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FULL PAPER

The Triazole ring as a Privileged Scaffold for Putative Antifungals: Synthesis and Evaluation of a Series of New analogues

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This paper is dedicated to Professor Angelo Carotti on the occasion of his 74th birthday

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Abstract: The significant antifungal activity of a series of novel 1,2,4-triazole derivatives against different strains of *Candida albicans*, *Candida krusei* and *Aspergillus fumigatus*, compared to the commercial fungicide ketoconazole and itraconazole, is reported. Systemic mycosis and invasive fungal infections, whether from immunodeficiency or hospital-acquired infection, have been on an upward trend for several years. The 1,2,4-triazole ring substituted with other aromatic and heteroaromatic systems plays an important role in the field of antifungal drug discovery and development. Thus, an extensive series of 29 triazoles, substituted in different positions with a variety of aromatic rings, were designed, synthesized, and evaluated for their fungicidal activity. Almost all the *in vitro* tested agents showed a high activity against all examined fungal strains. It is noteworthy, that in the case of *Aspergillus fumigatus* all the examined compounds achieved equal or higher antifungal activity than ketoconazole, but less activity than itraconazole. Among all the derivatives studied, the dichloro urea analogue and bromo substituted triazole, stand out as the most promising compounds. Quantitative structure activity relationship (QSAR) models were built for a systematic structure activity relationship (SAR) profile to explain and potentially explore the potency characteristics of 1,2,4-triazole analogs.

Introduction

In recent years, the prevalence of invasive fungal infections (IFIs) has been raised due to the increasing number of immunosuppressive population, the high frequency of bone marrow and organ transplants, the use of antineoplastic agents, the excessive use of antibiotics and the prolonged use of corticosteroids.[1-3] The contribution of invasive fungal infections to human morbidity and mortality is highlighted by the fact that they are responsible for over one million deaths per year.[4-5] *Candida albicans*, *Aspergillus fumigatus*, and *Cryptococcus neoformans* are the most common fungal pathogens, causing serious and usually life-threatening human infections.[6-7] *Candida albicans*, a common member of the normal human microbiome, constitutes the most frequent cause of severe systemic fungal infections in immunocompromised patients and it is classified as the fourth most common cause of hospitalized bloodstream infections.[8-9] Epidemiological results indicated that *Candida albicans* is associated with > 400,000 cases per year of systemic candidiasis in a global level and its mortality rate ranges from 46% to 75%.[5] Additionally, invasive candidiasis has mortality rates 40 to 60%, and are most commonly caused by *C. albicans*, *C. glabrata*, *C. tropicalis*, *C. parapsilosis*, and *C. krusei*. The latter is an emerging nosocomial pathogen, presenting a significant increase in the last decade.[10] Invasive aspergillosis, the disease caused mainly by *Aspergillus fumigatus*, has been estimated to induce over 200,000 cases in immunosuppressive hosts and the prevalence of mortality ranging from 30% to 95%.[5,11] Also, *Aspergillus fumigatus* is responsible for chronic pulmonary aspergillosis, affecting more than 3 million people worldwide.[5,12]

Despite the urgent need for effective confrontation of invasive mycoses, currently available antifungal pipeline includes only four major drug classes, polyenes, flucytosine, azoles and echinocandins, targeting three specific fungal metabolic pathways (the ergosterol biosynthesis, the fungal cell wall and the fungal DNA/RNA).[13] The number of antifungal drugs is restricted because of their limited clinical efficacy, narrow spectrum of fungal strains, adverse pharmacokinetic profiles, severe side effects, and interactions with other drugs.[14-15] The increasing antimicrobial drug resistance from the emerging fungal pathogens provides also a challenging task to be faced,[16-17] thus the discovery of novel therapeutic agents is of paramount importance. Since their discovery, azoles have gained widespread attention, exhibiting the most widely used category of antifungal agents in clinical practice.[18] Their antifungal mode of action is based on the

inhibition of the cytochrome P450 dependent lanosterol 14α demethylase enzyme (CYP51A), a key enzyme in the biosynthesis of ergosterol which is a significant component of the fungal cell membrane. Particularly, a lone pair of electrons on an unhindered nitrogen atom of azoles binds to the heme iron atom, located in the active site of the enzyme CYP51 (encoded by ERG11 gene), inducing the azoles mechanism of action.[19-21] Azole drugs are classified into two groups bearing characteristic (a) imidazole and (b) triazole rings. The firstly developed imidazole drugs, such as miconazole, clotrimazole and ketoconazole, exhibited high toxicity, unfavorable side effects and a plethora of interactions with other drugs. Triazoles overcome several limitations, displaying lower toxicity and stronger antifungal activity compared to imidazoles and other antifungals.[22] Recent evidences have proved that new generation triazoles,[23] such as voriconazole and posaconazole possess potent activity against *Candida* and *Aspergillus* species.[24] In 2015 isavuconazole was approved for the treatment of invasive aspergillosis, indicating the pivotal role of triazoles in the fungus treatment.[25] Consequently, the identification of novel triazoles remains still in the frontline of the pharmaceutical research for novel antifungals.[26] In line with this, the present study attempts to discover novel triazoles with putative antifungal activity. For this scope, a series of 29 triazole derivatives (**Table 1**) were synthesized and their activity was evaluated against three different pathogenic fungal strains namely *Candida albicans*, *Candida krusei* and *Aspergillus fumigatus*. In order to provide greater insight into the chemical features that may enhance antifungal activity, the polar triazole ring was substituted with a variety of chemically diverse but pharmacologically interesting groups in different positions of the heterocycle. Towards this direction, urea and amide groups were utilized as linkers and different electron withdrawing (EWG: -Cl, -Br, -F) and electron donating groups (EDG: $-NH_2$, $-OCH_3$) were added on the aromatic rings. Quantitative structure activity relationship models (QSAR) were generated in an effort to provide a putative explanation of the correlation among key parameters of the synthesized compounds that may influence their antifungal activity.

