4-(3H)-quinazolinones N-3 substituted with a five membered heterocycle: a promising scaffold towards bioactive molecules.

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ABSTRACT

The quinazolinone nucleus represents, among the class of fused heterocycles, a very important scaffold to obtain molecules with biological activities. A review of literature revealed how such kind of fused heterocycles, coming from natural or synthetic source, are associated with a wide range of biological activities. This review is mainly directed towards the 4-(3H)-quinazolinones N-3 substituted with a five membered heterocycle in which all the possible combinations of nitrogen, sulfur and oxygen atoms are present.

KEYWORDS N-3 substituted-4-(3H)-quinazolinones, five membered heterocycle, bioactive system

1. Introduction

Quinazolinone, a bicyclic system formed by benzene and pyrimidinone rings, is one of the most representative heterocycles in medicinal chemistry present in numerous compounds endowed with various biological activities. Idelalisib **1** [1], afloqualone (Arofuto) **2** [2], albaconazole **3** [3], mecloqualone **4** [4], balaglitazone **5** [5], nolatrexed **6** [6], ispinesib **7** [7], halofuginone **8** [8-9] and ratiltrexed **9** [10] (Figure 1, Table 1) are examples of just approved or marketed drugs endowed with several activities.

Figure 1. Examples of just approved or marketed drugs having the quinazolin-4-one scaffold (in red).

Table 1. Just approved or marketed drugs having the quinazolin-4-one scaffold.

COMPOUND	TRADING NAME	BIOLOGICAL ACTIVITY
Idelalisib **1**	Zydelig	Treatment of hematological malignancies
afloqualone **2**	Airomate, Arofuto, Arostowa, Mioben, Sekaron	Sedative and muscle-relaxant effects
albaconazole **3**	UR-9825	Triazole antifungal
Mecloqualone **4**	Casfen, Nubarene	Treatment of insomnia
balaglitazone **5**	DRF-2593	Type 2 Diabetes Mellitus
nolatrexed **6**	Thymitaq	Thymidylate synthase inhibitor

ispinesib **7**	CK-0238273, SB-715992	Anticancer agent
halofuginone **8**	Steronol, Tempostatin	Treatment of scleroderma, cancer, and restenosis
Ratiltrexed **9**	Tomudex	Dihydrofolate reductase inhibitor

Quinazolinone skeleton is well represented also in plants and microorganisms [11]. Example of such natural quinazolinones are Febrifugine **10** [9,12,13], Dictyoquinazol A **11** [14], Bouchardatine **12** [15], Neosartin C **13** [16], Isaindigotone **14** [17], Tryptoquivaline U **15** [18] and Chaetominine **16** [19](Figure 2, table 2).
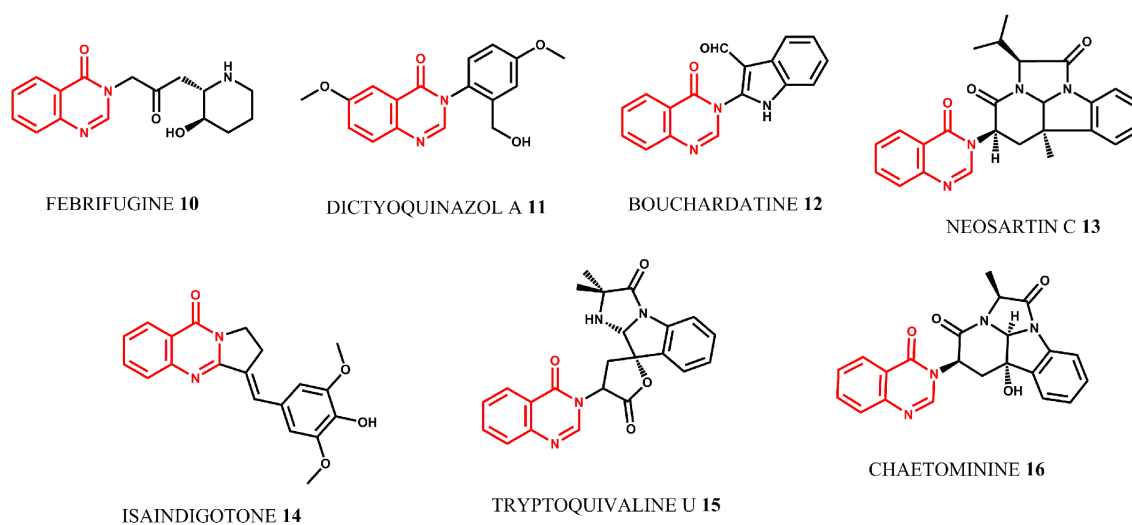
Figure 2. Examples of natural compounds having the quinazolin-4-one scaffold (in red).

Table 2. Examples of natural products containing the quinazolin-4-one scaffold.

COMPOUND	SOURCE	BIOLOGICAL ACTIVITY
Febrifugine **10**	Dichroa febrifuga, Hydrangea species	Antimalarial, coccidiostat (veterinary medicine)
Dictyoquinazol A **11**	Dictyophora indusiata	Neuronal cells protector, glutamate receptor antagonist
Bouchardatine **12**	Bouchardia neurococca	Inhibitor of adipogenesis/lipogenesis in 3T3-L1 adipocytes
Neosartin C **13**	Neosartorya pseudofischeri	No activity
Isaindigotone **14**	Isatis indigotica	Influenza, epidemic hepatitis, and epidemic encephalitis
Tryptoquivaline U **15**	Neosartorya takakii KUFC 7898	No activity
Chaetominine **16**	Chaetomium sp. IFB-E015	Cytotoxic (leukemia K562 and colon cancer SW1116 cell lines)

Three different types, namely quinazolin-2(1H)-one **17**, quinazoline-2,4-(1*H*,3*H*)-dione **18** and quinazolin-4(3*H*)-one **19** (Figure 3) are possible, based on the position of the keto or oxo group. Among these, the quinazolin-4-one **19** is the most common either as scaffold in synthetic route or as structural part of natural products [20]. This last is a very versatile scaffold considering that on it, as many as six different substitutions are possible in the positions 2, 3, 5, 6, 7 and 8.
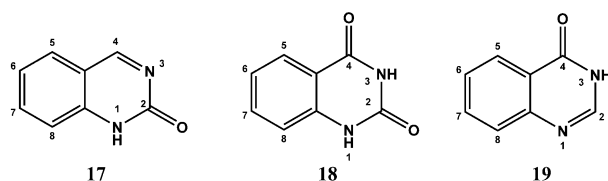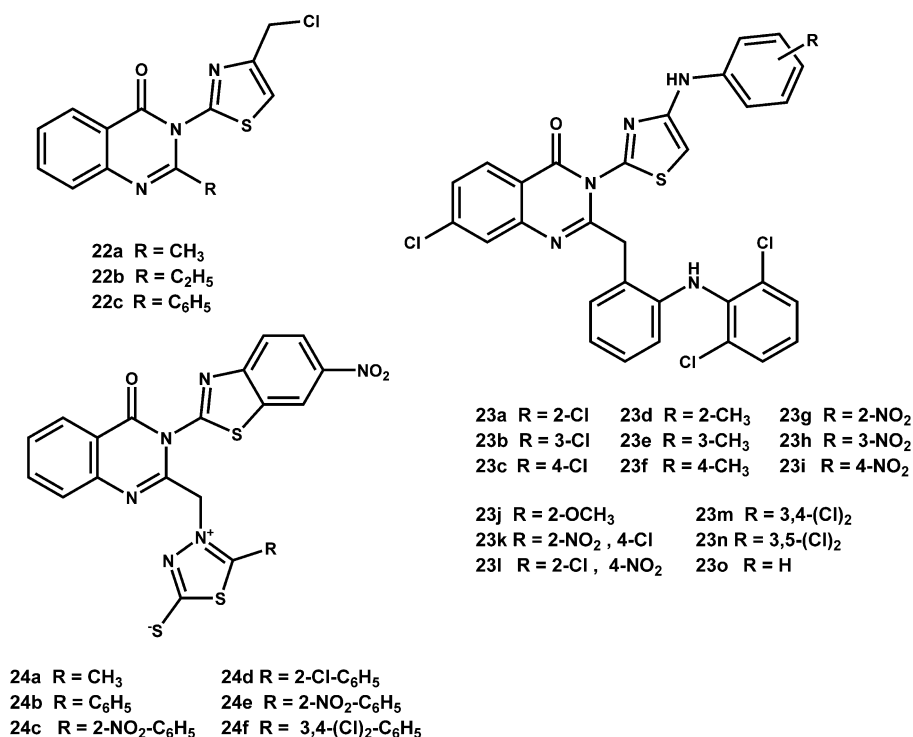

Figure 3. Different types of quinazolinones.

On the basis of this last statements, and considering that our research group has long been interested in the synthesis and biological activity of the isomer **19** derivatives [21-30], this last will be the object of the review. In particular, among the six different opportunities of substitution in this bicyclic system (position 2, 3, 5, 6, 7, 8), the attention will be focused on the quinazolin-4(3*H*)-one **19** linked with a five membered heterocycle at the 3 position such as pyrazole, indazole, isoxazole, imidazole and benzoimidazole, thiazole and benzothiazole, furane, thiophene and benzothiophene, oxadiazole, thiadiazole, triazole, tetrazole and 7*H*-purine (Figure 4).

Figure 4. Five membered heterocycles as substituents in the 3 position of quinazolin-4(3H)-one ring.

All the compounds described in this review will be divided and classified on the basis of the same pentatomic heterocyclic system describing the biological activities and, wherever possible, the targets, the mechanisms of action and the structure-activity relationships of the molecules.

2. Quinazolin-4(3H)-ones having substituted in the 3rd position with a thiazole or benzothiazole nucleus.

Literature survey revealed that, among the 3-heterociclo-quinazolin-4(3H)-ones, the most representative derivatives are 3-(thiazol-2-yl)quinazolin-4(3H)-ones **20** and 3-(benzo[d]thiazol-2-yl)quinazolin-4(3H)-ones **21** (figure 5). Systems containing thiazol-2-yl and benzo[d]thiazol-2-yl linked to quinazolin-4(3H)-one nucleus have been extensively studied for many applications including antimicrobial agents, anticancer agents, analgesic and antinflammatory agents, anticonvulsant agents, antitubercular agents, A2A receptor inhibitors, inverse agonists or antagonists of hH4R, antioxidant agents, antileishmanial agents and phosphodiesterase inhibitors.

Figure 5. General structure of 3-(thiazol-2-yl)quinazolin-4(3H)-ones **20** and 3-(benzo[d]thiazol-2-yl)quinazolin-4(3H)-ones **21**.

2.1. 3-Thiazole and 3-benzothiazole quinazolinones as antimicrobial agents.

Among some novel quinazolinone derivatives synthesized and screened by Sing et al.[31], the 3-(4-(chloromethyl)thiazol-2-yl)quinazolin-4(3H)-ones **22a-c** (figure 6) showed good antibacterial activity against two gram positive bacteria *Staphylococcus aureus* and *Bacillus subtilis* as well as two gram negative bacteria *Salmonella typhi* and *Escherichia coli*. As reported in table 3, first the

best antibacterial agent was **22c**, then E. coli and B. subtilis resulted the most and the least sensitive cell line respectively.

Figure 6. General structure of quinazolinones **22a-c**, **23a-o** and **24a-f**.

Table 3. Antibacterial activity of compounds **22a-c**.

Comp.	Gram positive bacteria		Gram negative bacteria	
	S. aureus	*B. subtilis*	*S. typhi*	*E.coli*
22a	++	+	+	-
22b	+	-	+	++
22c	+++	-	++	++

In a further study reported by Arora [32,33], the author wants to relate some semi-empirical quantum chemically computed properties with the activities against *streptococcus pyogenes* of 3-(1,3-Thiazol-2-yl-7-Chloroquinazolin-4-(3*H*)–one derivatives. In particular, the following descriptors: hydration energy (Hyd E), log P (log P), refractivity (REF), polarizability (POL), mass (mass), surface area approx. (SAA), surface area Grid (SAG), volume (Vol), heat of formation (HF), zero point energy (ZPE), HOMO energy (HOMO), LUMO energy (LUMO) and dipole

moment (DM) were used to perform a 3D-QSAR for compounds **23a-l** (figure 6). The final equation used in this study was the following:

$$p(MIC)=-0.00511 \, (SAA)-0.54732(LUMO)+0.175796(DM)-0.21124$$
$$(n = 15, \, r= 0.660166, \, SE = 0.278621, \, F= 2.832436).$$

Based on this method, the author showed how SAA, LUMO and DM are the parameters/descriptors that have a positive contribution on the MIC.

Antimicrobial activity was also showed by a series of 2-substituted-3-((3-(6-nitrobenzo[d]thiazol-2-yl)-4-oxo-3,4-dihydroquinazolin-2-yl)methyl)-1,3,4-thiadiazol-3-ium-5-thiolate described by Akbari et al. [34]. Ten benzothiazolyl quinazolinones were synthesized and tested for their antimicrobial activity against *S. aureus* and *B. subtilis* as Gram positive, *P. aeruginosa* and *E. coli* as Gram negative bacterial strains as well as against *C. albicans* as fungal strain. Among the tested compounds, **24a-i** (figure 6) showed the best antimicrobial activity.

