Advances in Molecular Hybridization Approaches for Anticancer, Antiparasitic, and Antiviral Drug Development

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***Abstract*—Molecular hybridization is a new concept in drug design and development based on the combination of pharmacophoric moieties of different bioactive substances to produce a new hybrid compound with improved affinity and efficacy, when compared to the parent drugs. Additionally, this strategy can result in compounds presenting modified selectivity profile, different and dual mode of action and reduced undesired side effects. So, in this paper, we described several examples of different strategies for drug design, discovery and pharmacomodulation focused on new innovative hybrid compounds presenting analgesic, anti-inflammtory, platelet anti-aggregating, anti-infectious, anti-cancer, cardio and neuroactive properties.**

I. INTRODUCTION

The process of drug discovery for diseases with complex pathogenic factors has been facing significant challenges since the traditional " one molecule, one target" drug discovery paradigm is not adequately addressing many diseases. The architecture of new drugs with better physicochemical properties like appropriate absorption, distribution, metabolism, and excretion, effective pharmacological activity and less toxicity is also a herculean task. Besides the exploitation of new targets, there is another approach in drug discovery which involves combining two or more pharmacophore or drugs into a single molecule. The review article presents insights into molecular hybridization in designing drugs.

The molecular hybridization (MH) is a strategy of rational design of new ligands or prototypes based on the recognition of pharmacophoric sub-unities in the molecular structure of two or more known bioactive derivatives which, through the adequate fusion of these sub-unities, lead to the design of new hybrid architectures that maintain pre-selected characteristics of the original templates. Considering the use of known template substances, already evaluated concerning the physicochemical and pharmacological features, toxicity and mechanism of action, it is possible the generation of extensive chemical libraries, constituted by hundreds or even thousands of homologous molecular hybrids, bringing a high level of accumulated information, e.g. structural requirements, ligand-protein interaction mode, site ligand receptor interactions and quantitative structure-activity relationships, which tends to become faster and more efficient the development of new drugs. On the other hand, if the degree of template-hybrid homology is either low or inexistent, the discovery of new lead-compounds should be made by massive screening of the generated chemical library.

Molecular hybridization is a molecular modification approach to obtain multiple-ligands/ compounds with pharmacokinetic advantages over concomitant administration of two different drugs.

II. TYPES OF MOLECULAR HYBRIDIZATION

Drug-drug molecular hybridization which involves hybridization between the drugs;

A. Directly linked drug-drug molecular hybridization: Merged type

Fused type

Cleavable conjugate

B. Indirectly linked drug-drug molecular hybridization: Linked by a flexible linker

Linked by a rigid linker

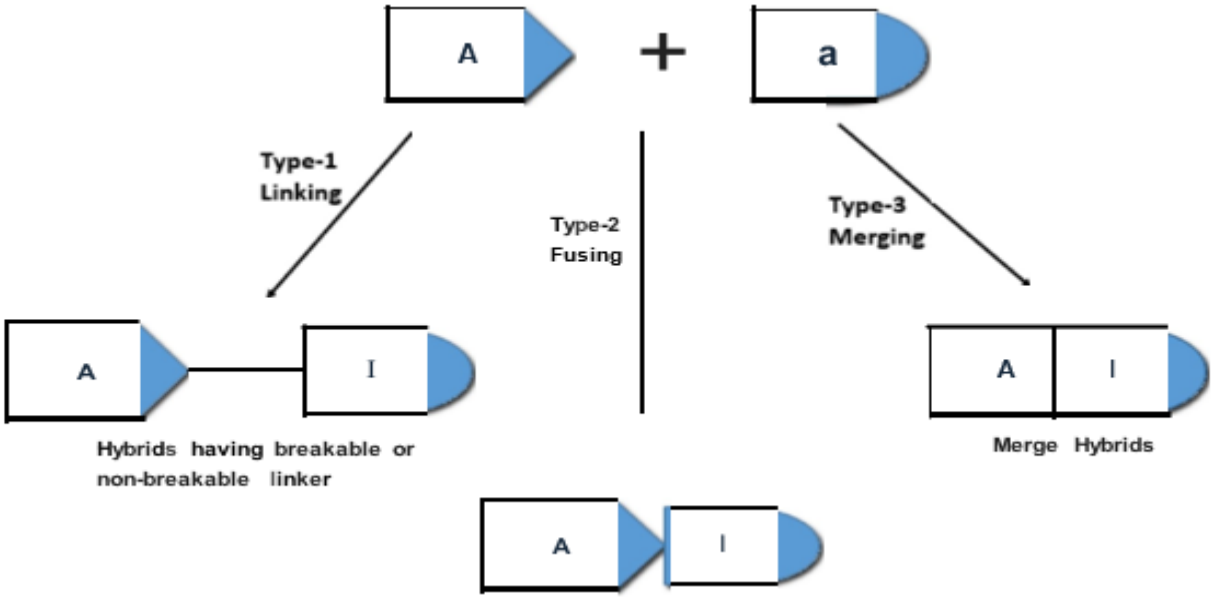
Pharmacophore hybridization which involves hybridization between pharmacophore;

A. Directly linked pharmacophore hybridization Merged type

Fused type

B. Indirectly linked pharmacophore hybridization Linked by flexible linker

Linked by a rigid linker



Fused Hybrids

Types of Hybridization

Opioids as well NSAIDS (Nonsteroidal anti-inflammatory drugs) have several adverse effects since ancient times like Gastro-intestinal itching, constipation, and most importantly dependence and resistance. So as to avoid these adverse effects associated with NSAIDS and opioids, an attempt has been made on the concept of Non-Opioid-Opioid hybrid drugs, in which two pharmacophores, viz. one non-opioid and another opioid are linked together with a spacer moiety, that are expected to dissociate and act independently, when introduced in-vivo.