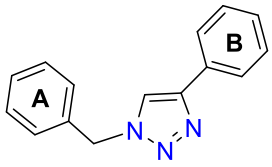
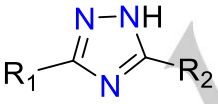
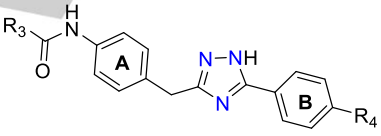
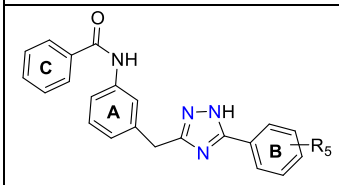
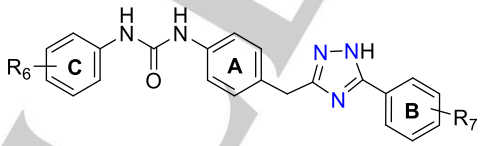
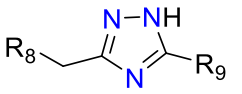
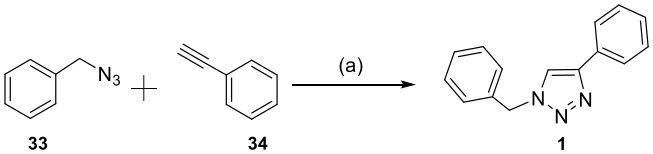
		
1	**2** R_1=-$CH_2C_6H_5$, R_2=-C_6H_5	**11** R_3=-C_6H_5, R_4=H
	3 R_1=-C_6H_5, R_2=-$CH_2C_6H_5$	**12** R_3=-C_6H_3(Cl)-2,(Cl)-4, R_4=H
	4 R_1=-$CH_2C_6H_4$(CH_3O)-4, R_2=-C_6H_5	**13** R_3=-C_6H_4(Cl)-3, R_4=H
	5 R_1=-$CH_2C_6H_4$(Br)-4, R_2=-C_6H_5	**14** R_3=-$CH_2C_6H_5$, R_4=H
	6 R_1=-$CH_2C_6H_3$(Cl)-3,(Cl)-4, R_2=-C_6H_5	**15** R_3=-$CH_2C_{10}H_7$, R_4=H
	7 R_1=-$CH_2C_6H_3$(Cl)-2,(F)-6, R_2=-C_6H_4(Cl)-4	**16** R_3=-C_6H_5, R_4=Cl
	8 R_1=-$CH_2C_6H_4$(CH_3O)-4, R_2=-C_6H_4(Cl)-4	**17** R_3=-$CH_2CH_2C_6H_5$, R_4=H
	9 R_1=-$CH_2C_6H_4$(NH_2)-4, R_2=-C_6H_4(Cl)-4	**18** R_3=-C_6H_{11}, R_4=H
	10 R_1=-$CH_2C_6H_4$(C_6H_5)-4, R_2=-C_6H_4(Cl)-4	
	30 R_1=-$CH_2C_6H_4$(NH_2)-4, R_2=-C_6H_5	
	31 R_1=-$CH_2C_6H_4$(NH_2)-3, R_2=-C_6H_4(Cl)-3	
	32 R_1=-$CH_2C_6H_4$(NH_2)-3, R_2=-C_6H_4(Cl)-4	
		
19 R_5=(Cl)-4	**21** R_6=H, R_7=H	**25** R_8=-C_6H_5, R_9=-$CH_2C_6H_5$
20 R_5=(Cl)-3	**22** R_6=(Cl)-4, R_7=H	**26** R_8=-C_6H_5, R_9=-C_4H_3S
	23 R_6=(Cl)-3, R_7=(Cl)-3	**27** R_8=-C_6H_5, R_9=-C_5H_4N
	24 R_6=(Cl)-3, R_7=(Cl)-4	**28** R_8=-$C_7H_5O_2$, R_9=-C_6H_4(Cl)-4
		29 R_8=-C_6H_4[-$NHSO_2C_6H_4$(CH_4)-4]-4, R_9=-C_6H_5

Table 1. The chemical structures of the synthesized triazole derivatives

Results and Discussion

Chemistry

In order to synthesize the 1-benzyl-4-phenyl-1*H*-1,2,3-triazole **1**,[27] we performed a Cu(I)-catalyzed [3+2]-dipolar cycloaddition of benzyl azide **33** and benzonitrile **34** (Scheme 1).[28]

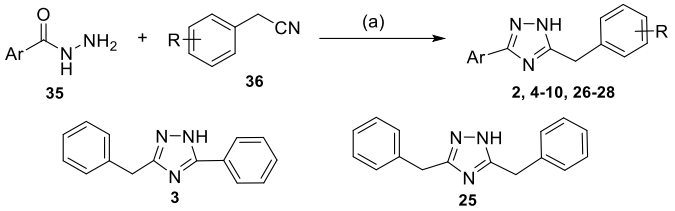


33 **34** **1**

Scheme 1. Reagents and conditions: (a) sodium ascorbate, $CuSO_4 \cdot 5H_2O$, *t*-BuOH/H_2O=1/1, rt, 16 h, (85%).

The synthesis of 3-aryl-5-benzyl-1*H*-1,2,4-triazole scaffold was achieved through a straightforward click procedure, starting from commercial benzhydrazides **35** and substituted phenylacetonitriles **36**. Dibenzyl derivative **25** and compound **3** were prepared with the same procedure, from 2-phenylacetohydrazide and phenylacetonitrile the first and 2-phenylacetohydrazide with benzonitrile the latter. The reaction

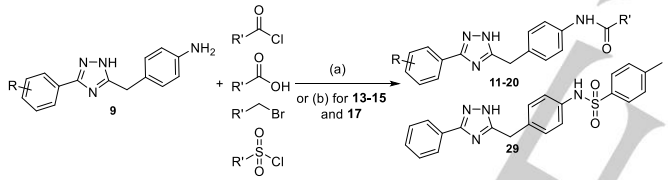
yields and times were successfully optimized by using microwave heating (**Scheme 2**). Specifically, in the case of compounds **2** and **3** the reaction times were reduced to 2 hours and the yields were considerable improved.[29]



Compounds	Ar	R	Yields (%)
2 and 3	phenyl	H	85 and 60
4		4-OCH_3	83
5		4-Br	89
6		3,4-diCl	85
7	4-chlorophenyl	2-F-6-Cl	65
8		4-OCH_3	55
9		4-NH_2	50
10		4-Ph	59
28		3,4-(OCH_2O)	55
26	thien-2-yl	H	37
27	pyrid-3-yl	H	64

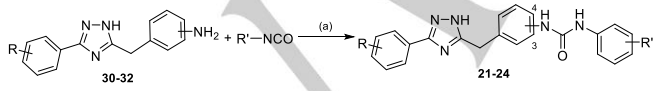
Scheme 2. Reagents and conditions: (a) K_2CO_3, *n*-BuOH, MW, 150 °C, 3-4 h (TLC monitoring), 40-90 %.

