UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL

FACULDADE DE FARMÁCIA

TRABALHO DE CONCLUSÃO DE CURSO

SYNTHESIS AND ANTIFUNGAL ACTIVITY OF 8-HYDROXYQUINOLINE DERIVATIVES BEARING 1,2,3-TRIAZOLE MOIETY

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PORTO ALEGRE, DEZEMBRO DE 2019

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Trabalho de Conclusão apresentado ao Curso de Farmácia da Universidade Federal do Rio Grande do Sul, como requisito para a obtenção do título de Farmacêutica.

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PORTO ALEGRE

2019

Este trabalho foi elaborado conforme as normas da revista *European Journal of Medicinal Chemistry,* apresentadas em anexo.

AGRADECIMENTOS

Primeiramente agradeço aos meus pais, Ricardo e Beatriz, pelas suas trajetórias de vida inspiradoras além de todo apoio e incentivo que serviram como base para minhas realizações.

A minha irmã Daniela, por sua ternura e carinho recebidos em momentos difíceis.

Ao Luis Henrique que esteve ao meu lado durante toda a jornada UFRGS, sempre apoiando e incentivando para chegar na reta final.

A todos meus amigos e colegas que sempre estiveram ao meu lado compartilhando momentos, em especial às amigas que fiz durante o curso, Julia e Victória.

Ao Professor Dr. Saulo Fernandes de Andrade pela oportunidade de trabalhar neste projeto, ótima orientação e companheirismo durante minha jornada.

À coorientadora Caroline Gentz pelos ensinamentos e todo suporte dado durante o desenvolvimento do TCC.

Ao Laboratório 705 e 105 por toda a disposição e parceria.

SYNTHESIS AND ANTIFUNGAL ACTIVITY OF 8-HYDROXYQUINOLINE DERIVATIVES BEARING 1,2,3-TRIAZOLE MOIETY

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Abstract

The lack of selective antifungal agents and the growth of fungal resistance to current treatments has become a worldwide concern, especially for immunocompromised patients. 8-Hydroxyquinolines and 1, 2 ,3 - triazoles have shown wide spectrum effects against several microorganisms. Thus, the purpose of this study was the synthesis of 1,4-triazole-substituted 8-hydroxyquinoline derivatives and evaluation of in vitro antifungal activity against strains of dermatophytes and *Candida* spp. The commercial available 8-hydroxyquinoline 1 was used to prepare triazole derivates **7a-7d** in eight-step synthesis: nitrosation of **1** followed by oxidation to 5-nitro-8-hydroxyquinoline **2**; reduction of **2** to 5-amino-8-hydroxyquinoline **3**; diazotization of **3** followed by azide replacement to 5-azido-8-hydroxyquinoline **4**; acetylation of **4** to 5-azidoquinolin-8-yl acetate **5**; copper (I) catalyzed cycloaddition of **5** and deprotection of acetylated intermediates **6a-6d** to triazole derivates **7a-7d**. The compounds prepared were characterized by ^{1}H and ^{13}C NMR. The evaluation of antifungal activity was determined by broth microdilution assay. The compound **7a** presented the most potent activity against dermatophytes, *C. albicans* and *C. glabrata* strains, and compounds **7c** and **7d** had good MIC values for the strains of *Trichophyton*, *C. krusei* and *C. glabrata*. These compounds have the potential to be developed as antifungal agents.

Keywords: 8-hydroxyquinoline; triazole; antifungal.

1. Introduction

Fungal infections represents a global health threat [1,2]. Dermatophytosis is among the most common public health problem in the hot and humid climate of tropical areas, particularly in developing and underdeveloped countries [3,4]. The genera *Trichophyton*, *Microsporum* and *Epidermophyton* are groups of dermatophytes which typically lead to circular, erythematous and pruritic lesions on the skin. In onychomycosis, nails become thickened, separated from the bed, even develop white spots or dystrophy [5]. Although dermatophytes generally cause cutaneous mycoses, they can be invasive, causing disseminated infection, especially in immunocompromised patients [3,5]. Some fungal species commonly found in human microbiota can behave as opportunistic pathogens when the immune system is impaired, resulting in mucosal or systemic infection. *Candida* spp. are the most prevalent pathogens implicated in those types of infection caused by *Candida albicans*, *Candida glabrata*, *Candida parapsilosis*, *Candida tropicalis* [6–8].

The treatment of human fungal infections has been limited by the challenging development of new antifungal. The high similarities between fungal and animal cells narrow the availability of specific cellular targets for antifungal agents and may result in therapies with significant toxic effects [2,9]. The current antifungal treatments are characterized by extended regiments to produce a complete cure, but poor patient compliance and increased risk of relapse or reinfection may be resulted by long-term treatments [10]. Also, the emergence of antifungal resistance has impaired patients at high risk for invasive infections and at immunosuppression, leading to high morbidity and mortality [7]. Intensive care unit (ICU), malignancy, blood/solid organ transplantation, HIV infection and poorly controlled diabetes are well-recognized risk factors for invasive fungal infections [11].

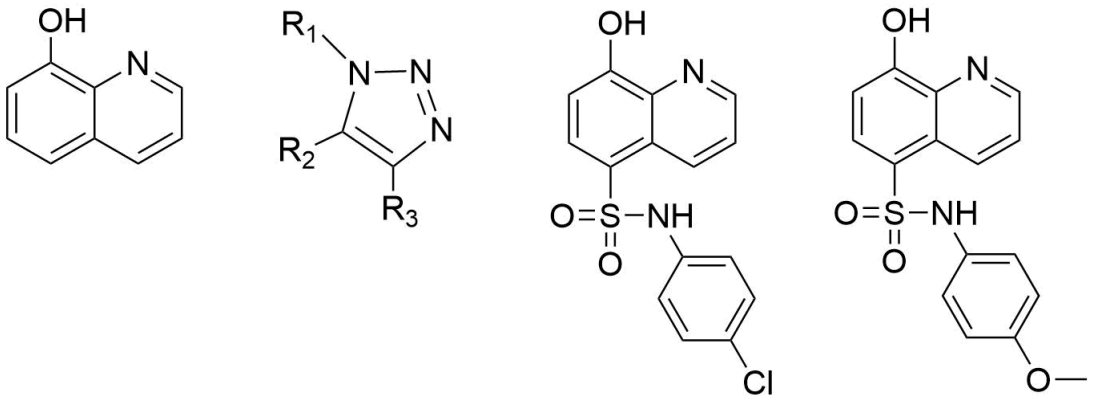
Five classes of antifungal agents are used orally, topically or intravenously for therapy: azoles, polyenes, echinocandins, pyrimidines and allylamines [2]. Conversely, several studies have reported the resistance of *Candida* strains to short-tailed azoles such as fluconazole and to echinocandins in different geographic regions. Further, dermatophytes isolates have demonstrated resistance to azoles and allylamines such as terbinafine [8,12]. There is a clear need for development of new antifungal derivatives that will help to expand the limited and available therapy against fungal infections.

8-hydroxyquinolines **1** are a subclass of quinolines – double-ring structures composed of a benzene and a pyridine fused rings - with a wide spectrum of biological activities (1,

Fig.1). In the last decades, the studies on 8-hydroxyquinolines have grown exponentially leading to new drug candidates with multifunctional uses as antibacterial, antifungal, antiviral, antiparasitic and anticancer agents [13–19]. Several studies have also shown 8-hydroxyquinoline derivatives as potential therapeutic agents against neurodegenerative diseases such as Alzheimer, Parkinson and Huntington [20–22]. Although the fungistatic activity of 8-hydroxyquinoline has been known since the early 1920s, its mechanism of action into fungal cells is poorly elucidated and some studies demonstrated that any modification of the 8-hydroxyquinoline substitution pattern could result in different antifungal mechanisms [17,23].

1,2,3-Triazoles **2** are other N-heterocycles organic compounds - five-membered rings with three nitrogen and two carbon atoms - displaying a wide range of biological effects [24–29] because they can act as pharmacophores, linkers, and an amide bond bioisostere (2, Fig.1). The recent developments in copper-catalyzed cycloaddition, the "click" reaction, has grown the interest in synthesis and biological evaluations of triazoles linked to other potential pharmacophores rings [30,31]. Quinoline based 1,2,3-triazoles emerged as a group of potent inhibitors against *C. albicans*, *C. glabrata* and *C. tropicalis* with low cytotoxicity [32,33]. Besides, selective antiproliferative activity [30,34] and promising antimicrobial activities [35–37] have been evaluated from diverse triazole-quinoline hybrids.

The antimicrobial activity of 8-hydroxyquinolines might be modulated by the type of the substituent at the 5- and 7- positions. Due to the hydroxyl group being an activating ortho-/para- directing substituent, these positions can be easily functionalized by electrophilic aromatic substitutions such as sulfonation, nitration and nitrosation [13,16,38]. Hybrids between the 8-hydroxyquinoline and sulfonamide **3** and **4** were recently reported as potential candidates for the treatment of dermatophytosis and candidiasis (3 and 4, Fig.1)[16]. Since 1,2,3 – triazoles also demonstrated antifungal effects [31], they could be conjugated with 8-hydroxyquinoline at 5-position using "click" chemistry. Thus, the purpose of this study was to synthesize 8-hydroxyquinolines substituted with an appropriate 1,2,3-triazole core at 5-position and to evaluate their *in vitro* antifungal activity.