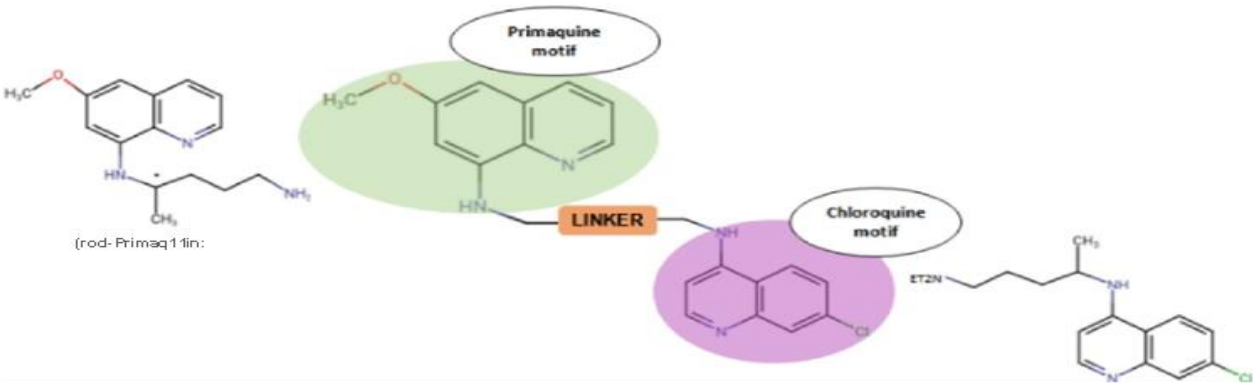
SYENTHETIC WORK:

NOVAL HYBRID MOLECULE AGAINST MALARIA (2015)

The drugs primaquine (1) and chloroquine (2) have been successfully used in combination for the weekly chemoprophylaxis against malaria during the Vietnam War. Both are approved and low-priced drugs, and they are active against most stages of the plasmodium infection in humans. Primaquine (1) has a very short half-life and accumulates potentially harmful metabolites. However, primaquine has been safe and an effective prophylactic agent for nonpregnent women and travelers with a normal glucose-6-phosphate dehydrogenase level; in endemic malaria regions up to 20% of the patients on average suffer from such a deficiency. Chloroquine has a long terminal half-life with a higher risk to develop resistant strains under sub therapeutic concentrations and is a safe medicament in therapeutic doses. In addition, primaquine can reduce the chloroquine efflux transport (a resistance mechanism) by binding to the PfCRT channels and support the activity of chloroquine.

Chemistry;

Hybrid molecule primaquine and chloroquine pharmacophore were designed and synthesized with different types of linkage; with an authentic linker part, without a linkage moiety, with an elongated piperazine diamine or diamide linker bond, and with an aromatic-type linkage.

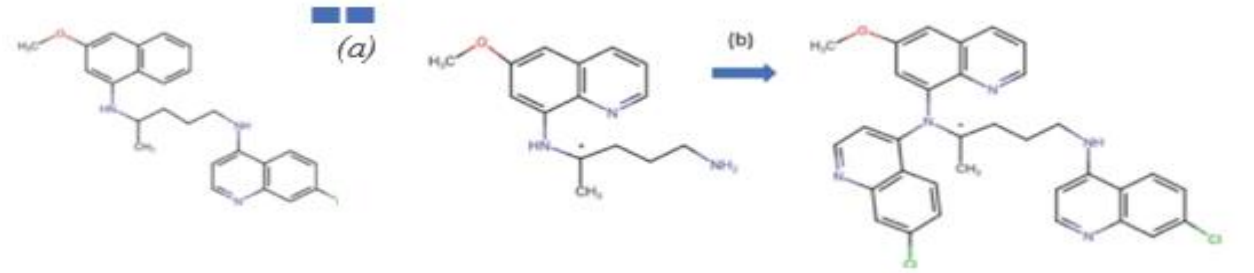


(roq- **thloroquin<e**

The first component of the hybrid drugs (rac) - primaquine and its pharmacophore moiety (in green) as well as the second drug (rac) - chloroquine and the corresponding pharmacophore structure (in blue).

Primaquine-Chloroquine Hybrid Molecules with Authentic linkage

The first dual molecules were synthesized with an authentic linkage part in order to avoid additional structural moieties on the pharmacodynamics and pharmacokinetics properties of the hybrid compounds. Earlier examples of primaquine derivatives showed that the linkage of primaquine can be performed via the primary amine without loss of activity. Therefore, hybrid structures of primaquine and chloroquine moiety were synthesized with a linker using original side chain of primaquine, with a pharmacophore ratio of 1: 1 and 1: 2 of primaquine to chloroquine. Since a Buchwald-Hartwig amination protocol leads merely to low yields (a decomposition of the palladium catalyst was observed), a nucleophilic substitution reaction of primaquine and 4, 7-dichloroquinoline was performed at 120c under neat conditions to obtain the hybrid molecules (rac)-5(82% yield) and (rac)-6 (77% yield).



***(rac)* (82%)** **(rac)-primaquine** ***(roe)* (77%)**

Synthesis of the primaquine-chloroquine hybrid molecules (radio 1: 1 and ratio 1: 2) with an authentic linkage part of primaquine.

Reagents and conditions: (a) 4, 7-dichloroquinoline (0.5 equivalents), heat 120° C ;

(b) 4, 7-dichloroquine (3 equivalents), heat 120° C

Synthesis, Trypanocidal and Antitumor activities of naphthoquinone-based 5-iodo-1, 4-disubstituted-1, 4-and 1, 5-disubstituted-1, 2, 3-triazoles :(2016)

Molecular hybridization based on the combination of pharmacophoric moieties has emerged as an important strategy for the development of new drug that are able to act as multitarget ligands. As suggested by Cavalli and bolognesi, multitargets ligands are a logical alternative for preparing small molecule that are able to interfere in vital targets in parasites 'metabolism. Modulating multiple protein targets

simultaneously can be beneficial for treating complex diseases. Recently, 2 phenoxy-1, 4-napthoquinones were identified as multitarget ligands.