Compound **24a** resulted significantly active against Gram negative bacteria *P. aeruginosa* and the compounds **24b-c** showed good activity against S. aureus and B. subtilis as Gram positive bacteria. Finally, good antifungal activity against C. albicans was shown by compounds **24d-f**.

Newer 3-thiazole substituted 2-styrylquinazolin-4(3*H*)-one derivatives were synthesized exploiting the synthesis by microwave [35]. Among the synthesized compounds, derivatives **25a-c** (figure 7) showed an *in vitro* antibacterial and antifungal activity against *Escherichia coli*, *Pseudomonas aeruginosa*, *Bacillus megaterium*, *Bacillus subtilis*, and *Aspergillus niger* comparable with the standards Norfloxacin and Clotrimazole.
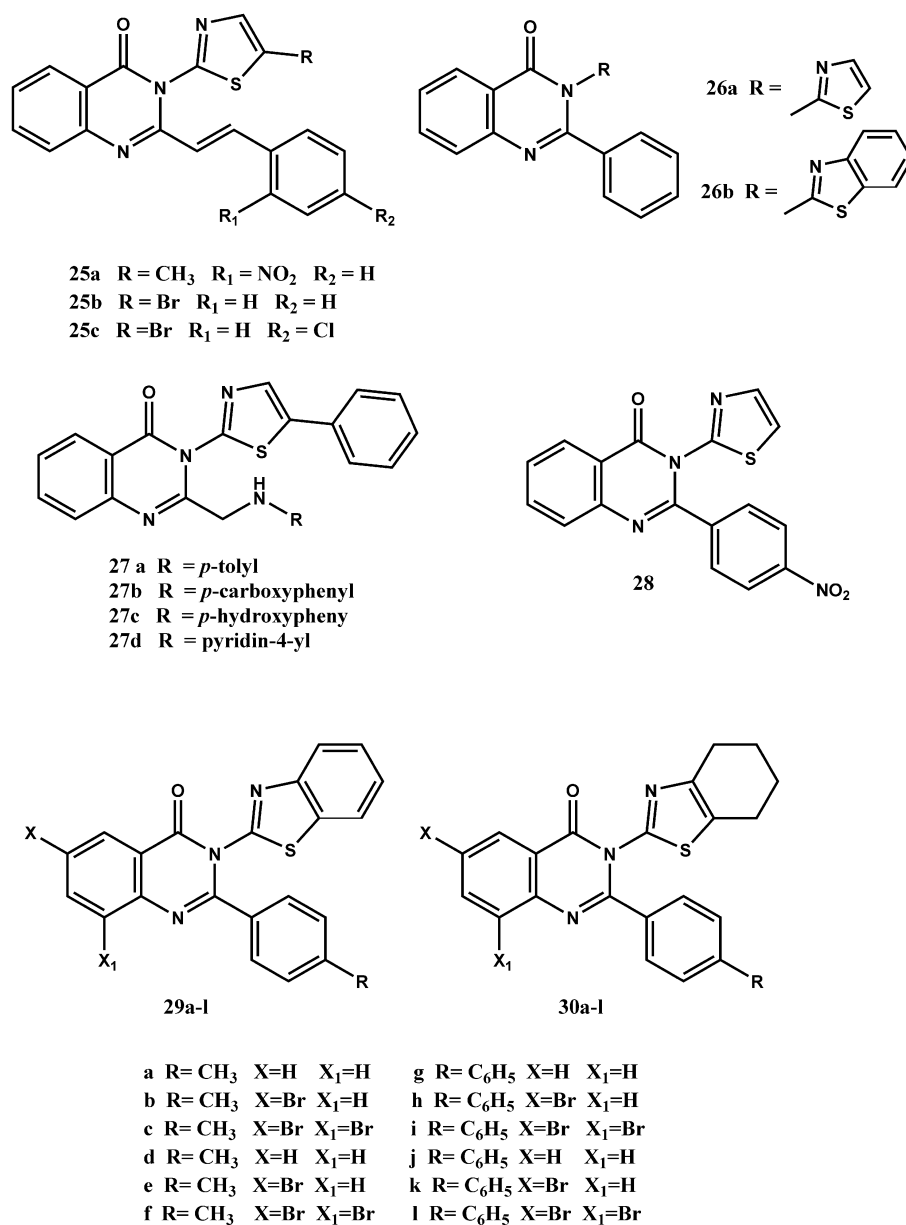
Figure 7. General structure of quinazolinones **25a-c**, **26a,b**, **27a-d**, **28**, **29a-l** and **30a-l**.

Among the twenty heterocycle compounds newly synthesized by Habib et. Al. [36] the 3-thiazole and 3-benzothiazole-2-phenylquinazolinones **26a,b** (figure 7) exhibited the better antimicrobial activity with a MIC (mg/mL) of 6.25 against gram positive bacteria *S. aureus* and *S. pyogenes*. Further studies on 3-benzothiazole 2-phenylquinazolinones have been conducted by Sharma [37] . A quantitative structure–activity relationship was also conducted to investigate the influence of substituents on the biological activity. Other examples of 3-thiazole and 3-benzothiazolequinazolinones are reported in the literature [38-40] (figure 7). In particular, the four

novel phenylthiazolyl-quinazolin-4(3H)-one derivatives, bearing in the 2 position of quinazolinone system the p-tolylaminomethyl, the p-carboxyphenylaminomethyl, the 4-hydroxyphenylaminomethyl and the pyridin-4-yl-aminomethyl moieties (**27a-d**, figure 7), were synthesized by Badwaik et. al [38] with an efficient route and showed a good antibacterial activity against *E.coli* and *S. aureus* with an average percentage of inhibitions of 76-88% against E.coli and 67-80 % against S.aureus.

Antileishmanial and antimicrobial activities were also showed by some 2,3-disubstituted 3*H*-quinazolin-4-ones [39]. Among these, the 2-(4-nitrophenyl)-3-(thiazol-2-yl)quinazolin-4(3*H*)-one **28** (figure 7) was also synthesized even if resulted to be inactive against the

tested bacteria and fungi. Finally, brominated 3-(4-phenylthiazol-2-yl) and 3-(3-carbethoxy-4,5,6,7-tetrahydrobenzothiophen-2-yl)quinazolin-4(3*H*)-one derivative (**29a-d** and **30a-l**, figure 7) were synthesized and tested for their antimicrobial activity by Saravanan et al. [40]. Derivatives **29** and **30** were screened for their anti-bacterial and anti-fungal activities against gram positive bacteria (*S. aureus* ATCC 9144, *S. epidermidis* ATCC 155, *M. luteus* ATCC 4698 and *B. cereus* ATCC 11778) and three gram negative bacteria (*E. coli* ATCC 25922, *P. aeruginosa* ATCC and *K. pneumoniae* ATCC 11298) as well as two fungi (*A. niger* ATCC 9029 and *A. fumigatus* ATCC). Based on the reported data, the authors state how brominated derivatives exhibited more activity than unsubstituted one. Also, in the series of thiazole derivatives the antibacterial activity is greater than anti-fungal activity whereas, among the tetrahydrobenzothiophene derivatives the best activity was the anti-fungal activity. Among the 3-(thiazol-2-yl)quinazolin-4(3*H*)-ones, showing antibacterial activity, they must also be counted derivatives **31a,b**. They were part of a group of thirty-seven quinazolin-4(3*H*)-ones synthesized as novel strategy in development of a new generation of antibacterial drugs acting as inhibitors of the zinc metalloproteinase thermolysin (TLN) [41]. Even if compounds **31a** and **31b** showed moderate or low inhibitory activity (IC50 76.85 µm, Ki 59.3 µm for **31a**; low activity for **31b**) they were very useful to obtain a structure-activity relationship which led to discover the potent inhibitors **32** and **33** (figure 8). A docking

study on the most active compound **32** highlighted the importance of the trifluoromethyl group in position 2.
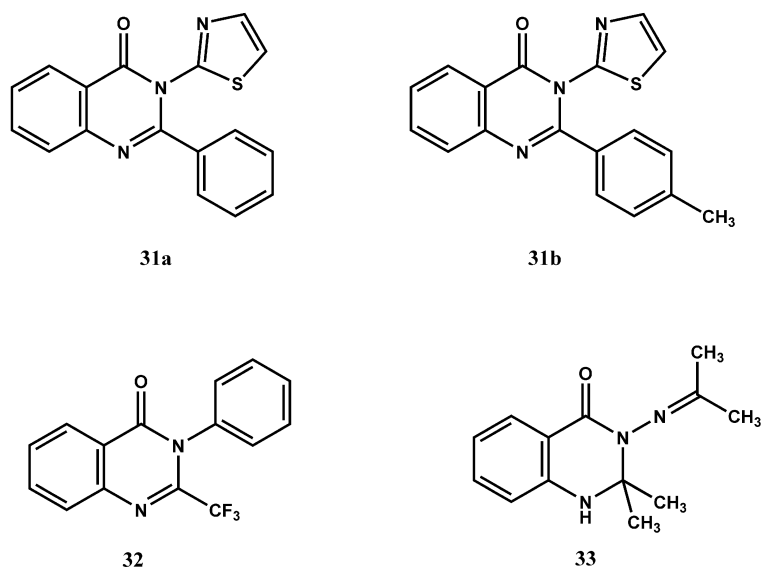
**Figure 8**. General structure of quinazolinones **31a,b**, **32**, and **33**.

2.2. Other biological activities of 3-Thiazole and 3-benzothiazole quinazolinones.

Although, as demonstrated in the previous paragraph, literature survey revealed that the most representative biological properties among 3-(thiazol-2-yl)quinazolin-4(3*H*)-ones **20** and 3-(benzo[d]thiazol-2-yl)quinazolin-4(3*H*)-ones **21** are the antibacterial and antifungal activities, other activities, such as anticonvulsant, antinflammatory, anticancer, antioxidant, antitubercular, antiparkinsonian, broncodilatatory and antagonistic Histamine H4 receptor ones, are reported but less represented respect to the antimicrobial activity.

2.2.1. Anticonvulsant activity.

The quinazolin-4(3*H*)-one nucleus has been recently studied as potential scaffold to obtain anticonvulsant agents. Starting from the well-known sedative-hypnotic and anticonvulsant methaqualone **34** (figure 10) it was highlighted that the presence of a methyl group at position 2 (site A) and a substituted aromatic ring at position 3 (site B) are required for the anticonvulsant activity of such kind of heterocyclic nucleus (figure 9a) [42,43]. Further, it was showed how, the methyl group at the position 2 is not always necessary and potent anticonvulsant agents have other

groups at position 2. Finally, considering that thiadiazole and benzothiazole nuclei exhibit anticonvulsant activity [44,45] a molecular hybridization between the quinazolinones and thiadiazole or benzothiazole was carried out to obtain more potent anticonvulsant (figure 9b).
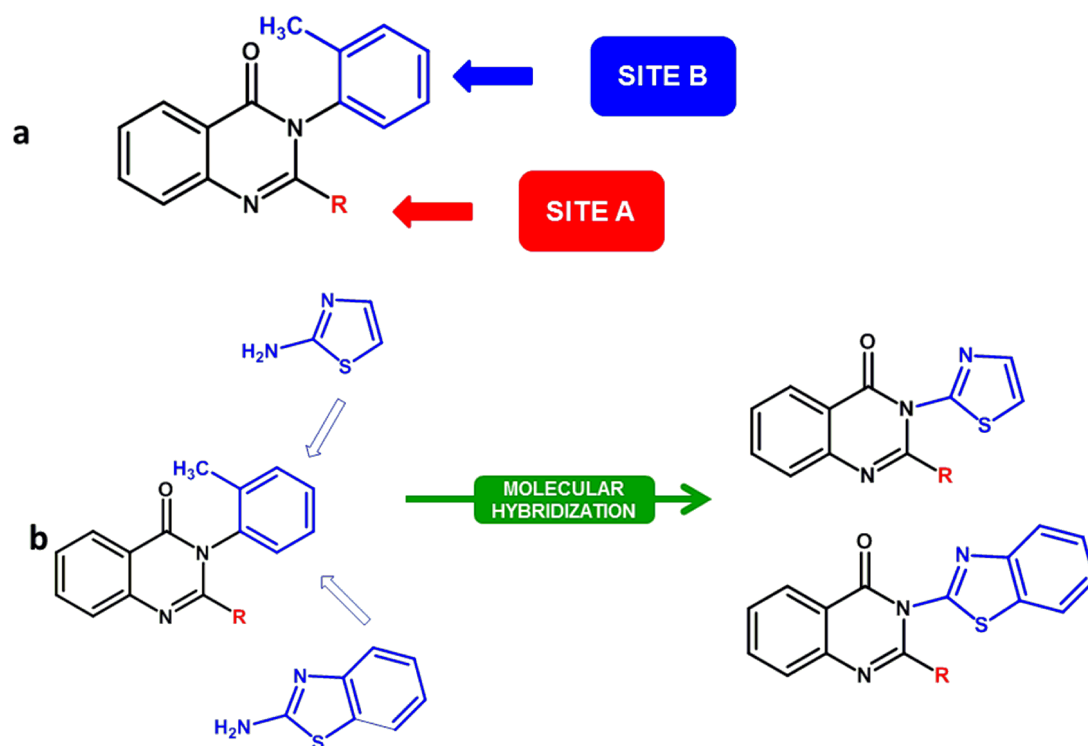
Figure 9. Molecular hybridization between the quinazolinones and thiadiazole or benzothiazole to obtain more potent anticonvulsant.