1 **2** **3** **4**

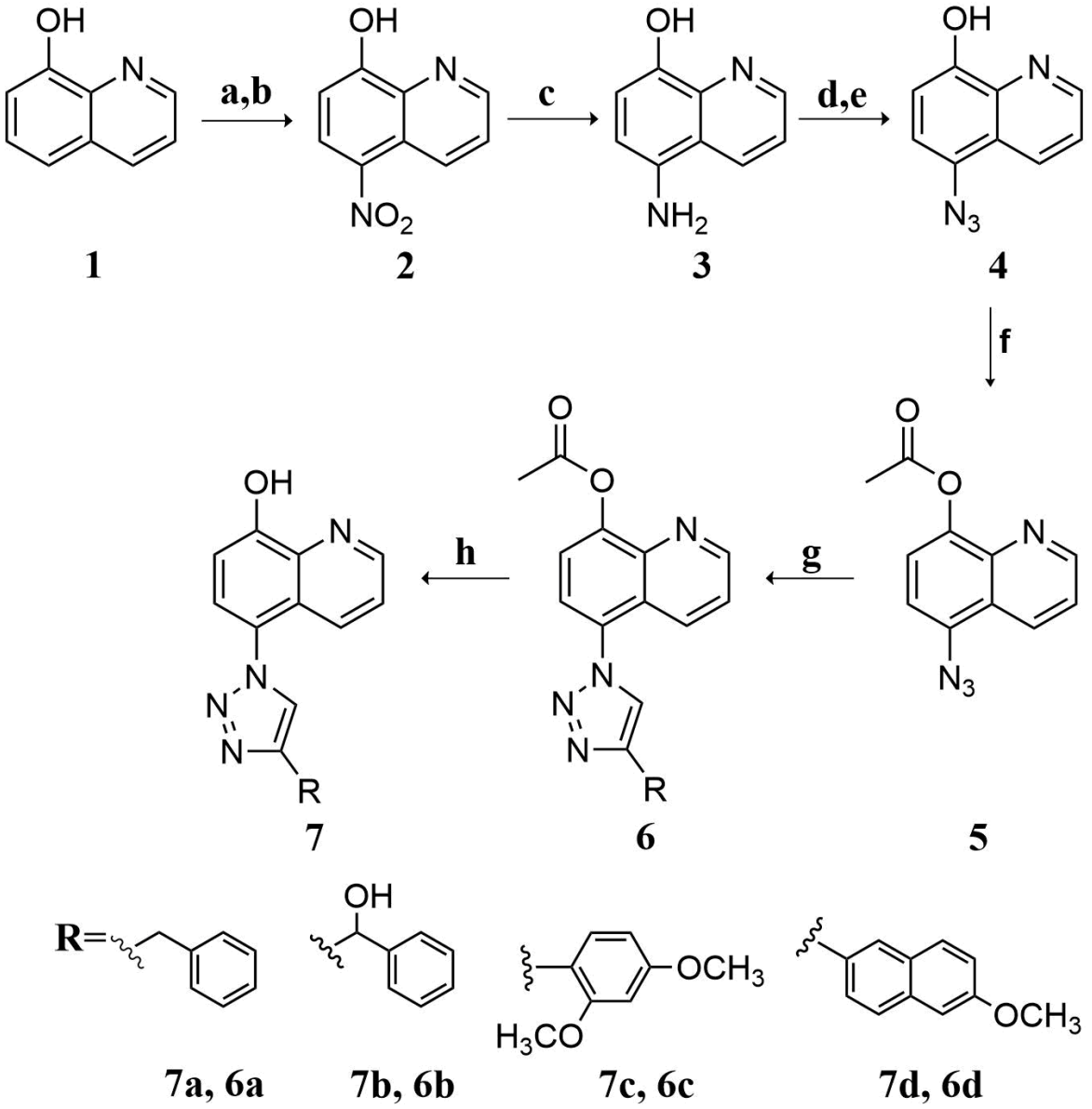
Fig. 1 – Chemical structure of 8–hydroxyquinoline **1**, 1,2,3-triazole **2**, 8-hydroxiquinoline-5-(*N*-4-chlorophenyl)sulfonamide **3**, 8-hydroxiquinoline-5-(*N*-4-methoxyphenyl)sulfonamide **4**.

2. Results and discussion

2.1 Chemistry

Initially, 5-nitro-8-hydroxyquinoline **2** was prepared as previously described by Mazumder et al. (**Scheme 1**) [39]. In brief, commercially available 8-hydroxyquinoline **1** was dissolved in HCl (37%) and treated with $NaNO_2$ to give 5-nitroso-8-hydroxyquinoline that was oxidized by HNO_3 to provide **2**. Secondly, it was proceeded the synthesis of 5-amino-8-hydroxyquinoline **3**. Palladium-on-carbon catalyzed the reduction of **2** with hydrazine solution (24%), affording **3**. Then, 5-azido-8-hydroxyquinoline **4** was formed by the diazotization of **3** with $NaNO_2$ and concentrated HCl, and further treatment with sodium azide.

The triazoles derivatives were prepared using “click” chemistry as previously described [40], specifically copper (I) catalyzed azide-alkyne cycloaddition. However, the cycloaddition of 5-azido-8-hydroxyquinoline and alkynes could not be carried out using the selected catalyst system, copper (II)/sodium ascorbate. This is due to 8-hydroxyquinolines being bidentate chelators that bind preferably copper (II) and zinc (II) through the phenol oxygen and pyridine nitrogen [13]. Based on that, it was decided to introduce an acetyl group at OH-8 before the cycloaddition in order to prevent copper chelation and a low-yielding reaction. Then, 5-azido-8-hydroxyquinoline was treated with acetic anhydride and pyridine to provide 5-azidoquinolin-8-yl acetate **5** (**Scheme 1**).



Scheme 1 – Synthesis of 1,4-triazole-substituted 8-hydroxyquinoline derivatives 7a-7d. Reagents and conditions: (a) HCl, $NaNO_2$, 0 ºC, 40 min; (b) HNO_3, 17 °C, 75 min; (c) Isopropanol, hydrazine, refluxed for 3 h; (d) HCl, $NaNO_2$,- 3 ºC, 30 min; (e) NaN_3, 0 °C (90 min), r.t. (24 h); (f) Acetic anhydride, pyridine, r.t., 60 min; (g) t-butanol, appropriate alkyne, $CuSO_4.5H_2O$, $NaHCO_3$, ascorbic acid, r.t., 18 h; (h) Ethanol, KOH, r.t., 60 min.

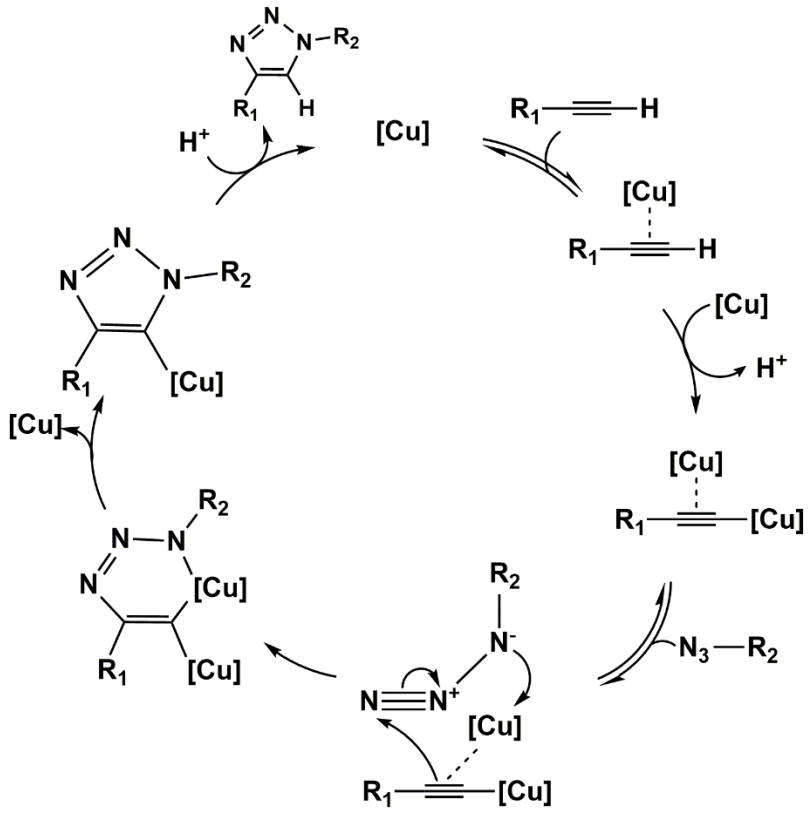


Fig.2 – Dinuclear mechanism of copper (I) catalyzed azide-alkyne cycloaddition [42– 44]

After protecting the hydroxyl at 8 position, copper (I) catalyzed azide-alkyne cycloaddition reaction promoted the formation of 1,4 – disubstituted 1,2,3 – triazoles (**6a-6d**) by coupling terminal alkynes and organic azides. Ascorbic acid and $NaHCO_3$ in aqueous solution resulted in sodium ascorbate which was used as a reducing agent to generate copper (I) in situ from copper (II) sulphate pentahydrate ($CuSO_4.5H_2O$). Inert atmosphere was not required despite the instability of the copper (I) oxidation state in the presence of oxygen [41]. The catalysis mechanism [42–44] starts with the formation of σ-bound copper (I) acetylide followed by the recruitment of a second π-bound copper atom. Then, the azide is activated by coordination to cooper, forming an intermediate complex. In the next step, the distal nitrogen of the azide is attacked by the C-2 carbon of the acetylide, generating a six-membered copper metallocycle. Finally, the ring contraction to triazole-copper derivatives is followed by protonation which results in triazole derivatives (**Fig. 2**). After deprotecting **6a-6d**, triazoles derivatives **7a-7d** was confirmed by ^{1}H and ^{13}C NMR spectra (Supplementary Information). The hydrogen signal of the 1,4-disubstituted-triazole group was detected at δ_H 8.28-7.50 ppm as a singlet confirming the formation of the planned derivative.