Chemistry
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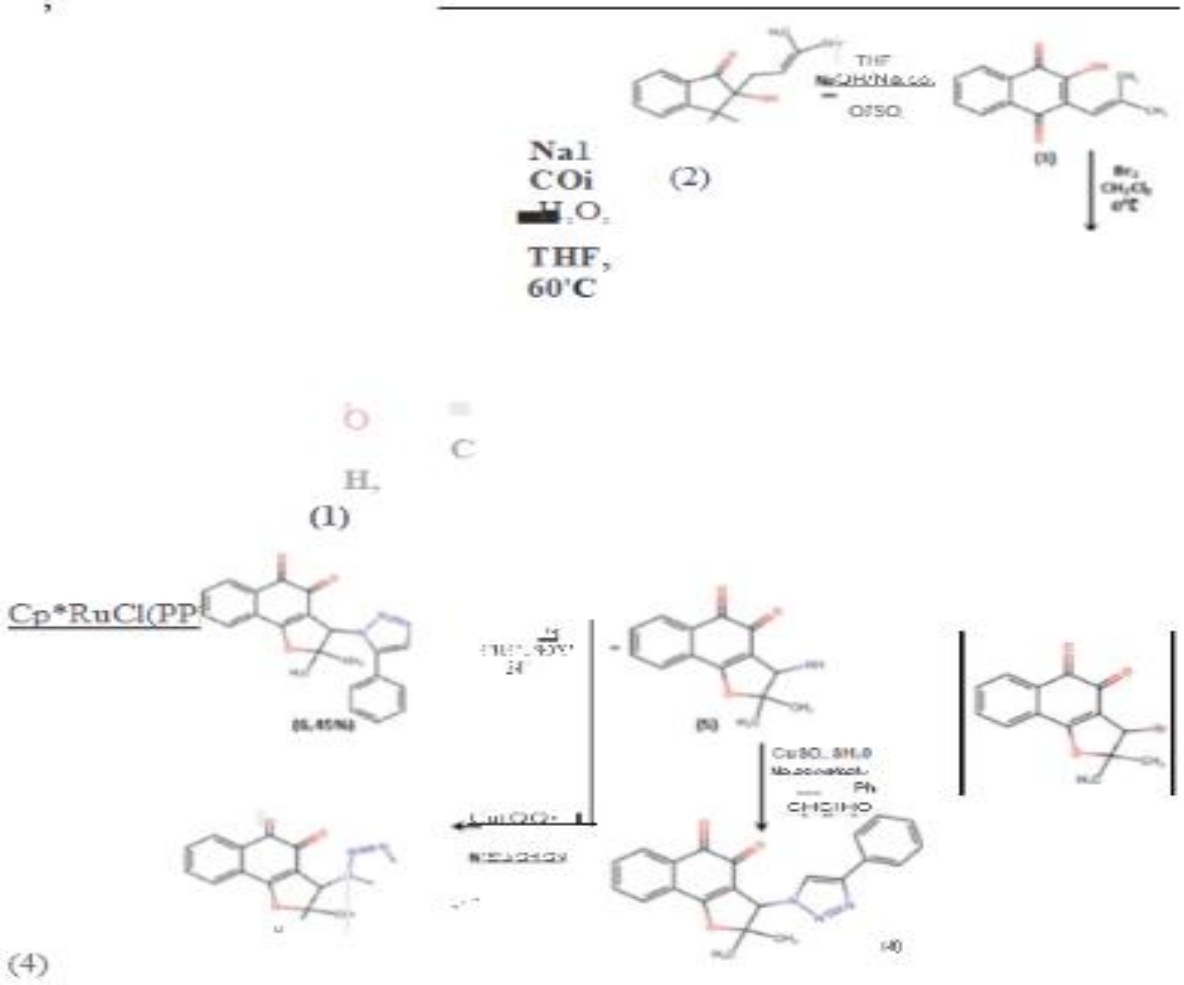
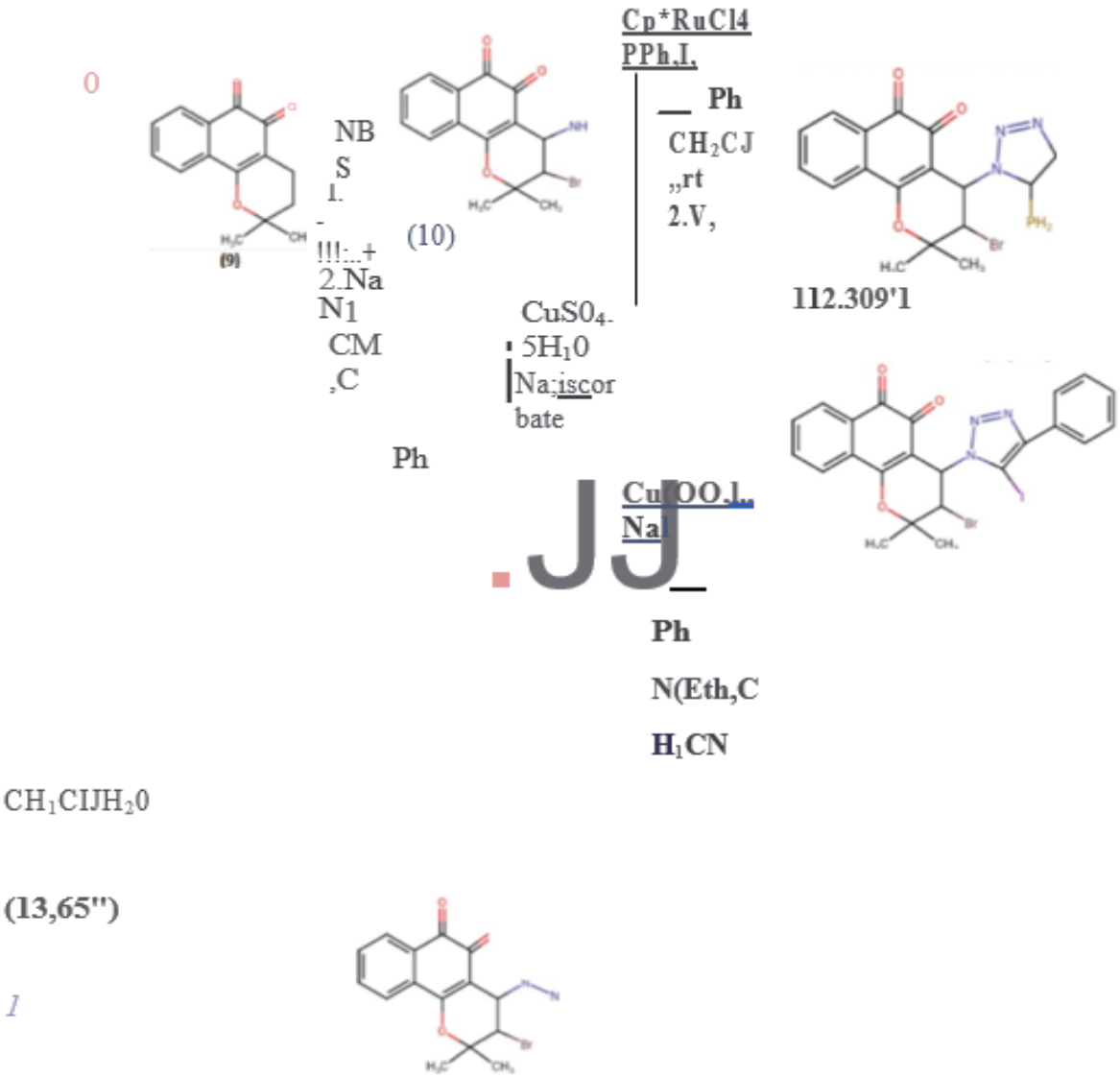