On the basis of such results, the chemical modifications at second and third position of methaqualone **34** (figure 10) lead to the more active anticonvulsant agents **35 a-j**, **36 a-j**, **37** and **38** (figure 10) [43,45,46,47].

In particular, the substitution of a methyl group with an ethyl one in the position 2 and the presence of the benzothiazole nucleus in the position 3 lead to compounds **35 a-j** [45] and **36 a-j** [47] (figure 10).
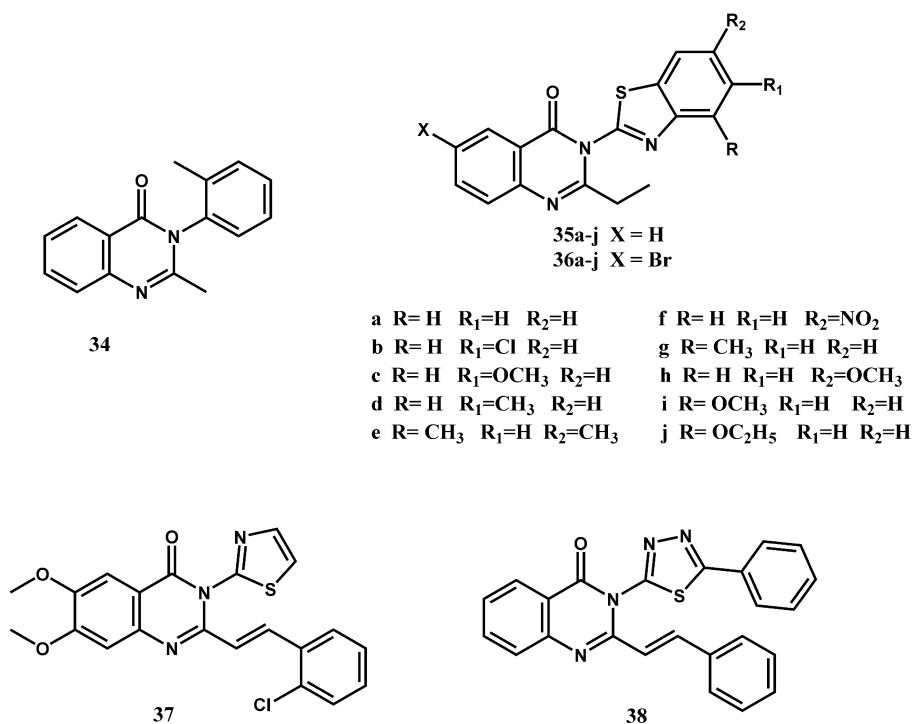
Figure 10. General structure of quinazolinones **34**, **35a-j**, **36a-j**, **37**, and **38**.

Quinazolinones **35** and **36** are equipped with the essential pharmacophoric elements common to various anticonvulsant agents with sodium channel blockade activity, namely presence of a hydrophobic unit (R, figure 11 in green), an electron donor group (D, figure 11 in blue) and hydrogen donor/acceptor unit (HAD, figure 11 in red) [48].
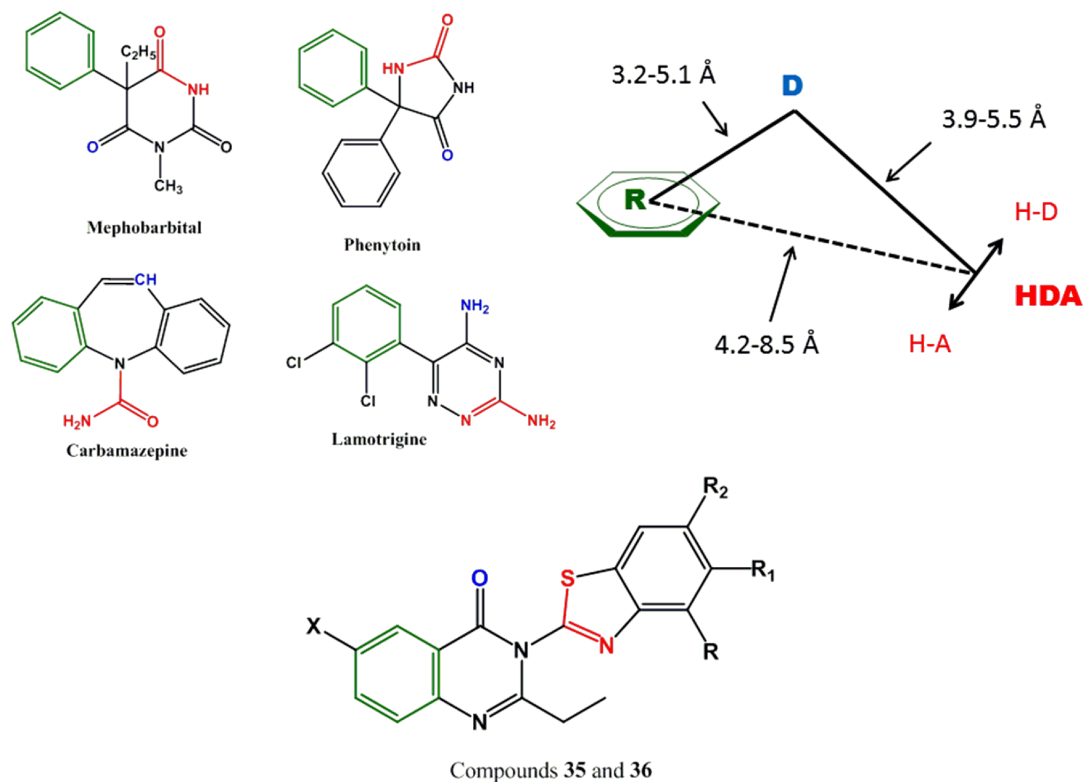
Figure 11. Pharmacophoric pattern of well-known anticonvulsant agents and compounds **35** and **36**.

The anticonvulsant efficacy of quinazolin-4(3*H*)-one nucleus is also linked to the presence of the 2-chlorophenyl and substituted (pyridin-2-yl)vinyl moieties at N3 and C2 position respectively (figure 12). Example of such compounds are CP-526,427 and CP-465,022 (figure 12, compounds **39** and **40**).
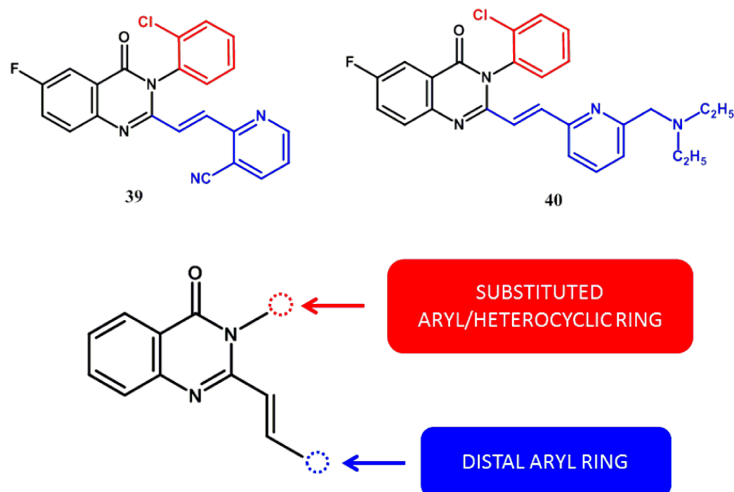
Figure 12. Compounds **39** and **40** as template for 2-styryl-quinazolin-4(3*H*)-ones **37** and **38**.

Starting from these statements, 2-styryl-quinazolin-4(3*H*)-ones bearing the 1,3,4-thiadiazole-2-yl nucleus (figure 10, compounds **37** and **38**) at the position 3 were synthesized and tested for their anticonvulsant activity in various physicochemically induced seizure models. In particular, compound **37** resulted scarcely active [46] while, among the eighteen synthesized compounds, compounds **38** showed potency similar to standard drug (phenytoin, carbamazepine) without any neurotoxicity [43].

2.2.2. Antinflammatory activity.

Some example of 2,3-disubstituted quinazolone derivatives endowed with analgesic and antinflammatory activities were reported [49,50]. Among four synthesized 2-chloromethyl-3-heterocyclo substituted quinazolin-4(3*H*)-ones, the 2-(chloromethyl)-3-(6-nitro-1,3-benzothiazol-2-yl)quinazolin-4(3*H*)-one **41** (figure 13) showed moderate analgesic activity in the Eddy's hot plate test [49]. With the same synthetic route Srivastav et al. [50] obtained sixteen (1,3-benzothiazole-2-yl)quinazolin-4(3*H*)-ones of type **42** (figure 13). Compounds under study showed moderato or significant antinflammatory activity at the dose of 200 mg/ kg in acute–inflammatory models in Rats. In this work the authors also highlight how the marked antinflammatory activity is linked to the presence of electron withdrawing group as substituents on benzothiazole ring.

41

42 R = CH$_3$, OCH$_3$, Cl, F
R$_1$ = H, CH$_3$, OCH$_3$, Cl

43

44a R= OCH$_3$
44b R = CH$_3$

45a-e

a R= CH$_3$ R$_1$=H R$_2$= H
b R= CH$_3$ R$_1$=Br R$_2$= H
c R= CH$_3$ R$_1$=Br R$_2$= Br
f R= C$_6$H$_5$ R$_1$=H R$_2$= H
d R= C$_6$H$_5$ R$_1$=H R$_2$= H
e R= C$_6$H$_5$ R$_1$=H R$_2$= H

46a-i

a R= 4-chlorophenylaminomethyl
b R= 4-fluorophenylaminomethyl
c R= 4-nitrophenylaminomethyl
d R= 4-tolylaminomethyl
e R= 4-methoxyphenylaminomethyl
f R= N-methylhydrazidoisonicotinic acid
g R= 2-(methylamino)pyrazine
h R= 2-(methylamido)pyrazine
i R= 2-hydroxy-4-aminomethylbenzoic acid

Figure 13. General structure of quinazolinones **41**, **42**, **43**, **44a-b**, **45a-e** and **46a-i**.

2.2.3. Anticancer activity.

The anticancer activity of quinazolin-4(3*H*)-ones **19** linked with a five membered heterocycle at the 3 position is reported by Bhatta and Pattanaik [51]. The study is based on the synthesis of eight molecules including the 3-(4-(*p*-methoxyphenyl)thiazol-2-yl)quinazolin-4(3*H*)-ones **43** and **44a,b** (figure 13). The compounds were screened for their anticancer activity at five different concentrations in a battery of about 60 cell lines of 8-types of human cancer. Among these, compounds **43** and **44a,b** (figure 13) showed low activity.

2.2.4. Antioxidant activity.

The antioxidant activity of quinazolin-4(3H)-ones of type **19** (figure 4) were described by Saravanan et al. [52]. Considering that a number of synthetic compounds such as quinazolinones and thiazoles exert antioxidant activity, they synthesized and tested the quinazolin-4(3H)-one ring system associated with thiazole. In particular, compounds **45a-e** (figure 13) were screened for antioxidant activity by DPPH radical scavenging activity method. Experimental data showed how the brominated compound and the presence of a phenyl ring at position 2 of quinazolinone nucleus are crucial for the antioxidant activity; compound **45i** having two bromine atoms at positions 6, 8 and a phenyl group at position 2 of quinazolin-4(3*H*)-one ring resulted the best antioxidant agent.

