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Article

Quinolinotriazole antiplasmodials via click chemistry: synthesis and *in vitro* studies of 7-Chloroquinoline-based compounds

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Malaria is nowadays one of the most serious health concerns in a global scale and, although there is an evident increase in research studies in this area, pointed by the vast number of hits and leads, it still appears as a recurrent topic every year due to the drug resistance shown by the parasite exposing the urgent need to develop new antimalarial medications. In this work, 38 molecules were synthesized *via* copper(I)-catalyzed alkyne-azide cycloaddition (CuAAC) or "click" chemistry, following different routes to produce 2 different organic azides, obtained from a 4,7 dicholoquinoline, reacted with 19 different commercially available terminal alkynes. All those new compounds were evaluated for their *in vitro* activity against the chloroquine resistant malaria parasite *Plasmodium falciparum* (W2). The cytotoxicity evaluation was accomplished using Hep G2 cells and SI index was calculated for every molecule. Some of the quinoline derivatives have shown high antimalarial activity, with IC_{50} values in the range of 1.72–8.66 μM, low cytotoxicity, with CC_{50}>1000 μM and selectivity index (SI) in the range of 20-100, with some compounds showing SI>800. Therefore, the quinolinotriazole hybrids could be considered a very important step on the development of new antimalarial drugs.

Keywords: 7-Chloroquinolinotriazoles. Quinolines. Click reaction. *Plasmodium falciparum*. Antimalarial activity.

INTRODUCTION

Malaria is a deadly disease that affects mostly third-world countries, being responsible for 219 million cases and 435.000 deaths in 2017 alone, according to the World Health Organization 2018 report (WHO, 2018). The transmission of malaria occurs through blood transfusions or the mosquito bite of the genus *Anopheles* and it is caused by protozoan parasites of the genus *Plasmodium*, including the human parasites *P. malariae, P. ovale, P. knowlesi, P. vivax* and *P. falciparum*. The last two are responsible for the majority of human infections around the world, with *P. falciparum* being the most lethal (Harvard Medical School, 2013).

If not treated soon enough, the *P. falciparum* malaria, can become severe and often leads to death, therefore, it is important to have fast and effective treatment measures. The resistance of *Plasmodium* sp. to different medicines is a constant concern, because it has already shown resistance to previous aminoquinoline drug generations, such as quinine(**1**) and its molecular simplification (Barreiro,

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2002), mefloquine (**2**), mepacrine (**3**) and its well-known molecular simplification chloroquine (**CQ**) (**4**) (2017) (**Figure I**). Other drug classes, including artemisinin and atovaquone have recent cases of resistance (Mishra *et al.*, 2016). Due to this fact, research studies seeking new compounds are increasing, and it is evidenced by the vast number of leads and exploratory drugs against malaria (Okombo, Chibale, 2017).

Once the host is infected, several events take place. Firstly, the parasite goes to the liver and replicates several times until it reaches the blood stream. After that, the parasite settles inside the red blood cells of its host, where it degrades hemoglobin (Hb) to use it as a source of amino acids for its own proteins (Sherman, Tanigoshi, 1970). When the Hb is degraded inside the food vacuole, heme is released and autoxidated in hematin, that is converted by the parasite in hemozoin by biocrystallization (Pagola *et al.*, 2000), which then can be disposed (Brown, 1911). Both free heme and free hematin are toxic to the parasite (Ladan, Nitzan, Malik, 1993), subsequently, the formation of hemozoin is essential to its survival. The chloroquinoline core present in **CQ** is the pharmacophoric group, since it has a binding functionality with hematin (Sullivan *et*

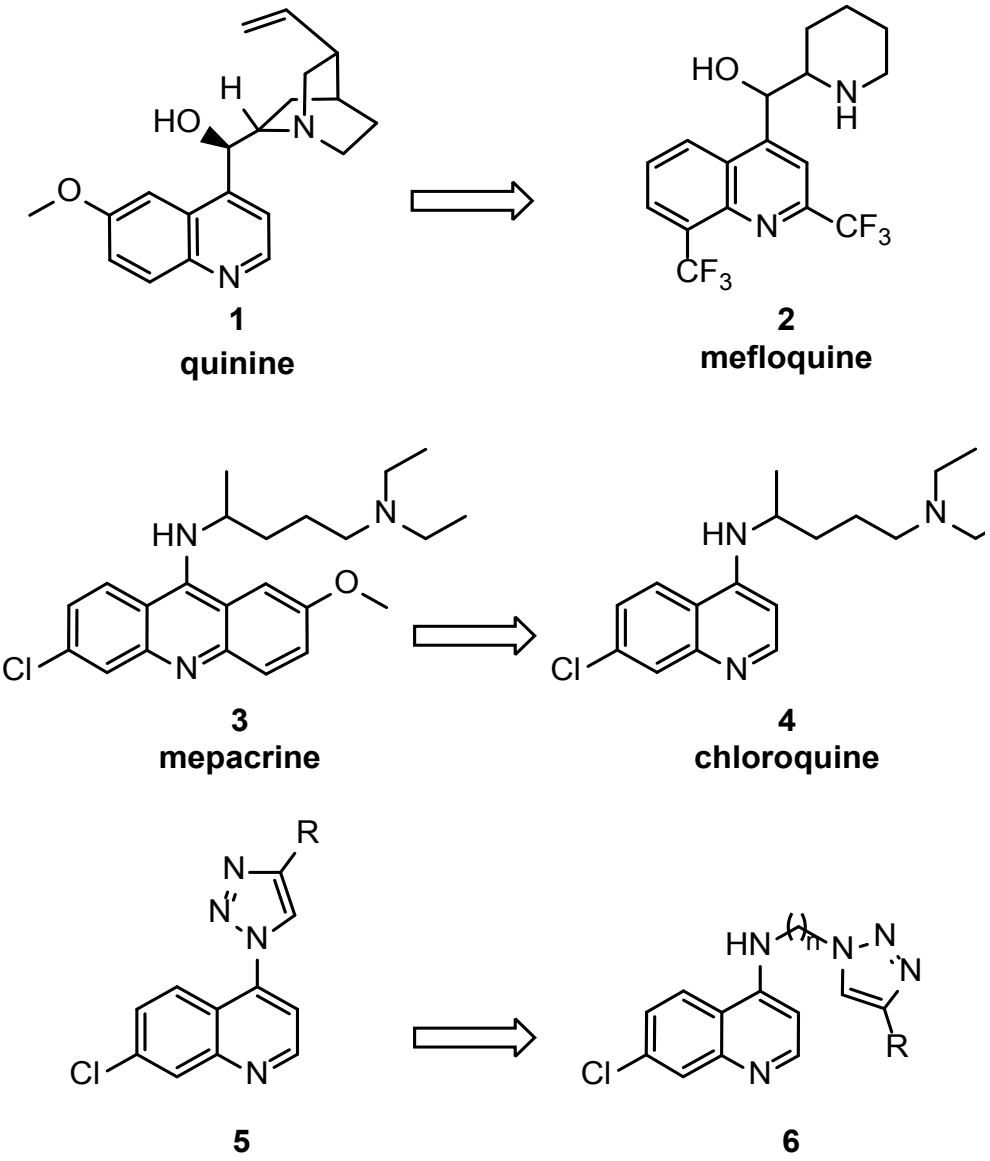

FIGURE 1 – Structures of quinine (**1**), mefloquine (**2**), mepacrine (**3**) chloroquine (**4**), compounds synthesize in previous projects (**5**) and proposed compounds (**6**).

al., 1996), thus preventing the polymerization from the toxic heme (Ziegler, Linckand, Wright, 2001), which then, accumulates inside the food vacuole, leading to parasitic death (Coronado, Nadovichand, Spadafora, 2014). This antimalarial effect is improved by the nitrogen binder in the side chain, increasing the core activity due to electron donation. Besides, **CQ** is widely studied because of its easy preparation and low toxicity and side-effects (Kouznetsov, Gó Mez-Barrio, 2009).

Several compounds were made in some of those studies (Guillon *et al*., 2011; Kumar *et al*., 2008; Melato *et al*., 2008; Pérez *et al*., 2012; Sunduru *et al*., 2009), combining different molecules with **CQ** core with several molecular groups, such as amides (Joshi *et al*., 2013) chalcones (Guantai *et al.,* 2010; Kumar *et al.,* 2017), naphthoquinones (da Silva *et al*., 2012), isatins (Raj *et al.,* 2013), pyrimidines (Chopra, Chibale, Singh, 2018) and also a previous work from the group (Pereira *et al*., 2014), consisting on the union of the triazole moiety straight to the quinoline ring, which has shown that the activity decreased due to inductive and mesomeric effects. More studies have shown that the quinoline nucleus containing achloromoiety at the seventh position and a basic side chain at the terminal position has very good antimalarial activity (O'Neill *et al*., 1998). Despite many molecules with the chloroquinoline core were already made, containing small modifications in the side chain (Manohar, Khanand Rawat, 2011), there are still many different groups in the end of these chairs that still need to be exploited.

Thereby, several molecules have been made to fulfill this approach, this time with an aliphatic chain containing 2 or 3 carbons between these centers, becoming more similar to chloroquine, as well as a nitrogen linker, that improves activity due to its capability of donating electron density to the ring, raising the antiplasmodial activity. These new compounds were made using the process known as Cu-mediated "click" chemistry (Rostovtsev *et al*., 2002), which is presently being extensively used (Kolb, Finnand, Sharpless, 2001), as well for the enhancement of the activity in natural products (Bakka *et al*., 2017; Hou *et al*., 2017; Mistry, Pateland, Keum, 2017; Yamada *et al*., 2016). This method made it possible to easily produce hybrid molecules by combining several terminal alkynes and two different organic azides, with a chloroquinoline core and a side chain linked at the terminal position, with changes in the number of carbon atoms. Once it a study has shown that hybrid compounds present advantages over a single drug or multicomponent combination therapy related to drug resistance, solubility and formulation (Chopra, Chibale, Singh, 2018), hence the click chemistry emerged as a promising alternative on antimalarials chemotherapy.

CHEMISTRY

The building blocks for the final molecules (**9**) were obtained through a synthesis route started with the commercial reagent 4,7-dichloroquinoline (**6**). The inception of a carbonic chain was carried out using ethanolamine and 3-amino-1-propanol providing a 4-aminoquinoline (**7**) and then the hydroxyl moiety was replaced for bromine (**8**) with hydrobromic acid in toluene. At the end, an azide was introduced to the molecule through a bimolecular nucleophilic substitution (S_N2) providing the key intermediaries for the synthesis (Figure 2).

The final products were obtained through click chemistry according to the methodology described by Sharpless and co-workers (Rostovtsev *et al*., 2002) that consists on a Cu(I)-catalyzed azide-alkyne 1,3 dipolar cycloaddition (CuAAC) and provided *1,2,3*-triazole 1,4 disubstituted hybrids (Melato *et al*., 2008; da Silva *et al*., 2012; Sunduru *et al*., 2009). The reactions of the obtained azide and commercial alkynes were carried out in methanol and water, in the presence of $CuSO_4.5H_2O$, $NaHCO_3$ and ascorbic acid, stirring at room temperature overnight. Afterwards, the products were purified via chromatographic column and the yields varied around 68 to 89% (Figure 3).

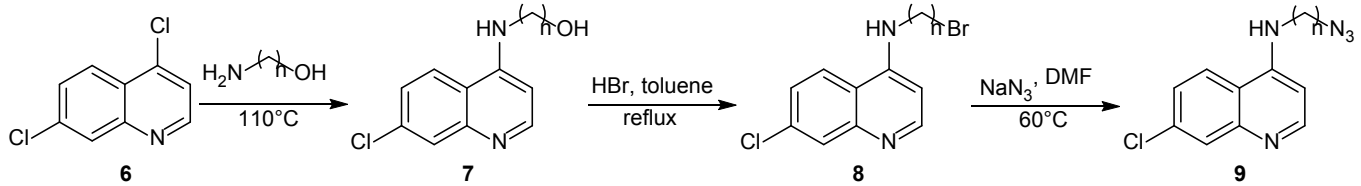

FIGURE 2 – Obtainment of the building block (**9**) from 4,7-dichloroquinoline employed on the synthesis.