Amides **11**-**20** (Scheme 3) and ureas **21**-**24** (Scheme 4) were obtained from aniline derivatives **9** and **30**-**32**, by the reaction with commercial acyl chlorides, carboxylic acids (Scheme 3) and isocyanates (Scheme 4), respectively. Sulfonamide **29** was prepared from benzenesulfonyl chloride according to the conditions shown in Scheme 3.



Compounds	R	R´	Subst. position
11	H	Ph	4
12		2,4-diClPh	4
13		3-ClPh	4
14		CH_2Ph	4
15		CH_2Naphth-2-yl	4
16	4-Cl	Ph	4
17	H	$(CH_2)_2Ph$	4
18		CyHexyl	4
19	4-Cl	Ph	3
20	3-Cl	Ph	3

Scheme 3. Reagents and conditions: (a) DIPEA (3eq), dry THF, 0 ° to rt, 3-5 h (TLC monitoring), 29-92 %; (b) For compounds **13**-**15** and **17**: *N*-Methyl morpholine (NMM), HOBt, THF, EDC, 0 ˚C to rt, under argon, (TLC monitoring) 16 h, 44-72 %.



Compounds	R	R´	Subst. position
21	H	H	4
22	H	4-Cl	4
23	3-Cl	3-Cl	3
24	4-Cl	3-Cl	3

Scheme 4. Reagents and conditions: (a) Dry THF, 0 ˚C to rt, up to 48 h (TLC monitoring), 26-80 %.

Antifungal activity evaluation

For the identification of antifungal activity of the synthesized triazole derivatives, *in vitro* assays were performed against different strains of *Candida albicans* (strains *475/15, 10/15* and *ATCC10231*), *Candida krusei* (strain *H1/16*) and *Aspergillus fumigatus* (strain *ATCC9197*). The minimal inhibitory concentrations (MIC values) and the minimal fungicidal concentrations (MFC values) of the tested compounds were detected in comparison to **ketoconazole** (an imidazole) and **itraconazole** (a triazole), the azole drugs used as positive control (**Table 2**).

From the *in vitro* results, it is obvious that all synthetic derivatives displayed significant antifungal activity against all examined fungal strains. The comparison of the antifungal activity against the different strains of *Candida albicans* proved that all compounds present equivalent activity and, in some cases (compounds **2**, **5**, **12**, **17**, **18**, **22**, **26**, **29**) *Candida albicans ATCC10231* characterized as the most sensitive strain. Against the latter strain the amide analogues (**11**-**20**) proved to be more potent than the less bulky triazoles (**1-9** and **25-28**) and slightly more potent than the urea counterparts (**11** *vs* **21**), with the exception of compound **24**. As far as the substitution of the less bulky triazoles (**1**-**9**) is concerned, the amino group in compound **9** (hydrogen bond donor) seems to play a pivotal role, probably via hydrogen bonding interaction. Additionally, the observed MIC (0.288-3.369 μmol·mL^{-1}) and MFC (0.575-6.738 μmol·mL^{-1}) values of the tested triazoles against *Candida krusei* H1/16 are equal or higher compared to *Candida albicans* strains, with six exceptions (compounds **1**, **3**, **4**, **9**, **16** and **29**), rendering it as the most resistant species for the studied class of compounds, for which the same SAR trend was generally observed.

It is noteworthy that, in the case of *Aspergillus fumigatus ATCC9197* all the examined compounds achieved equal or higher antifungal activity than ketoconazole (MIC=0.433 μmol·mL^{-1} and MFC=1.261 μmol·mL^{-1}) apart from compounds **18** (MIC=0.860 μmol·mL^{-1} and MFC=1.720 μmol·mL^{-1}) and **29** (MIC=0.922 μmol·mL^{-1} and MFC=1.818 μmol·mL^{-1}) (**Table 2**). However, they were less active than **itraconazole**. Compound **24** possessed the highest potency. Compounds **24**, **5**, **4**, and **6** were the most potent against *Aspergillus fumigatus*, with MIC values ranged from 0.114 to 0.230 μmol·mL^{-1} and MFC values among 0.228-0.920 μmol·mL^{-1} (**Table 2**). Interestingly, against *Aspergillus fumigatus* amide analogues (**11**-**20**), appear to follow a similar trend that was observed for the other species, with similar potencies as the urea counterparts (**11** *vs* **21**). The effect of the substitution position on ring C on fungicidal activity was also investigated. It seems that substitution on ring C did not seem to play a pivotal role on potency. Finally, replacement of the aromatic ring B with a heterocycle (thiophene, pyridine) (**26** or **27** *vs* **2**) led to a 2.2 and 1.5-fold decrease in potency respectively. Interestingly, tautomers **2** and **3** present different activities against *Candida albicans ATCC10231* and *Aspergillus fumigatus* with compound **2** presenting higher antifungal activity in both strains.

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Table 2. Minimal inhibitory (MIC) and fungicidal (MFC) concentration values of the synthesized compounds (μmol·mL^{-1}).

