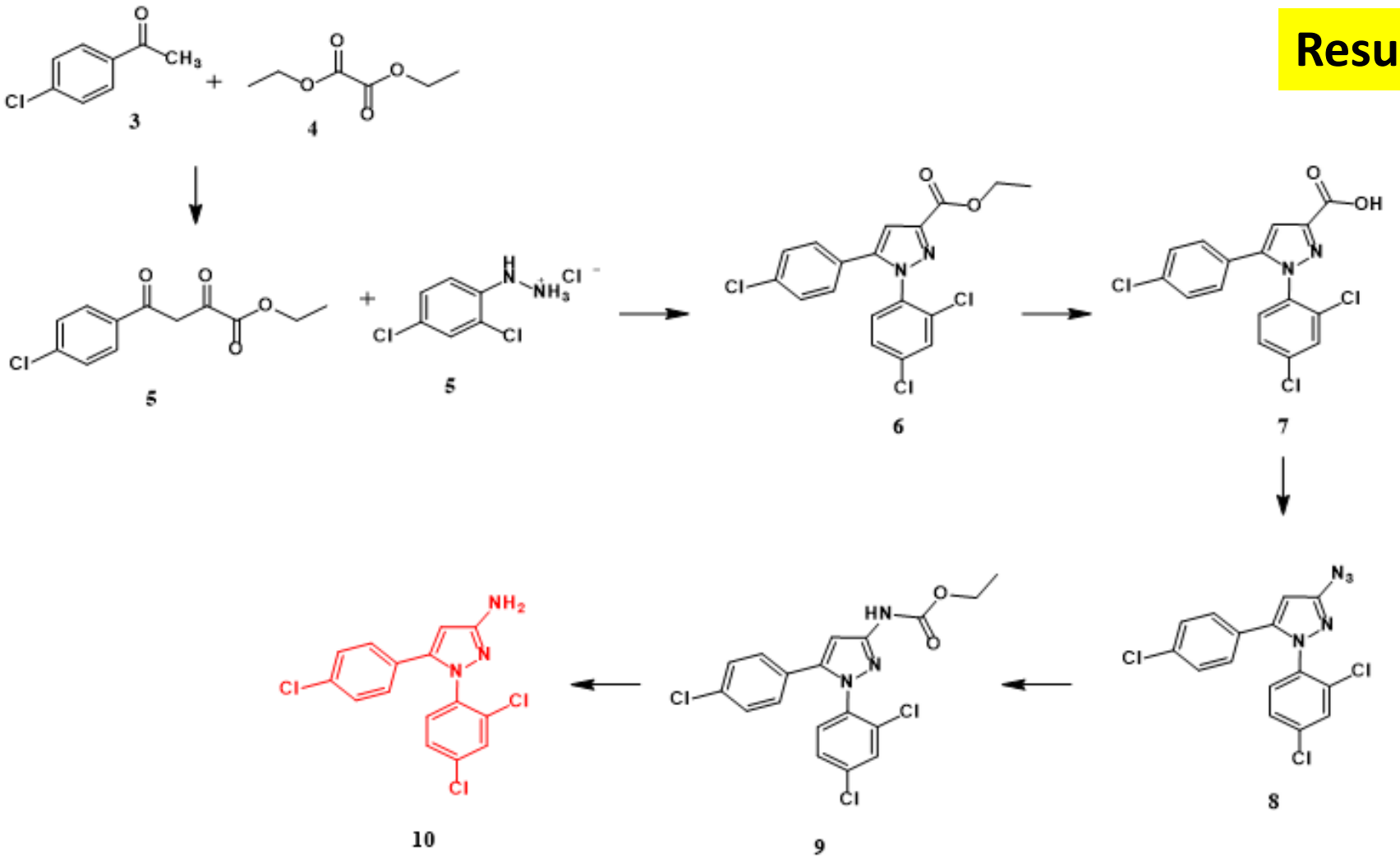
ARM 3: quinazolinones group bulky is essential on arm 3 for the antagonism of the CB1