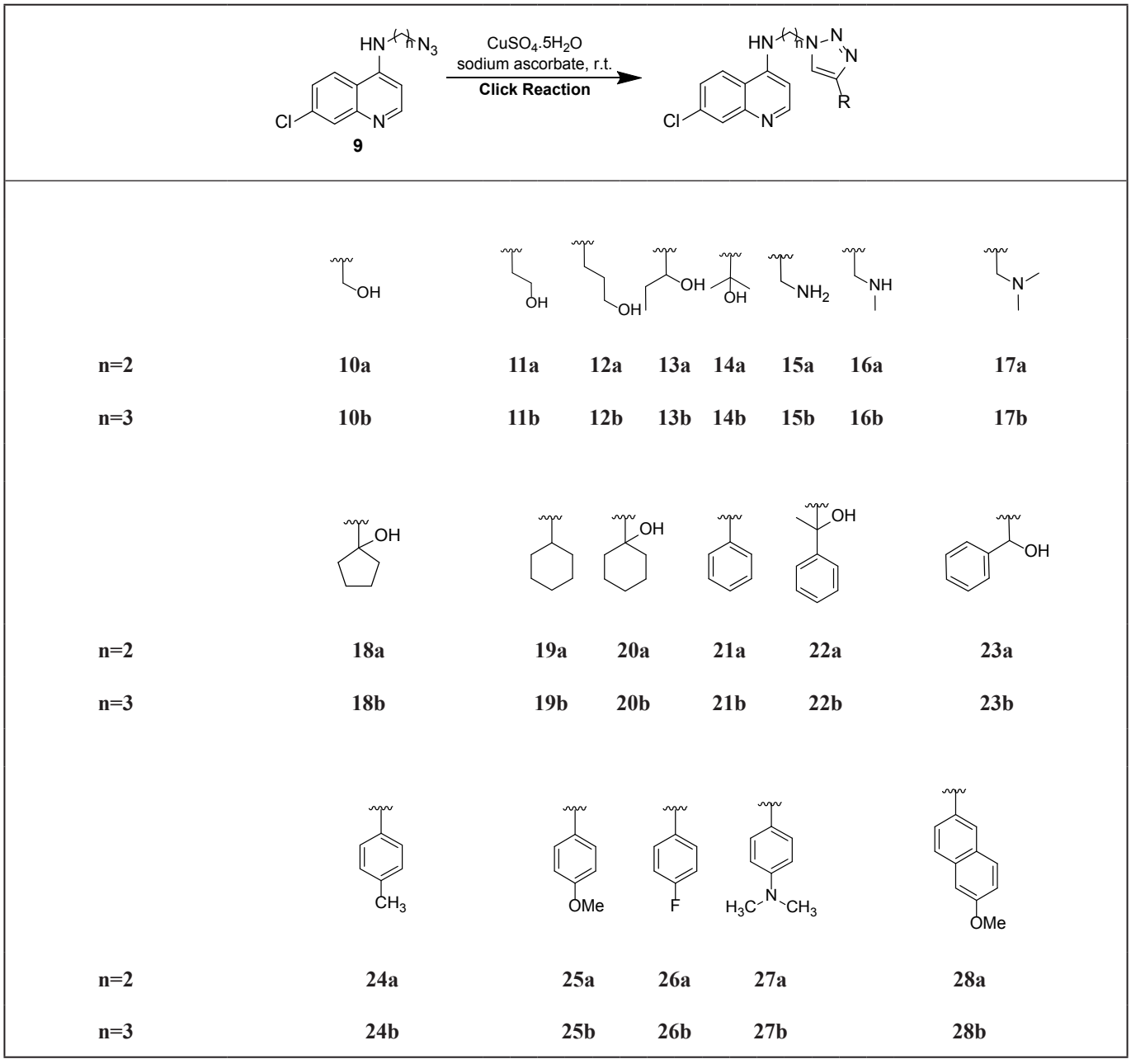

FIGURE 3 – Obtainment of quinolyl triazole hybrids *via* click reaction.

The aminoquinolinotriazole hybrid structures were assigned on the basis of spectrometric data including HRMS-ESI-IT-TOF, IR, ^{1}H and ^{13}C NMR.

BIOLOGICAL ACTIVITY

Continuous cultures of *Plasmodium falciparum*

The chloroquine-resistant and mefloquine-sensitive (De Andrade-Neto *et al.*, 2004) *P. falciparum* W2 clone was kept in a continuous culture at 37 ºC in human erythrocytes using the candle jar method (Trager, Jensen, 1976). The antimalarial effect of the compounds was measured by the pLDH assay (Noedl *et al.*, 2005). The parasites were kept in complete culture medium (RPMI) containing hypoxanthine (300 µM), sodium bicarbonate (21 mM), HEPES (25 mM), gentamicin (40 µg/mL) and D-glucose (11 mM), which were supplemented by 10% human plasma on culture dishes, with daily changes of medium. All experiments were performed in

triplicate. The compounds were tested in triplicate at each concentration. The cultures with predominantly ring-stage parasites were concentrated by sorbitol-synchronization (Lambros, Vanderberg, 1979). A suspension of red blood cells with 1.5% hematocrit and 0.05% parasitemia was distributed in a 96-well microtiter plate (180 µL/well). The parasite growth was evaluated by the pLDH assay, as summarized below.

Evaluation of the *in vitro* antimalarial activity by the pLDH assay

The antimalarial effects of the compounds and controls were measured by the lactate dehydrogenase of *Plasmodium falciparum* (pLDH) assay as previously described (Piper *et al.*, 1993), with slight modifications. Briefly, ring-stage parasites in sorbitol-synchronized blood cultures were added to 96-well culture plates at 1% hematocrit and 2% parasitemia and then incubated with the test drugs that were diluted in complete medium, from 50 mg/mL stock solutions in DMSO, at a final concentration of 0.002% (v/v) and stored at –20 ºC. After 48 h of incubation, the plates were frozen at –20 ºC for 24 h and thawed for the pLDH assay. The hemolyzed cultures were transferred to another 96-well culture plate. Then, Malstat® reagents, tetrazolium nitroblue and phenazine etazulfate salt (NBT/PES) were added. After 1 h of incubation at 37 ºC in the dark, the absorbance was read at 570 nm in a spectrophotometer (Infinite®200 PRO, Tecan). The results were evaluated with the software Microcal Origin 8.5 for determination of the dose-response curves plotted with sigmoidal fit (de Pilla Varotti *et al.*, 2008). The IC_{50} was determined by comparison with the controls using standard drugs and without drugs.

Cytotoxicity evaluation in human hepatoma cell cultures – Hep G2 cells

The hepatoma cells Hep G2 were maintained in 75 cm^2 sterile culture flasks (Corning®), in 5% CO_2 and at 37 ºC, with RPMI 1640 culture medium supplemented with penicillin (10 U/mL), streptomycin (100 g/mL) and 5% FBS, the medium being changed twice a week. The cells were maintained in weekly passages (at 1:3 dilutions in sterile culture flasks) and grown to 80% (Twentyman, Luscombe, 1987). After being trypsinized (0.05% trypsin/0.5 mM EDTA) and plated on 96 well microplates (Calvocalle *et al.*, 1994), they were used for experiments. When confluent, the monolayers were trypsinized, washed, counted, diluted in complete medium, distributed in 96-well microplates (4 x 103 cells/well) and then incubated for another 24 h at 37 ºC. The test samples and controls were diluted to a final concentration of 0.02% DMSO in culture medium to yield four concentrations in serial dilutions starting at 1000 mg/mL. After24 h incubation at 37 ºC, 18 µL of MTT solution (5 mg/mL in PBS) were added to each well, followed by another 90 min incubation at the same temperature. Then, the supernatant was removed and 180 µL of DMSO were added to each well. The culture plates were read in a spectrophotometer with a 570 nm filter (Twentyman, Luscombe, 1987). The minimum cytotoxicity concentration was determined as described previously, with minor modifications (DMSO was used instead of ethanol for solubilizations and chloroquine was used instead of primaquine for the positive control). Each test was performed in duplicate, the concentration that killed 50% of the cells (CC_{50}) was determined (Madureira *et al.*, 2002). Then the selectivity index (SI) for the antimalarial activity was calculated based on the ratio between CC_{50} and IC_{50} for the *in vitro* activity against *P. falciparum* (de Sá *et al.*, 2009).

RESULTS AND DISCUSSION

The initial proposed route using mesylation was optimized through the substitution of this step for the bromination, being far more easily to obtain the intermediate employed in the final compounds. The size influence of the side chain was taken in consideration for this work. After synthesize molecules with side chains with 2 carbon atoms, a different approach was made with a 3-carbon atom side chain, since it is more similar to chloroquine. The thirty-eight quinolinotriazole hybrids obtained had their antiplasmodic activity evaluated *in vitro* against *P. falciparum* W2 strain sensitive to mefloquine and chloroquine-resistant. The values of CC_{50} for the cytotoxicity (Hep G2A16 cells), IC_{50}values according to pLDH method and the respective SI of the molecules are shown in Table I.

TABLE I – Quinolinotriazole products 10-28, *in vitro* antimalarial activity (IC50 μM) against P. falciparum (W2 clone), cytotoxicity (CC50 μM, Hep G2A16 cells) and selectivity index (SI)

	IC_{50}	CC_{50}	SI		IC_{50}	CC_{50}	SI
10a	21.84±1.10	>3299.15	>151.06	**10b**	29.49±3.06	788.62	26.74
11a	15.86±1.45	>1438.17	>91.94	**11b**	37.93±1.99	810.80±6.87	21.37
12a	140.60±3.02	>3020.09	>21.48	**12b**	33.14±1.53	806.20±14.64	24.32
13a	36.39±6.83	781.08	21.46	**13b**	34.39±2.72	>869.21	>25.27
14a	39.13±0.13	>1018.16	>26.02	**14b**	16.31±0.15	425.90±7.12	26.11
15a	29.36±4.34	534.19	18.19	**15b**	18.88±0.57	97.38±16.16	5.16
16a	7.78±2.28	109.89	14.12	**16b**	7.35±1.06	75.48±4.44	10.28
17a	5.66±0.39	272.73	48.15	**17b**	6.84±0.14	790.81±14.53	115.56
18a	47.60±1.27	>2798.88	>58.80	**18b**	7.50±0.39	>1007.33	>134.31
19a	7.94± 0.30	>2815.60	>354.61	**19b**	6.58±1.55	78.66±6.22	11.95
20a	38.55±2.37	>1064.37	>27.61	**20b**	6.85±0.46	736.60±2.02	107.50
21a	12.90±1.60	>2858.64	>221.60	**21b**	2.03±0.30	>2748.39	>1351.35
22a	12.62±3.40	332.17±26.25	25.53	**22b**	12.53±4.14	97.40±18.68	7.77
23a	35.72±2.92	>2632.61	>73.69	**23b**	26.07±5.03	534.68±9.17	20.51
24a	17.70±1.40	>2754.12	>155.60	**24b**	17.12±0.06	>2650.18	>154.80
25a	64.90±2.83	20.81±1.80	0.32	**25b**	32.38±2.62	84.60±2.31	2.61
26a	8.66±0.92	>2723.22	>314.46	**26b**	4.98±0.70	>4048.79	>813.01
27a	6.98±0.26	>2549.79	>365.30	**27b**	11.80±1.71	>2462.07	>208.65
28a	1.72±0.39	75.52±9.31	43.89	**28b**	15.16±0.36	70.00±3.82	4.61
CQ	0.28	364.96	1297.11				

[a]IC50: concentration that inhibits 50% of the parasite growth in relation to control cultures with no drugs.
[b]CC50: concentration that kills 50% of HepG2 cells, 24 h after incubation with the compounds determined by the MTT method.
[c]SI: Selectivity Index = CC_{50}/IC_{50}.

Despite, other groups have already exploited triazol quinolinic moieties similar to these compounds, therefore, it is essential to fulfill the empty spaces and investigate small changes that could answer a number of questions in the path of finding new antimalarial drugs. Several side chain groups were produced including aliphatic and aromatic moieties, alcohol, halide, amine and ether side chain compounds. The most active compound (**21b**) was ever more active then **CQ** and its SI of 1351.35 demonstrate a promising compound for future *in vivo* evaluation. In addition, a similar compound (**26b**) containing 3 side chain carbons and a phenyl substituted group also had promising results.