Synthesis of nor-f3-lapachone derivatives 6-8.

The synthesis of novel lapachone-based triazole were accomplished by using the methodologies discussed above. The first classes of compounds, ortho-quinone, were prepared from a naturally occurring naphthoquinone lapachol) (1). Initially, 1 was used for preparing nor-lapachol (3) by Hooker oxidation reaction. With compound 3 in hands, the reaction with bromine in dichloromethane afforded 3-bromo-nor-J3-lapachone (4), and dichloromethane provided 5 as previously described (scheme1). The click adducts 6 and 7were obtained from the action of Azide-nor-J3-lapachone (5) and phenyl acetylene .the structure of the product was determined by detailed spectral analysis. However, the radiochemistry of the 1, 5-disubstituted triazole 6 was also further confirmed by single crystal X-ray analysis.



(II)

Synthesis of J3-lapachone derivatives 11-13

8-lapachone-based 1, 5-disubbstitutedd- (12) and 5-iodo-1, 4-disubstituted-1, 2, 3-triazoles {13) were also prepared from 13-lapachone (9). Previously, our group has obtained 3-bromo-4-azide-13-lapachone (10) for the synthesis of triazole derivative 11. Compound 12 was synthesized from 10 in 30% yield and the structure was also re-confirmed by crystallographic methods (scheme 2). The iodotriazole 13 was synthesized in moderate yield and isolated as yellow crystalline solid.

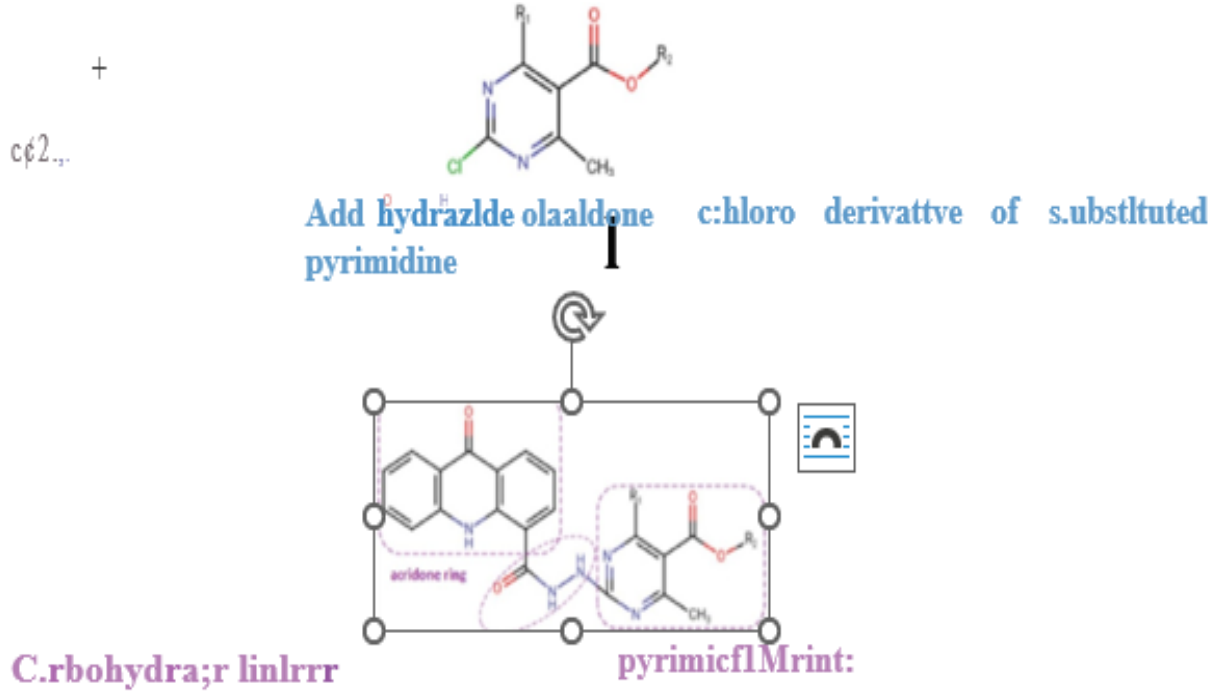
Acridone-pyrimidine hybrids molecule against cancer cells (2017)