Results

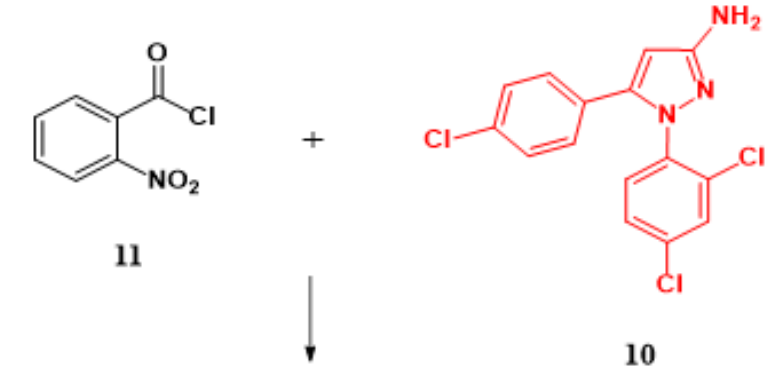


The 2-d compound (in light blu), also presents the styril moiety bonded to position 2 of the quinazolinones group which is positioned in the same space occupied by the agonist CP 55.940 (in blue)

Results



Results



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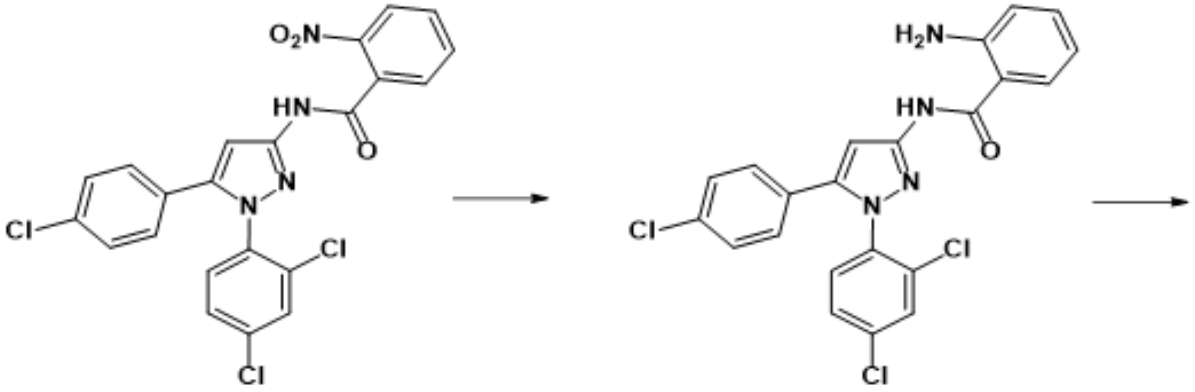

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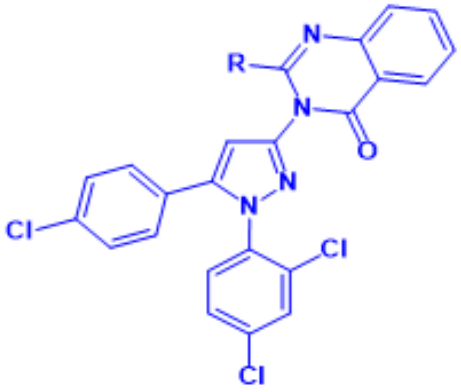


2a-d

R = H, CH_3, C_2H_5, C_6H_5

CONCLUSIONS

The antagonist CB1 we have synthesized is structurally similar to rimonabant

Compound 1 is active in counteracting the effects induced by the administration of the known synthetic agonist CP 55940 taken as a reference

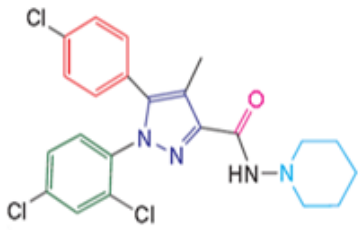
Compound 1 proved to be a good candidate for future therapeutic uses.

Its antagonism could be exploited for the treatment of addiction as well as for disease related to obesity

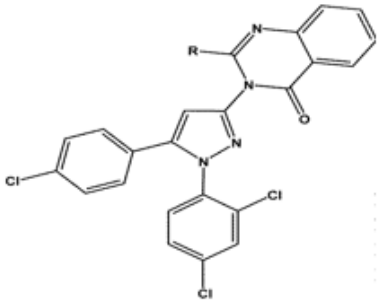
The docking study showed that 2 a-d derivatives occupy the same space and the same orientation of rimonabant in the cannabinoidergic site of the CB1 receptor making these molecules excellent candidates for antagonizing the activity of the aforementioned receptor.

Binding and pharmacological studies are currently underway in order to experimentally confirm the antagonist efficiency.

RIMONABANT



2a-d



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University of Palermo for financial support FFR project 2018-2020

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THANKS FOR YOUR KIND ATTENTION