SAR analysis of the most active compounds confirmed that side chain containing 3 carbons and a phenyl group increase activity and future work could exploit other substitutions in the aromatic ring. The most active compounds containing 2 side chain carbons are a ciclohexyl moiety (**19a**) and a napthyl substituted moiety in the end, demonstrating a pattern that a hydrophobic pocket might be responsible for the most active compounds in this study. Molecules containing different amines (**15**, **16** and **17a** and **b**) were also active and their SAR with **CQ** demonstrated that the inclusion of a triazol ring between this amine and quinoline group increase cytotocixity and low SI. Previous work from this group, demonstrated that some quinolyl terminal alcohol compounds were active, but in this work, it could be concluded that despite moderate results, other substitutions were more promising. Several aromatic side chain compounds were evaluated, including compounds **21-28a 21-28b** and they showed more promising results than the non-aromatic side chains. Thirteen compounds presented IC_{50}<10 μM. By analyzing the selectivity index, it is possible to assume that the most promising compounds were **21b** and **26b** with SI of 1351.35 and 813.01 respectively, the first one being more selective than **CQ**.

The resistance to the currently used drugs and the complex life cycle are the main reasons that *Plasmodium* sp is responsible for most deaths caused by malaria. For this reason, the research of new effective antimalarial drugs is of essential and scientists all over the world are using different approaches and methods to create a compound to satisfy this need.

The concept used in this work was the design of new molecules, created of a chroloquinoline moiety, known for its antimalarial activity, linked with different side chains containing 2 or 3 carbon atoms to prevent the decreasing of activity due to inductive and mesomeric effects, a nitrogen atom to donate density to the ring and a chloro moiety at the seventh position of the ring, improving even more the antimalarial effect. Several commercially terminal alkynes were then combined with this core *via "*click" chemistry by the copper(I)-catalyzed alkyne-azide cycloaddition (CuAAC) reaction, creating unprecedented ntiplasmodial hybrid drugs. Triazole quinolyl molecules are a promising class of molecules in finding new antimalarial prototypes.

CONCLUSION

The search for a new arsenal of antimalarial medicines with effectiveness is an important approach. Thus, small changes in existing molecules is an interesting procedure to find new molecules.

Thus, new molecules were created based on chloroquinoline moiety, known for its antimalarial activity. Created molecules have side chains containing 2 or 3 carbon atoms still containing a nitrogen atom linked to 7-cloroquine core. The introduction of the triazole in the end of these aliphatic chairs produced several interesting molecules. This approach used commercially terminal alkynes *via "*click" or copper(I)-catalyzed alkyne-azide cycloaddition (CuAAC) reaction, thus creating unprecedented antiplasmodial hybrid molecules. Triazole quinolyl molecules are a promising class of molecules in finding new antimalarial prototypes.

EXPERIMENTAL SECTION

General

All the chemicals and reagents were acquired commercially and used as received. The reactions were carried out without inert atmosphere in standard dry glassware. They were also controlled via thin layer chromatography (TLC) using silica gel 60 with fluorescent indicators (e.g., silica F-254 gel, Macherey-Nagel) unless noted otherwise and visualized by exposure on iodine chamber, by spraying anisaldehyde acid, Hanissam reagent (ceric ammonium molibidate-CAM), Dragendorff solution or even using ultraviolet light source at 254 nm. The intermediaries were purified via crystallization, liquid phase extraction or filtration and the products with silica chromatographic column (Sigma-Aldrich, 0.040 to 0063 mm, 230-400 mesh American Society for Testing and Materials (ASTM)). Concentration and evaporation were performed on standard Ika rotavapor under low pressure using vacuum pump. Melting points (mps) were measured with a Buchi M-560 melting point apparatus and are uncorrected. Infrared spectra were recorded on FT-IR, Shimadzu IRAffinity-1 with ATR system and are reported in wave numbers (cm^{-1}). Mass spectra data were obtained by liquid chromatography coupled to a Waters Acquity TQD UPLC/MS/MS system mass spectrometer using electrospray ionization (ESI). The ^{1}H and ^{13}C NMR spectra were measured on a Bruker Advance DPX 200, Fourier 300HDand DRX400 with FT analysis. The chemical shifts δ (ppm) relates to $SiMe_4$ and coupling constants (J) are given in hertz. The deuterated solvent used were MeOD, CD_3OD, $CDCl_3$ or DMSO-d_6. All 2D NMR data were recorded at 400 MHz (Bruker DRX400),

heteronuclear single quantum coherence (HSQC) using *J* 145 Hzand heteronuclear multiple-bond correlation (HMBC) using *J* 8 Hz.

Materials

The following materials were used: 4,7-Dichloroquinoline, ethanolamine, 3-amino-1-propanol, bromidric acid, prop-2-yn-1-ol, but-3-yn-1-ol, pent-4-yn-1-ol, pent-1-yn-3-ol, 2-methylbut-3-yn-2-ol, prop-2-yn-1-amine, *N*-methylprop-2-yn-1-amine, *N*,*N*-dimethylprop-2-yn-1-amine, 1-ethynylcyclopentanol, ethynylcyclohexane, 1-ethynylcyclohexanol, ethynylbenzene, 2-phenylbut-3-yn-2-ol, 1-phenylprop-2-yn-1-ol, 1-ethynyl-4-methylbenzene, 1-ethynyl-4-methoxybenzene, 1-ethynyl-4-fluorobenzene, 4-ethynyl-*N*,*N*-dimethylaniline, 2-ethynyl-6-methoxynaphthalene, D-glucose, HEPES, hypoxanthine, gentamicin, D-sorbitol, PBS, BSA, TMB, FBS, penicillin, streptomycin, tripsin/EDTA and DMSO were obtained from Sigma-Aldrich® USA, Ltd. The glassware was purchased from Hialoquímica Ltda; Toluol, sodium azide, dimethylformamide, methanol, sodium ascorbate, sodium bicarbonate and copper(I) sulphate pentahydrate were obtained from Synth; MPFG-55P and MPFM-55A antibodies were purchased from ICLLABS®; sulfuric acid, sodium bicarbonate and sodium sulphate were obtained from FMaia and used without further purification.

Synthesis and Characterization

All the compounds were synthesized and characterization was made by NMR, IR and MS.

Obtainment of the chloroquinolinyl alcohol

The 4,7-dichloroquinoline was mixed with the respective aminoalcohol in 1:12.5 equivalent (ethanolamine for **7a** or 3-amine-1-propanol for **7b**) and the system stayed at 110 ºC for two hours. Then the brown solution obtained was crystallized with ethyl acetate and water, while the precipitate was filtered under vacuum. After dried, the product presented itself as a white powder with yield of 91%.

2-((7-chloroquinolin-4-yl) amino) ethan-1-ol (**7a**)

White crystalline powder. m.p. 217.0-219.0 ºC, IR (λ_{max}, cm^{-1}): 3306, 3066, 2923, 2816, 1614, 1580, 1063, 800, 763. ^{1}H NMR (200 MHz, MeOD): δ8.32 (d, 1H, *J* = 5.8, H-2), 8.06 (d, 1H, *J* = 9.0, H-5), 7.74 (d, 1H, *J* = 2.2, H-8), 7.36 (dd, 1H, *J* = 2.2 e 9.0, H-6), 6.53 (d, 1H, *J* = 5.8, H-3), 3.86 (2H, t, *J* = 5.7, $ArNHCH_2CH_2$-), 3.47 (2H, t, *J* = 5.7, $ArNHCH_2$-). ^{13}C NMR (50 MHz, $CDCl_3$): δ151.8 (C-2), 150.2 (C-3), 149.0 (C-8), 133.3 (C-6), 127.4 (C-7), 123.9 (C-4), 123.9 (C-5), 117.4 (C-9), 98.6 (C-2), 58.7 (C-11), 45.0 (C-10).

3-((7-chloroquinolin-4-yl) amino) propan-1-ol (**7b**)

White crystalline powder. m.p. 149.7-151.7 ºC, IR (λ_{max}, cm^{-1}): 3374, 3312, 2896, 2757, 1612, 1584, 854, 800. ^{1}H NMR (200 MHz, MeOD): δ8.22 (d, 1H, *J* = 5.8, H-2), 7.89 (d, 1H, *J* = 8.8, H-5), 7.65 (d, 1H, *J* = 2.0, H-8), 7.23 (dd, 1H, *J* = 2.0 e 9.0, H-6), 6.37 (d, 1H, *J* = 5.8, H-3), 3.66 (2H, t, *J* = 6, H-13), 3.34 (2H, t, *J* = 6.8, H-11), 1.87 (2H, q, *J* = 6.2 e 12.8, H-12).^{13}C NMR (50 MHz, $CDCl_3$): δ152.6 (C-2), 152.3 (C-3), 149.5 (C-8), 136.2 (C-6), 127.5 (C-7), 125.9 (C-4), 124.1 (C-5), 118.6 (C-9), 99.5 (C-2), 60.8 (C-12), 41.3 (C-10), 32.1 (C-11).

Obtainment of the chloroquinolinyl bromide

The quinolinyl alcohol was mixed with hydrobromic acid and toluene and maintained under reflux for one hour. After this period, a Dean-Stark Apparatus was docked and the system maintained under reflux for one more hour. Then the solution was eluted with dichloromethane and methanol, then it was washed with a 1M solution of sodium bicarbonate. The solvent extraction was carried out with a rotavapor coupled with a vacuum pump and the product obtained was a light-yellow powder with yield of 88%.

N-(2-bromoethyl)-7-chloroquinolin-4-amine (**8a**)

Yellowish powder. m.p. 142.0-144.4 ºC, IR (λ_{max}, cm^{-1}): 3628, 2970, 2378, 2347, 2309, 1582, 810. 1H NMR (300 MHz, MeOD)*: d* 8.27 (d, 1H, *J1-2* = 6.23, H-1), 7.97 (d, 1H, *J4-5* = 9.4, H-4), 7.69 (s, 1H, H-7), 7.31 (d, 1H, *J5-4* = 9.26, H-5), 6.46 (d, 1H, *J2-1* = 5.39, H-2), 3.69-3.75 (m, 2H, H-11 and H-11'), 3.53-3.56 (m, 2H, H-10 and H-10'), 3.21 (s, 1H, -NH).^{13}C NMR (100 MHz, $CDCl_3$): δ154.8 (C-3), 152.0 (C-1), 151.8 (C-8), 139.2 (C-6), 130.1 (C-7), 129.0 (C-4), 126.8 (C-5), 121.2(C-9), 102.3 (C-2), 48.2 (C-10), 32.8 (C-11).

N-(3-bromopropyl)-7-chloroquinolin-4-amine (**8b**)

Yellowish powder. m.p. 323.2-325.0 ºC, IR (λ_{max}, cm^{-1}): 3728, 3701, 3628, 2384, 2351, 2307, 1580, 814. ^{1}H NMR (300 MHz, MeOD)*: d* 8.72 (d, 1H, J_{1-2} = 5.48, H-1), 8.30

(d, 1H, J_{4-5} = 8.96, H-4), 8.17 (s, 1H, H-7), 7.70 (d, 1H, J_{5-4} = 9.08, H-5), 6.81 (d, 1H, J_{2-1} = 5.49, H-2), 3.88-3.92 (m, 4H, H-11, H-11', H-12 and H-12'), 2.62-2.66 (m, 2H, H-10 and H-10'), 1.62 (s, 1H, -NH).^{13}C NMR (50 MHz, MeOD): δ151.4 (C-3), 148.6 (C-1), 135.7 (C-8), 127.3 (C-6), 125.7 (C-7), 122.9 (C-4), 117.8 (C-5), 99.0(C-9), 41.6 (C-2), 31.5 (C-10), 31.2 (C-11), 30.1 (C-12).

Obtainment of the chloroquinolinyl azide

In anhydrous DMF, sodium azide was mixed with the quinolinyl bromide and stirred overnight. The work-up employed dichloromethane and water, then the product was filtered with silica gel. After dried with rotavapor, it presented itself as a white-yellow powder with 89% yield.