Cancer is one of the leading cause of death in the world till today. Advancement of technology, climate change and life style has aggravated the situation of cancer as a disease, due to its abnormal cell mutation that can cause in any human at any given time through multiple mechanisms in different environment compared to normal health human cell. If a drug molecule acting against cancer has the ability to reach target site and specific to cancer cell,

capable of binding to multiple target might be beneficial and may also prevent in acquiring drug resistance to combine Acridone and pyrimidine scaffolds and synthesized a series of novel hybrid molecules which would have ability to display anticancer activity by interacting with multiple targets. The linker used for the conjugation of Acridone with pyrimidines was an hydrazide. Hydrazide and substituted hydrazides have been used as versatile building blocks for

the conjugation of heterocyclic systems. Carbohydrazide contaiing molecules have shown diverse pharmacological activities. Hydrazide of Acridone is synthesized by treating ester of Acridone with hydrazine hydrate. The study also helps in identifying the potential of Acridone with hydrazide linker against sensitive and resistant cancer decrease the ability of cancer cells acquiring resistance.

Chemistry;



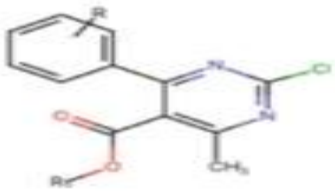
Design approach of" Acridone-pyrimidine" hybrids

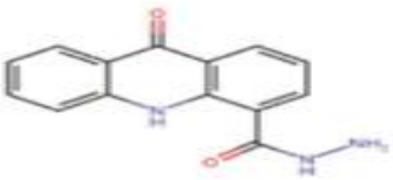
Synthetic scheme for hybrid molecules of Acridone with ethyl/methyl ester of substituted pyrimidines:

Then Acridone-pyrimidine hybrids were synthesized by linking carbohydrazide of Acridone with different

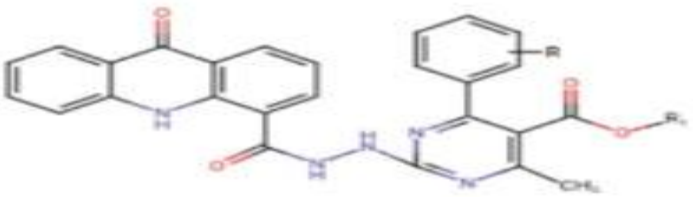
Anticancer activity has not been reported for hybrid structures of Acridone nucleus with substituted pyrimidines and Acridone hydrazide. Synthesis of Acridone starts with the Ulmann condensation of halobenzoic acid and anthranilic acid in the presence of copper as catalyst. Cyclization with polyphosphoric acid yields substituted Acridone-1-carboxylic acid. Further esterification and treating with hydrazine hydrate gives carbohydrazide of Acridone in the presence of solvent ethanol. Synthesis of pyrimidine ring started with the well reported Biginelli reaction by one pot synthesis using monochloroacetic acid as catalyst under solvent free conditions gave good yields. Two manuscript accepted 9 series of pyrimidine were prepared using substituted Benzaldehydes, urea and ethyl acetoacetate (Sa-Sh) and substituted Benzaldehydes, urea and methyl acetoacetate (8a-8g). Further oxidation with 60 HNO3 yielded 6a-6h and 9a-9g. Later chlorination with phosphorus oxychloride yielded different chloro substituted pyrimidine derivatives 7a-7h and 10a - 10g.

chloro substituted pyrimidines in acetonitrile in the presence of anhydrous potassium carbonate, yielded the hybrid derivatives 11a-11h and 12a-12g.





R1: -CH1CH1(70-'71t)
: -Ob (10a,-1Qc) !



Ri= ·CH,CH,(11>11h)
: -CH, (12•·1:ZS)

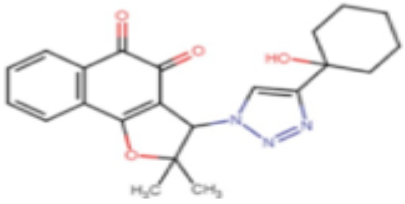
Reagents and Conditions: (1) CH3CN, anhydrous K2CO3, Reflux 4-6 h.

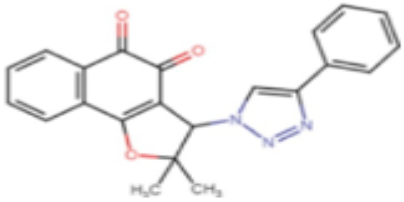
Synthetic scheme for hybrid molecules of Acridone with ethyl/methyl ester of substituted pyrimidines.

Synthesis and Evaluation of the cytotoxic activity of Furanaphthoquinones Tetherd to lH-1,2,3-Triazoles in caco-2,calu-3,MDA-MB231 cells. (2018)

Introduction:

There are several synthetic and natural low molecular weight. Naphthoquinone with many application in various scientific and technological fields. In this sense, Quinone' s have already been described with a diversity of bioactivities such as anticancer molluscicides, antiparasitics, antimalarial, leischmanicides, anti-inflammatory, antifungal, antimicrobial and trypanocydal.Although the scaffold Quinone' s and 1,2,3-triazoles are of major importance separately, molecules containing this two nuclei only have been studied in recent year against various diseases showing that this molecular combination have great potential synergism, i.e. , napthaquinone-1,2,3-triazole conjugates 1and 2 with good antitumor activity.





1 2

ICSOO, 43 µM
Melanoma (
MDAMB-435)

ICSOO, 75 µM
Leukemia cell (MOLT)

Example of hybrid napthaquinone-1, 2, 3-triazole with high activities in cancer.