2.2.5. Antitubercular activity.

The antitubercular activity of a set of 52 compounds possessing 2,3-substituted quinazolin-4(3*H*)-one moiety has been studied in silico to obtain useful molecular models to provide better insight into the designing of more potent antitubercular agents [53]. Among the 52 compounds were also selected the 3-(4-(4-chlorophenyl)thiazol-2-yl)quinazolin-4(3*H*)-ones **46a-i** (figure 13). 2D and 3D computational study highlighted the positive contribution of a bulky group introduced at 3rd position of quinazolin-4(3*H*)-one nucleus, as well as the presence of an electronegative atom like iodine or hydrogen at 6rd position. Finally, electronegative substitution is essential at 2 and 3-position of quinazolinone rings.
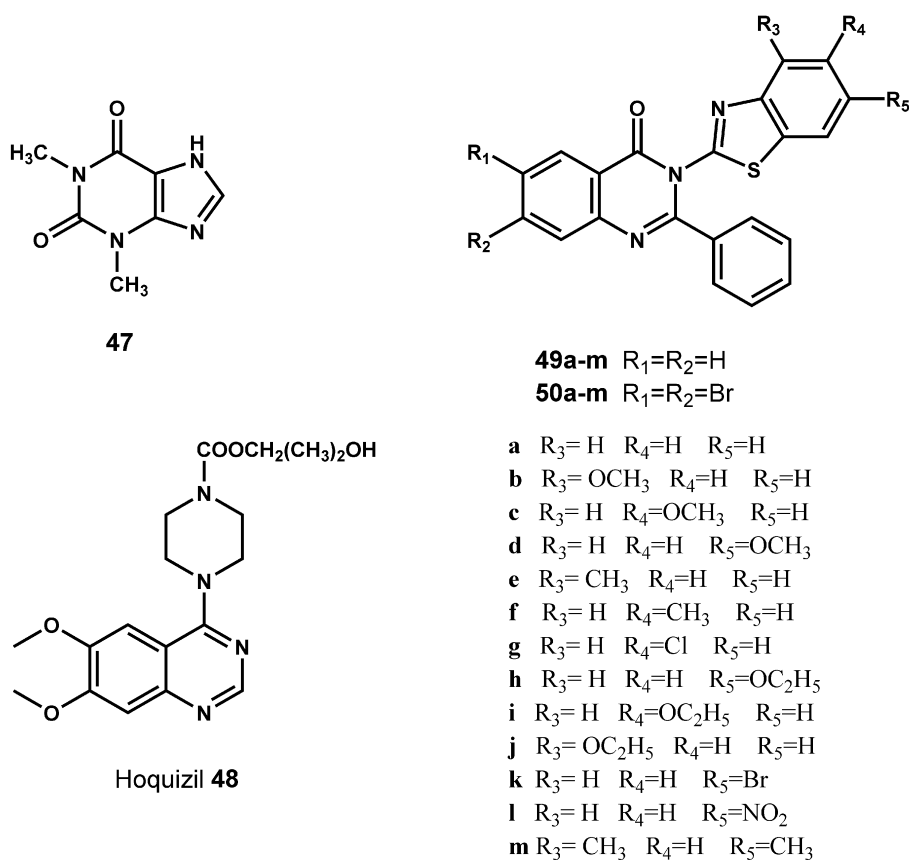
2.2.6. Bronchodilatory activity.

Bronchodilatory activity is somewhat related to phosphodiesterase activity (PDE). Agents that interfere with the catabolism of cyclic AMP and cyclic GMP *via* inhibition of phosphodiesterase are useful as therapeutic tool for various diseases including all those pathologies that require the use of bronchodilators. Starting from the xanthine **47** skeleton and the bronchodilator Hoquizil **48** structure, Laddha et al. synthesized two series of 6,8-disubstituted-2-phenyl-3-(substituted benzothiazole-2-yl)quinazolin)-4(3*H*)-ones **49a-m** and **50a-m** (figure 14) and tested them for their ability to inhibit bovine heart phosphodiesterase [54]. Data reported showed that the quinazolinone

derivatives **49a-m** and **50a-m** (figure 14) are significantly more potent inhibitors of PDE than theophylline **47**, chosen as standard. In particular, derivatives **50a-m**, containing the 6,8-dibromo-quinazol-4(3*H*)-one ring system are more active than the unsubstituted ones. Moreover, an electron-releasing group at R3 in the benzothiazole nucleus afforded greater activity than the presence of an electron-releasing group at R4 and R5.

According with this statement, compounds **50g** and **50l** are the more potent phosphodiesterase inhibitors.

47

Hoquizil **48**

49a-m $R_1=R_2=H$
50a-m $R_1=R_2=Br$

a $R_3=$ H $R_4=$H $R_5=$H
b $R_3=$ OCH$_3$ $R_4=$H $R_5=$H
c $R_3=$ H $R_4=$OCH$_3$ $R_5=$H
d $R_3=$ H $R_4=$H $R_5=$OCH$_3$
e $R_3=$ CH$_3$ $R_4=$H $R_5=$H
f $R_3=$ H $R_4=$CH$_3$ $R_5=$H
g $R_3=$ H $R_4=$Cl $R_5=$H
h $R_3=$ H $R_4=$H $R_5=$OC$_2$H$_5$
i $R_3=$ H $R_4=$OC$_2$H$_5$ $R_5=$H
j $R_3=$ OC$_2$H$_5$ $R_4=$H $R_5=$H
k $R_3=$ H $R_4=$H $R_5=$Br
l $R_3=$ H $R_4=$H $R_5=$NO$_2$
m $R_3=$ CH$_3$ $R_4=$H $R_5=$CH$_3$

Figure 14. General structure of compounds **47**, **48**, **49a-m** and **50a-m**.

3. Quinazolin-4(3*H*)-ones substituted in the 3rd position with an oxadiazole or thiadiazole nucleus.

Oxadiazole and thiadiazole rings lead to 3-heterociclo-quinazolin-4(3*H*)-ones endowed of several biological properties. They are five-membered rings which contain three heteroatoms, that is oxygen and two nitrogen for oxadiazole and sulfur and two nitrogen for thiadiazole. Furthermore

four different isomers, namely 1,2,3-, 1,2,4-, 1,3,4- and 1,2,5- are possible for both rings (Figure 15) even if only for 3-(1,2,4-oxadiazol-3-yl)quinazolin-4(3*H*)-one **51**, 3-(1,3,4-oxadiazol-2-yl)quinazolin-4(3*H*)-one **52** and 3-(1,3,4-thiadiazol-2-yl)quinazolin-4(3*H*)-one **53** (figure 15) some biological activities, that is antimicrobial, antinflammatory, anticancer and anticonvulsant, are reported.

1,2,3-oxadiazole **1,2,4-oxadiazole** **1,3,4-oxadiazole** **1,2,5-oxadiazole**

1,2,3-thiadiazole **1,2,4-thiadiazole** **1,3,4-thiadiazole** **1,2,5-thiadiazole**

51   **52**   **53**

Figure 15. Possible isomers of oxadiazole and thiadiazole linked to the quinazolin-4(3*H*)-one nucleus.

3.1. Antimicrobial activity.

A review on oxadiazole derivatives [55] showed, among several class of therapeutic oxadiazoles, fifteen 3-(1,3,4-oxadiazol-2-yl)-2-styrylquinazoline-4(3*H*)-one analogues **54a-o** (figure 16) possessing antibacterial activity against *Staphylococcus aureus*, *Bacillus subtilis*, *Pseudomonas aeruginosa* and *Escherichia coli* as well as antifungal activity against *Aspergillus niger* and *Fusarium oxysporum*.

Figure 16. General structure of compounds **54a-o**, **55a-h**, **56**, **57a-f**, **58a-f** and **59a-f**.

The activity is linked to the presence of the unsubstituted styryl group. Furthermore, compounds **54a-o** have shown greater antibacterial activity than antifungal. Finally, the best compound of the series was **54d** which showed an antibacterial activity of 79 μg/mL for *Staphylococcus aureus*, 75 μg/mL for *Bacillus subtilis*, 86 μg/mL for *Pseudomonas aeruginosa* and 70 μg/mL for *Escherichia coli*. 3-(1,3,4-Oxadiazol-2-yl)-2-styrylquinazolin-4(3*H*)-ones were object of study also by Sowjanya et al. [56] which synthesized and tested against *Bacillus subtilis*, *Escherichia coli*, *Staphylococcus aureus* (gram-positive) and *Proteus vulgaris* (gram-negative) compounds **55a-h** (figure 16). In analogy to compounds **54**, the activity is showed only by the unsubstituted derivative **55a**. Any

substitution either by electron-releasing or electron-attracting moieties at the styryl group resulted in decreased activity. Antibacterial and anthelmintic activity were also showed by 3-(1,2,4-oxadiazol-3-yl)quinazolin-4(3*H*)-one derivative **56** [57]. It was synthesized together with other three 3-heterociclo-quinazolin-4(3*H*)-ones in the effort to get new and more safe antibacterial and anthelmintic drugs. Compound **56** resulted active both as antibacterial and as anthelmintic although less active than the other synthesized compounds. Finally, Patel N. B. and Patel J. C. [58] studied the influence of the 1,3,4-oxadiazole ring attached directly as well as with a phenylene or methylene link to the quinazolin-4(3*H*)-one nucleus. They synthesized and tested against two gram positive bacteria (*S. aureus*, *S. pyogenes*) and two gram negative bacteria (*E. coli*, *P. aeruginosa*) as well as against three fungal species *C. albicans*, *A. niger* and *A. clavatus*, compounds **57a-f**, **58a-f** and **59a-f**. Most of the compounds showed very good antibacterial activity compared to ampicillin taken as a reference. In particular, gram positive bacteria *S. aureus* was more sensitive to derivatives **57b**, **58a,c,f** and **59e** (MBC 50-150 µg/ml) than to ampicillin (MBC 250 µg/ml). Compound **59f** resulted the best antibacterial against gram negative bacteria (MBC 50 and 150 µg/ml vs *E. coli* and *P. aeruginosa* respectively). To whom concern the antifungal activity, noteworthy is the compound **59c** which showed the best activity among the synthesized compounds (MFC 100, 200 and 200 µg/ml vs *C. albicans*, *A. niger* and *A. clavatus* respectively). Ultimately, methylene link between 3rd position of quinazolinone and 2nd position of oxadiazole is the best choice in this type of antimicrobial.

3.2. Anticancer activity.

Among the several biological properties owned by quinazolin-4(3*H*)-ones bearing the oxadiazole or thiadiazole rings, the anticancer activity is sufficiently represented [59-61]. Kumar et al. [59], explored the anticancer activity on human myelogenous leukemia K562 cells of six new 3-[5-(4-substituted-phenyl)-1,3,4-oxadiazol-2-yl]-2-phenylquinazolin-4(3*H*)-ones **59a-f**. The Percent growth inhibition on K562 cell lines was evaluated at five different concentration (0.01 µM, 0.1 µM, 1 µM, 10 µM and 100 µM). Compounds **59** exert the anticancer activity at 1 µM being inactive

below this concentration. Compounds which showed the best activity were **59d,e** with an IC_{50} of 1 µM and 1.5 µM respectively.
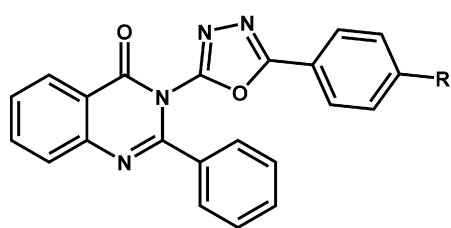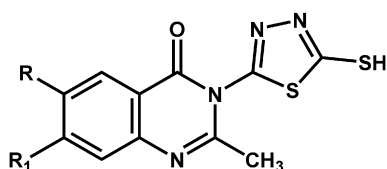

59a-f

a R= H   d R= CH₃
b R= Cl   e R= NO₂
c R= OCH₃ f R= F
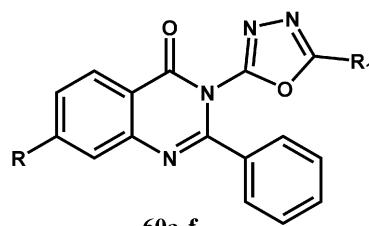
60a-f

a R= H R_1= 4-Cl-phenyl
b R= H R_1= 2-cyclopropyl
c R= Cl R_1= 2-methyl
d R= Cl R_1= phenyl
e R= Cl R_1= 2-cyclopropyl
f R= Cl R_1= 4-OMe-phenyl

61a R = H R_1 = H
61b R = H R_1 = Br
61c R = Br R_1 = Br
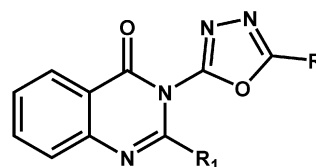
62a-l

a R= (CH)₂-C₆H₅ R_1= C₆H₅   g R= 4-NH₂-C₆H₄ R_1= C₆H₅
b R= (CH)₂-C₆H₅ R_1= CH₃   h R= 4-NH₂-C₆H₄ R_1= CH₃
c R= C₆H₄N R_1= C₆H₅   i R= 2-COOH-C₆H₄ R_1= C₆H₅
d R= C₆H₄N R_1= CH₃   j R= 2-COOH-C₆H₄ R_1= CH₃
e R= 2-NH₂-C₆H₄ R_1= C₆H₅   k R= SH R_1= C₆H₅
f R= 2-NH₂-C₆H₄ R_1= CH₃   l R= SH R_1= CH₃

Figure 17. General structure of compounds **59a-f**, **60a-f**, **61a-c** and **62a-l**.