N-(2-azidoethyl) -7-chloroquinolin-4-amine (**9a**)

White fine powder. m.p. 146.2-147.7 ºC, IR (λ_{max}, cm^{-1}): 3229, 3065, 2924, 2856, 2091; 1571, 1549. ^{1}H NMR (200 MHz, $CDCl_3$): δ8.26 (d, 1H, J = 5.6, H-2), 7.95 (d, 1H, J = 9.0, H-5), 7.67 (d, 1H, J = 2.0, H-8), 7.27 (dd, 1H, J = 2.0 e 9.0, H-6), 6.44 (d, 1H, J = 5.6, H-3), 3.49 (4H, sl, 2 H-11 e 2 H-12). ^{13}C NMR (50 MHz, $CDCl_3$): δ152.4 (C-2), 152.3 (C-3), 149.6 (C-8), 136.4 (C-6), 127.6 (C-7), 126.2 (C-5), 124.2 (C-5), 118.7 (C-9), 99.7 (C-2), 50.6 (C-11), 43.3 (C-10).

N-(3-azidopropyl) -7-chloroquinolin-4-amine (**9b**)

White fine powder. m.p. 153.9-156.5 ºC, IR (λ_{max}, cm^{-1}): 3217, 3066, 2940, 2092, 1611, 1574, 1492, 1282. ^{1}H NMR (200 MHz, $CDCl_3$): δ8.54 (d, 1H, J = 5.2, H-2), 7.96 (d, 1H, J = 2.0, H-8), 7.67 (d, 1H, J = 9.0, H-5), 7.37 (dd, 1H, J = 2.0 e 9.0, H-6), 6.44 (d, 1H, J = 5.4, H-3), 3.54 (t, 2H, J = 6.0, H-13), 3.44 (t, 2H, J = 5.6, H-11), 2.02 (q, 2H, J = 6.6 e 12.8, H-12). ^{13}C NMR (50 MHz, MeOD): δ152.6 (C-3), 152.3 (C-2), 149.5 (C-8), 136.3 (C-6), 127.5 (C-7), 126.0 (C-5), 124.4 (C-5), 118.7 (C-9), 99.6 (C-2), 50.3 (C-12), 41.1 (C-10), 28.7 (C-11).

General procedure of click reaction

Commercial alkyne-compounds and chloroquinoline azide were dissolved in MeOH (1 mL), followed by the addition of $NaHCO_3$ (0.3 equivalents), $CuSO_4.5H_2O$ (0.3 equivalents) and an aqueous solution of sodium ascorbate (0.6 equivalents) (0.5 mL) freshly prepared. The system stirred overnight and it was stopped when the TLC indicated the end of the reaction. The work-up of the reaction mixture was done with CH_2Cl_2 and water (3x10 mL), dried over Na_2SO_4 and finally purified by column chromatography with DCM/MeOH (98:2 v/v).

(1-(2-((7-chloroquinolin-4-yl) amino) ethyl) -1*H*-1,2,3-triazol-4-yl) methanol (**10a**)

White powder. m.p. 201.9-203.9 ºC, IR (λ_{max}, cm^{-1}): 3285, 3123, 2955, 2924, 2384, 2349, 2307, 1585, 1456, 1049, 810. ^{1}H NMR (400 MHz, MeOD): δ8.33 (d, 1H, J = 7.2, H-2), 8.27 (d, 1H, J =9.2, H-5), 8.00 (s, 1H, H-13), 7.86 (d, 1H, J = 2, H-8), 7.63 (dd, 1H, J = 2.0 e 9.2, H-6), 6.71 (d, 1H, J = 6.8, H-3), 4.81 (t, 2H, J = 5.2, H-12), 4.63 (s, 2H, H-15), 4.14 (t, 2H, J = 5.6, H-11). ^{13}C NMR (100 MHz, $CDCl_3$): δ157.9 (C-3), 144.1 (C-2), 141.2 (C-8), 140.0 (C-13), 128.9 (C-7), 125.8 (C-4), 120.4 (C-5), 116.9 (C-9), 99.6 (C-2), 56.2 (C-14), 49.7 (C-11), 44.4 (C-10). HRMS-ESI-IT-TOF: m/z was calculated as $C_{14}H_{15}ClN_5O$ 303.09, and found 303.05 as a result.

(1-(3-((7-chloroquinolin-4-yl)amino)propyl)-1*H*-1,2,3-triazol-4-yl)methanol (**10b**)

White powder. m.p. 193.2-195.0 ºC, IR (λ_{max}, cm^{-1}): 3351, 3123, 3069, 2958, 2924, 2802, 2366, 2340, 1588, 1374, 1058, 799. ^{1}H NMR (300 MHz, MeOD)*: d* 8.41 (d, 1H, J_{1-2} = 4.78, H-1), 8.01-8.11 (m, 1H, H-4), 7.84-7.89 (m, 2H, H-7 and H-13), 7.46-7.49 (m, 2H, H-5 and –NH), 6.48 (d, 1H, J_{2-1} = 5.71, H-2), 4.59-4.62 (m, 5H, H-12, H-12', H-15, H-15' and –OH), 3.46-3.51 (m, 2H, H-11 and H-11'), 2.40-2.44 (m, 2H, H-10 and H-10').^{13}C NMR (100 MHz, $CDCl_3$): δ155.2 (C-3), 155.3 (C-1), 154.1 (C-8), 152.1 (C-14), 151.2 (C-6), 139.7 (C-7), 130.1 (C-13), 129.5 (C-4), 126.7 (C-5), 121.2 (C-9), 102.4 (C-2), 59.5 (C-15), 51.8 (C-12), 43.7 (C-10), 32.4 (C-11). HRMS-ESI-IT-TOF: m/z calculated $C_{15}H_{17}ClN_5O$ 317.10, found 317.05.

2-(1-(2-((7-chloroquinolin-4-yl)amino)ethyl)-1*H*-1,2,3-triazol-4-yl)ethan-1-ol(**11a**)

Yellow powder. m.p. 148.3-152.6 ºC, IR (λ_{max}, cm^{-1}): 3277, 3138, 2955, 2924, 2384, 2349, 2307, 1585, 1456, 1049, 810. ^{1}H NMR (200 MHz, MeOD): δ8.33 (d, 1H, J = 5.0, H-2), 7.97 (d, 1H, J = 8.8, H-5), 7.75 (sl, 2H, H-8 e H-13), 7.38 (dd, 1H, J = 1.4 e 8.8, H-6), 6.49 (d, 1H, J = 5.2, H-3), 4.68 (t, 2H, J = 5.6, H-12), 3.90 (t, 2H, J = 5.2, H-16), 3.73 (t, 2H, J = 6.8, H-11), 2.84 (t, 2H, J = 6.6, H-15).^{13}C NMR (50 MHz, MeOD): δ152.6 (C-3), 151.8 (C-2), 148.9 (C-8),

146.4 (C-13), 136.8 (C-6), 127.1 (C-7), 126.5 (C-4), 124.7 (C-12), 124.3 (C-5), 118.6 (C-9), 99.6 (C-2), 62.0 (C-15), 49.7 (C-11), 43.1 (C-10), 29.8 (C-14). HRMS-ESI-IT-TOF: m/z calculated $C_{15}H_{17}ClN_5O$ 317.10, found 317.10.

2-(1-(3-((7-chloroquinolin-4-yl)amino)propyl)-1*H*-1,2,3-triazol-4-yl)ethan-1-ol(**11b**)

Yellow powder. m.p. 90.1-93.2 ºC, IR (λ_{max}, cm^{-1}): 3273, 3127, 2955, 2928, 2388, 2353, 2307, 1593, 1456, 745. ^{1}H NMR (200 MHz, MeOD): *δ*8.40-8.31 (m, 2H, H-2 e H-5), 7.94 (s, 1H, H-14), 7.87 (d, 1H, *J* = 1.6, H-8), 7.66 (dd, 1H, *J* = 1.8 e 9.2, H-6), 6.83 (d, 1H, *J* = 7.2, H-3), 4.60 (t, 2H, *J* = 6.6, H-13), 3.84-3.74 (m, 2H, H-17), 3.67 (t, 2H, *J* = 6.8, H-11) 2.86 (sl, 2H, H-16), 2.43 (q, 2H, *J* = 6.4 e 13, H-12). ^{13}C NMR (100 MHz, $CDCl_3$): *δ*157.6 (C-3), 143.9 (C-13), 141.0 (C-8), 140.0 (C-6), 128.7 (C-7), 126.0 (C-4), 120.3 (C-5), 116.9 (C-9), 99.8 (C-2), 61.8 (C-16), 47.7 (C-12), 42.1 (C-10), 29.6 (C-15), 28.7 (C-11). HRMS-ESI-IT-TOF: m/z calculated $C_{16}H_{19}ClN_5O$ 331.12, found 331.10.

3-(1-(2-((7-chloroquinolin-4-yl)amino)ethyl)-1*H*-1,2,3-triazol-4-yl)propan-1-ol(**12a**)

White powder. m.p. 65.2-68.0 ºC, IR (λ_{max}, cm^{-1}): 3285, 2944, 2881, 1610, 1581, 1548. ^{1}H NMR (400 MHz, MeOD)*: δ*8.33 (d, 1H, *J* = 5.2, H-2), 7.99 (d, 1H, *J* = 8.8, H-5), 7.77 (sl, 1H, H-8), 7.69 (s, 1H, H-13), 7.41 (dd, 1H, *J* = 1.6 e 9.6, H-6), 6.47 (d, 1H, *J* = 5.6, H-3), 4.87 (t, 2H, *J* = 5.2, H-12), 3.91 (t, 2H, *J* = 5.2, H-11), 3.50 (t, 2H, *J* = 6, H-17), 2.69 (t, 2H, J = 7.2, H-15), 1.76 (q, 2H, *J* = 6.4 e 13.6, H-16). ^{13}C NMR (50 MHz, DMSO-d_6)*: δ*151.7 (C-2), 149.6 (C-3), 148.8 (C-8), 146.6 (C-13), 133.4 (C-6), 127.4 (C-7), 124.3 (C-5), 123.8 (C-4), 122.2 (C-12), 117.3 (C-9), 98.7 (C-2), 59.9 (C-16), 47.6 (C-11), 42.3 (C-10), 32.2 (C-14), 21.5 (C-15).

3-(1-(3-((7-chloroquinolin-4-yl)amino)propyl)-1*H*-1,2,3-triazol-4-yl)propan-1-ol(**12b**)

White powder. m.p. 140.0-142.5 ºC, IR (λ_{max}, cm^{-1}): 3289, 3150, 2909, 2862, 1612, 1583, 1490. ^{1}H NMR (200 MHz, DMSO-d_6)*: δ*8.38 (d, 1H, *J* = 5.4, H-2), 8.25 (d, 1H, *J* = 9.2, H-5), 7.88 (s, 1H, H-14), 7.78 (d, 1H, *J* = 2.2, H-8), 7.45 (dd, 1H, *J* = 2.2 e 9.0, H-6), 6.42 (d, 1H, *J* = 5.4, H-3), 4.44 (t, 2H, *J* = 6.8, H-13), 3.26 (t, 2H, *J* = 6.6, H-11), 2.63 (t, 2H,*J* = 7.4, H-16), 2.19 (q, 2H, J = 7.0 e 13.8, H-12), 1.72 (q, 2H, *J* = 6.6 e 14.4, H-17). ^{13}C NMR (50 MHz, DMSO-d_6)*: δ*151.8 (C-2), 149.8 (C-3), 148.9 (C-8), 146.7 (C-14), 133.3 (C-6), 127.4 (C-7), 124.0 (C-4), 124.0 (C-13), 121.8 (C-5), 117.4 (C-9), 98.6 (C-2), 59.9 (C-17), 47.1 (C-12), 39.5 (C-10), 32.2 (C-15), 28.4 (C-16), 21.6 (C-11).

1-(1-(2-((7-chloroquinolin-4-yl)amino)ethyl)-1*H*-1,2,3-triazol-4-yl)propan-1-ol(**13a**)

White powder. m.p. 208.1-209.0 ºC, IR (λ_{max}, cm^{-1}): 3725, 3698, 3630, 2386, 2367, 2351, 2299, 1582, 673. ^{1}H NMR (300 MHz, MeOD)*: d* 8.47 (d, 1H, $J_{1\text{-}2}$ = 5.26, H-1), 7.94-7.97 (m, 2H, H-7 and H-13), 7.73 (s, 1H, H-4), 7.44-7.52 (m, 1H, H-5), 6.48 (d, 1H, $J_{1\text{-}2}$ = 5.24, H-2), 4.35-4.50 (m, 5H, H-11, H-11', H-15, -NH and -OH), 3.97 (d, 2H, $J_{10\text{-}10'}$ = 4.79, H-10 and H-10'), 1.89-1.94 (m, 2H, -CH_2-), 1.00-1.02 (m, 3H, -CH_3).^{13}C NMR (100 MHz, $CDCl_3$): *δ*155.7 (C-3), 155.1 (C-1), 154.1 (C-8), 152.2 (C-14), 139.4 (C-6), 131.0 (C-7), 129.5 (C-13), 126.2 (C-4), 126.0 (C-5), 121.2(C-9), 102.3 (C-2), 71.7 (C-15), 52.4 (C-11), 46.5 (C-10), 34.0 (C-16), 13.4 (C-17).HRMS-ESI-IT-TOF: m/z calculated $C_{16}H_{19}ClN_5O$ 331.12, found331.10.