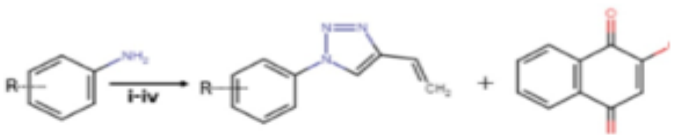
On this synthesis of biological active Quinone, we became interested in synthesis and antitumor evaluation of hybrid napthaquinone-1, 2, 3-triazoles. Among the mentioned hybrids, a series of eight 2-(1-phenyl-1 H-1,2,3-triazoles-4-yl)-2,3-dihydronapthol[1,2-b]furan-4,9-dione(6a-h) and eight2-(1-phenyl-1H-1,2,3-triazole-4-yl)-dihydronapthol[2,3-b]furan-4,9-dione (7a-h) were

synthesized and screened against MDA-MB231,Caco-2 and Calu-3 human cancer cell lines and also evaluated there cell viability on Vero cells.

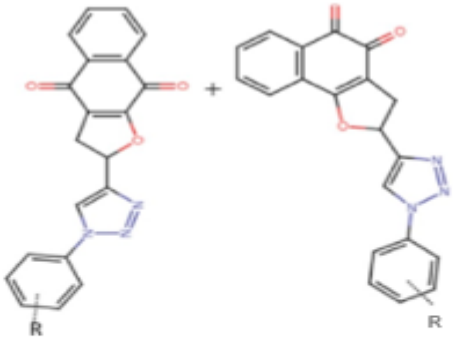
Chemistry:

Initially, the 4-vinyl-1H-1, 2, 3-triazoles 4a-h were prepared according to the reported methodology from the protocol based on a Huisgen 1, 3-dipolar cycloaddition. The reaction between several aryl azides (from anilines 3a-h) and propargylic alcohol was catalysed by Cu(I) providing only the 1,4-disubstituted regioisomer, followed by partial oxidation of the alcohol to generate 4-carboxyldehyde-1H-1,2,3- triazole. The wittige reaction allowed to prepare the 4-vinyl 1H-1, 2, 3-triazoles (4a-h) with overall yield ranging from 80-90%.

The reaction proposed to synthesize the hybrid napthaquinone-1, 2, 3-triazoles was a radical electrocyclic reaction between 2-hydroxy-1, 4-napthoquinone 5 and the 4-vinyl-1H-1, 2, 3-triazoles (4a-h) that have been reported in the literature by several authors. Thus, the reactions were carried on in the presence of excess cerium (IV) ammonium nitrate as one-electrone oxidizing agent, dried acetonitrile, at low temperature and monitored by thin layer chromatography (TLC). After three hours of reaction time it was observed total consumption of 5 a remaining small amount of unreacted 4 and the formation of two more polar products. after the evaporation of the solvent and purification of the reaction mixture by column chromatography using chloroform/ethyl acetate gradient as eluent, followed by spectroscopic analysis of each synthesized compound, it was possible to identify the compounds 6a-h (yellow solid compounds) and 7a-h (orange solid compounds) considering the concentration of 5 in these isolated two isomers the yield range from 40-59%. In the table 1 are the described ratio of between 6:7 and the overall.



3a-h 4■·h, 80·90 % 5



6a·h 7a-h

(i) NANO2, HCL,) 0-5° C, 30 min then NAN3 (aq) 1h

(ii) Propargylic alcohol, CuSO4.H2O.sodium ascorbate, tBuOH: H2O, RT, 24h.

(iii) IBX, DMSO, 24H

BrCH3PPh3,NaH,THF,20 min, 75° C, ultrasound, then triazole aldehyde, RT, 30-40 min.

(v) CAN, NaHCO3, acetonitrile, 0° C to RT 3h.

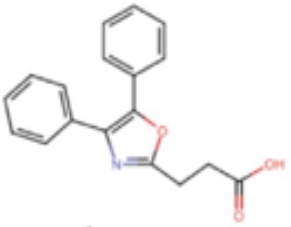
The hybrid napthaquinone-1,2,3-triazole 6a-h and 7a-h were screened in vitro activity against MDA-MB231,Caco-2 and Calu-3 human cancer cell lines and by the absence of toxic effects (cell viability 70%) on Vero cells, using MTT reduction assay.

Synthesis of Novel acylhydrazone-oxazole Hybrids and docking studies of SARS-CoV-2 Main protease (2020)

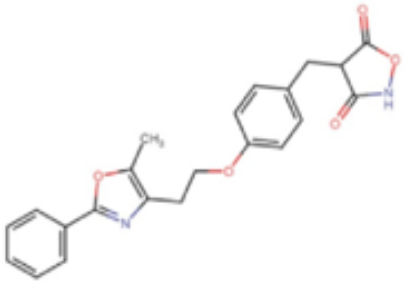
Introduction:

Both 1, 3-oxazole and acylhydrazone based molecule are of biological and pharmaceutical relevance as they are considered as pharmacophoric subunits. Some examples of drugs or drugs candidates

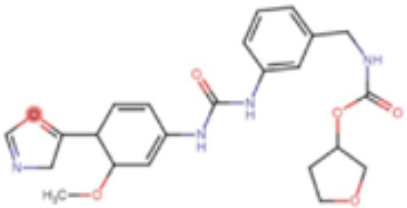
containing this pharmacophoric. also, the biological diversity of acylhydrazone is due to the nitrogen atom of the azomethine group having the lone pair of electrons in its sp^2 hybridized orbital and to the presence of geometrical isomers E and Z of azomethine group



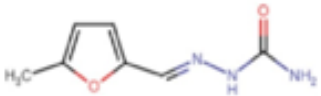
1
Oxaprozin
I non-steroidal anti-inflammatory)