2.2 Biological activity

The minimal inhibitory concentration (MIC, μg/mL) against strains of dermatophytes and *Candida* spp. was determined for the four synthesized triazole-derivatives **7a-7d** (**Table 1** and **2**). Fluconazole and ciclopirox were used as positive controls for *Candida* strains and dermatophytes, respectively. Compound **7a** was the most potent derivative being active against all dermatophyte species tested, with MIC values comparable to the positive control. The activity of **7c** against strains of *Trichophyton rubrum* and *Microsporum canis* was comparable to **7a**. Compound **7d** had values of MIC comparable with the positive control for both species of *Trichophyton* tested. Despite being against *Microsporum gypseum* isolate, **7b** has shown poor activity for other dermatophytes strains. All triazole derivates have presented good MIC values for *Candida glabrata* strain RL 37. Compound **7a** was the most active derivative against all *Candida* spp. strains tested.

Table 1 - *In vitro* evaluation of MIC (minimal inhibitory concentration) values in μg/mL for ciclopirox (positive control) and derivates 7a-7d against dermatophytes strains*.

Species (Strain)	**Compound**				
	Ciclopirox	**7a**	**7b**	**7c**	**7d**
T. mentagrophytes (TME 40)	1	2	32	8	2
T. rubrum (TRU 51)	1	1	32	2	1
M. canis (MCA 01)	>1	1	32	2	4
M. gypseum (MGY ATCC)	0.25	4	4	16	64

*According to CLSI - Clinical and Laboratory Standards Institute.

Table 2 - *In vitro* evaluation of MIC* (minimal inhibitory concentration) values in μg/mL for fluconazole (positive control) and derivates 7a-7d against *Candida* spp. strains*.

Species (Strain)	**Compound**				
	Fluconazole	**7a**	**7b**	**7c**	**7d**
C. albicans (CAMS5)	0.5	4	>64	>64	64
C. parapsilosis (RL33)	0.06	8	ND	32	16
C. krusei (CK02)	32	8	ND	4	1
C. glabrata (RL37)	8	2	8	0.5	4

Note: ND - Not determined; 50% inhibition reading compared to positive control. *According to CLSI - Clinical and Laboratory Standards Institute.

The 8-hydroxyquinolines substituted at 5- position have shown potential antifungal activity, especially those with sulfonamide groups that presented MIC values (3 – 12 µM) similar to fluconazole [16]. Further, 1,2,3-triazoles are important pharmacophores groups displaying several biological effects and the nature of the substituent on the 4-position influences on antimicrobial activity due to electronic and steric factors [45]. This present study explored the antifungal activity of **7a-7d** varying substituents at 4-position of the triazole moiety. The compound **7a** and **7b** contain a benzyl group – hydrophobic group with spacer chain – but the introduction of OH at Csp3 reduced the activity of **7b** against strains of *T.mentagrophytes, T.rubrum, M.canis. C.albicans* and *C.glabrata.* The compound **7c** contains a 2,4-dimetoxiphenyl group – hydrophobic group without spacer chain – that presented low MIC values for *C.glabrata* and *C.krusei* strains. The compound **7d** containing methoxynaphtol group – hydrophobic group without spacer chain – exhibited similar activity to **7a** against both strains of *Trichophyton*. The best antifungal activities may occur due to hydrophobic groups on the 4-position of triazole ring, especially those with spacer carbon chain (**7a**).

Previous studies performed the synthesis of several triazole hybrids and revealed promising MIC results. 1,2,3–Triazoles derivatives of quinazolin-4-ones [46], benzene [47] and oxazolones [48] exhibited activity against *Candida* spp. strains as good as compounds **7a**, **7c** and **7d**. However, these 8-hydroxynoline-triazole hybrids were more potent against *T.rubrum* and *M.canis* (MIC = 1 – 4 µg/mL) than 1,2,3 – triazoles conjugates of benzenes (MIC = 6.25 - 12.5 µg/mL) [47]. Besides, compound **7a** showed MIC values ranging 1 – 4 µg/mL in dermatophytes while 1,2,3–triazoles derivatives of chalcones and flavones showed MIC values ranging 6.25 – 25 µg/mL or > 100 µg/mL [49].

3. Conclusions

The synthesis of the 1,4-triazole-substituted 8-hydroxyquinoline derivatives was achieved using 8-hydroxyquinoline **1** as a starting material. The intermediates **2-5** were obtained successfully without purification. In order to avoid copper chelation during the "click" reaction, **4** was acetylated by acetic anhydride to give **5**. The copper (I) catalyzed azide-alkyne cycloaddition lead to the formation of 1,4 – disubstituted 1,2,3 – triazoles for terminal alkynes affording organic azides. This reaction was tested for four different alkynes with success and, after deprotecting OH-8, it was given the derivates **7a-7d** with 66-39% of overall yield.

Among all prepared compounds, **7a** had the most potent activity against the strains of dermatophytes and *Candida* spp. with MIC value between 1 – 8 µg/mL. The compound **7a** has a hydrophobic group (benzyl) at 4-position of the triazole. The compounds **7c** and **7d** also have electron-releasing substituents (-OCH_3) on naphthalene and benzene rings, respectively, resulting in good activity against the strains of *Trichophyton*, even better MIC values for *C. krusei* and *C. glabrata* than fluconazole. Thus, these compounds are considered as potential candidates for the treatment of fungal infections.

4. Experimental section

4.1 Materials and instruments

8-hydroxyquinoline **1** and other reactants were obtained from commercial suppliers. Proton and carbon NMR spectra were performed by Bruker 400 or Varian 400 nuclear magnetic resonance spectrometer, which proton and carbon shifts (δ) are related to TMS. Column chromatography was performed on silica gel Fluka (Sigma-Aldrich) 0.035-0.070 mm.

4.1.1 Synthesis of 5-nitro-8-hydroxyquinoline (2)

It was obtained as described previously by Mazumder et al. [39]. Bright yellow crystal. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.34 (dd, 1H, J = 1.5, 9.0 Hz), 8.89 (dd, 1H, J = 1.5, 4.3 Hz), 8.60 (d, 1H, J = 8.8 Hz), 7.74 (dd, 1H, J = 4.3, 9.0 Hz), 7.20 (d, 1H, J = 8.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 158.64, 148.93, 137.21, 136.26, 133.91, 129.23, 125.37, 122.70, 108.28.

4.1.2 Synthesis of 5-amino-8-hydroxyquinoline (3)

To a solution of 5-nitro-8-hydroxyquinoline (3.50 g, 18.40 mmol) in isopropanol (174.10 mL) were added palladium-on-carbon 10% catalyst (440 mg) and hydrazine solution (24% w/v, 13.10 mL, 64.40 mmol), and the mixture was heated to 82 °C. The reaction was stirred, refluxed for 3 h and monitored by TLC. Thereafter the mixture was filtered in hot and washed with heated isopropanol, the filtrate was concentrated under reduced pressure to give the 5-amino-8-hydroxyquinoline as a black solid that was used in the next step without further purification. ^{1}H NMR (400 MHz, DMSO – d_6) δ (ppm): 8.76 (dd, 1H, J = 1.7, 4.1 Hz), 8.47 (dd, 1H, J = 1.7, 8.6 Hz), 7.42 (dd, 1H, J = 4.1, 8.6 Hz), 6.85 (d, 1H, J = 8.2 Hz), 6.63 (d, 1H, J = 8.2 Hz). ^{13}C NMR (100 MHz, DMSO – d_6) δ (ppm): 147.69, 143.83, 138.59, 136.73, 131.59, 119.46, 118.66, 111.82, 108.66.

4.1.3 Synthesis of 5-azido-8-hydroxyquinoline (4)

5-amino-8-hydroxyquinoline (3.0 g, 18.73 mmol) was dissolved in a solution of concentrated hydrochloric acid (1.66 mL) and water (20.7 mL), cooled to - 3 °C in an ice

bath and stirred for 10 min. Then, a cold solution of sodium nitrite (2.07 g, 29.97 mmol) in water (20.7 mL) was added dropwise to the mixture. After 20 min, a solution of sodium azide (2.44 g, 37.46 mmol) in water (89.10 mL) was added dropwise to the mixture and stirred at 0 °C for 1.5 h. The reaction was kept at room temperature for 24 h in the dark, with stirring. After 24h, ethyl acetate (100 mL) was added to the resulting mixture, which was filtered and extracted by ethyl acetate. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the 5-azido-8-hydroxyquinoline as a brown solid that was used in the next step without purification. ^{1}H NMR (400 MHz, DMSO – d_6) δ (ppm): 9.92 (s, 1H), 8.91 (dd, 1H, J = 1.6, 4.1 Hz), 8.34 (dd, 1H, J = 4.1, 8.5 Hz), 7.59 (dd, 1H, J = 4.1, 8.5 Hz), 7.37 (d, 1H, J = 8.2 Hz), 7.13 (d, 1H, J = 8.2 Hz). ^{13}C NMR (100 MHz, DMSO – d_6) δ (ppm): 150.82, 149.10, 138.59, 130.82, 125.28, 122.00, 121.55, 116.18, 111.35.

4.1.4 Synthesis of 5-azidoquinolin-8-yl acetate (5)

To a solution of 5-azido-8-hydroxyquinoline (150 mg, 0.810 mmol) in acetic anhydride (114.20 µL, 1.21 mmol) was added pyridine (39.15 µL, 0.486 mmol). The reaction was stirred under room temperature. After 1 h, ethyl acetate (10 mL) was added to the resulting mixture, which was transferred to a separation funnel. Acetic acid and solution of sodium acetate (1 M) were used to adjust the organic layer pH to 7.0. The resulting organic layer was washed with water (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the 5-azidoquinolin-8-yl acetate that was used in the next step without purification.