1-(1-(3-((7-chloroquinolin-4-yl)amino)propyl)-1*H*-1,2,3-triazol-4-yl)propan-1-ol(**13b**)

White powder. m.p. 195.5-197.9 ºC, IR (λ_{max}, cm^{-1}): 2959, 2920, 2855, 2378, 2347, 2309, 1728, 1582, 1464, 1267, 748. ^{1}H NMR (300 MHz, MeOD)*: δ*9.32 (d, 1H, $J_{1\text{-}2}$ = 5.64 Hz, H-1), 9.00 (d, 1H, $J_{4\text{-}5}$ = 9.02 Hz, H-4), 8.76-8.79 (m, 2H, H-7 and H-13), 8.49 (s, 1H, -NH), 8.37-8.40 (m, 1H, H-5), 7.39 (d, 1H, $J_{2\text{-}1}$ = 5.73 Hz, H-2), 5.66-5-69 (m, 3H, -CH_3), 5.51-5.54 (m, 2H, H-16 and H-16'), 4.32-4.40 (m, 2H, H-12 and H-12'), 4.31 (s, 1H, -OH), 3.30-3.36 (m, 2H, H-10 and H-10'), 3.19 (s, 1H, H-11'), 2.26-2.30 (m, 1H, H-11), 0.93-0.96 (m, 1H, H-15).^{13}C NMR (100 MHz, $CDCl_3$): *δ*155.1 (C-3), 154.4 (C-1), 152.0 (C-8), 151.5 (C-14), 139.6 (C-6), 130.3 (C-7), 129.4 (C-13), 126.7 (C-4), 126.6 (C-5), 121.2(C-9), 102.4 (C-2), 81.3 (C-15),59.4 (C-12), 43.7 (C-11), 36.6 (C-10), 32.4 (C-16), 13.1 (C-17).HRMS-ESI-IT-TOF: m/z calculated $C_{17}H_{21}ClN_5O$ 345.14, found345.10.

2-(1-(2-((7-chloroquinolin-4-yl)amino)ethyl)-1*H*-1,2,3-triazol-4-yl)propan-2-ol (**14a**)

White powder. m.p. 180.2-183.0 ºC, IR (λ_{max}, cm^{-1}): 3354, 3146, 2984, 2928, 1610, 1579, 1486, 1455. ^{1}H NMR (200 MHz, DMSO-d_6): *δ*8.38 (d, 1H, *J* = 5.4, H-2), 8.18 (d, 1H, *J* = 9.0, H-5), 7.90 (s, 1H, H-13), 7.80 (d, 1H, *J* = 2.2, H-8), 7.47 (dd, 1H, *J* = 2.2 e 9.0, H-6), 6.49 (d, 1H, *J* = 5.4, H-3), 4.60 (t, 2H, *J* = 6.2, H-12), 3.78-3.75 (m, 2H,

H-11), 1.40 (s, 6H, H-16). ^{13}C NMR (50 MHz, DMSO-d_6): δ155.7 (C-3),151.8 (C-2), 149.7 (C-8), 148.9 (C-13), 133.4 (C-6), 127.4 (C-7), 124.3 (C-4), 123.8 (C-12), 121.0 (C-5), 117.3 (C-9), 98.7 (C-2), 66.9 (C-14), 47.6 (C-11), 42.43 (C-10), 30.6 (C-15).

2-(1-(3-((7-chloroquinolin-4-yl)amino)propyl)-1*H*-1,2,3-triazol-4-yl)propan-2-ol (**14b**)

White powder. m.p. 149.7-151.7 ºC, IR (λ_{max}, cm^{-1}): 3354, 3146, 2984, 2928, 1610, 1579, 1486, 1455. ^{1}H NMR (200 MHz, DMSO-d_6): δ8.38 (d, 1H, J = 5.4, H-2), 8.18 (d, 1H, J = 9.0, H-5), 7.90 (s, 1H, H-13), 7.80 (d, 1H, J = 2.2, H-8), 7.47 (dd, 1H, J = 2.2 e 9.0, H-6), 6.49 (d, 1H, J = 5.4, H-3), 4.60 (t, 2H, J = 6.2, H-12), 3.78-3.75 (m, 2H, H-11), 1.40 (s, 6H, H-16). ^{13}C NMR (50 MHz, DMSO-d_6): δ155.7 (C-3),151.8 (C-2), 149.7 (C-8), 148.9 (C-13), 133.4 (C-6), 127.4 (C-7), 124.3 (C-4), 123.8 (C-12), 121.0 (C-5), 117.3 (C-9), 98.7 (C-2), 66.9 (C-14), 47.6 (C-11), 42.43 (C-10), 30.6 (C-15).

N-(2-(4-(aminomethyl)-1*H*-1,2,3-triazol-1-yl) ethyl)-7-chloroquinolin-4-amine (**15a**)

Redish powder.m.p. 233.0-235.3 ºC, IR (λ_{max}, cm^{-1}): 3300, 3134, 2963, 2878, 2388, 2347, 2305, 1578, 1144, 1053, 810. ^{1}H NMR (300 MHz, MeOD): *d* 8.45 (d, 1H, H-1), 8.02-8.06 (m, 1H, H-4), 7.94 (s, 1H, H-7), 7.75-7.76 (m, 1H, H-13), 7.50 (d, 1H, H-2), 6.48-6.51 (m, 1H, H-5), 4.00 (s, 2H, -NH$_2$), 1.64-2.08 (m, 6H, H-11, H-11', H-15, H-15', H-10 and H-10'), 1.32 (s, 1H, -NH).^{13}C NMR (100 MHz, CDCl$_3$): δ155.2 (C-3), 150.2 (C-1), 148.2 (C-8), 135.4(C-14), 127.9 (C-6), 126.9 (C-7), 125.5 (C-13), 124.9 (C-4), 122.2 (C-5), 117.2 (C-9), 98.2 (C-2), 71.4 (C-11), 42.4 (C-10), 29.6 (C-15). HRMS-ESI-IT-TOF: m/z calculated $C_{14}H_{16}ClN_6$302.10, found 302.10.

N-(3-(4-(aminomethyl)-1*H*-1,2,3-triazol-1-yl) propyl)-7-chloroquinolin-4-amine (**15b**)

Brown oil. IR (λ_{max}, cm^{-1}): 3296, 3065, 2955, 2388, 2347, 2309, 1582, 1456, 1140, 802, 737. 1H NMR (300 MHz, MeOD): δ8.62-8.65 (m, 2H, -NH2), 8.39-8.46 (m, 2H, H-4 and H-7), 8.07-8.22 (m, 3H, H-1, H-13 and -NH), 7.67-7.72 (m, 2H, H-5 and H-2), 3.69-3.72 (m, 2H, H-12 and H-12'), 3.57 (s, 1H, H-11'), 3.24-3.30 (m, 1H, H-11), 2.89 (s, 1H, H-15'), 2.60-2.70 (m, 2H, H-10 and H-10'), 1.55-1.58 (m, 1H, H-15).^{13}C NMR (100 MHz, CDCl$_3$): δ155.4 (C-3), 154.7 (C-1), 148.9 (C-8), 139.3 (C-14), 130.2 (C-6), 129.1 (C-7), 128.5 (C-13), 127.6 (C-4), 127.5 (C-5), 121.4 (C-9), 102.6 (C-2), 49.1 (C-15), 46.2 (C-12), 32.6 (C-11), 30.7 (C-10). HRMS-ESI-IT-TOF: m/z calculated$C_{15}H_{18}ClN_6$ (M+H) 317.7966, found 317.3698.

7-chloro-*N*-(2-(4-((methylamino)methyl)-1*H*-1,2,3-triazol-1-yl)ethyl)quinolin-4-amine (**16a**)

Brown oil. IR (λ_{max}, cm^{-1}): 3308, 2951, 2382, 2344, 2317, 1578, 1452, 1144, 1053, 806. 1H NMR (300 MHz, MeOD): δ8.45 (s, 1H, H-1), 7.89-8.01 (m, 2H, H-4 and H-7), 7.39 (s, 1H, H-13), 6.46 (s, 2H, H-2 and H-5), 3.96 (s, 3H, -CH3), 3.50 (s, 1H, -NH), 2.99 (s, 2H, H-11 and H-11'), 2.55 (s, 2H, H-15 and H-15'), 2.05 (s, 1H, -NH), 1.21-1.38 (m, 2H, H-10 and H-10').^{13}C NMR (100 MHz, CDCl$_3$): δ154.8 (C-3), 154.4(C-1), 151.8 (C-8), 147.6 (C-14), 139.4 (C-6), 130.7 (C-7), 129.4 (C-13), 128.1 (C-4), 126.6 (C-5), 121.2(C-9), 102.2 (C-2), 49.7 (C-11), 48.9 (C-15), 46.5 (C-10), 38.3 (C-16).

7-chloro-*N*-(3-(4-((methylamino)methyl)-1*H*-1,2,3-triazol-1-yl)propyl)quinolin-4-amine (**16b**)

Brown oil. IR (λ_{max}, cm^{-1}): 3317, 3141, 2958, 2882, 2363, 2344, 1585, 1451, 1367, 1138, 1054, 806. ^{1}H NMR (300 MHz, MeOD): *d* 9.54 (d, 1H, J_{1-2} = 6.69 Hz, H-1), 8.97-9.12 (m, 3H, H-4, H-7 and H-13), 8.52 (d, 1H, H-5), 7.52 (d, 1H, J_{2-1} = 5.96 Hz, H-2), 5.07 (s, 2H, H-15 and H-15'), 4.52-4.56 (m, 2H, H-12 and H-12'), 4.04-4.09 (m, 3H, -CH$_3$), 3.66 (s, 1H, -NH), 3.47-3.52 (m, 2H, H-10 and H-10'), 3.13 (s, 1H, -NH), 2.35-2.45 (m, 2H, H-11 and H-11').^{13}C NMR (100 MHz, CDCl$_3$): δ150.8 (C-3), 147.9(C-1), 144.3 (C-8), 135.4 (C-14), 131.2 (C-6), 127.0 (C-7), 125.5 (C-13), 123.5 (C-4), 122.3 (C-5), 117.2(C-9), 98.5 (C-2), 47.9 (C-11), 45.4 (C-15), 39.6 (C-12), 34.8 (C-10), 28.2 (C-16).

7-chloro-*N*-(2-(5-((dimethylamino)methyl)-1*H*-1,2,3-triazol-1-yl)ethyl)quinolin-4-amine (**17a**)

Brown oil. IR (λ_{max}, cm^{-1}): 3273, 3092, 2970, 2946, 2759, 2706, 2363, 2340, 1585, 1458, 1241, 852. ^{1}H NMR (300 MHz, MeOD): *d* 9.05 (d, 1H, J_{1-2} = 5.55 Hz, H-1), 8.52-8.56 (m, 2H, H-4 and H-5), 8.32 (s, 1H, H-7), 8.02-8.06 (m, 1H, H-13), 7.07 (d, 1H, J_{2-1} = 5.43 Hz, H-2), 5.35-5.38 (m, 2H, H-15 and H-15'), 4.54-4.57 (m, 2H, H-11 and H-11'), 4.23-4.28 (m, 2H, H-10 and H-10'), 2.89 (s, 6H, 2 CH$_3$), 1.96 (s, 1H, -NH).^{13}C NMR (100 MHz, CDCl$_3$): δ155.1 (C-3), 154.2 (C-1), 152.2 (C-8), 147.8 (C-14), 139.5 (C-6), 131.1 (C-7), 129.6 (C-13), 128.2 (C-4), 126.1 (C-5),

121.2 (C-9), 102.3 (C-2), 67.3 (C-15), 57.6 (C-10), 48.5 (C-16, C-16'), 46.5 (C-11). HRMS-ESI-IT-TOF: m/z calculated $C_{16}H_{20}ClN_6$ 330.14, found 330.15.