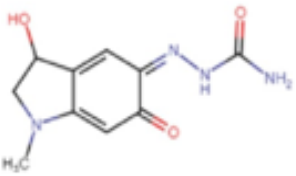
2
Reglitazar
(Diabetes treatment)



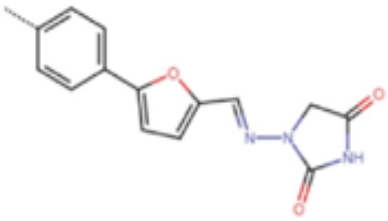
3
Merimepodib
(Hepatits c treatment)



4
Nitrofurazone
(antibacterial)



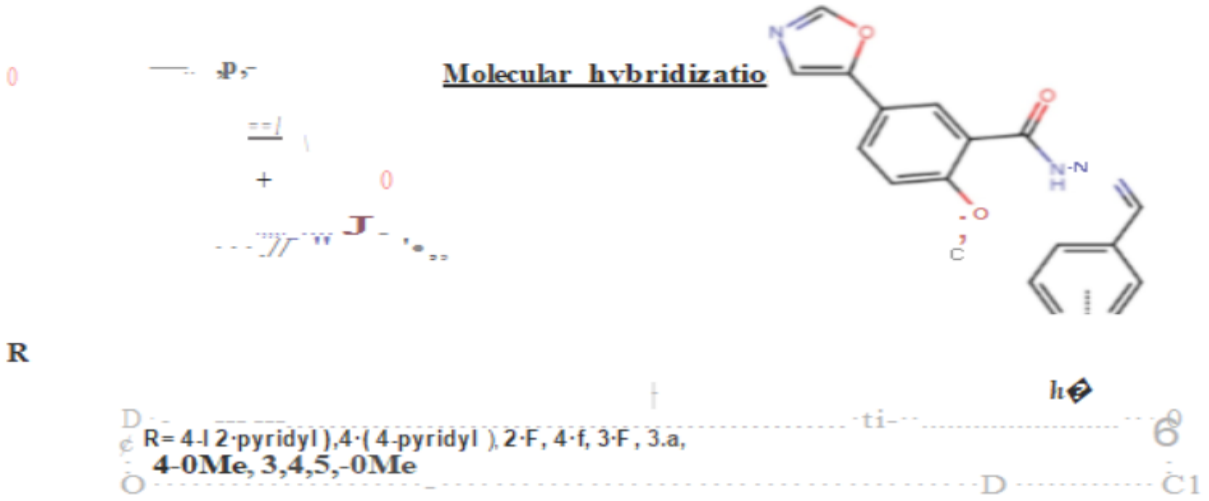
5
Carbazochrome
(hereditary hemorrhagic treatment)



6
Dantrolene
(malignant hyperthermia treatment)

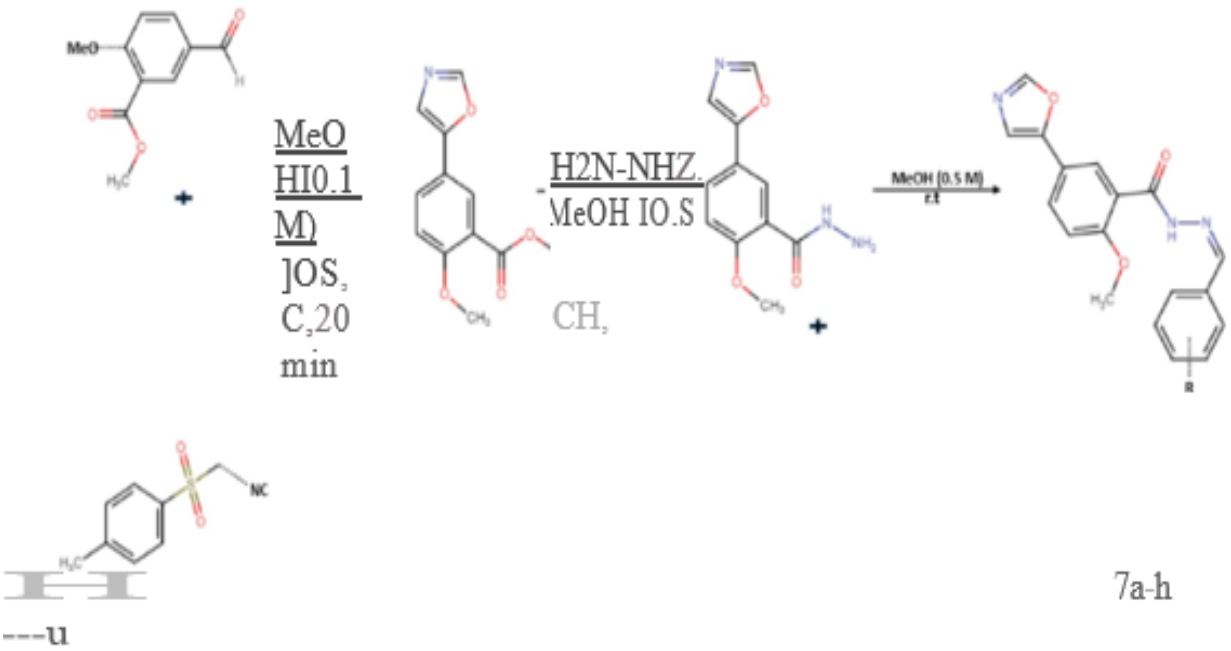
Drugs and Drugs candidates containing 1, 3-oxazole and acylhydrazone scaffolds.

On the other hand, molecular hybridization is a novel strategy within medicinal chemistry that has its main objective the search and efficient development of new candidate drug molecule. It is based on the combination of two or more Pharmacophore of different bioactive substance to produce a hybrid compound with better biological activities and pharmacokinetics profile when compared to parent drugs hybrid molecule can be prepared by linking the pharmacophoric directly or with spacer agents. Herein, we report the novel synthetic strategy to obtain the acylhydrazone-oxazole hybrids by using the molecular hybridization strategy and based on the pharmacological relevance of 1, 3-oxazole and acylhydrazone derivatives.