Patel et al. developed new anticancer agent based on a quinazolone core scaffold, whose target was the epidermal growth factor receptor (EGFR) [60]. The rationale of this work starts from the known EGFR inhibitors (figure 18).
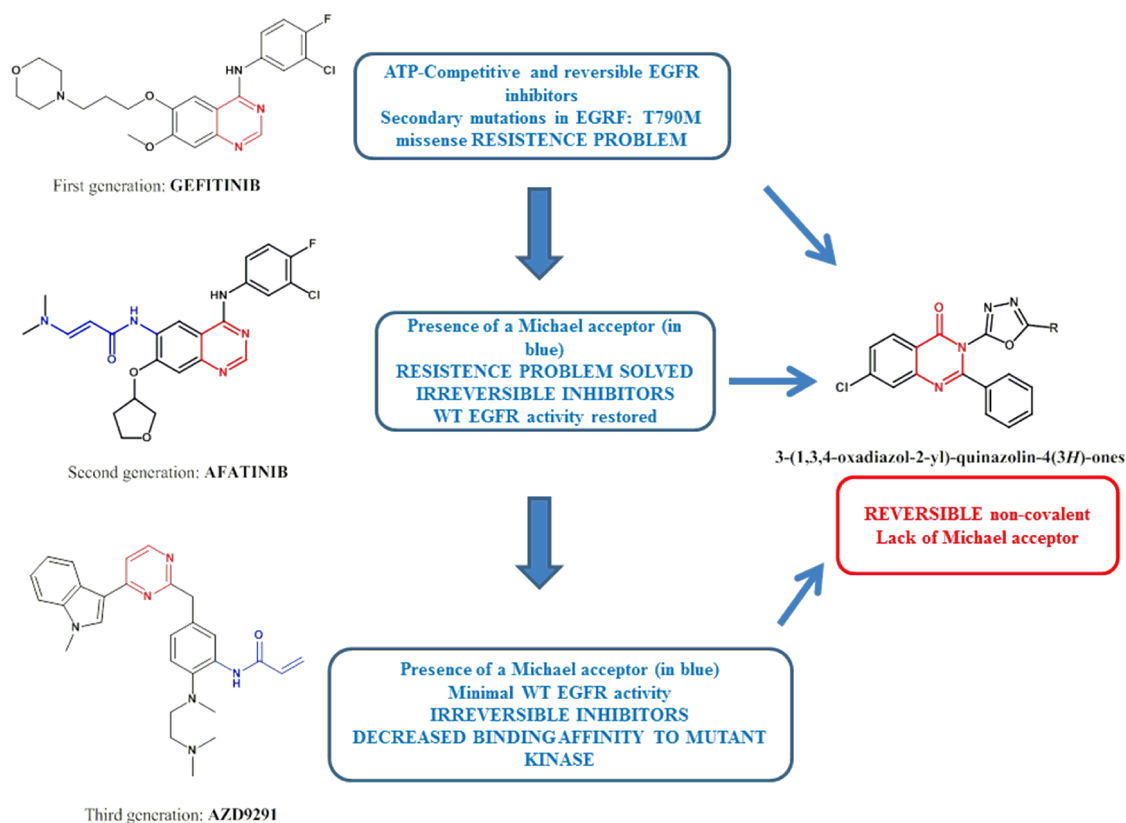
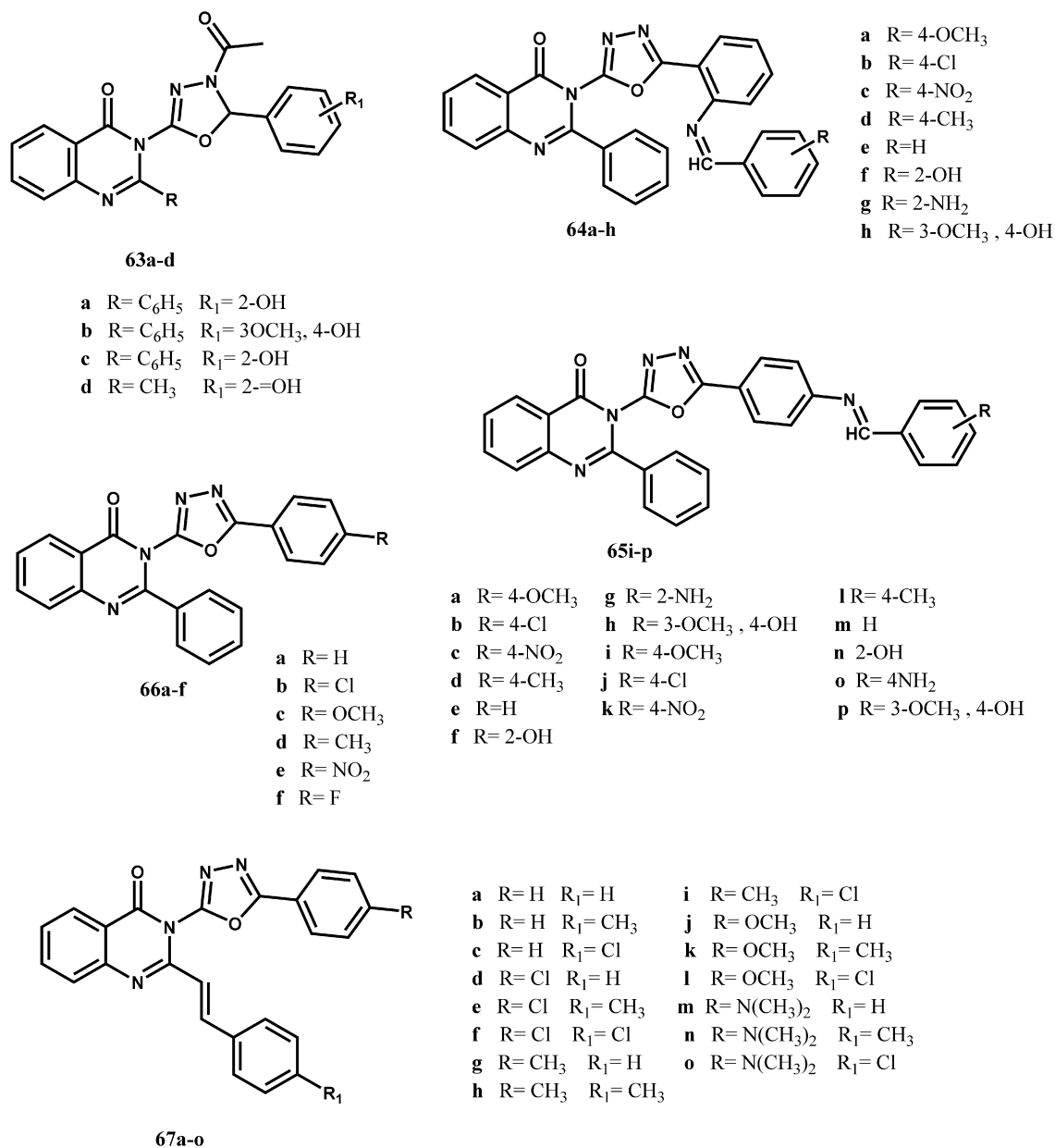**Figure 18**. Rationale to obtain the new EGFR inhibitors 3-(1,3,4-oxadiazol-2-yl)-quinazolin-4(3*H*)-ones.

In particular, the first generation ATP-competitive and reversible EGFR inhibitors such as gefitinib are effective on some somatic EGFR mutations (L858R and delE746_A750). A secondary mutation namely T790M missense in EGFR, developed a drug resistance problem: EGFR T790M mutation restores the affinity for ATP similar to that of wild type. This resistance was overcome with the second generation of such inhibitors (afatinib). However, the presence of a Michael acceptor (figure 18 in blue), responsible for a covalent interaction with the conserved residue cys797 of EGFR, makes these molecules irreversible inhibitors with a restored WT EGFR activity. The problem was bypassed with the third generation of inhibitors (AZD9291) which showed again a minimal WT EGFR activity but a decreased binding affinity to mutant kinase. So, far from solving the problem, they showed limited clinical efficacy as well as relatively high toxicity. Substitution of pyrimidine ring (figure 18 in red) with the pyrimidin-4(3*H*)-one to give the quinazolin-4(3*H*)-ones **60a-f** (figure 17), lead to reversible non-covalent inhibitors. The SAR revealed the importance of the presence of

the 7-chloro substitution and of the 1,3,4-thiadiazole ring in the third position of the quinazolinones. Compounds **60e,f** showed IC50 values in the nanomolar range (0.102 µM and 0.021 µM respectively). A docking study was also carried out revealing how synthesized quinazolinones bind in a quite different way respect to the first, second and third generation agents to the ATP-binding site of the T790M EGFR tyrosine kinase domain.

Finally, El-Naggar et al. evaluated the anticancer activity of newly synthesized twenty-five compounds among which the (1,3,4-thiadiazol-2-yl)quinazolin-4(3*H*)-ones **61a-c** (figure 17) [61]. They were synthesized and tested against Ehrlich ascites carcinoma (EAC) model *in vivo* by measurements of several parameter: changes in the total body weight, total ascitic volume, number of live and death tumor cells, median survival time. Some biochemical parameter such as transaminases (AST and ALT), alkaline phosphatase (ALP), catalase, superoxide dismutase (SOD), glutathione reduced (GSH) and lipid peroxidation (MDA) were also evaluated. Although active, compounds **61a-c** are not among the most active ones. In particular, compound **61a** caused a decrease in the total ascitic volume of 28% and a decrease in the total cell count of tumor cell of 12%.

3.3. Antinflammatory activity.

1,3,4-Oxadiazoles linked with quinazolin-4-one ring revealed attractive biological properties among which analgesic and anti-inflammatory activities. Dewangan et al. explored the analgesic and antiinflammatory activity in mice and rats, of two series of quinazolin-4(3H)-ones bearing in the position 3 the 1,3,4-oxadiazole nucleus [62,63]. In the first study [62] compounds **62a-l** (figure 17) were synthesized. Among the twelve synthesized derivatives, compounds **62** showed fair analgesic (38-46% of inhibition) and antinflammatory activities (32-42% of inhibition) in the acetic acid induced writhing reflex method and carrageenan-induced paw edema model respectively even if the best activity was showed by 4,5-dihydro-1,3,4-oxadiazol-2-yl derivatives **63a-d** (figure 17).

a   R= 4-OCH$_3$
b   R= 4-Cl
c   R= 4-NO$_2$
d   R= 4-CH$_3$
e   R=H
f   R= 2-OH
g   R= 2-NH$_2$
h   R= 3-OCH$_3$, 4-OH

63a-d

a   R= C$_6$H$_5$ R$_1$= 2-OH
b   R= C$_6$H$_5$ R$_1$= 3OCH$_3$, 4-OH
c   R= C$_6$H$_5$ R$_1$= 2-OH
d   R= CH$_3$ R$_1$= 2-=OH

64a-h

65i-p

66a-f

a   R= H
b   R= Cl
c   R= OCH$_3$
d   R= CH$_3$
e   R= NO$_2$
f   R= F

a R= 4-OCH$_3$	**g** R= 2-NH$_2$	**l** R= 4-CH$_3$
b R= 4-Cl	**h** R= 3-OCH$_3$, 4-OH	**m** H
c R= 4-NO$_2$	**i** R= 4-OCH$_3$	**n** 2-OH
d R= 4-CH$_3$	**j** R= 4-Cl	**o** R= 4NH$_2$
e R=H	**k** R= 4-NO$_2$	**p** R= 3-OCH$_3$, 4-OH
f R= 2-OH		

67a-o

a R=H R$_1$=H	**i** R= CH$_3$ R$_1$= Cl
b R=H R$_1$= CH$_3$	**j** R= OCH$_3$ R$_1$= H
c R=H R$_1$= Cl	**k** R= OCH$_3$ R$_1$= CH$_3$
d R= Cl R$_1$= H	**l** R= OCH$_3$ R$_1$= Cl
e R= Cl R$_1$= CH$_3$	**m** R= N(CH$_3$)$_2$ R$_1$= H
f R= Cl R$_1$= Cl	**n** R= N(CH$_3$)$_2$ R$_1$= CH$_3$
g R= CH$_3$ R$_1$= H	**o** R= N(CH$_3$)$_2$ R$_1$= Cl
h R= CH$_3$ R$_1$= CH$_3$	

Figure 19. General structure of compounds **63a-d, 64a-h**, **65i-p**, **66a-f** and **67a-o**.

Dewangan et al. also studied the analgesic and antinflammatory activities of Schiff bases of 3-(1,3,4-Oxadiazol-2-yl)quinazolin-4(3*H*)-ones [63]. The rationale of this study is based on the well-known biological activities of 1,3,4-oxadiazole and 4(3H)-quinazolinone nuclei but also on capacity of the Schiff bases to produce a broad range of biological activities. Sixteen Schiff bases of 3-(1,3,4-oxadiazol-2-yl)quinazolin-4(3*H*)-ones **64a-h** and **65i-p** (figure 19), were synthesized and tested in animal studies (mice and rat) to evaluate their potential as analgesic and antinflammatory

agents. Compared with the other derivatives, compounds **65i** and **64f** showed more potent analgesic and antinflammatory activity respectively.