7-chloro-*N*-(3-(4-((dimethylamino)methyl)-1*H*-1,2,3-triazol-1-yl)propyl)quinolin-4-amine (**17b**)

Brown oil. IR (λ_{max}, cm^{-1}): 3377, 3123, 3065, 3034, 2990, 2955, 2689, 2378, 2355, 2309, 1582, 1456, 806. ^{1}H NMR (300 MHz, MeOD)*: d* 8.84 (d, 1H, J_{1-2} = 10.55 Hz, H-1), 8.70-8.72 (m, 2H, H-4 and H-5), 8.26 (s, 1H, H-7), 7.86 (s, 1H, H-13), 7.00 (d, 1H, J_{2-1} = 6.84 Hz, H-2), 5.64 (s, 1H, -NH), 4.52 (s, 2H, H-15 and H-15'), 3.96-3.98 (m, 2H, H-12 and H-12'), 3.55-3.58 (m, 2H, H-10 and H-10'), 3.06 (s, 6H, 2 CH_3), 2.85-2.87 (m, 2H, H-11 and H-11').^{13}C NMR (100 MHz, $CDCl_3$): *δ*154.7 (C-3), 144.1(C-1), 140.4 (C-8), 139.3 (C-14), 138.6 (C-6), 127.0 (C-7), 126.3 (C-13), 124.7 (C-4), 120.8 (C-5), 115.8(C-9), 98.2 (C-2), 62.5 (C-15), 46.1 (C-12), 43.1 (C-16, C-16'), 40.4 (C-10), 28.1 (C-11). HRMS-ESI-IT-TOF: m/z calculated$C_{17}H_{22}ClN_6$ (M+H) 345.85, found 345.40.

1-(1-(2-((7-chloroquinolin-4-yl)amino)ethyl)-1*H*-1,2,3-triazol-4-yl)cyclopentan-1-ol (**18a**)

Yellow powder. m.p. 227.6-230.2 ºC, IR (λ_{max}, cm^{-1}): 3386, 3196, 3107, 3054, 3002, 2945, 9861, 2364, 2340, 1587, 1451, 1337, 1163, 803. ^{1}H NMR (400 MHz, $CDCl_3$): *δ*8.31-8.27 (m, 2H, H-2 e H-5), 7.90 (s, 1H, H-13), 7.87 (d, 1H, J = 1.6, H-8), 7.65 (dd, 1H, *J* = 2.0 e 8.8, H-6), 6.63 (d, 1H, *J* = 7.2, H-3), 4.79 (t, 2H, *J* = 5.6, H-12), 4.14 (t, 2H, *J* = 5.6, H-11), 1.97-1.73 (m, 8H, H-16, H-17, H-18 e H-19). ^{13}C NMR (100 MHz, MeOD): *δ*158.0 (C-3), 144.0 (C-1), 141.2 (C-6), 140.0 (C-13), 129.0 (C-7), 125.8 (C-4), 123.7 (C-5), 120.4 (C-5), 116.9 (C-9), 99.4 (C-2), 79.4 (C-14), 49.8 (C-11), 44.4 (C-10), 41.9 (C-15), 37.5 (C-18), 24.4 (C-16), 23.9 (C-17).

1-(1-(3-((7-chloroquinolin-4-yl)amino)propyl)-1*H*-1,2,3-triazol-4-yl)cyclopentan-1-ol (**18b**)

Yellow powder. m.p. 180.2-183.0 ºC, IR (λ_{max}, cm^{-1}): 3728, 3694, 2659, 2928, 2853, 2386, 2361, 2295, 1541, 1194. ^{1}H NMR (200 MHz, $CDCl_3$): *δ*8.31-8.27 (m, 2H, H-2 e H-5), 7.90 (s, 1H, H-13), 7.87 (d, 1H, J = 1.6, H-8), 7.65 (dd, 1H, *J* = 2.0 e 8.8, H-6), 6.63 (d, 1H, *J* = 7.2, H-3), 4.79 (t, 2H, *J* = 5.6, H-12), 4.14 (t, 2H, *J* = 5.6, H-11), 1.97-1.73 (m, 8H, H-16, H-17, H-18 e H-19). ^{13}C NMR (100 MHz, MeOD): *δ*158.0 (C-3), 144.0 (C-1), 141.2 (C-6), 140.0 (C-13), 129.0 (C-7), 125.8 (C-4), 123.7 (C-5), 120.4 (C-5), 116.9 (C-9), 99.4 (C-2), 79.4 (C-14), 49.8 (C-11), 44.4 (C-10), 41.9 (C-15), 37.5 (C-18), 24.4 (C-16), 23.9 (C-17).

7-chloro-*N*-(2-(4-cyclohexyl-1*H*-1,2,3-triazol-1-yl)ethyl)quinolin-4-amine (**19a**)

Yellowish powder. m.p. 215.3-217.9 ºC, IR (λ_{max}, cm^{-1}): 3277, 3142, 2886, 2806, 1619, 1580, 1426. ^{1}H NMR (200 MHz, MeOD): *δ*8.33 (d, 1H, *J* = 7.0, H-2), 8.27 (d, 1H, *J* = 9.2, H-5), 7.88 (d, 1H, *J* = 1.8, H-8), 7.85 (s, 1H, H-13), 7.69 (dd, 1H, *J* = 2.0 e 9.2, H-6), 6.68 (d, 1H, *J* = 7.2, H-3), 4.79 (t, 2H, *J* = 5.2, H-12), 4.14 (t, 2H, *J* = 5.4, H-11), 1.91-1.73 (m, 6H, H-15, H-16, H-17 e H-18), 1.42-1.27 (m, 5H, H-15, H-16, H-17 e H-18). ^{13}C NMR (50 MHz, DMSO-d_6): *δ*151.9 (C-3), 151.7 (C-1), 149.6 (C-8), 148.9 (C-13), 133.4 (C-6), 127.4 (C-7), 124.2 (C-5), 123.8 (C-4), 121.0 (C-12), 117.4 (C-9), 98.7 (C-2), 47.7 (C-11), 42.3 (C-10), 34.4 (C-14), 32.4 (C-15), 25.5 (C-17), 25.4 (C-16).

7-chloro-*N*-(3-(4-cyclohexyl-1*H*-1,2,3-triazol-1-yl)propyl)quinolin-4-amine (**19b**)

Yellowpowder. m.p. 136.1-138.9 ºC, IR (λ_{max}, cm^{-1}): 3283 e 3115 (N-H); 3060 (C-H aromático); 2927, 2853, 1608, 1582, 1446. ^{1}H NMR (200 MHz, MeOD): *δ*8.17 (d, 1H, *J* = 5.6, H-2), 7.86 (d, 1H, *J* = 9.2, H-5), 7.61 (d, 1H, *J* = 2.0, H-8), 7.56 (s, 1H, H-14), 7.21 (dd, 1H, *J* = 2.0 e 9.0, H-6), 6.27 (d, 1H, *J* = 5.6, H-3), 4.40 (t, 2H, *J* = 6.6, H-13), 3.27-3.25 (m, 2H, H-11), 2.20 (q, 2H, *J* = 6.4 e 13.2, H-12), 1.80-1.60 (m, 5H, H-16 e H-17), 1.27-1.07 (m, 6H, H-18 e H-19). ^{13}C NMR (50 MHz, MeOD): *δ*154.5 (C-3), 152.4 (C-8), 152.2 (C-1), 149.3 (C-14), 136.3 (C-6), 127.4 (C-7), 126.0 (C-4), 124.3 (C-5), 122.0 (C-13), 118.6 (C-9), 99.5 (C-2), 49.2 (C-12), 41.2 (C-10), 36.3 (C-15), 33.9 (C-16), 29.6 (C-11), 27.1 (C-17), 27.0 (C-18).

1-(1-(2-((7-chloroquinolin-4-yl)amino)ethyl)-1*H*-1,2,3-triazol-4-yl)cyclohexan-1-ol (**20a**)

White powder. m.p. 191.0-193.0 ºC, IR (λ_{max}, cm^{-1}): 3386, 3196, 3111, 3047, 2998, 2942, 2861, 2368, 2340, 1584, 1535, 1447, 1337, 1163, 807. ^{1}H NMR (200 MHz, $CDCl_3$): *δ*8.29 (d, 1H, *J* = 6.8, H-2), 8.28 (d, 1H, *J* = 8.8, H-5), 7.89 (s, 1H, H-13), 7.87 (d, 1H, *J* = 1.6, H-8), 7.67 (dd, 1H, *J* = 1.6 e 8.8, H-6), 6.62 (d, 1H, *J* = 7.2, H-3), 4.79 (t, 2H, *J* = 5.2, H-12), 4.15 (t, 2H, *J* = 5.2, H-11), 1.93-1.52 (m, 10H, H-16, H-17, H-18, H-19 e H-20). ^{13}C NMR (50 MHz, MeOD): *δ*160.8 (C-3), 158.0 (C-8), 144.0 (C-1),

141.2 (C-6), 140.0 (C-13), 129.0 (C-7), 125.8 (C-4), 123.7 (C-12), 120.4 (C-5), 116.9 (C-9), 99.4 (C-2), 73.0 (C-14), 49.4 (C-11), 44.4 (C-10), 40.8 (C-15), 38.8 (C-19), 26.4 (C-17), 24.2 (C-16), 23.0 (C-18).

1-(1-(3-((7-chloroquinolin-4-yl)amino)propyl)-1*H*-1,2,3-triazol-4-yl)cyclohexan-1-ol (**20b**)

Yellowish powder. m.p. 149.7-151.7 ºC, IR (λ_{max}, cm^{-1}): 3726, 3127, 2932, 2855, 2382, 2355, 2301, 1570, 1368, 845, 669. ^{1}H NMR (200 MHz, $CDCl_3$): δ8.29 (d, 1H, J = 6.8, H-2), 8.28 (d, 1H, J = 8.8, H-5), 7.89 (s, 1H, H-13), 7.87 (d, 1H, J = 1.6, H-8), 7.67 (dd, 1H, J = 1.6 e 8.8, H-6), 6.62 (d, 1H, J = 7.2, H-3), 4.79 (t, 2H, J = 5.2, H-12), 4.15 (t, 2H, J = 5.2, H-11), 1.93-1.52 (m, 10H, H-16, H-17, H-18, H-19 e H-20). ^{13}C NMR (50 MHz, MeOD): δ160.8 (C-3), 158.0 (C-8), 144.0 (C-1), 141.2 (C-6), 140.0 (C-13), 129.0 (C-7), 125.8 (C-4), 123.7 (C-12), 120.4 (C-5), 116.9 (C-9), 99.4 (C-2), 73.0 (C-14), 49.4 (C-11), 44.4 (C-10), 40.8 (C-15), 38.8 (C-19), 26.4 (C-17), 24.2 (C-16), 23.0 (C-18).

7-chloro-*N*-(2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)ethyl)quinolin-4-amine (**21a**)

Yellowish powder. m.p. 268.0-271.0 ºC, IR (λ_{max}, cm^{-1}): 3306, 3007, 1611, 1585, 1543, 1450, 1436. ^{1}H NMR (200 MHz, $CDCl_3$): δ8.58 (s, 1H, H-13), 8.55 (sl, 1H, H-2), 8.41 (d, 1H, J = 9.2, H-5), 7.92 (d, 1H, J = 1.8, H-8), 7.79-7.73 (m, 3H, H-6 e H-16), 7.44-7.25 (m, 3H, H17 e H-18), 6.93 (d, 1H, J = 7.2, H-3), 4.75 (t, 2H, J = 5.2, H-12), 4.11 (t, 2H, J = 4.8, H-11). ^{13}C NMR (100 MHz, MeOD): δ156.4 (C-3), 151.6 (C-1), 148.8 (C-8), 136.2 (C-14), 127.4 (C-7), 126.2 (C-13), 123.1 (C-15), 118.0 (C-7), 98.9 (C-17), 69.8 (C-16), 43.2 (C-4), 40.1 (C-5), 38.2 (C-9), 25.9 (C-2), 23.7 (C-11), 22.4 (C-10). HRMS-ESI-IT-TOF: m/z calculated $C_{19}H_{17}ClN_5$ 349.11, found 349.10.