III. CHEMISTRY

The novel acylhydrazone-1, 3-oxazoles hybrids were synthesized via three step reaction. The first step reaction is the global key step due to the formation of first pharmacophoric fragment (1, 3-oxazole moiety) via a van leusen reaction by the previously described method by research team. The reacting TOSMIC and the bifunctional aldehyde component 8 that contain methyl ester group provided intermediate methyl ester-1, 3-oxazole 10 in good yield. The second step is the hydrazinolysis reaction of methyl ester group by using hydrazine hydrate to give the intermediate hydrazide-11, 3 oxazole 12 in moderate yield. Finally, the third step was the Schiff condensation of hydrazide-1, 3-oxazole 12 with different functionalized aldehydes 13 to give the novel acylhydrazone - oxazole hybrids in moderate to good yields. In addition, fluorinated aromatic aldehydes were used in the given biological and pharmacological relevance of fluorine in medicinal chemistry.



C.Ol11)0llld	R	Yield
7a	4-(2-pyridyl)	59%
7b	4-(4-pyridyl)	36%
7c	2-F	86%
7d	4-F	7.Jllo
7e	4-0Me	*7Z'lo*
7f	3-F	65%
7g	3-0	81%
7h	3,4,5-tri-Ovle	85%

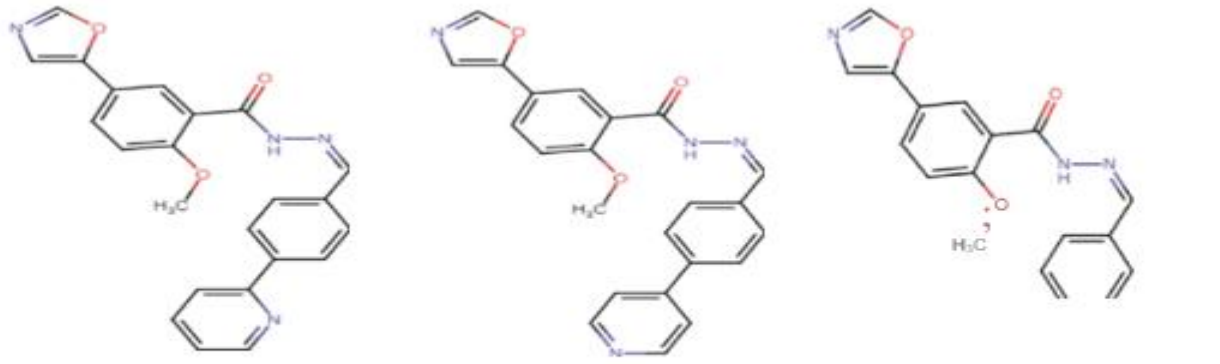
General synthetic route for the synthesis of acylhydrazone-1, 3-oxazoles hybrids

Moreover, to explore the possible mode or modes of interactions of compounds against the Mpro of SARS-CoV-2, molecular docking studies were carried out. N3 was the reference compound as a co-crystalized ligands in the receptor (PDB:6LU7) which has the active site in the position His41 and Cyst145, as some key residues for the Mpro protease inhibition. The predicted free energy constant values are listed.

Table 1. Result of docking studies of the tested acylhydrazone-oxazole hybrids.

C.Ol11)0llld	.6. G(kcal/irol)	Ki(µM)	pKi
7a	*-1.n*	219	5.66
7b	-7.76	205	5.69
7c	-7.53	3.04	5.52
7d	-7.21	5.14	5.29
7e	*-7.'lB*	4.6	5.34
7f	-7.58	279	5.55
7g	-8.22	0.94	6.03
7h	-7.5	3.17	5.50
N3	-7.7	1.70	5.77

Almost all the predicted energy for all the acylhydrazone-oxazole hybrids are comparable N3. Nevertheless, only 7a, 7b and 7g, showed the lowest free energy with some interesting ligand-receptor interaction such as -sulfur interaction between Cyst145 and Met161 residue in the active site with the 1, 3-oxazole moiety



7a **7b** **7c**

Acylhydrazone-oxazole hybrids with the best predicted free energy in docking studies.

mCurrent efforts to inhibit the Mpro of SARS-CoV-2 take into account the presence of cys145 as a site of inhibition.

Notably, this residue is capable of interaction with aromatic system like the 1, 3-oxazole moiety, which is present in the synthesized compounds in our research group

Table.2 Result of docking studies of

Corrpot.Jnd	Residuesofinteraction	typeofinteraction
7a	Cys145 Mat165 lhr190	n-sulfur n-sulfur n-Ellide
7b	Cys145 t.Aet165 1hr190	!-¥1rogenbond n-sulfur n-cmde
7g	Cys145 t.Aet165	n-alkyl n-sulfur

A novel synthetic strategy to obtain acylhydrazone-oxazole hybrids in three-step reaction in moderate to good yields (36-86%) is reported. The developed synthetic methodology offers operational simplicity and allow electronic environment. The production of -sulfur interaction opens the possibilities to investigate the chemical characteristics that these ligands may present in diverse environment including the active site of Mpro of SARS-CoV-2.

IV. FUTURE OUTLOOK CONCLUSION

In this article we tried to demonstrate the versatility of the molecular hybridization approach as structural modification strategy. Useful in the design of new drugs with new molecular architectures. New chemical classes were discovered coming from the combination of pharmacophoric sub-unities of known prototypes, resulting frequently, in more potent and selective hybrid derivatives. Molecular hybridization is used to combine two distinct pharmacological profile in only one molecule, characterizing new potential dual-acting drugs, able of reproducing the effect of associations of more than one therapeutic agent. The molecular hybridization strategy is particularly interesting for the development of new prototypes for the treatment of various diseases.

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