3.4. Anticonvulsant activity.

1,3,4-oxadiazole ring linked to the quinazoline-4(3H)-one nucleus are also of considerable interest as anticonvulsant agents for the treatment of seizures[64,65]. In particular, the new 2-phenyl-3-(5-(4-substituted-phenyl)-1,3,4-oxadiazol-2-yl)quinazolin-4(3H)-ones **66a-f** (figure 19) were synthesized and tested in the maximal electroshock induced seizures (MES) and subcutaneous pentylenetetrazole (sc PTZ) induced seizure models in mice by Gupta et al. [64]. Among the synthesized compounds, derivatives **66a** and **66f** resulted as the best anticonvulsant agents at 300 mg/kg body weight even if the second one showed also neurotoxicity at the same dose. The authors highlighted the importance of the electronegativity of 4-phenyl substituent: the higher the electronegativity the greater anticonvulsant activity and duration of action. A similar study has been conducted by Kashaw et al. [65] which synthesized derivatives **67a-o** (figure 19) and evaluated them for their anticonvulsant, neurotoxicity, sedative-hypnotic, and phenobarbitone-induced hypnosis potentiation test activities. The results showed how all compounds **67a-o** (figure 19) are endowed with more potent sedative, hypnotic and CNS-depressant activity compared with anticonvulsant, being compounds **67e** and **67o** the only ones with significant anticonvulsant activity in MES screen after 0.5 hours at 300 mg/kg and 100 mg/kg, respectively. Unfortunately, compound **67o** showed also neurotoxicity after 0.5 hours at 100 mg/kg.

4. Quinazolin-4(3*H*)-ones substituted in the 3rd position with a pyrazole, triazole, tetrazole indazole or benzimidazole nucleus.

Pyrazole, triazole, tetrazole or indazole are five-membered rings in which there are two to four nitrogen atoms. These nitrogen-containing heterocycles are excellent substituents for the third position of quinazolin-4(3*H*)-ones endowed with biological activity. In particular, examples of 1*H*-

pyrazol-3-yl-, 1,2,4-triazol-3-yl-, 1,2,3,4-tetrazol-5-yl-, 1,2-indazol-3-yl-, and 1,3-imidazol-2-yl-quinazolin-4(3*H*)-ones (figure 20) are reported as anticancer, antinflammatory, antiulcer agents, and for Alzheimer, schizophrenia and sleep disorders.
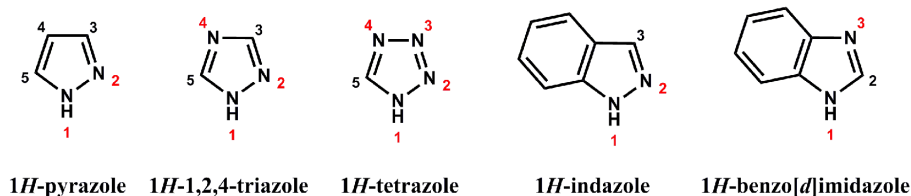

1*H*-pyrazole   1*H*-1,2,4-triazole   1*H*-tetrazole   1*H*-indazole   1*H*-benzo[*d*]imidazole

Figure 20. Possible five-membered rings, in which there are two to four nitrogen atoms, linked to the quinazolin-4(3*H*)-one nucleus.

4.1. Anticancer activity.

Several compounds containing the pyrazole or tetrazole ring on the 3rd position of quinazolinone nucleus are good candidates to develop new anticancer agents [66-69]. One of the most frequent mechanisms observed in human malignancy is the abnormal activation of the PI3K/AKT pathway. This anomaly is the basis of the tumorigenesis, cancer progression, and resistance. In the PI3K/AKT pathway, the activation of the phosphoinositide 3-kinase (PI3K) causes phosphorylation of the ATK protein and consequently a number of downstream effects. A lot of known factors can enhance or antagonize the PI3K/AKT pathway. Among these, factor PTEN which is often deficient in cancer cells elicit an over activation of the PI3K/AKT pathway [70]. The attenuation of this pathway by inhibitors can lead to several benefits in cancer treatment. Four different class, namely class I , II, II and IV, of PI3K are known and among these the class I is somehow involved in cancer. In particular, class I PI3Ks is further divided between IA and IB subsets which in turn are splitted in several isoforms. This diversity is responsible of the side effects resulting in dose reductions which in turn causes reduction in activity. It is described [66,67] the synthesis of new potent, selective, and metabolically stable PI3Kβ inhibitors starting from the previously described PI3Kδ-selective inhibitor Idealisib. The selectivity has been achieved considering that, in the hydrophobic region II of PI3K, only the isoform β has the variation Asp856. Adding a hydrogen bond donor to the inhibitor allow to form an interaction with Asp856 causing a 1000-fold
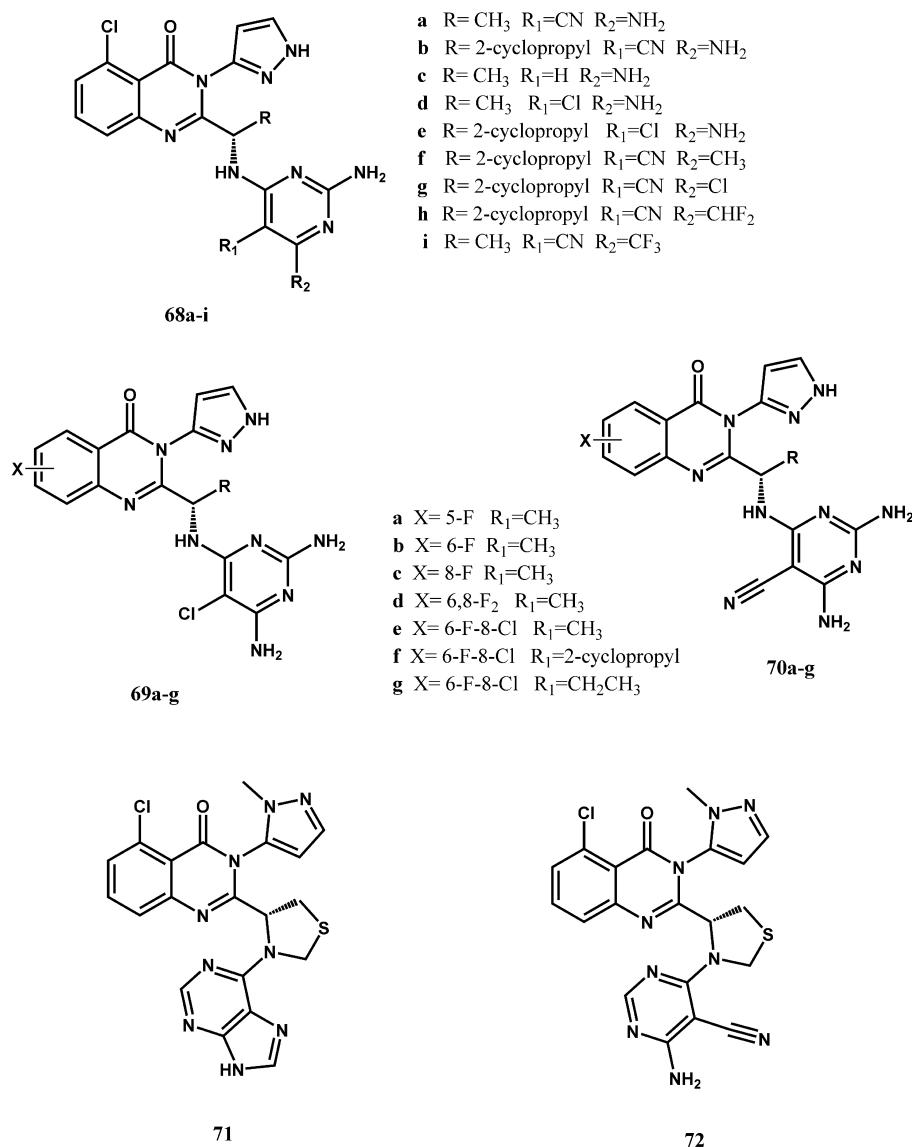
improvement in PI3Kβ potency. To substitute the phenol group, responsible of pharmacokinetic and/or toxicological limitations, pyrazol-3-yl and pyrazol-4-yl moieties are good substitutes as hydrogen bond donor. Among these, the best was the pyrazol-3-yl moiety owing to their lower selectivity for the PI3Kα isoform. Perreault et al. [66,67] also investigate alternative substitutions around the pyrimidine hinge binder (figure 21).
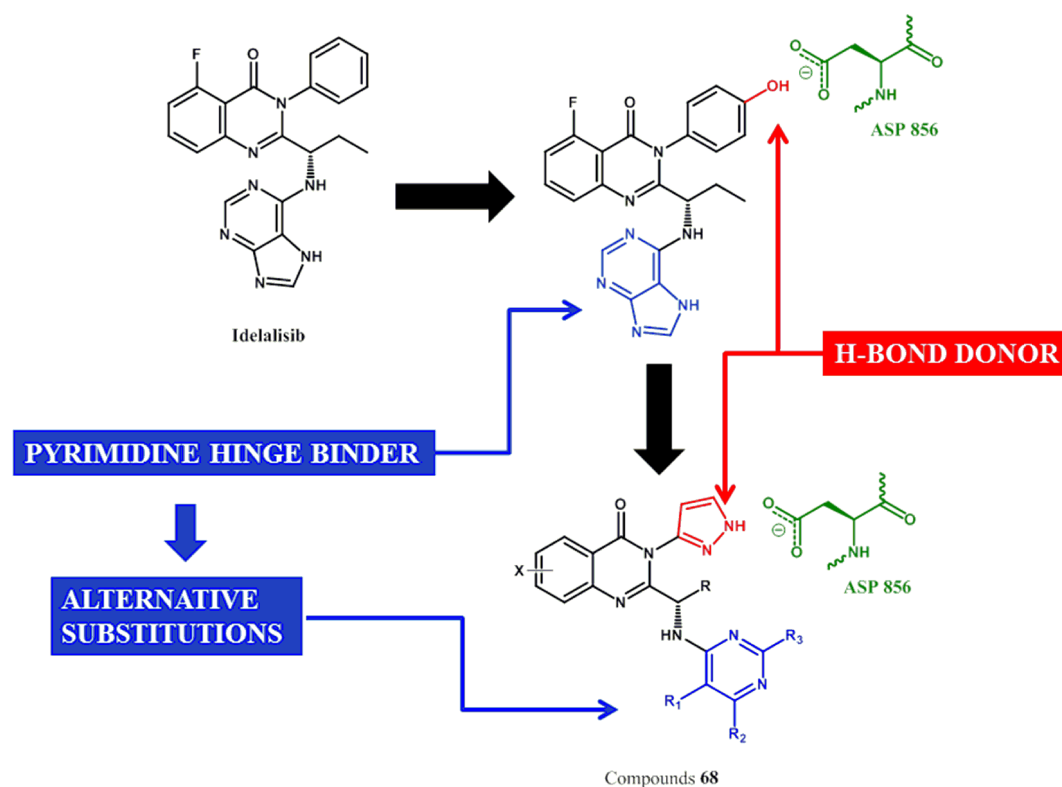
Figure 21. Optimization of PI3Kβ-selective inhibitors.

This resulted in the synthesis of the twenty-three compounds **68a-i**, **69a-i** and **70a-i** (figure 21) which led to the optimization of pyrimidine hinge binder and the subsequent improvement of the isoform selectivity. This has allowed the discovery of compound **69e** (figure 22) as potent and selective inhibitor of PI3Kβ/δ with good pharmacokinetic properties and efficacy in a human PTEN-deficient LNCaP prostate carcinoma xenograft tumor model.

Other quinazolinones containing the pyrazole ring on the 3rd position, namely compounds **71** and **72** (figure 22), are useful to treat disease in which the PI3K/AKT pathway is involved, being **71** selective for PI3Kδ (table 4) [68].

a R= CH₃ R₁=CN R₂=NH₂
b R= 2-cyclopropyl R₁=CN R₂=NH₂
c R= CH₃ R₁=H R₂=NH₂
d R= CH₃ R₁=Cl R₂=NH₂
e R= 2-cyclopropyl R₁=Cl R₂=NH₂
f R= 2-cyclopropyl R₁=CN R₂=CH₃
g R= 2-cyclopropyl R₁=CN R₂=Cl
h R= 2-cyclopropyl R₁=CN R₂=CHF₂
i R= CH₃ R₁=CN R₂=CF₃

68a-i

a X= 5-F R₁=CH₃
b X= 6-F R₁=CH₃
c X= 8-F R₁=CH₃
d X= 6,8-F₂ R₁=CH₃
e X= 6-F-8-Cl R₁=CH₃
f X= 6-F-8-Cl R₁=2-cyclopropyl
g X= 6-F-8-Cl R₁=CH₂CH₃

69a-g

70a-g

71

72

Figure 22. General structure of compounds **68a-i**, **69a-g**, **70a-g**, **71** and **72**.

Table 4. Enzymatic and cellular assays on compounds **71**, **72**, **84** and **85**.

	Enzymatic assay			Cellular assay		
Comp.	PI3Kα	PI3Kδ	PI3Kγ	PI3Kα	PI3Kδ	PI3Kγ
71	>9.1	0.056	0.42	>10	0.222	nt
72	>10	7.2	>10	>10	>10	nt
84	>10	0.082	>10	>10	0.262	nt
85	>10	0.140	1.1	>10	0.509	nt

nt not tested.