4.1.5 General procedure for the synthesis of 6a-6d

To a stirred solution of 5-azidoquinolin-8-yl acetate (100 mg, 0.438 mmol) in t-butanol (2 mL) was added, in order, a proper alkyne (0.876 mmol), $CuSO_4.5H_2O$ (44 mg, 0.175 mmol) and a solution of ascorbic acid (46 mg, 0.263 mmol) and $NaHCO_3$ (22 mg, 0.263 mmol) in water (2 mL). The reaction was stirred under room temperature. After 18 h, the resulting mixture was extracted by ethyl acetate. The organic layer was dried over Na_2SO_4, filtered, concentrated under reduced pressure and purified by silica gel column chromatography (cyclohexane/ethyl acetate).

4.1.6 General procedure for the deprotection of 7a-7d

It was added ethanol (50 µl) to solubilize one of the derivatives (**6a-6d**, 50 mg). After adding KOH (25.93 mg), the reaction was stirred under room temperature for 1 h. The resulting mixture was concentrated under reduced pressure. Water was added and acetic acid solution

(1 M) was used to adjust the pH < 7. Then the mixture was extracted by ethyl acetate. The organic layer was dried over Na_2SO_4, filtered, concentrated under reduced pressure.

4.1.6.1. 5-(4-benzyl-1*H*-1,2,3-triazol-1-yl)quinolin-8-ol (7a)

Red solid, 39% yield.^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.85 (d, 1H, J = 4.0 Hz), 8.09 (d, 1H, J = 8.8 Hz), 7.53 – 7.47 (m, 3H), 7.38 – 7.30 (m, 4H), 7.20 (d, 1H, J = 8.0 Hz), 4.23 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 153.76, 148.95, 148.03, 138.89, 137.88, 132.22, 128.95, 128.90, 126.83, 125.02, 124.82, 124.34, 124.13, 123.45, 108.88, 32.43, 29.84.

4.1.6.2. 5-(4-(hydroxy(phenyl)methyl)-1*H*-1,2,3-triazol-1-yl)quinolin-8-ol (7b)

Yellow solid, 66% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.86 (d, 1H, J = 4.4 Hz), 8.07 (d, 1H, J = 8.8 Hz), 7.60 (s, 1H), 7.57 – 7.45 (m, 5H), 7.41 (t, 3H, J = 7.4 Hz), 7.53 (t, 2H, J = 7.2 Hz), 7.21 (d, 2H, , J = 8.0 Hz), 6.19 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 153.94, 151.53, 149.03, 141.81, 137.86, 132.11, 128.91, 128.40, 126.59, 125.17, 124.53, 124.27, 123.94, 123.54, 108.89, 69.43, 29.84.

4.1.6.3. 5-(4-(2,4-dimethoxyphenyl)-1*H*-1,2,3-triazol-1-yl)quinolin-8-ol (7c)

Yellow solid, 57% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.88 (dd, 1H, J = 1.4, 4.2 Hz), 8.39 (d, 1H, J = 8.8 Hz), 8.28 (s, 1H), 8.17 (dd, 1H, J = 1.6, 8.8 Hz), 7.64 (d, 1H, J = 8.4 Hz), 7.53 (dd, 1H, J = 4.2, 8.8 Hz), 7.28 (s, 1H), 6.70 (dd, 1H, J = 2.4, 8.8 Hz), 6.58 (d, 1H, J = 2.4 Hz), 3.92 (s, 3H), 3.89 (s, 3H). ^{13}C NMR (100 MHz, CDCl3) δ (ppm): 149.06, 132.51, 128.80, 125.29, 124.72, 123.55, 112.35, 109.02, 105.30, 98.89, 55.75, 55.68.

4.1.6.4. 5-(4-(6-methoxynaphthalen-2-yl)-1*H*-1,2,3-triazol-1-yl)quinolin-8-ol (7d)

Yellow solid, 40% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.91 (d, 1H, J = 4.0 Hz), 8.43 (d, 1H, J = 8.0 Hz), 8.38 (d, 1H, J = 9.2 Hz), 8.29 (d, 1H, J = 8.8 Hz), 8.11 (s, 1H), 7.80 (d, 1H, J = 8.0 Hz), 7.71 (d, 1H, J = 8.0 Hz), 7.65 – 7.50 (m, 4H), 7.30 (d, 1H, J = 8.4 Hz), 6.94 (d, 1H, J = 8.0 Hz), 4.08 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 156.27, 153.94, 149.08, 138.01, 132.32, 132.19, 127.98, 127.45, 126.00, 125.61, 125.21, 125.09, 124.66, 124.46, 123.61, 122.63, 120.05, 109.00, 103.66, 55.81.

4.2 Biological assay

The antifungal activity of prepared compounds was assessed on *Candida* spp. and dermatophyte isolates, such as *Trichophyton mentagrophytes* (TME 40), *Trichophyton rubrum* (TRU 51), *Microsporum canis* (MCA 01), *Microsporum gypseum* (MGY ATCC), *Candida albicans* (CAMS5), *Candida parapsilosis* (RL33), *Candida krusei* (CK02),

Candida glabrata (RL37). The MIC values (µg/mL) were determined by broth microdilution assay according to M27-A3 for yeasts and M38-A2 for filamentous fungi [50,51].

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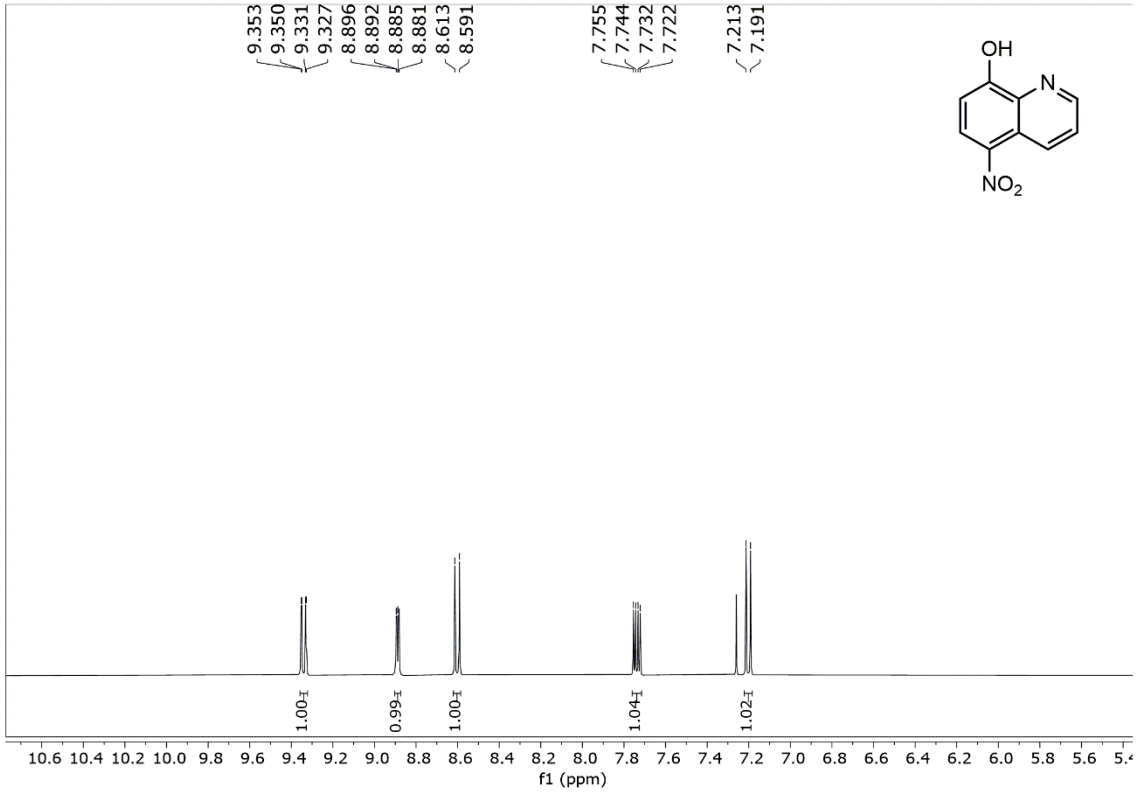