Compounds	*Candida albicans* 475/15		*Candida albicans* 10/15		*Candida albicans* ATCC10231		*Candida krusei* H1/16		*Aspergillus fumigatus* ATCC9197	
	MIC	*MFC*	*MIC*	*MFC*	*MIC*	*MFC*	*MIC*	*MFC*	*MIC*	*MFC*
1	0.637±0.004	1.275±0.01	0.637±0.004	1.275±0.01	0.637±0.004	1.275±0.01	0.297±0.001	0.637±0.004	0.382±0.004	0.765±0.004
2	1.062±0.01	2.125±0.02	1.062±0.01	2.125±0.02	0.510±0.004	2.125±0.02	0.510±0.004	2.125±0.02	0.340±0.004	1.232±0.01
3	1.062±0.01	2.125±0.01	1.062±0.01	2.125±0.02	1.062±0.02	2.125±0.03	0.510±0.004	1.062±0.01	0.637±0.004	1.275±0.01
4	1.696±0.02	3.392±0.02	1.696±0.02	3.392±0.02	0.867±0.01	1.696±0.02	0.867±0.01	1.696±0.03	0.226±0.001	0.980±0.01
5	1.528±0.01	3.024±0.02	1.528±0.01	3.024±0.02	0.764±0.004	1.528±0.02	1.528±0.02	3.024±0.02	0.223±0.001	0.891±0.004
6	0.789±0.004	1.578±0.02	0.789±0.004	1.578±0.02	0.789±0.004	1.578±0.02	0.953±0.01	1.910±0.02	0.230±0.001	0.920±0.01
7	0.869±0.004	1.738±0.02	0.869±0.004	1.738±0.02	0.869±0.004	1.738±0.02	2.080±0.02	4.159±0.05	0.497±0.005	0.993±0.01
8	0.801±0.004	1.601±0.02	0.801±0.005	1.601±0.01	0.801±0.005	1.601±0.02	1.935±0.02	3.903±0.05	0.467±0.005	0.934±0.01
9	0.562±0.004	1.124±0.015	0.562±0.005	1.124±0.01	0.562±0.004	1.124±0.02	0.316±0.004	0.632±0.01	0.632±0.005	1.264±0.01
10	0.549±0.005	1.041±0.01	0.549±0.005	1.041±0.01	1.014±0.01	2.082±0.02	2.573±0.02	5.118±0.04	0.636±0.005	1.272±0.01
11	0.508±0.008	1.016±0.01	0.508±0.008	1.016±0.01	0.508±0.008	1.016±0.01	1.129±0.01	2.257±0.02	0.282±0.004	0.564±0.008
12	0.992±0.02	1.984±0.03	0.992±0.02	1.984±0.02	0.496±0.01	0.992±0.02	0.590±0.004	1.181±0.02	0.283±0.001	0.567±0.004
13	0.463±0.002	0.926±0.01	0.463±0.004	0.926±0.01	0.463±0.004	0.926±0.02	0.540±0.004	1.080±0.02	0.257±0.001	0.514±0.004
14	0.488±0.002	0.977±0.01	0.488±0.004	0.977±0.01	0.488±0.004	0.977±0.01	0.597±0.004	1.194±0.01	0.298±0.002	0.597±0.003
15	0.645±0.003	1.290±0.01	0.645±0.004	1.290±0.01	0.645±0.004	1.290±0.01	2.867±0.04	5.735±0.06	0.765±0.004	1.529±0.02
16	0.566±0.005	1.131±0.01	0.566±0.005	1.131±0.01	0.566±0.005	1.131±0.01	0.334±0.004	0.669±0.01	0.643±0.005	1.286±0.01
17	0.497±0.004	0.993±0.01	0.497±0.004	0.993±0.01	0.235±0.002	0.497±0.006	0.288±0.002	0.575±0.004	0.288±0.002	0.575±0.004
18	0.721±0.004	1.443±0.01	0.721±0.004	1.443±0.01	0.361±0.002	0.721±0.01	0.444±0.002	0.888±0.01	0.860±0.01	1.720±0.015

19	0.746±0.004	1.517±0.02	0.746±0.004	1.517±0.01	0.746±0.004	1.517±0.01	0.900±0.01	1.800±0.02	0.437±0.006	0.874±0.004
20	1.440±0.01	2.880±0.04	1.440±0.01	2.880±0.02	1.440±0.02	2.880±0.02	3.369±0.02	6.738±0.04	0.411±0.005	0.823±0.01
21	0.568±0.008	1.137±0.01	0.568±0.008	1.137±0.01	0.568±0.008	1.137±0.01	1.380±0.01	2.761±0.04	0.325±0.004	0.650±0.004
22	1.040±0.01	2.080±0.02	1.040±0.01	2.080±0.02	0.520±0.004	1.040±0.01	1.238±0.01	2.476±0.02	0.297±0.001	0.594±0.01
23	0.730±0.004	1.460±0.02	0.730±0.004	1.460±0.01	0.730±0.004	1.460±0.01	1.734±0.02	3.468±0.02	0.433±0.003	0.867±0.004
24	0.182±0.002	0.365±0.002	0.182±0.002	0.365±0.004	0.182±0.002	0.365±0.004	0.456±0.004	0.912±0.01	0.114±0.002	0.228±0.002
25	1.043±0.01	2.086±0.02	1.043±0.01	2.086±0.02	1.043±0.01	2.086±0.02	1.243±0.01	2.487±0.02	0.602±0.004	1.203±0.01
26	1.285±0.01	2.569±0.02	1.285±0.01	2.569±0.02	0.622±0.004	1.285±0.01	1.285±0.01	2.569±0.02	0.746±0.004	1.492±0.02
27	0.889±0.004	1.777±0.02	0.889±0.02	1.777±0.02	0.889±0.01	1.777±0.02	1.058±0.01	2.116±0.02	0.508±0.004	1.016±0.01
28	0.733±0.004	1.466±0.02	0.733±0.004	1.466±0.01	0.733±0.004	1.466±0.02	1.753±0.02	3.506±0.04	0.414±0.005	0.829±0.01
29	1.562±0.015	3.124±0.02	1.562±0.01	3.124±0.02	0.768±0.01	1.562±0.02	0.461±0.004	0.922±0.01	0.922±0.01	1.818±0.02
Ketoconazole	0.003±0.00002	0.012±0.0001	0.013±0.0001	0.094±0.0002	0.003±0.00002	0.012±0.0001	0.003±0.00002	0.006±0.0001	0.433±0.005	1.261±0.01
Itraconazole	0.026±0.0002	0.052±0.0004	0.013±0.0002	0.026±0.0004	0.026±0.0002	0.052±0.0004	0.052±0.0004	0.104±0.002	0.035±0.0006	0.07±0.0006

Experiments were performed in duplicate and repeated three times. Values are expressed as means ± SD ($p < 0.05$).

Dataset collection and QSAR model analysis

The antifungal activity values (Table 2) clearly indicate that the examined compounds possessed higher antifungal activity against *Aspergillus fumigatus* (strain *ATCC9197*) compared to *Candida albicans* (strains *475/15, 10/15* and *ATCC10231*) *and Candida krusei* (strain H1/16). Based on this observation the MIC values against *Aspergillus fumigatus* were selected as dependent variables to develop QSAR models. Specifically, MICs together with molecular descriptors were employed as dependent and independent variables, respectively and a multiple linear regression (MLR) analysis was performed to identify the structural and/or physicochemical properties' effects on the antifungal activity. The QSAR analysis suggested a variety of models (see Supporting Information) which were evaluated for reliability according to statistically significant parameters including the square of correlation coefficient (R^2), the square of correlation coefficient for cross validation (Q^2), the sequential Fischer test (F-test) and Root-Mean-Square Error (RMSE).