4.2. Antinflammatory and analgesic activity.

Potential non-steroidal anti-inflammatory and analgesic activity among the quinazolin-4(3*H*)-ones 3-substituted with 4*H*-1,2,4-triazole and 3-indazole rings is reported [71,72]. In the first study, the combination of the well-known antinflammatory and analgesic quinazolinones with other biologically active heterocyclic nuclei, such as thiazolidinone, azetidinones and Triazole rings led to the new series of quinazolinone derivatives **73a-l**, **74a-l** and **75a-l** (figure 23) [71]. Compounds **73**, **74** and **75** were studied *in vivo* for their anti-inflammatory, analgesic and ulcerogenic activity as well as for their acute toxicity. Varying degree of anti-inflammatory activity against carrageenan-induced edema have been detected in the range of 10-46% at a dose of 50 mg/kg given orally. Compounds **73g** and **74g** showed the best antinflammatory activity which is greater than phenylbutazone as well as good analgesic activity. They also resulted less ulcerogenic compared to phenylbutazone and very safe with an approximate lethal dose greater than 1400 mg./kg. p.o..

In vitro antinflammatory activity by inhibitory activity test against COX-1 and COX-2 was evaluated on 3-indazolyl-substituted 4(3*H*)-quinazolinones [72]. Data reported in this study showed how, the 3-(indazol-3-yl)-quinazolin-4(3*H*)-one derivatives **76a-d** (figure 23) possess a moderate COX2 selectivity with a selectivity index (SI= IC50COX-1/ IC50COX-2) of 3.59, 2.55 and 1.05 for **76b**, **76c** and **76d** respectively.

Antinflammatory activity was also showed when the 4(3H)-quinazolinone ring is substituted in the 3rd position with benzimidazole moiety [73]. Based on the well-known antinflammatory activity showed by the quinazolinone and benzimidazole rings, a rationale design led to the synthesis of compounds **77a-h** (figure 23) starting from the two potent anti-inflammatory agents rutaecarpine and diproqualone (quinazolinone core) and the antimicrobial rings thiabendazole and benzimidazole ring). The majority of compounds **77** showed good to moderate anti-inflammatory activity being **77b,c,f,h** the most promising. Derivatives **77b** and **77f** resulted equivalent to the prednisolone.

Good analgesic activity was shown also by compound **78**, synthesized and tested in the Eddy's hot plate test by Thirugnanasambanthan and Sankarnarayanan [49].

73a-l

74a-l

75a-l

a R = 2-Cl
b R = 4-Cl
c R = 2-Br
d R = 4-Br
e R = 2,4-Cl$_2$
f R = 2,4-Br$_2$
g R= 2,6-Br$_2$
h R= 2,6-Cl$_2$
i R= 2-OCH$_3$
j R= 4-OCH$_3$
k R= 2-CH$_3$
l R= 4-CH$_3$

77a-h

a R= CH$_3$ R$_1$= H R$_2$= H
b R= CH$_3$ R$_1$= Br R$_2$= Br
c R= CH$_3$ R$_1$= Cl R$_2$= Cl
d R= C$_6$H$_5$ R$_1$= H R$_2$= H
e R= C$_6$H$_5$ R$_1$= Br R$_2$= Br
f R= C$_6$H$_5$ R$_1$= Cl R$_2$= Cl
g R= CH$_3$ R$_1$= NO$_2$ R$_2$= H
h R= CH$_3$ R$_1$= I R$_2$= H

76a-d

a R = H
b R = CH$_3$
c R = Cl
d R = Br

78

79a R = H
79b R = OCHF$_2$
79c R = OCH$_3$
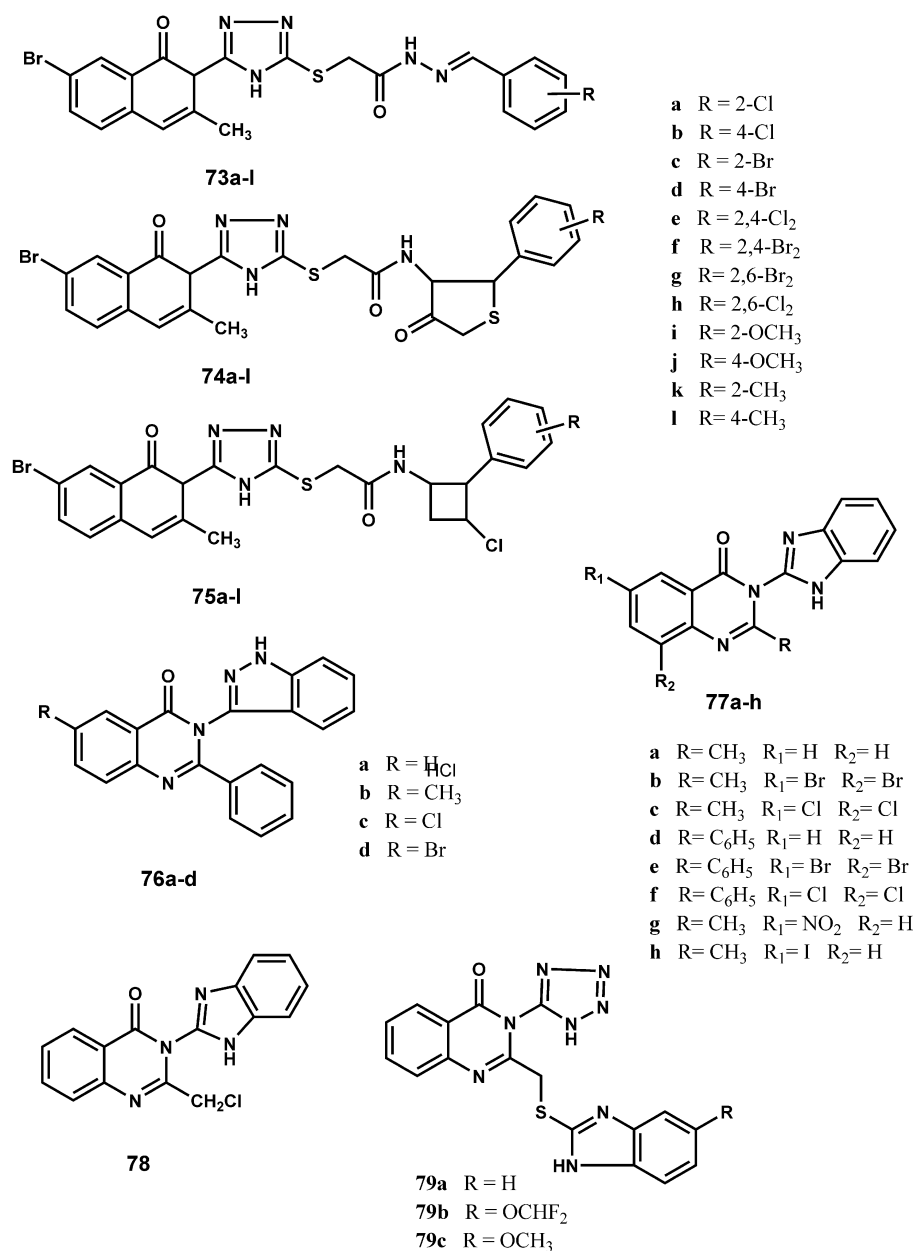
Figure 23. General structure of compounds **73a-l**, **74a-l**, **75a-l**, **76a-d**, **77a-h**, **78** and **79a-c**.

4.3. Antiulcer activity.

The treatment of acute and chronic ulcer conditions has taken several advantage of the biological properties of the quinazolin-4(3*H*)-ones. In particular, the enzyme H+/K+ATPase, responsible for gastric acid production, is a good target to design inhibitors, able to reduce the gastric acid secretion, to be used in anti-ulcer therapy. Some of these inhibitors were developed starting from the combination of two antiulcer and antisecretory agents, that is benzimidazole sulfinyl methyl

pyrimidines with quinazolin-4(3*H*)-ones to give the 3-(1*H*-tetrazol-5-yl)quinazolin-4(3*H*)-ones **79a,b** (figure 23) [74]. These last belong to a set of fifteen compounds variously substituted in the 3rd position of quinazolin-4(3H)-one nucleus. The antiulcer screening was evaluated by three different tests such as pylorus ligation-induced gastric ulcer, aspirin induced gastric ulcer and ethanol-induced gastric ulcer. Acute toxicity (LD50) was also evaluated. Among the tested quinazolinones, compound **79b** resulted in a moderate antiulcer agent with no toxicity. Compounds **79a,b** were also investigated for their antiulcer activity through virtual ligand screening and docking studies [75]. They were inserted, together with **79c** (figure 23), in a selection of fifty one 2-(5-substituted-1*H*-benzo[d]imidazole-2-yl-sulfinyl)methyl-3-substituted quinazoline-4(3H)ones and docked into a generated homology model of H+/K+ ATPase based on the template crystal structure of the sodium-potassium pump. Even if compounds **79a-c** are not among the derivatives which showed higher dock score, they have good docking score. This can be due to the presence of methoxy and difluromethoxy at fifth position of benzimidazole. However, this study can result of utility to be used for virtual screening of antiulcer activity.

5. Quinazolin-4(3*H*)-ones substituted in the 3rd position with a furane, thiophene, benzothiophene, isoxazole or oxazole nucleus.

Several biological properties such as antiinflammatory, antiviral, anticancer, antitubercolar, antioxidant and antimicrobial activity, were reported for quinazolin-4(3*H*)-ones substituted on 3rd position with thiophene, benzothiophene, or isoxazole rings.

5.1. Antinflammatory and analgesic activity.

The antinflammatory activity of 2,3-disubstituted-quinazolin-4(3*H*)-ones, targeting the COX-II, was investigated, by docking procedure, to identify new ligands structurally related to celecoxib [76]. The study has been based on a set of seventy-five quinazolin-4(3H)-one substituted with five or six membered heterocycle in the 3 position. The 3-substituted quinazolinones with a pentatomic

heterocyclic ring in the set were compounds **80a-o** and **81a-o** (figure 24) carrying a furanyl or thienyl ring respectively.
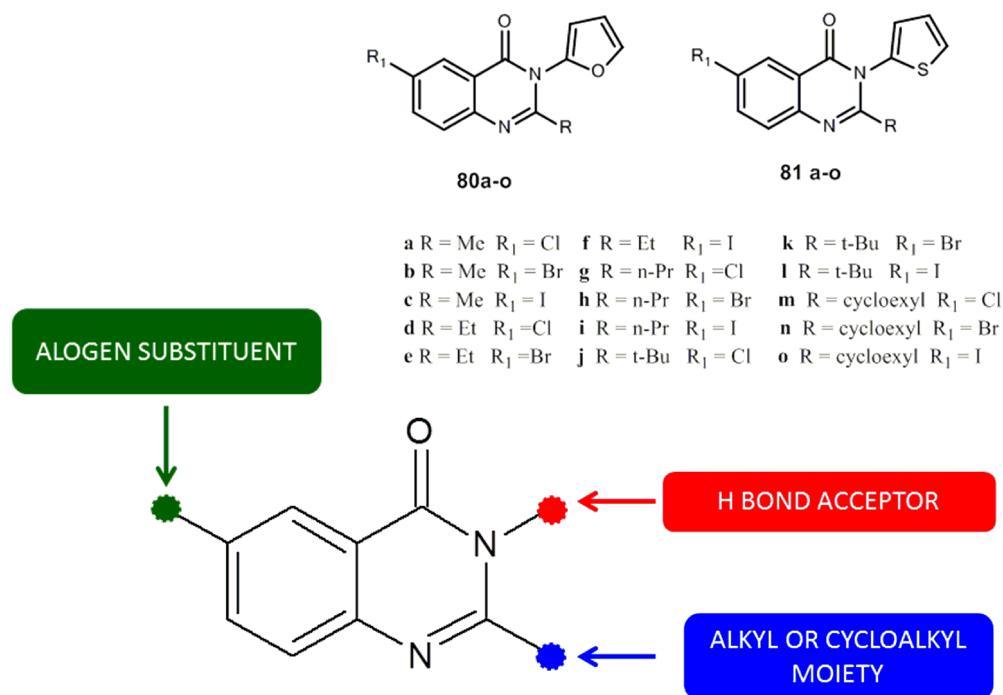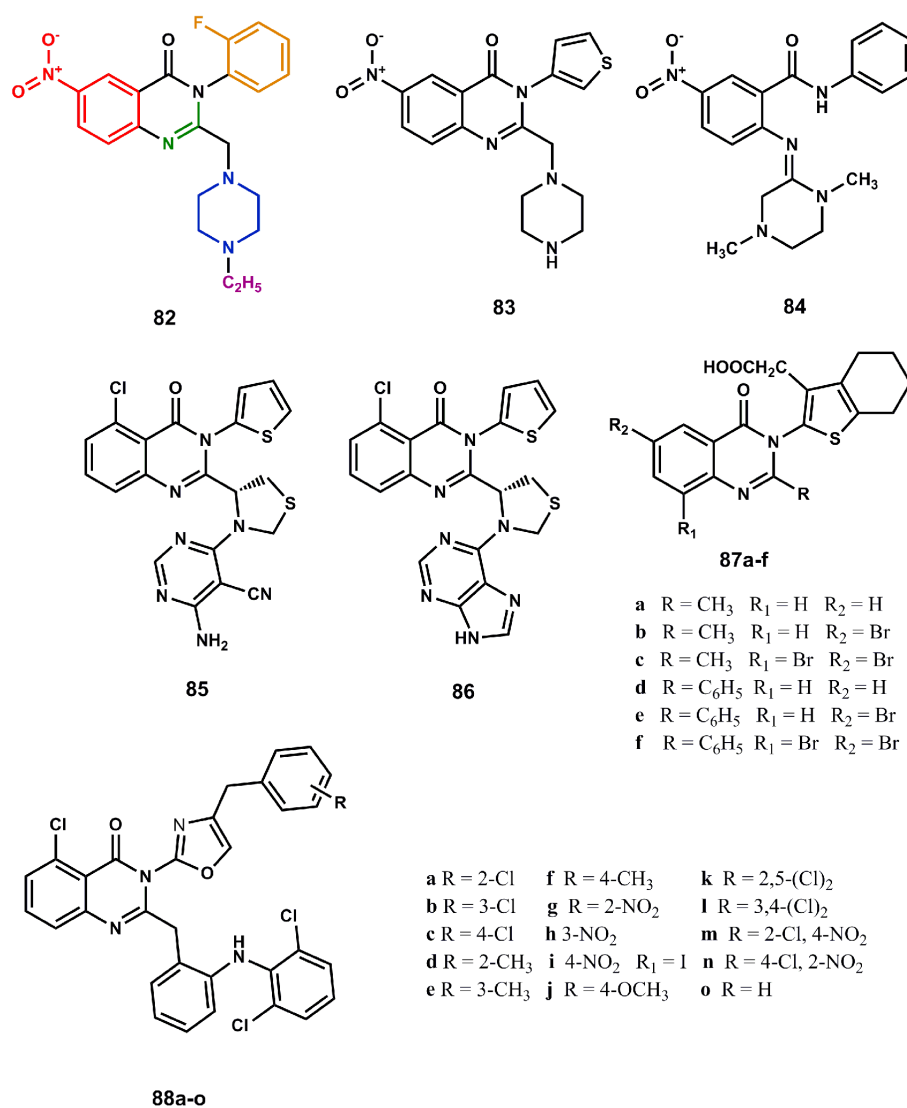