Figure 1 - NMR ^{1}H spectrum in $CDCl_3$ of **2.**

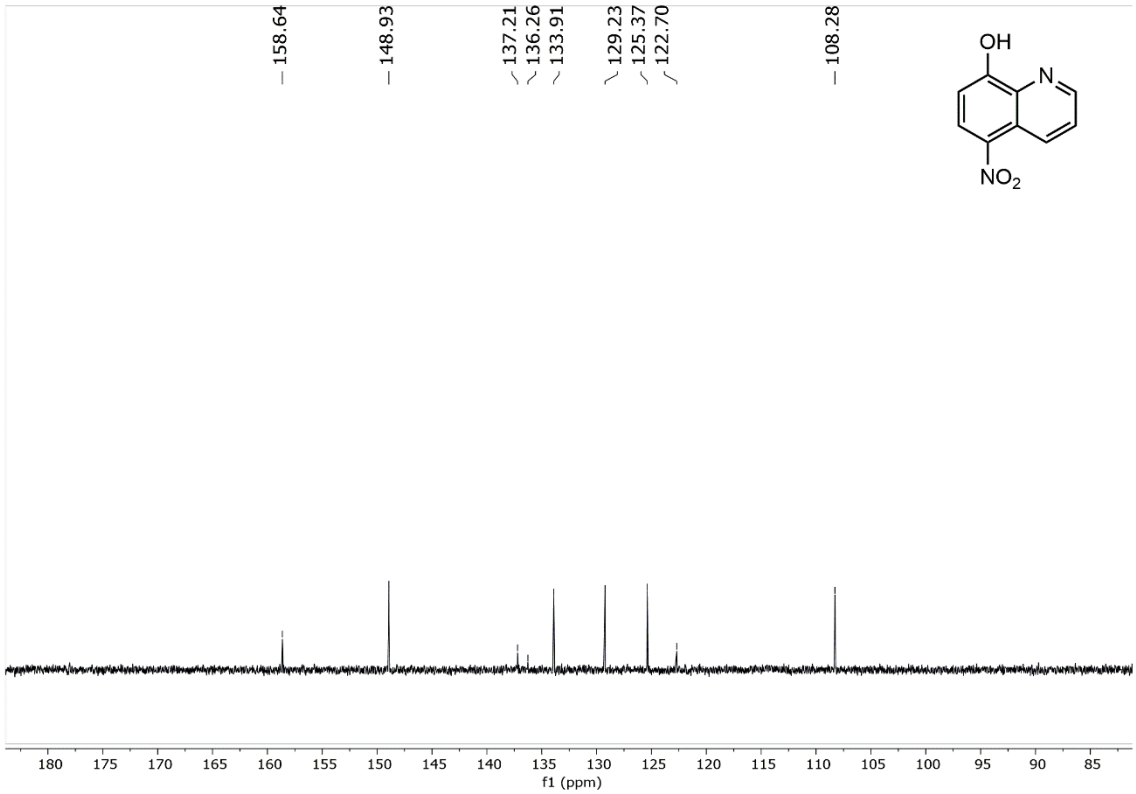

Figure 2 - NMR ^{13}C spectrum in $CDCl_3$ of **2**.

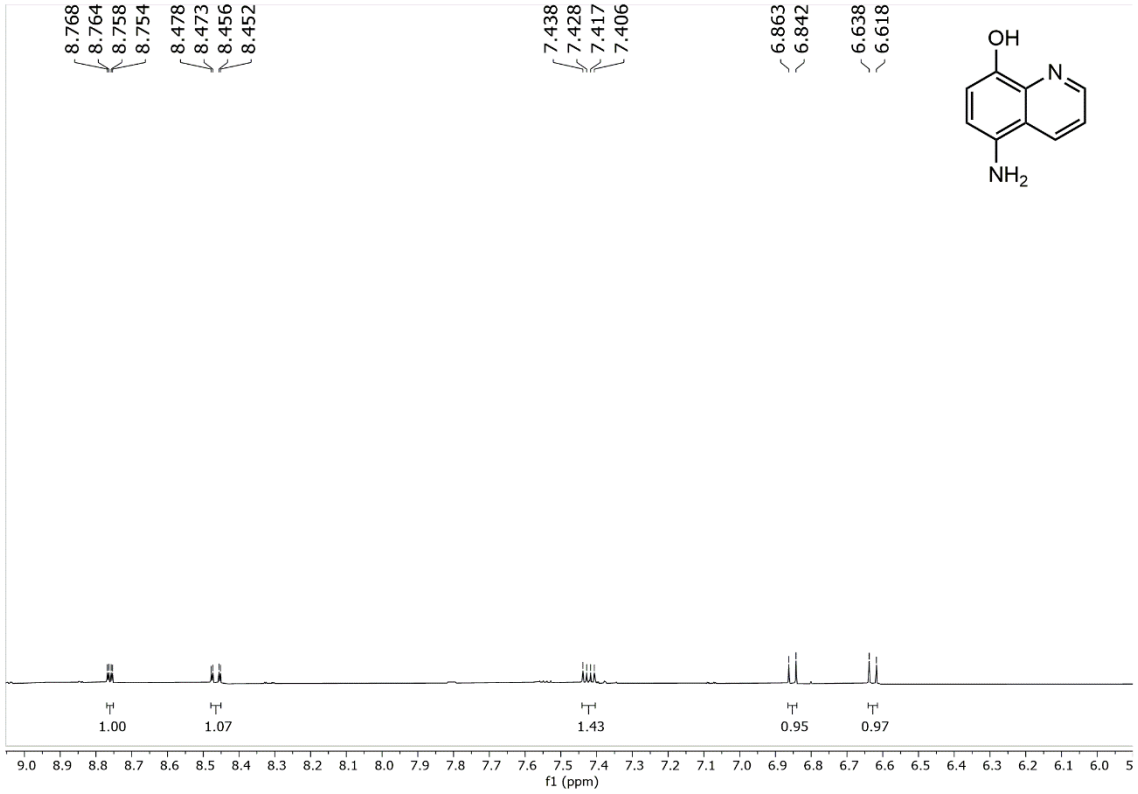

Figure 3 - NMR ^{1}H spectrum in DMSO – d_6 of **3**.

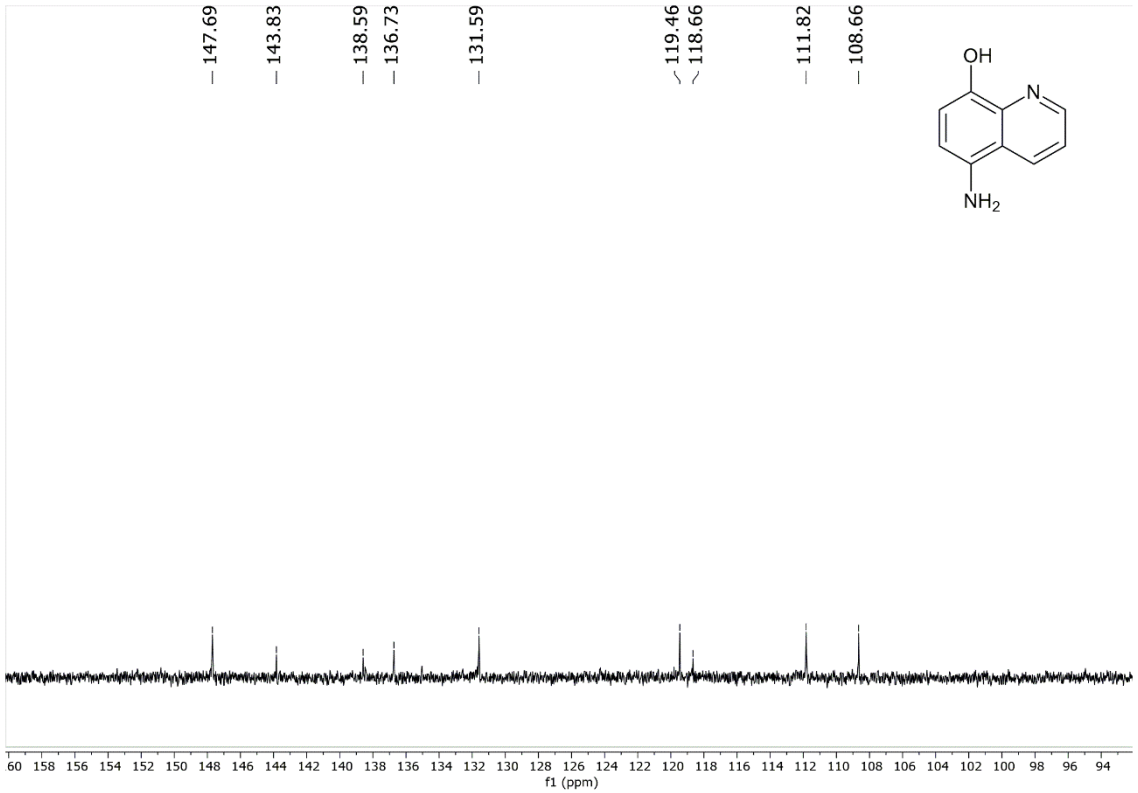

Figure 4 - NMR ^{13}C spectrum in DMSO – d_6 of **3**.

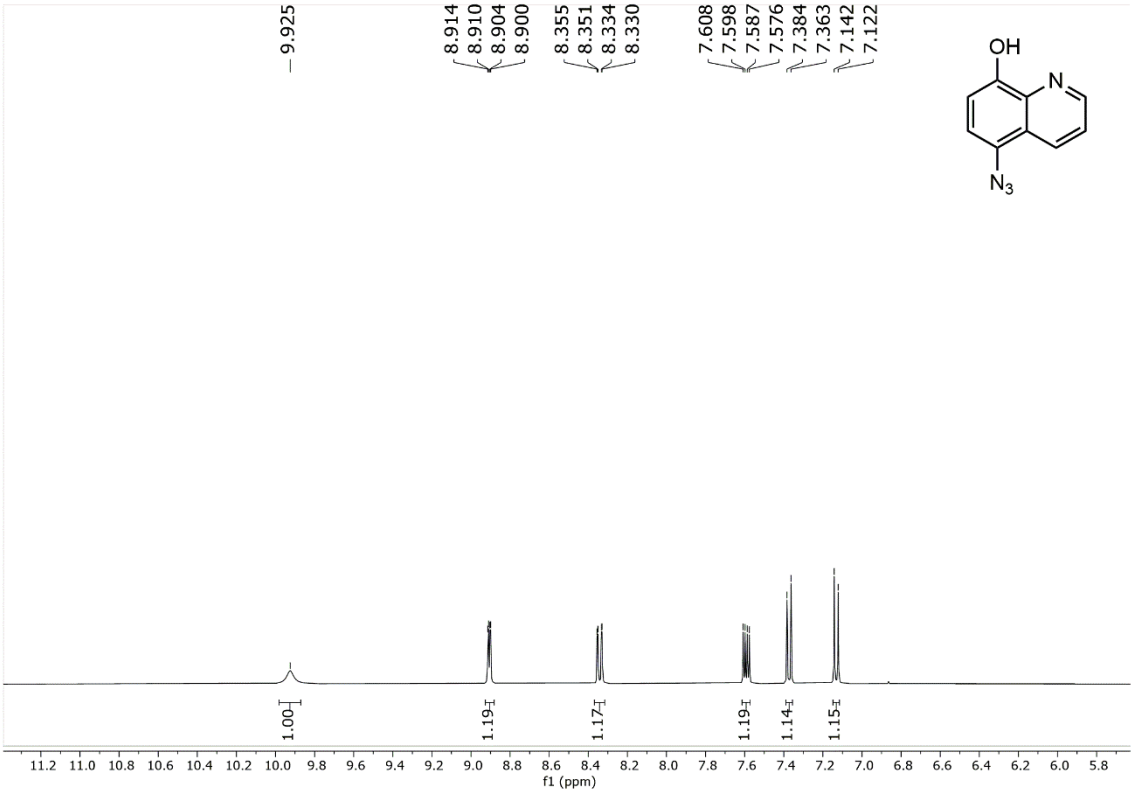

Figure 5 - NMR ^{1}H spectrum in DMSO – d_6 of **4**.