The most reliable model included all agents bearing 1*H*-1,2,4 triazole ring and a methylene linker in position 5, except compounds **3** and **19** (Table 1). MLR analysis generated a model described by a good correlation (R^2=0.98) among 12 molecular descriptors and the antifungal activity (Figure 1). The expression of the key properties that may influence the antifungal activity (Equation 1) and the statistically significant parameters obtained from model analysis (Model 2), are described in Table 3. Also, the crucial descriptor's calculated values of the examined compounds and the observed and predicted antifungal activity values estimated by equation 1 are illustrated in Tables 4 and 5, respectively.

For the case of *Aspergillus fumigatus ATCC9197* strain, the QSAR model revealed that the dipole-dipole nature of the intermolecular forces, measured using the square of the dipole moment divided by the molecular volume, ($dipole^2/V$) descriptor,[30] contributes significantly and positively to MIC values. Thus, the higher $dipole^2/V$ values are the greater the MIC and therefore the antifungal activity is decreased, such as in the case of compound **18** ($dipole^2/V$=0.047), which possessed weaker antifungal activity compared to compounds **11** ($dipole^2/V$=0.013) and **16** ($dipole^2/V$=0.007). The mean topological charge index of order 9, which evaluates the charge transfers between pairs of atoms and therefore the global charge transfers in the molecule[31] also constitutes an important explanatory descriptor where an increase in its value, reduces the MIC thus increases the antifungal activity. Representatively, the descriptor's value for compound **6** which presents strong antifungal activity is 9.3 10^{-3}, compared to the corresponding value of the less active compounds **2** and **1** (2.8 10^{-3}). Another descriptor that emerges from this model is the Path/Walk 3 - Randic shape index, which describes the branching of the carbon-atom skeleton and also is used to differentiate molecules based on their size, flexibility and overall shape.[32] This descriptor contributes negatively to MIC values, thus higher values demonstrate lower MIC hence improved activity against *Aspergillus fumigatus ATCC9197* strain, such as in the case of compound **12** (0.333) compared to **25** (0.308). Also, the correlation analysis proved that the valence connectivity indexes chi-3 and chi-4, which are related to the position and influence of heteroatoms, play a critical role in antifungal activity.[33] Particularly, the examination of these descriptor's values showed that in the case of compound **29** the sulfonamide group substitution is responsible for the significant antifungal activity reduction. Furthermore, the predicted conformation-independent aqueous solubility and the dipole moment variables correlate positively and negatively to MIC values, respectively. According to solubility values, compounds **5** (logS=-5.594) and **6** (logS=-5.388), bearing halogenated benzyl rings, are more active compared to compound **1** (logS=-3.929). The comparison of the dipole moment values of structurally similar compounds **23** (dipole=5.027) and **24** (dipole=9.615) could partially explain the higher activity of **24**. To a lesser extent, the number of nitrogen and oxygen atoms as well as the sum of their topological distances and the Modified Randic connectivity descriptor, also contribute to MIC values (Equation 1). Regarding the observed differences in activity between tautomers **2** and **3**, and since compound **3** was excluded from the final model, these could be attributed to electron affinity differences (0.55eV for compound **2** and 0.095eV for compound **3**). Electron affinity is a parameter which has been correlated with anti-candidal activity of *N*-heterocyclic thioamides.[34]

Conclusions

We have developed a novel series of 1,2,4-triazole derivatives that inhibit different strains of *Candida albicans*, *Candida krusei* and *Aspergillus fumigatus* with low micromolar or submicromolar MIC and MFC values. These inhibitors were derived from 1,2,4-triazole ring by incorporating a variety of chemically diverse but pharmacologically interesting groups in different positions of the heterocycle. The tested compounds exhibited significant antifungal activity, especially in the case of *Aspergillus fumigatus*, where most of them proved to be equally or more active than ketoconazole. The most active of them, compounds **24** and **5**, were 4 and 2-fold more active than ketoconazole. On the other hand, these compounds were less active than itraconazole. Our studies demonstrate that: (i) the fungicidal activity of this class of compounds is greatly dependent upon the substitution on ring A; (ii) amide substitution was mostly more favorable than urea or halogen; (ii) addition of an extra aromatic ring (ring C) had a positive influence on the potency against most of the fungi and (iv) replacement of ring B with a heterocycle reduced potency.

Moreover, from the MLR analysis three interesting points arise. Specifically, the MIC values significantly depend on: (i) the dipole-dipole nature of the intermolecular forces ($dipole^2/V$), (ii) the global charge transfers (Mean topological charge index of order 9) and (iii) the branching of the carbon-atom skeleton (Path/Walk 3 - Randic shape index). Also, the descriptors of aqueous solubility, dipole moment and the position and influence of heteroatoms contribute, but to a lesser extent, on the activity.

Our findings suggest that the 1,2,4-triazole ring offers a promising motif for further development of new analogues with optimized antifungal properties through appropriate substitution.

Table 3. Selected QSAR equation (Equation 1) and the statistical significance parameters, obtained from Model 2 analysis.

QSAR Model 2	N	R^2	Q^2	F-value	RMSE
Equation (1): **MIC** = 0.126(±0.011) **logS** - 5.380(±1.181) **Mean topological charge index of order 9** - 0.0074(±0.0006) **Modified Randic connectivity** + 0.039(±0.006) **Number of N** – 0.037(±0.007) **Number of** - 0.0013(±0.0003) **Sum of topological distance between N…O** + 0.137(±0.009) **Valence connectivity index chi-3** + 0.575(±0.0382) **Valence connectivity index chi-4** + 20.666(±4.17375) **Dipole²/V** - 0.277(±0.042) **Dipole** - 2.346(±0.540) **Path/walk 3 – Randic shape index** + 1.22(±0.237)	**27**	**0.98**	**0.72**	**92.52**	**0.10**