Figure 24. General structure of compounds **80a-o**, **81a-o** and possible substitution on quinazolin-4(3*H*)-one ring.

The study was led by comparing the docking scores and the hydrogen bonds formed among the seventy-five derivatives and the surrounding amino acids of COX-II (PDB id 3LN1). The results showed the importance of the 6-halo substitution irrespective of the halogen substituent. The highest binding energy of ligands was obtained when a cyclo aliphatic substituent, in particular the cycloexyl one, is present in the 2nd position. Finally, the best activity was showed only when in the 3rd position, the heterocycle has a hydrogen acceptor atom. The lack of such hydrogen bond is the major reason for the moderate binding energies to the COX-II binding site of ligands. Thienyl or isoxazolyl ring in the 3rd position (compounds **80** and **81**, figure 24) are able to form such an interaction and are therefore endowed with good binding energy.

5.2. Antiviral activity.

Alphavirus, among which Venezuelan equine encephalitis virus (VEEV) is one of the most significant representatives, can cause significant disease in humans. Due to its easy to be detected in blood and cerebral-spinal fluid samples as well as a good safety margin, VEEV could be useful to facilitate the discovering of new antiviral agents. Schroeder et al. [77], developed a new series of potent inhibitors of venezuelan equine encephalitis virus starting from a high throughput screen which led to the hit compound **82** (figure 25).

Figure 25. General structure of compounds **82**, **83**, **84**, **85**, **86**, **87a-f** and **88a-o**.

Through a optimization process which involved the synthesis of sixty-eight new compounds, the C-6 nitro functionality (red), the N-aryl (orange), the piperazine (blue), the alkylpiperazine appendage

(magenta) and the quinazolinone opening ring to give ammidines (green) groups of compound **82** (figure 25) were examined. Among the synthesized compounds, the 3-thiophenyl quinazolinone **83** showed an IC50 of 1.4 µM in a cell-based assay that measured the ability of a compound to inhibit a VEEV-induced cytopathic effect. The results of their study highlighted the high potent inhibition of the ammidine being compound **84** the most active of the series with an IC50 of 0.03 µM.

5.3. Anticancer activity.

As already reported in the section 4.1, together with several compounds containing the pyrazole or tetrazole ring on the 3rd position of quinazolinone nucleus, also 3-(tiazol-2-yl) ring was reported as good substituent to develop new quinazolinones as anticancer agents [68]. Such derivatives are useful to treat disease in which the PI3K/AKT pathway is involved and, among the other, (5-methylthiophen-2-yl)quinazolin-4(3H)-ones **85** and **86** (figure 25) showed good anticancer activity and selectivity against the PI3K isoforms (table 4, section 4.1).

5.4. Antioxidant activity.

New quinazolin-4(3*H*)-ones substituted in the 3rd position with 4-phenyl thiazole (see section 2.2.4) or 4,5,6,7-tetrahydrobenzothiophene ring were synthesized and tested for the antioxidant activity [52]. In particular, 4,5,6,7-tetrahydrobenzothiophene **87a-f** together with 4-phenyl thiazole **45a-e** (figure 13) derivatives were screened for their DPPH radical scavenging activity to test their antioxidant activity. The best antioxidant activity was showed when bromine, a phenyl ring and benzothiophene ring are present in the quinazolin-4(3*H*)-one nucleus (Figure 26).

For this reason compound **87f**, bearing two bromide atoms in the 6 and 8 positions, the benzothiophene ring in the 3rd position and a phenyl ring in the 2nd position of quinazolinone system resulted endowed with the best antioxidant activity.

5.5 Antimicrobial activity.

Patel and Shaikh studied the antimicrobial activity of 1,3-oxazol-2-yl-quinazolin-4(3H) ones [78-80]. They synthesized derivatives **88a-o** (figure 25) and tested them against some bacterial cell lines (Gram negative: *S. aureus* and *S. pyogenes*; gram positive: *P. aeruginosa* and *E. coli*) as well as fungal species (*C. albicans*, *A. niger* and *A. clavatus*) by Broth dilution method. The biological results highlighted the good antibacterial activity of some derivatives which are comparable or slightly greater than ampicillin. A SAR showed that the compounds substituted with chlorine, a methyl or a nitro group, are more potent than the other compounds.
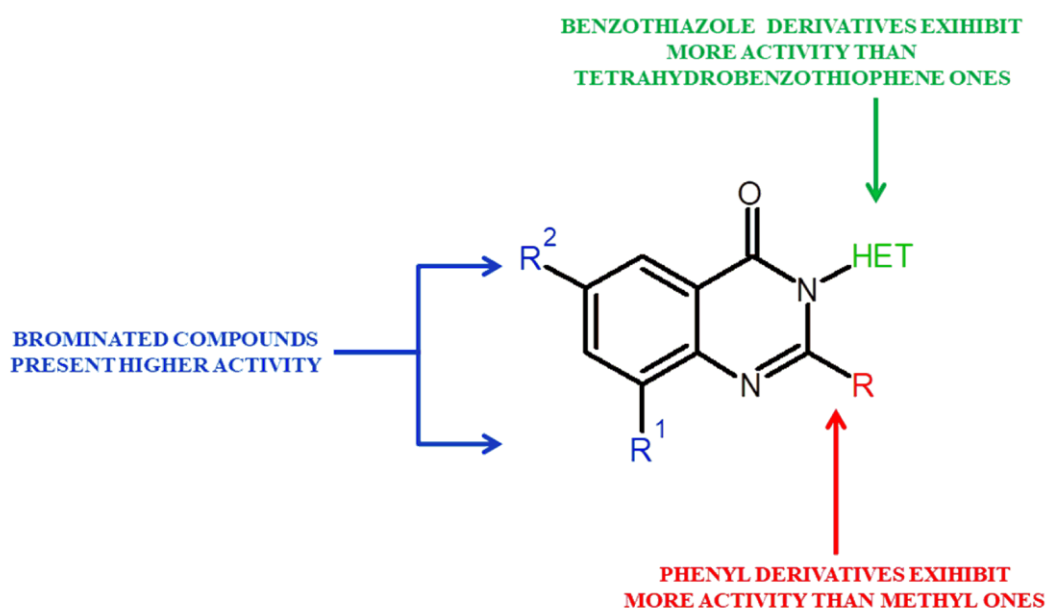
Figure 26. Best modifications to have to optimize antioxidant quinazolin-4(3H)-ones.

6. Conclusion.

In this review we showed the state of art over the past decade of the quinazolin-4(3*H*)-one system as well as the biological properties associated with its 3-substitution with a pentatomic heterocycle. We have wanted to highlight how the quinazolin-4(3*H*)-one ring often represents the central body of the pharmacophore in a very large number of biologically active compounds. Also, owing to the six different opportunities of substitution, this bicyclic system represents a very all-around scaffold to obtain new active compounds with structural diversity. Literature is full of examples of bioactive quinazolin-4(3*H*)-ones with a more or less complex structure. We have narrowed the field on

quinazolin-4-(3*H*)-ones N-3 substituted with a five membered heterocycle or its benzofused derivative with the certainty of having provided a useful tool for medicinal chemists who could use the structures reported in this review as start point to obtain new and more potent compounds.

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FIGURE LEGENDS

Figure 1. Examples of just approved or marketed drugs having the quinazolin-4-one scaffold (in red).

Figure 2. Examples of natural compounds having the quinazolin-4-one scaffold (in red).

Figure 3. Different types of quinazolinones.

Figure 4. Five membered heterocycles as substituents in the 3 position of quinazolin-4(3*H*)-one ring.

Figure 5. General structure of 3-(thiazol-2-yl)quinazolin-4(3*H*)-ones **20** and 3-(benzo[d]thiazol-2-yl)quinazolin-4(3*H*)-ones **21**.

Figure 6. General structure of quinazolinones **22a-c**, **23a-o** and **24a-f**.

Figure 7. General structure of quinazolinones **25a-c**, **26a,b**, **27a-d**, **28**, **29a-l** and **30a-l**.

Figure 8. General structure of quinazolinones **31a,b**, **32**, and **33**.

Figure 9. Molecular hybridization between the quinazolinones and thiadiazole or benzothiazole to obtain more potent anticonvulsant.

Figure 10. General structure of quinazolinones **34**, **35a-j**, **36a-j**, **37**, and **38**.

Figure 11. Pharmacophoric pattern of well-known anticonvulsant agents and compounds **35** and **36**.

Figure 12. Compounds **39** and **40** as template for 2-styryl-quinazolin-4(3*H*)-ones **37** and **38**.

Figure 13. General structure of quinazolinones **41**, **42**, **43**, **44a-b**, **45a-e** and **46a-i**.

Figure 14. General structure of compounds **47**, **48**, **49a-m** and **50a-m**.

Figure 15. Possible isomers of oxadiazole and thiadiazole linked to the quinazolin-4(3*H*)-one nucleus.

Figure 16. General structure of compounds **54a-o**, **55a-h**, **56**, **57a-f**, **58a-f** and **59a-f**.

Figure 17. General structure of compounds **59a-f**, **60a-f**, **61a-c** and **62a-l**.

Figure 18. Rationale to obtain the new EGFR inhibitors 3-(1,3,4-oxadiazol-2-yl)-quinazolin-4(3*H*)-ones.

Figure 19. General structure of compounds **63a-d, 64a-h**, **65i-p**, **66a-f** and **67a-o**.

Figure 20. Possible five-membered rings, in which there are two to four nitrogen atoms, linked to the quinazolin-4(3*H*)-one nucleus.

Figure 21. Optimization of PI3Kβ-selective inhibitors.

Figure 22. General structure of compounds **68a-i**, **69a-g**, **70a-g**, **71** and **72**.

Figure 23. General structure of compounds **73a-l**, **74a-l**, **75a-l**, **76a-d**, **77a-h**, **78** and **79a-c**.

Figure 24. General structure of compounds **80a-o**, **81a-o** and possible substitution on quinazolin-4(3*H*)-one ring.

Figure 25. General structure of compounds **82**, **83**, **84**, **85**, **86**, **87a-f** and **88a-o**.

Figure 26. Best modifications to have to optimize antioxidant quinazolin-4(3H)-ones.

Table 1. Just approved or marketed drugs having the quinazolin-4-one scaffold.

Table 2. Examples of natural products containing the quinazolin-4-one scaffold.

Table 3. Antibacterial activity of compounds **22a-c**.

Table 4. Enzymatic and cellular assays on compounds **71**, **72**, **84** and **85**.