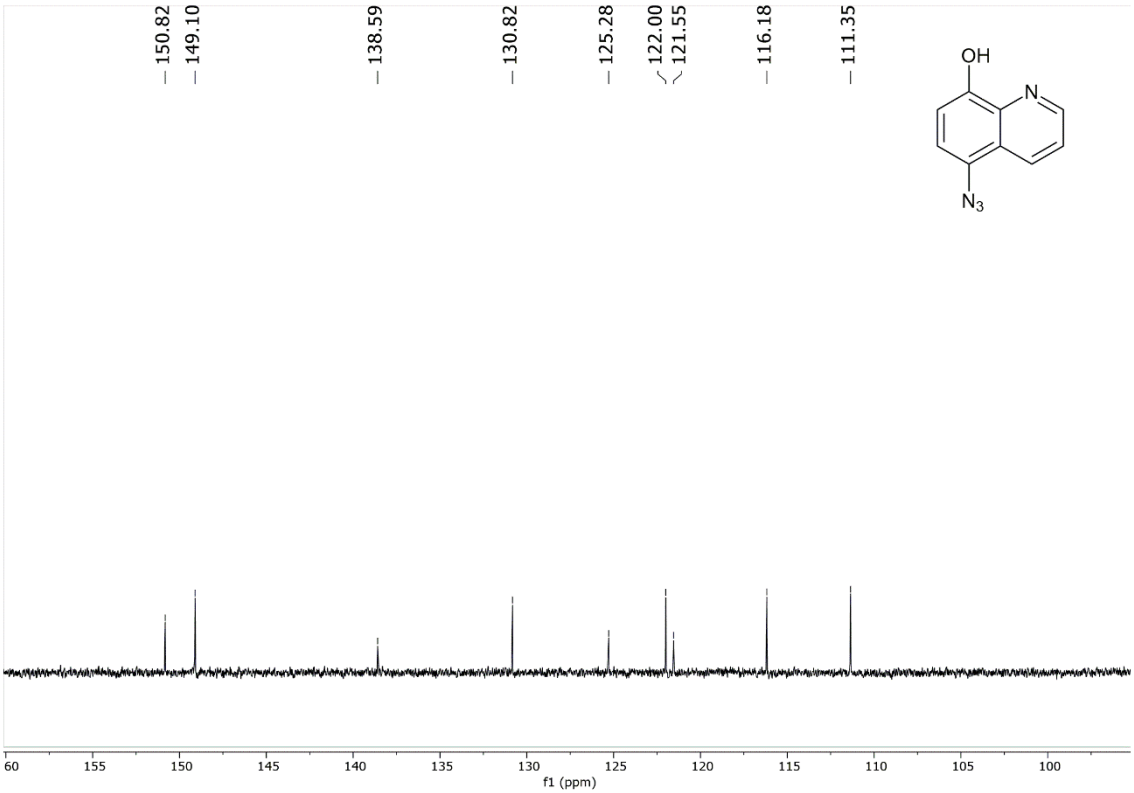

Figure 6 - NMR ^{13}C spectrum in DMSO – d_6 of **4**.

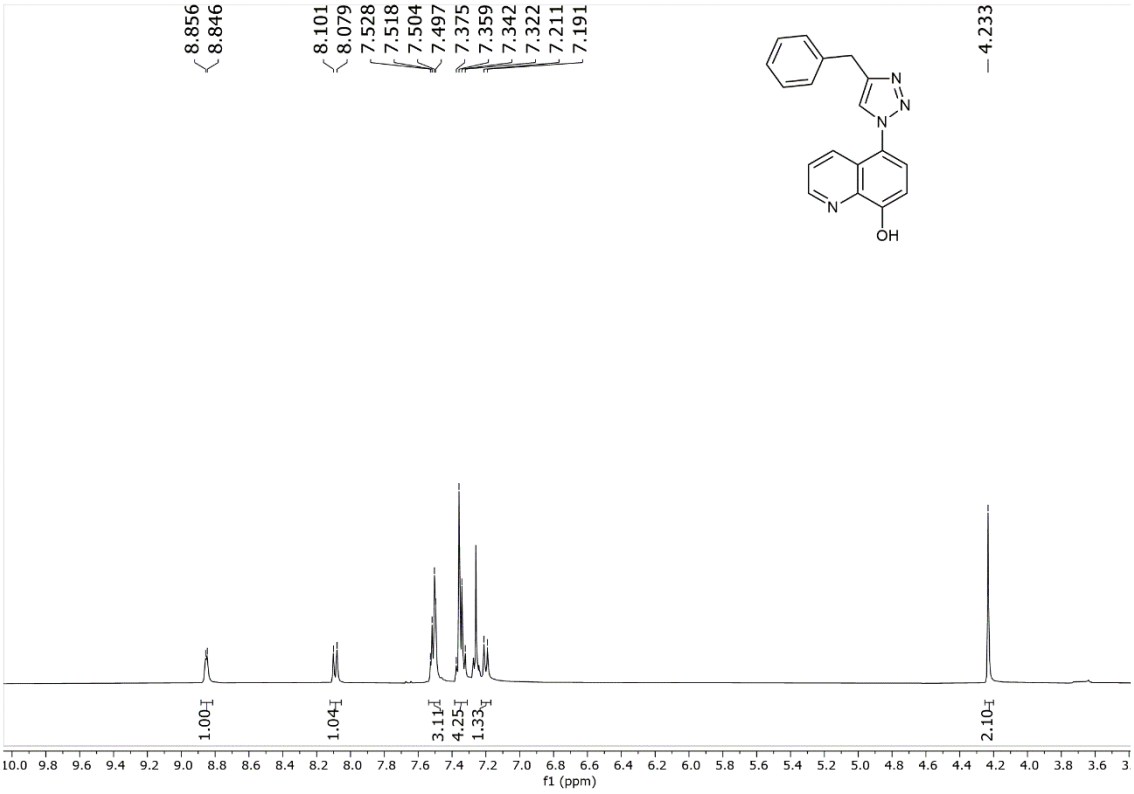

Figure 7 - NMR ^{1}H spectrum in $CDCl_3$ of **7a**.

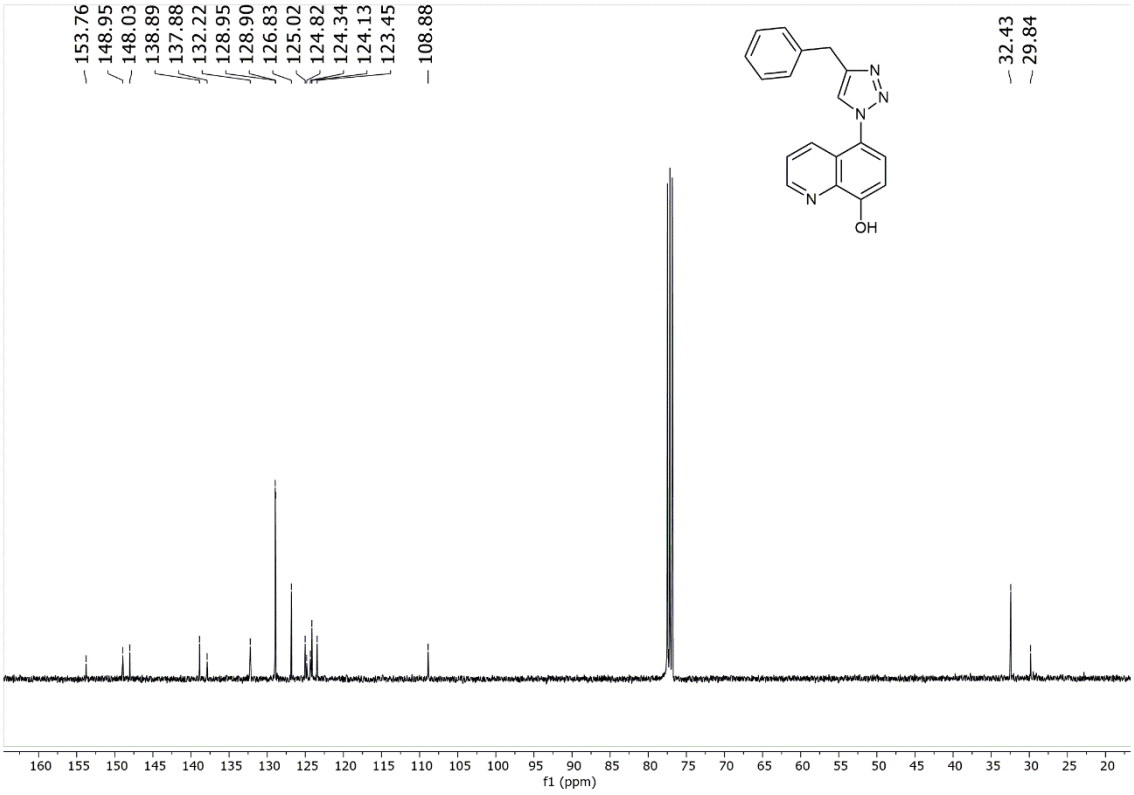

Figure 8 - NMR ^{13}C spectrum in $CDCl_3$ of **7a**.