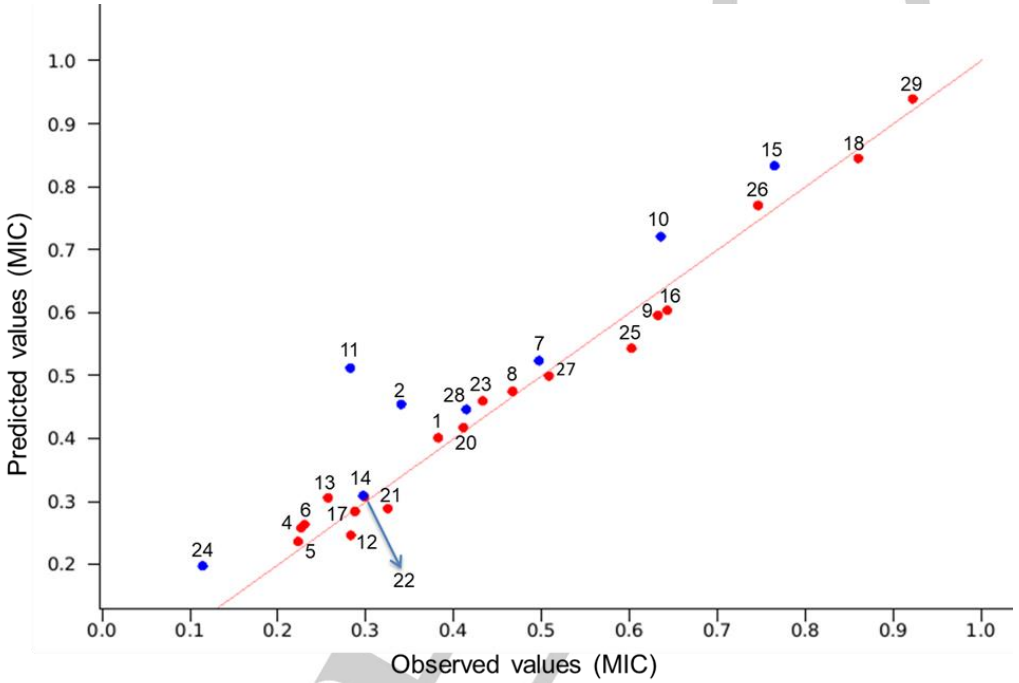

Figure 1. Correlation plot of the observed versus predicted MIC (μmol·mL^{-1}) values of triazole derivatives, including to Model 2. Compounds that comprise the training and test set are illustrated with red and blue dots, respectively.

Table 4. Predicted values of QSAR Model 2 significant descriptors.

Compounds	logS	Mean topological Charge Index of order 9	Modified Randic connectivity	Number of N	Number of O	Sum of topological distance Between N..O	Valence connectivity index chi-3	Valence connectivity index chi-4	Dip^ 2/V	Dipole	Path/walk 3 – Randic Shape index
1	-3.929	$2.8\ 10^{-3}$	55.015	3	0	0	2.796	1.887	0.033	4.311	0.317
2	-3.984	$2.8\ 10^{-3}$	54.811	3	0	0	2.784	1.879	0.021	4.177	0.317
4	-4.313	$7.9\ 10^{-3}$	61.518	3	1	22	3.100	2.027	0.022	4.441	0.327
5	-5.594	$6.9\ 10^{-3}$	65.546	3	0	0	3.383	2.149	0.033	5.44	0.320
6	-5.388	$9.3\ 10^{-3}$	65.989	3	0	0	3.664	2.253	0.046	6.518	0.332
7	-5.758	$6.7\ 10^{-3}$	69.319	3	0	0	3.652	2.327	0.006	2.444	0.338
8	-5.01	$10.6\ 10^{-3}$	67.056	3	1	22	3.423	2.164	0.006	2.318	0.328
9	-4.477	$10.2\ 10^{-3}$	63.002	4	0	0	3.243	2.056	0.008	2.79	0.321
10	-6.607	$6.1\ 10^{-3}$	78.148	3	0	0	4.325	2.867	0.006	2.632	0.329
11	-5.736	$6.6\ 10^{-3}$	81.958	4	1	30	4.189	2.782	0.013	3.899	0.327
12	-7.12	$6.2\ 10^{-3}$	93.136	4	1	30	4.876	3.355	0.061	8.768	0.333
13	-6.424	$8.0\ 10^{-3}$	87.496	4	1	30	4.475	3.012	0.026	5.689	0.327
14	-6.015	$5.7\ 10^{-3}$	84.857	4	1	30	4.386	2.976	0.037	6.803	0.317
15	-7.262	$4.8\ 10^{-3}$	96.655	4	1	30	5.357	3.728	0.012	4.041	0.327
16	-6.424	$8.2\ 10^{-3}$	87.496	4	1	30	4.511	2.920	0.007	2.993	0.327
17	-6.296	$5.8\ 10^{-3}$	87.857	4	1	30	4.662	3.115	0.050	8.065	0.316
18	-5.468	$6.6\ 10^{-3}$	81.958	4	1	30	5.139	3.598	0.047	7.608	0.327
20	-6.424	$5.3\ 10^{-3}$	87.496	4	1	27	4.448	3.065	0.020	5.014	0.326
21	-5.468	$5.7\ 10^{-3}$	85.265	5	1	32	4.185	2.804	0.052	7.964	0.317
22	-6.156	$6.9\ 10^{-3}$	90.804	5	1	32	4.507	2.942	0.028	5.942	0.319
23	-6.85	$6.7\ 10^{-3}$	96.342	5	1	32	4.756	3.269	0.019	5.027	0.318
24	-6.85	$7.0\ 10^{-3}$	96.342	5	1	32	4.793	3.177	0.071	9.615	0.319

25	-4.267	$0.9\ 10^{-3}$	57.710	3	0	0	2.997	2.061	0.018	4.060	0.308
26	-4.045	$3.4\ 10^{-3}$	56.353	3	0	0	3.368	2.341	0.027	4.690	0.321
27	-3.464	$2.8\ 10^{-3}$	55.311	4	0	0	2.672	1.786	0.026	4.619	0.317
28	-5.121	$9.1\ 10^{-3}$	70.964	3	2	41	3.700	2.472	0.012	3.423	0.336
29	-5.707	$7.6\ 10^{-3}$	92.504	4	2	60	5.598	3.867	0.027	5.742	0.329

Table 5. Observed and Predicte dantifungal activity (MIC - μmol·mL^{-1}) against *Aspergillus fumigatus ATCC9197* by Model 2 QSAR equation.