7-chloro-*N*-(3-(4-phenyl-1*H*-1,2,3-triazol-1-yl)propyl)quinolin-4-amine (**21b**)

Yellowish powder. m.p. 222.8-225.9 ºC, IR (λ_{max}, cm^{-1}): 3327, 3057, 3023, 2944, 2893, 1611, 1579, 1541, 1444. ^{1}H NMR (200 MHz, MeOD): δ8.18 (d, 1H, J = 7.4, H-2), 8.14 (s, 1H, H-14), 8.02 (d, 1H, J = 9.2, H-5), 7.57 (d, 1H, J = 2.0, H-8), 7.46 (dd, 2H, J = 1.8 e 8.2, H-18), 7.36 (dd, 1H, J = 2.0 e 9.2, H-6), 7.27-7.16 (m, 3H, H-17 e H-19), 6.67 (d, 1H, J = 7.2, H-3), 4.50 (t, 2H, J = 6.2, H-13), 3.58 (t, 2H, J = 6.6, H-11), 2.35 (q, 2H, J = 6.6 e 13.0, H-12). ^{13}C NMR (50 MHz, DMSO-d_6): δ151.8 (C-1), 149.9 (C-3), 148.9 (C-8), 146.2 (C-14), 133.3 (C-6), 130.7 (C-15), 128.8 (C-17), 127.7 (C-18), 127.4 (C-13), 125.0 (C-16), 124.0 (C-7), 124.0 (C-4), 121.4 (C-5), 117.4 (C-9), 98.7 (C-2), 47.5 (C-12), 39.5 (C-10), 28.3 (C-11). HRMS-ESI-IT-TOF: m/z calculated $C_{20}H_{19}ClN_5$ (M+H) 364.85, found 364.35.

1-(1-(2-((7-chloroquinolin-4-yl)amino)ethyl)-1*H*-1,2,3-triazol-4-yl)-1-phenylethan-1-ol (**22a**)

White powder. m.p. 225.0-227.5 ºC, IR (λ_{max}, cm^{-1}): 3277, 3119, 2955, 2924, 2384, 2349, 2307, 1585, 1456, 1019, 810, 745. ^{1}H NMR (300 MHz, MeOD)*: d* 8.72 (d, 1H, $J_{1\text{-}2}$ = 7.12 Hz, H-1), 8.23-8.27 (m, 2H, H-4 and H-7), 7.84 (d, 1H, $J_{2\text{-}1}$ = 10.75 Hz, H-2), 7.72-7.78 (m, 3H, H-5, H-17, H-17'), 7.60-7.63 (m, 3H, H-18, H-18', -NH), 6.73-6.75 (m, 1H, H-13), 5.00-5.05 (m, 2H, H-11 and H-11'), 4.22-4.27 (m, 2H, H-10 and H-10'), 2.29-2.31 (m, 3H, -CH_3), 1.65 (s, 1H, -OH).^{13}C NMR (100 MHz, $CDCl_3$): δ159.3 (C-3), 155.0 (C-1), 154.3 (C-8), 152.2 (C-17), 150.4 (C-6), 139.5 (C-14), 131.9 (C-7), 131.0 (C-19, C-19'), 130.9 (C-20), 129.5 (C-18, C-18'), 128.9 (C-4), 126.3 (C-13), 126.2 (C-5), 121.2 (C-9), 102.2 (C-2), 75.4 (C-15), 52.5 (C-11), 46.4 (C-10), 33.6 (C-16). HRMS-ESI-IT-TOF: m/z calculated $C_{21}H_{21}ClN_5O$ (M+H) 394.88, found 394.20.

1-(1-(3-((7-chloroquinolin-4-yl)amino)propyl)-1*H*-1,2,3-triazol-4-yl)-1-phenylethan-1-ol(**22b**)

Yellowish powder. m.p. 65.7-69.6 ºC, IR (λ_{max}, cm^{-1}): 3294, 2982, 1748, 1666, 1584, 1538, 1447, 1371, 1219, 1138. ^{1}H NMR (300 MHz, MeOD)*: δ*8.37 (s, 1H, H-1), 8.05-8.07 (m, 2H, H-4 and H-7), 7.82-7.88 (m, 3H, H-5, H-13 and -NH), 7.63-7.78 (m, 6H, -Ar and H-2), 3.76-3.80 (m, 3H, -CH3), 3.40 (s, 1H, H-11'), 3.29 (s, 1H, H-11), 2.73 (s, 2H, H-12 and H-12'), 2.38 (s, 2H, H-10 and H-10'), 2.17 (s, 1H, -OH). ^{13}C NMR (100 MHz, MeOD): δ163.7 (C-3), 147.2 (C-1), 145.8 (C-8), 135.9 (C-17), 128.5 (C-6), 127.9 (C-14), 127.5 (C-7), 126.1 (C-19, C-19'), 125.6 (C-20), 125.3 (C-18, C-18'), 72.8 (C-4), 69.5 (C-13), 50.0 (C-5), 46.4 (C-9), 40.2 (C-2), 37.1 (C-15), 33.5 (C-12), 31.8 (C-11), 31.1 (C-10), 28.7 (C-16). HRMS-ESI-IT-TOF: m/z calculated $C_{22}H_{23}ClN_5O$ 407.15, found 407.25.

(1-(2-((7-chloroquinolin-4-yl)amino)ethyl)-1*H*-1,2,3-triazol-4-yl)(phenyl)methanol (**23a**)

Yellowish powder. m.p. 238.3-240.0 ºC, IR (λ_{max}, cm^{-1}): 3119, 2384, 2349, 2307, 2924, 1585, 1456, 810, 749. ^{1}H NMR (300 MHz, MeOD)*: d* 9.02 (d, 1H,

J_{1-2} = 4.92 Hz, H-1), 8.49-8.53 (m, 2H, H-4 and H-7), 7.91-8.07 (m, 7H, H-13, H-5, H-17, H-17', H-18, H-18' and H-19), 7.04 (d, 1H, J_{2-1} = 5.31 Hz, H-2), 6.58 (s, 1H, -NH), 5.28-5.31 (m, 2H, H-11 and H-11'), 4.49-4.52 (m, 2H, H-10, H-10'), 2.86 (s, 1H, -OH), 1.81-1.85 (m, 1H, H-15).^{13}C NMR (100 MHz, $CDCl_3$): δ155.7(C-3), 155.1 (C-1), 154.0 (C-8), 152.3 (C-17), 146.0 (C-6), 139.4 (C-14), 132.3 (C-7), 131.7 (C-19, C-19'), 131.2 (C-20), 130.0 (C-18, C-18'), 129.6 (C-4), 126.6 (C-13), 126.0 (C-5), 121.2 (C-9), 102.3 (C-2), 72.4 (C-15), 52.4 (C-11), 46.4 (C-10). HRMS-ESI-IT-TOF: m/z calculated $C_{20}H_{19}ClN_5O$ (M+H) 380.85, found 380.35.

(1-(3-((7-chloroquinolin-4-yl)amino)propyl)-1*H*-1,2,3-triazol-4-yl)(phenyl)methanol (**23b**)

Yellowish powder. m.p. 160.2-162.7 ºC, IR (λ_{max}, cm^{-1}): 3361, 3307, 2955, 2921, 2851, 2361, 2341, 1585, 1455, 1048, 853, 670. ^{1}H NMR (300 MHz, MeOD)*: d* 9.32-9.34 (m, 1H, H-4), 8.93 (d, 1H, J_{1-2} = 8.57 Hz, H-1), 8.84 (s, 1H, H-7), 8.51 (s, 1H, H-13), 8.28-8.42 (m, 7H, H-5, H-17, H-17', H-18, H-18, H-19 and –NH), 7.33 (d, 1H, J_{2-1} = 5.25, H-2), 6.96 (s, 1H, -OH), 5.44-5.48 (m, 1H, H-15), 4.35-4.39 (m, 2H, H-12 and H-12'), 3.27-3.33 (m, 2H, H-10 and H-10'), 2.26-2.34 (m, 2H, H-11 and H-11').^{13}C NMR (100 MHz, $CDCl_3$): δ151.9 (C-3), 150.9 (C-1), 150.2 (C-8), 147.2 (C-17), 142.1 (C-6), 135.8 (C-14), 128.5 (C-7), 127.8 (C-19, C-19'), 126.4 (C-20), 126.3 (C-18, C-18'), 125.6 (C-4), 122.1 (C-13), 117.0 (C-5), 98.4 (C-2), 68.6 (C-15), 47.8 (C-11), 39.6 (C-10). HRMS-ESI-IT-TOF: m/z calculated $C_{21}H_{21}ClN_5O$ (M+H) 394.88, found 394.34.

7-chloro-*N*-(2-(4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl)ethyl)quinolin-4-amine (**24a**)

Yellowish powder. m.p. 276.8-278.2 ºC, IR (λ_{max}, cm^{-1}): 3303, 3142, 2922, 1608, 1579, 1498, 1443. ^{1}H NMR (400 MHz, DMSO-d_6): δ8.58 (d, 1H, *J* = 6.8, H-2), 8.56 (s, 1H, H-13), 8.42 (d, 1H, *J* = 9.2, H-5), 7.96 (d, 1H, *J* = 1.6, H-8), 7.79 (dd, 1H, *J* = 1.6 e 9.2, H-6), 7.64 (d, 2H, *J* = 8, H-16), 7.22 (d, 2H, *J* = 8, H-17), 6.94 (d, 1H, *J* = 7.2, H-3), 4.74 (t, 2H, *J* = 5.6, H-12), 4.09 (t, 2H, *J*= 5.2, H-11), 2.30 (s, 3H, H-19). ^{13}C NMR (100 MHz, DMSO-d_6): δ155.5 (C-3), 146.4 (C-8), 143.3 (C-1), 138.6 (C-13), 138.0 (C-6), 137.1 (C-17), 129.3 (C-16), 127.8 (C-14), 127.0 (C-12), 125.2 (C-7), 124.9 (C-15), 121.5 (C-4), 119.3 (C-5), 115.4 (C-9), 98.6 (C-2), 47.7 (C-11), 42.8 (C-10), 20.7 (C-18).

7-chloro-*N*-(3-(4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl)propyl)quinolin-4-amine (**24b**)

Yellow powder. m.p. 237.8-238.4 ºC, IR (λ_{max}, cm^{-1}): 3263, 3024, 2771, 1612, 1594, 1568, 1498, 1453. ^{1}H NMR (400 MHz, $CDCl_3$): δ8.26 (d, 1H, *J* = 7.0, H-2), 8.22 (s, 1H, H-14), 8.11 (d, 1H, *J* = 9.0, H-5), 7.66 (d, 1H, *J* = 1.8, H-8), 7.44 - 7.39 (m, 3H, H-6 e H-17), 7.13 (d, 2H, *J* = 8, H-18), 6.75 (d, 1H, *J* = 7.2, H-3), 4.62 (t, 2H, J = 6.2, H-13), 3.69 (t, 2H, *J* = 6.8, H-11), 2.47 (q, 2H, *J* = 6.0 e 12.2, H-12), 2.31 (s, 3H, H-20). ^{13}C NMR (100 MHz, MeOD): δ157.2 (C-3), 148.7 (C-8), 143.6 (C-1), 140.8 (C-14), 139.7 (C-6), 130.5 (C-17), 128.6 (C-13), 128.0 (C-18), 126.3 (C-16), 125.7 (C-7), 122.4 (C-4), 120.1 (C-5), 116.7 (C-15), 114.0 (C-9), 99.6 (C-2), 49.6 (C-12), 42.4 (C-10), 28.8 (C-11), 21.3 (C-19).