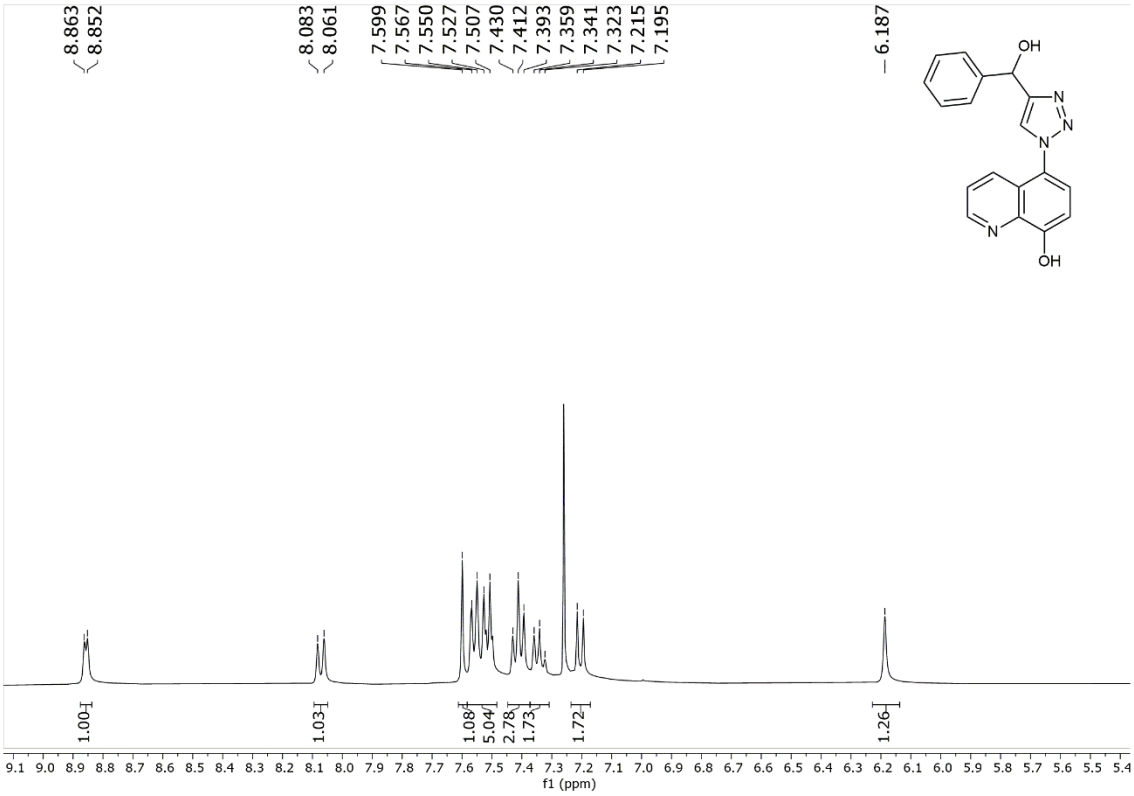

Figure 9 - NMR ^{1}H spectrum in $CDCl_3$ of **7b**.

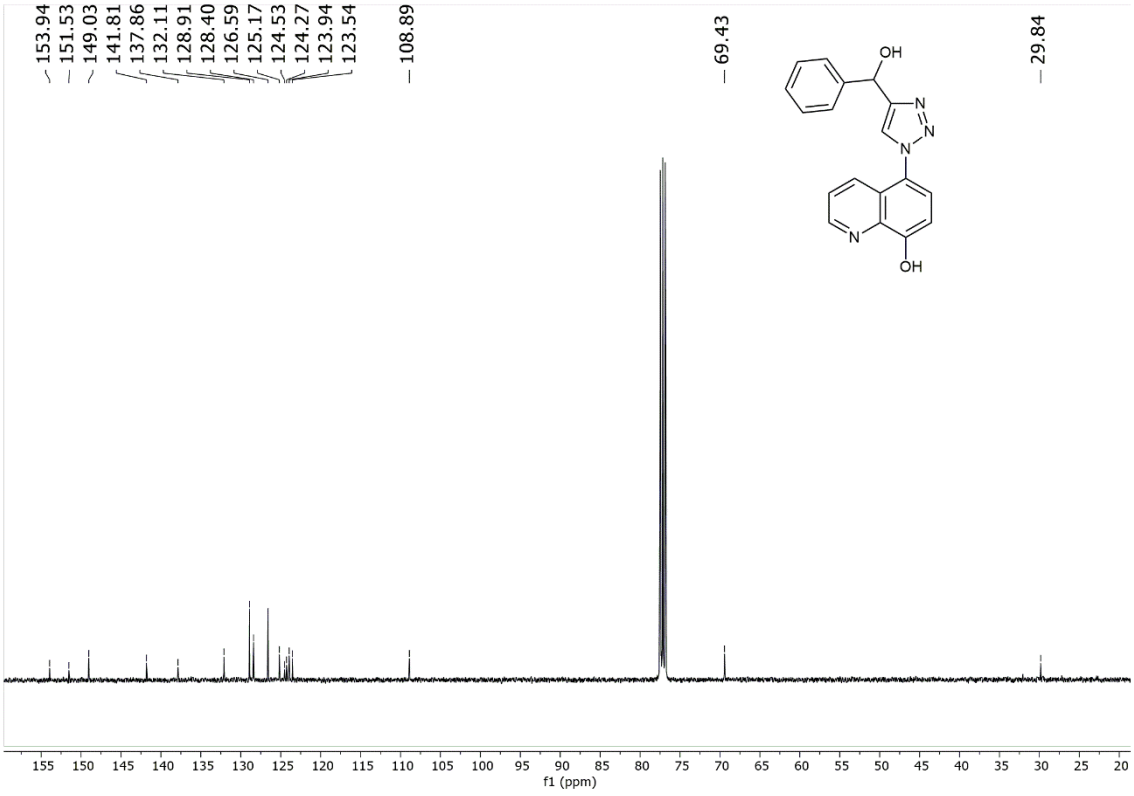

Figure 10 - NMR ^{13}C spectrum in $CDCl_3$ of **7b**.

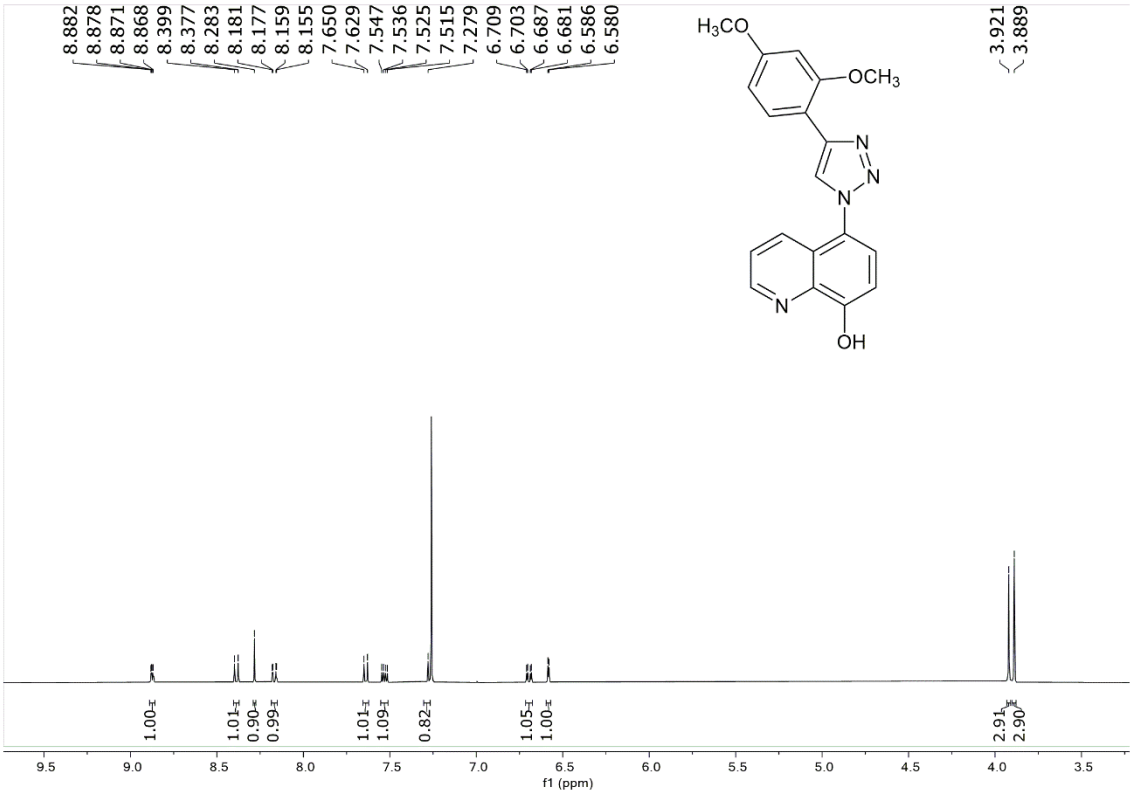

Figure 11 - NMR ^{1}H spectrum in $CDCl_3$ of **7c**.