Compounds	Observed Antifungal Activity	Predicted Antifungal Activity	$\Delta_{Obs-Pred}$
Training Set			
1	0.382	0.401	-0.019
4	0.226	0.258	-0.032
5	0.223	0.236	-0.013
6	0.230	0.263	-0.006
8	0.467	0.474	-0.007
9	0.632	0.595	0.037
12	0.283	0.246	0.037
13	0.257	0.305	-0.048
16	0.643	0.603	0.048
17	0.288	0.284	0.004
18	0.860	0.845	0.015
20	0.411	0.417	-0.006
21	0.325	0.288	0.037
22	0.297	0.309	-0.012
23	0.433	0.459	-0.026
25	0.602	0.543	0.059
26	0.746	0.769	0.023
27	0.508	0.498	0.010
29	0.922	0.939	-0.017
Test Set			
2	0.340	0.454	-0.114
7	0.497	0.523	-0.026
10	0.636	0.720	-0.084
11	0.282	0.512	-0.230
14	0.298	0.307	-0.009
15	0.765	0.833	-0.068
24	0.114	0.198	-0.084
28	0.414	0.446	-0.032

Experimental Section

Chemistry. General

Starting materials, reagents, and analytical grade solvents were purchased from Sigma-Aldrich Europe (Germany). All reactions were routinely checked by TLC using Merck Kieselgel 60 F254 aluminum plates and visualized by UV light. The purity of all the intermediates was checked by ^{1}H NMR. ESI-MS analyses were performed on an Agilent 1100 LC–MSD trap system VL. Flash chromatographic separations were performed on a Biotage SP1 purification system using flash cartridges prepacked with KP-Sil32–63 lm, 60 Å silica. Elemental analyses were performed on a EuroEA 3000 analyzer; the measured values for C, H, and N had a maximum deviation of ± 0.4% from the theoretical value. Melting points (mp) were taken on a Gallenkamp MFB 595010M apparatus (open capillary method). Nuclear magnetic resonance (NMR) spectra were recorded at 300 MHz on a Varian Mercury 300 instrument at ambient temperature in the specified deuterated solvent. Chemical shifts (d) are quoted in parts per million (ppm) and are referenced to the residual solvent peak. The coupling constants *J* are given in hertz (Hz). The following abbreviations were used: s (singlet), d (doublet), t (triplet), q (quadruplet), qn (quintuplet), dd (doublet of doublet), td (doublet of triplet), m (multiplet), brs (broad signal). Signals due to NH/OH protons were located by deuterium exchange with D_2O.

1-Benzyl-4-phenyl-1*H*-1,2,3-triazole (1)[27]**:** Benzyl azide (125 µL, 1.0 mmol) and ethynylbenzene (110 µL, 1.0 mmol) were suspended in a 1:1 mixture of water and tert-butyl alcohol (4 mL). Sodium ascorbate (0.1 mmol, 100 µL of freshly prepared 1M solution in water) was added, followed by copper (II) sulfate pentahydrate (2.5 mg, 0.01 mmol, in 100 µL of water). The heterogeneous mixture was stirred vigorously overnight, at which point it cleared and TLC analysis indicated complete consumption of the reactants. The reaction mixture was diluted with water (30 mL) and extracted with ethyl acetate. The organic extracts were washed with water and brine, dried (Na_2SO_4) and evaporate under vacuum. The residue was purified by flash column chromatography, using as eluent $CHCl_3$ to afford 200 mg (85%) of pure product as an off-white powder. ^{1}H-NMR (300 MHz, $CDCl_3$): δ [ppm]= 5.58 (s, 2H, CH_2), 7.32 (complex m, 3H, aromatic-H), 7.40 (complex m, 5H, aromatic-H), 7.66 (s, 1H, NH), 7.80 (m, 2H, aromatic-H); elemental analysis: calcd for $C_{15}H_{13}N_3$: C 76.57, H 5.57, N 17.86; found: 76.22, H 5.40, N 18.03.

5-Benzyl-3-phenyl-1*H*-1,2,4-triazole (**3**)[28]: 2-Phenylacetohydrazide (150.1 mg, 1.0 mmol) and benzonitrile (309 mg, 3.0 mmol) were suspended in *n*-butanol (3 mL). Potassium carbonate (68 mg, 0.5 mmol) was added and the heterogeneous mixture was stirred under microwave irradiation at 150 °C for 3 h (TLC monitoring). The solvents evaporated and the residue was purified with column chromatography using $CHCl_3$/MeOH 10/1 as eluents to give 140 mg (60%) of a pure white solid; ^{1}H-NMR (300 MHz, $CDCl_3$): δ [ppm]= 4.15 (s, 2H, CH_2), 7.29 (complex m, 6H, aromatic-H, NH), 7.40 (complex m, 3H, aromatic-H), 7.98 (m, 2H, aromatic-H); elemental analysis: calcd for $C_{15}H_{13}N_3$: C 76.57, H 5.57, N 17.86; found: 76.34, H 5.38, N 18.00.

General procedure for the synthesis of triazole derivatives 2, 4, 5, 6, 7, 8, 9, 10, 30, 31 and 32.

The corresponding hydrazides (1.0 mmol) and benzonitriles (3.0 mmol) were suspended in *n*-butanol (3 mL). Potassium carbonate (68 mg, 0.5 mmol) was added and the heterogeneous mixture was stirred under microwave irradiation at 150 °C for 3 h (TLC monitoring) [700 W, with temperature rising from ambient to 150 °C (5 min)]. The solvents evaporated and the residue was purified with column chromatography.

3-Benzyl-5-phenyl-1*H*-1,2,4-triazole (**2**)[28]: Column chromatography using CH_2Cl_2/AcOEt 4/1 as eluents gave 200 mg (85%) of a pure light orange solid; ^{1}H-NMR (300 MHz, $CDCl_3$): *δ* (ppm): 4.13 (s, 2H, C*H*$_2$), 7.28 (complex m, 5H, aromatic-H), 7.39 (complex m, 3H, aromatic-H), 7.96 (m, 2H, aromatic-H), 11.83 (br s, 1H, N*H*); elemental analysis: calcd for $C_{15}H_{13}N_3$: C 76.57, H 5.57, N 17.86; found: 76.39, H 5.47, N 17.96.