7-chloro-*N*-(2-(4-(4-methoxyphenyl)-1*H*-1,2,3-triazol-1-yl)ethyl)quinolin-4-amine (**25a**)

Yellowish powder. m.p. 234.3-237.0 ºC, IR (λ_{max}, cm^{-1}): 3295, 2999, 2936, 2834, 1618, 1580, 1498, 1460, 1220, 1162. ^{1}H NMR (200 MHz, DMSO-d_6): δ8.47 (s, 1H, H-13), 8.42 (d, 1H, *J* = 5.2, H-2), 8.16 (d, 1H, *J* = 9.0, H-5), 7.80 (d, 1H, *J* = 2.2, H-8), 7.72 (d, 2H, *J* = 8.8, H-16),7.46 (dd, 1H, *J* = 2.2 e 9.0, H-6), 6.99 (d, 2H, *J* = 8.8, H-17), 6.61 (d, 1H, *J* = 5.4, H-3), 4.66 (t, 2H, *J* = 6.0, H-12), 3.85 (t, 2H, *J* = 5.6, H-11), 3.77 (s, 3H, H-19). ^{13}C NMR (50 MHz, DMSO-d_6): δ158.8 (C-17), 151.8 (C-1), 149.5 (C-3), 148.9 (C-8), 146.1 (C-13), 133.4 (C-6), 127.4 (C-12), 126.3 (C-15), 124.2 (C-7), 123.8 (C-4), 123.2 (C-14), 120.8 (C-5), 117.3 (C-9), 114.1 (C-16), 98.7 (C-2), 55.0 (C-18), 47.7 (C-11), 42.2 (C-10).

7-chloro-*N*-(3-(4-(4-methoxyphenyl)-1*H*-1,2,3-triazol-1-yl)propyl)quinolin-4-amine (**25b**)

Yellowish powder. m.p. 189.6-191.5 ºC, IR (λ_{max}, cm^{-1}): 3319, 3111, 2929, 1612, 1581, 1498, 1453, 1224, 1177. ^{1}H NMR (200 MHz, DMSO-d_6): δ8.14 (d, 1H, *J* = 7.2, H-2), 8.00 (s, 1H, H-14), 7.97 (d, 1H, *J* = 9.0, H-5), 7.53 (d, 1H, *J* = 1.8, H-8), 7.35 – 7.29 (m, 3H, H-6 e H-17),6.73 (dd, 1H, *J* = 2.2 e 9.0, H-6), 6.99 (d, 2H, *J* = 8.8, H-17), 6.61 (d, 1H, *J* = 5.4, H-3), 4.66 (t, 2H, *J* = 6.0, H-12), 3.85 (t, 2H, *J* = 5.6, H-11), 3.77 (s, 3H, H-19). ^{13}C NMR (50 MHz, DMSO-d_6): δ158.8 (C-17), 151.8 (C-1), 149.5 (C-3), 148.9 (C-8), 146.1 (C-13), 133.4 (C-6), 127.4 (C-12), 126.3 (C-15), 124.2 (C-7), 123.8 (C-4), 123.2 (C-14), 120.8 (C-5), 117.3 (C-9), 114.1 (C-16), 98.7 (C-2), 55.0 (C-18), 47.7 (C-11), 42.2 (C-10).

7-chloro-*N*-(2-(4-(4-fluorophenyl)-1*H*-1,2,3-triazol-1-yl)ethyl)quinolin-4-amine (**26a**)

Yellowishpowder. m.p. 278.5-281.0 ºC, IR (λ_{max}, cm^{-1}): 3316, 3138, 2925, 1609, 1578, 1559, 1494, 1459.^{1}H NMR (200 MHz, MeOD): δ8.32 – 8.24 (m, 3H, H-2, H-5 e H-13), 7.85 (d, 1H, *J* = 1.8, H-8), 7.76 – 7.64 (m, 3H, H-6 e H-16), 7.17 – 7.08 (m, 2H, H-17), 6.77 (d, 1H, *J* = 7.2, H-3), 4.84 (t, 2H, *J* = 5.4, H-12), 4.18 (t, 2H, *J* = 5.4, H-11) ^{13}C NMR (50 MHz, DMSO-d_6): δ151.9 (C18), 151.8 (C-1), 149.6 (C-3), 148.9 (C-8), 145.3 (C-13), 133.4 (C-6), 127.4 (C-15), 127.1 (C-12), 126.9 (C-14), 124.3 (C-7), 123.9 (C-4), 121.7 (C-5), 115.9 (C-9), 115.5 (C-16), 98.7 (C-2), 47.9 (C-11), 42.2 (C-10).

7-chloro-*N*-(3-(4-(4-fluorophenyl)-1*H*-1,2,3-triazol-1-yl)propyl)quinolin-4-amine (**26b**)

Yellowish powder. m.p. 229.4-230.3 ºC, IR (λ_{max}, cm^{-1}): 3339, 3133, 2948, 1610, 1582, 1540, 1495, 1455. ^{1}H NMR (200 MHz, MeOD): δ8.32 (d, 1H, *J* = 7.2, H-2), 8.26 (s, 1H, H-14), 8.18 (d, 1H, *J* = 9, H-5), 7.73 (d, 1H, *J* = 1.8, H-8), 7.66 – 7.59 (m, 2H, H-17), 7.51 (dd, 1H, J = 1.6 e 9.0, H-6), 7.14 – 7.05 (m, 2H, H-18), 6.82 (d, 1H, *J* = 7.2, H-3), 4.64 (t, 2H, *J* = 6.2, H-13), 3.73 (t, 2H, *J* = 6.6, H-11), 2.53 (q, 2H, *J* = 6.2 e 12.8, H-12). ^{13}C NMR (50 MHz, MeOD): δ157.4 (C19), 148.0 (C-3), 143.8 (C-1), 140.9 (C-8), 139.9 (C-14), 128.5 (C-13), 128.3 (C-7), 127.8 (C-6), 125.8 (C-4), 122.4 (C-16), 120.2 (C-5), 119.7 (C-15), 117.0 (C-17), 116.9 (C-9), 99.7 (C-2), 49.5 (C-12), 42.5 (C-10), 28.9 (C-11).

7-chloro-*N*-(2-(4-(4-(dimethylamino)phenyl)-1*H*-1,2,3-triazol-1-yl)ethyl)quinolin-4-amine (**27a**)

Yellowish powder. m.p. 220.0-222.7 ºC, IR (λ_{max}, cm^{-1}): 3277, 3142, 2886, 2806, 1619, 1580, 1458. ^{1}H NMR (200 MHz, DMSO-d_6): δ8.50 (s, 1H, H-13), 8.36 (d, 1H, J = 7.2, H-2), 8.28 (d, 1H, J = 9.2, H-5), 7.93 (d, 1H, *J* = 1.8, H-8), 7.87 (d, 2H, J = 8.6, H-16), 7.67 (dd, 1H, J = 2.0 e 9.2, H-6), 7.60 (d, 2H, J = 8.6, H-17), 6.83 (d, 1H, *J* = 7.2, H-3), 4.88 (t, 2H, *J* = 5.2, H-12), 4.20 (t, 2H, *J* = 5.4, H-11) and 3.27 (s, 6H, H-19). ^{13}C NMR (50 MHz, DMSO-d_6): δ151.9 (C-1), 149.9 (C-17), 149.6 (C-3), 149.0 (C-8), 146.8 (C-13), 133.4 (C-6), 127.5 (C-7), 125.9 (C-5), 124.3 (C-4), 123.9 (C-12), 119.9 (C-15), 118.6 (C-14), 117.4 (C-9), 112.2 (C-16), 98.8 (C-2), 47.7 (C-11), 42.3 (C-10), 39.9 (C-18).

7-chloro-*N*-(3-(4-(4-(dimethylamino)phenyl)-1*H*-1,2,3-triazol-1-yl)propyl)quinolin-4-amine (**27b**)

Yellowish powder. m.p. 185.1-187.9 ºC, IR (λ_{max}, cm^{-1}): 3245, 3122, 3040, 2918, 2851, 1615, 1597, 1573, 1453. ^{1}H NMR (200 MHz, MeOD): δ8.37 (s, 1H, H-14), 8.27 (d, 1H, *J* = 7.2, H-2), 8.11 (d, 1H, *J* = 9.2, H-5), 7.75 (d, 2H, *J* = 8.6, H-17), 7.66 (d, 1H, *J* = 2.0, H-8), 7.55 (d, 2H, *J* = 8.6, H-18), 7.40 (dd, 1H, *J* = 1.8 e 9.0, H-6), 6.77 (d, 1H, *J* = 7.2, H-3), 4.62 (t, 2H, *J* = 6.2, H-13), 3.69 (t, 2H, *J* = 6.2, H-11), 3.69 (s, 6H, H-20), 2.46 (q, 2H, *J* = 5.8 e 12.2, H-12). ^{13}C NMR (50 MHz, MeOD): δ157.2 (C19), 147.1 (C-3), 144.4 (C-8), 143.7 (C-1), 140.6 (C-14), 139.7 (C-6), 128.5 (C-7), 128.1 (C-16), 125.9 (C-7), 123.3 (C-4), 123,2 (C-15), 121.3(C-5), 120.1 (C-17), 116.7 (C-9), 99.7 (C-2), 49.6 (C-12), 46.4 (C-19), 42.4 (C-10), 28.8 (C-11).

7-chloro-*N*-(2-(4-(6-methoxynaphthalen-2-yl)-1*H*-1,2,3-triazol-1-yl)ethyl)quinolin-4-amine (**28a**)

Yellowish powder. m.p. 244.3-246.3 ºC, IR (λ_{max}, cm^{-1}): 3341, 3063, 2936, 1610, 1580, 1452, 1220, 1162. ^{1}H NMR (200 MHz, MeOD):δ8.41 (s, 1H, H-24), 8.29 (d, 1H, *J* = 1.6, H-8), 8.25 (d, 1H, *J* = 6.0, H-2), 8.08 (s, 1H, H-13), 7.81 (d, 1H, *J* = 3.2, H-21), 7.77-7.75 (m, 2H, H-2 e H-19), 7.20 (d, 1H, *J* = 3.2, H-22), 7.13 (dd, 1H, *J* = 2.4 e 8.9, H-6), 7.70-7.64 (m, 2H, H-16 e H-17), 6.74 (d, 1H, *J* = 7.2, H-3), 4.87 (t, 2H, *J* = 5.2, H-12), 4.19 (t, 2H, *J* = 5.8, H-11), 3.90 (s, 3H, OCH_3). ^{13}C NMR (50 MHz, DMSO-d_6): δ157.4 (C-19), 151.8 (C-1), 149.6 (C-3), 149.0 (C-8), 146.4 (C-13), 133.8 (C-6), 133.5 (C-17), 129.4 (C-16), 128.4 (C-14), 127.5 (C-12), 127.3 (C-21), 124.3 (C-7), 124.4 (C-5), 124.0 (C-15), 123.9 (C-4), 123.2 (C-5), 121.7 (C-23), 119.0 (C-20), 117.4 (C-9), 105.9 (C-18), 98.9 (C-2), 55.1 (OCH_3), 47.9 (C-11), 42.3 (C-10).

7-chloro-*N*-(3-(4-(6-methoxynaphthalen-2-yl)-1*H*-1,2,3-triazol-1-yl)propyl)quinolin-4-amine (**28b**)

Yellowish powder. m.p. 197.8-199.0 ºC, IR (λ_{max}, cm^{-1}): 3322, 3062, 2924, 1611, 1582, 1543, 1481, 1451, 1219, 1163. ^{1}H NMR (200 MHz, DMSO-d_6): δ8.67 (s, 1H, H-25), 8.39 (d, 1H, *J* = 5,4, H-2), 8.29 (sl, 1H, H-5), 8.25 (sl, 1H, H-23), 7.89 - 7.79 (m, 3H,H-8, H-17 e H-18), 7.47 - 7.33 (m, 3H, H-14, H-20 e H-22), 7.18 (dd, 1H, *J* = 1.4 e 8.8, H-6), 6.48 (d, 1H, *J* = 5,4, H-3), 4.87 (t, 2H, *J* = 6.4, H-13), 3.88 (s, 3H, OCH_3), 3.38 (sl, H-11), 2.31 (q, 2H, *J* = 5.8 e 12.4, H-12). ^{13}C NMR (50 MHz, DMSO-d_6): δ157.3 (C-20), 151.8 (C-1), 149.9 (C-3), 148.9 (C-8), 146.5 (C-14), 133.8 (C-6),

133.3 (C-18), 129.4 (C-17), 128.4 (C-15), 127.4 (C-13), 127.2 (C-22), 125.9 (C-23), 124.0 (C-7/C-16), 123.3 (C-4/C-8), 121.3 (C-24), 19.0 (C-21), 117.4 (C-9), 105.9 (C-19), 98.7 (C-2), 55.1 (OCH_3), 47.5 (C-12), 39.5 (C-10), 28.3 (C-11).

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