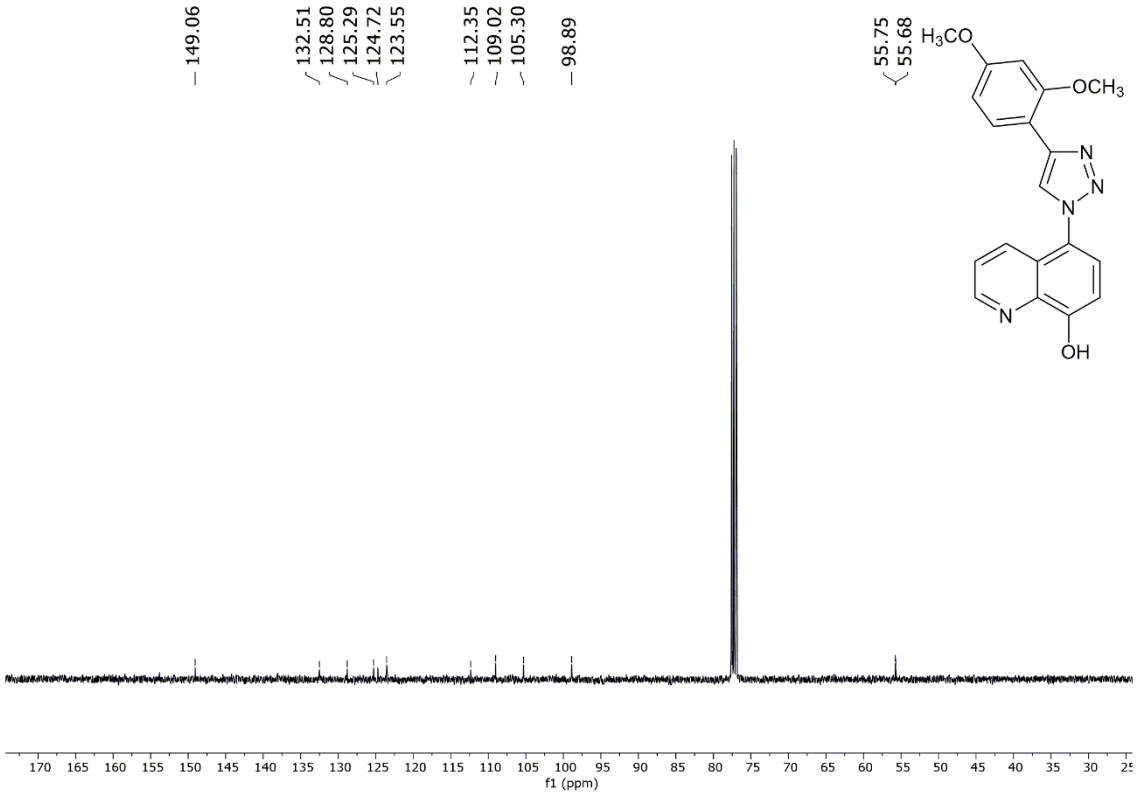

Figure 12 - NMR ^{13}C spectrum in $CDCl_3$ of **7c**.

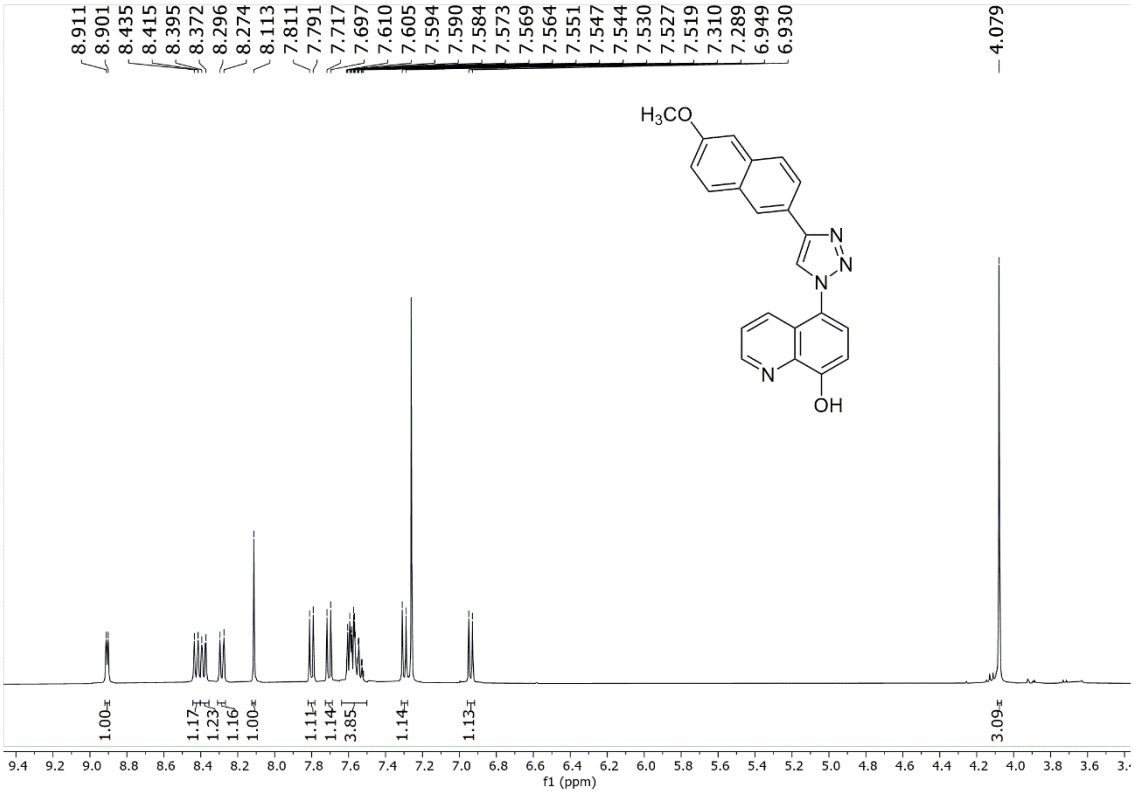

Figure 13 - NMR ^{1}H spectrum in $CDCl_3$ of **7d**.

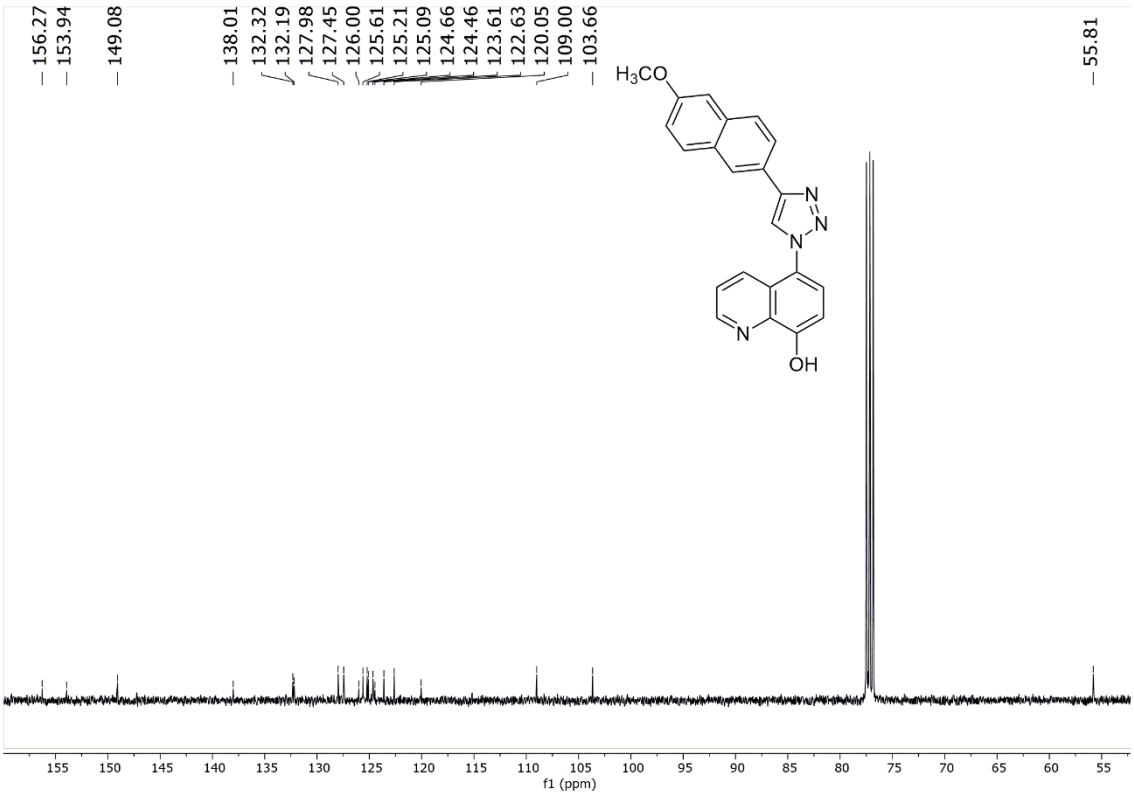

Figure 14 - NMR ^{13}C spectrum in $CDCl_3$ of **7d**.

ANEXO

EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY

AUTHOR INFORMATION PACK

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DESCRIPTION

The *European Journal of Medicinal Chemistry* is a global journal that publishes studies on all aspects of medicinal chemistry. It provides a medium for publication of original papers and also welcomes critical review papers.

A typical paper would report on the organic synthesis, characterization and pharmacological evaluation of compounds. Other topics of interest are drug design, QSAR, molecular modeling, drug-receptor interactions, molecular aspects of drug metabolism, prodrug synthesis and drug targeting. The journal expects manuscripts to present the rational for a study, provide insight into the design of compounds or understanding of mechanism, or clarify the targets.

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