3-(4-Methoxybenzyl)-5-phenyl-1*H*-1,2,4-triazole (**4**): Column chromatography using CH_2Cl_2/MeOH 10/1 as eluents to give 219 mg (83%) of a pure white solid; ^{1}H-NMR (300 MHz, $CDCl_3$): δ [ppm]= 3.69 (s, 3H, OC*H*$_3$), 4.13 (s, 2H, C*H*$_2$), 6.73 (d, 2H, *J* =11.6 Hz, aromatic-H), 7.08 (d, 2H, *J* =11.2 Hz, aromatic-H), 7.39 (complex m, 3H, aromatic-H), 7.94 (m, 2H, aromatic-H); elemental analysis: calcd for $C_{16}H_{15}N_3O$: C 72.43, H 5.70, N 15.84; found: C 72.73, H 5.85, N 15.62.

3-(4-bromobenzyl)-5-phenyl-1H-1,2,4-triazole (**5**): Column chromatography using CH_2Cl_2/MeOH 10/1 as eluents gave, after trituration with PE/Et_2O, 280 mg (89%) of a pure white solid; ^{1}H-NMR (300 MHz, $CDCl_3$): δ [ppm]= 4.13 (s, 2H, C*H*$_2$), 7.16 (d, 2H, *J* =11.2 Hz, aromatic-H), 7.43 (complex m, 5H, aromatic-H), 7.96 (m, 2H, aromatic-H, NH), 11.23 (br s, 1H, N*H*); elemental analysis: calcd for $C_{15}H_{12}BrN_3$: C 57.34, H 3.85, N 13.37; found: C 57.70, H 4.10, N 13.14.

3-(3,4-dichlorobenzyl)-5-phenyl-1*H*-1,2,4-triazole (**6**): Column chromatography using CH_2Cl_2/MeOH 10/1 as eluents gave, after trituration with MeOH, 260 mg (85%) of a pure crystalline white solid; ^{1}H-NMR (300 MHz, $CDCl_3$): δ [ppm]= 4.03 (s, 2H, CH2), 7.04 (d, 1H, *J* = 10.4 Hz, aromatic-H), 7.36 (complex m, 5H, aromatic-H), 7.86 (d, 2H, *J* = 8.8 Hz aromatic-H), 12.48 (br s, 1H, N*H*); elemental analysis: calcd for $C_{15}H_{11}Cl_2N_3$: C 59.23, H 3.65, N 13.81; found: C 59.50, H 3.81, N 14.11.

3-(2-chloro-6-fluorobenzyl)-5-(4-chlorophenyl)-1H-1,2,4-triazole (**7**): Column chromatography using $CHCl_3$, $CHCl_3$/AcOEt, 7:3 as eluents gave 243 mg (65%) of a yellow solid;^{1}H-NMR (300 MHz, $CDCl_3$): δ [ppm]= 4.11 (s, 2H, CH_2), 6.52 (s, H, N*H*), 7.08 (m, 1H, 3-aromatic-H), 7.30 (complex m, 2H, 1,2-aromatic-H), 7.51 (d, 2H, *J* = 5.1 Hz 3,5-aromatic-H), 8.03 (d, 2H, *J* = 5.1 Hz 2,6-aromatic-H); elemental analysis: calcd for $C_{15}H_{10}Cl_2FN_3$: C 55.92, H 3.13, N 13.04; found: C 55.61, H 3.47, N 13.40.

5-(4-Chlorophenyl)-3-(4-methoxybenzyl)-1*H*-1,2,4-triazole (**8**): Column chromatography using $CHCl_3$, $CHCl_3$/AcOEt, 7:3 as eluents gave 142mg of a white pearl solid (55%); R*f* 0.58 (AcOEt/ CH_2Cl_2, 25:75); mp: 152-153 °C; ^{1}HNMR (DMSO-*d*$_6$): δ [ppm]= 3.69 (s,3H,CH_3), 4.01 (s, 2H, C*H*$_2$), 6.84 (d,2H, *J* = 8.8 Hz), 7.20 (d, 2H, *J* = 8.8 Hz), 7.47 (d, 2H, *J* = 8.4 Hz), 7.94 (d, 2H, *J* = 6.2 Hz), 13.91 (s,1H, N*H*$_{triazole}$); elemental analysis: calcd for $C_{16}H_{14}ClN_3O$: C 64.11, H 4.71, N 14.02; found: C 64.37, H 4.95, N 14.30.

4-((5-(4-Chlorophenyl)-1*H*-1,2,4-triazol-3-yl)methyl)aniline (**9**): Column chromatography using $CHCl_3$, $CHCl_3$/AcOEt, 7:3 as eluents gave 786mg of a light yellow solid (50%); R*f* 0.29 (AcOEt/ CH_2Cl_2, 9:1); mp: 189-191 °C; ^{1}HNMR (DMSO-*d*$_6$): δ [ppm]= 3.88 (s, 2H, CH_2), 4.91 (s, 2H, NH_2), 6.49 (d, 2H, *J* = 8.4 Hz), 6.93 (d, 2H, *J* = 8.0 Hz), 7.47 (d, 2H, *J* = 8.4 Hz), 7.93 (d, 2H, *J* = 6.5 Hz), 13.8 (s, N*H*$_{triazole}$); elemental analysis: calcd for $C_{15}H_{13}ClN_4$: C 63.27, H 4.60, N 19.68; found: C 63.50, H 4.34, N 19.95.

3-(Biphenyl-4-ylmethyl)-5-(4-chlorophenyl)-1*H*-1,2,4-triazole (**10**): Column chromatography using $CHCl_3$, $CHCl_3$/AcOEt, 7:1 as eluents gave 237mg of a white pearl solid (59%);R*f* 0.29 (*n*-Hex 7:3); mp: 204-205 °C; ^{1}HNMR (DMSO-*d*$_6$): δ [ppm]= 4.10 (s, 2H, C*H*$_2$), 7.32-7.49 (m,7H), 7.58-7.63 (m,4H), 7.95 (d, 2H, *J* = 8.3 Hz), 14.02 (s, N*H*$_{triazole}$); elemental analysis: calcd for $C_{21}H_{16}ClN_3$: C 72.93, H 4.66, N 12.15; found: C 73.21, H 4.86, N 12.32.

3,5-Dibenzyl-1*H*-1,2,4-triazole (**25**): Column chromatography using $CHCl_3$, $CHCl_3$/AcOEt, 7:1 gave 110mg of a white pearl solid (73%); R*f* 0.57 (CH_2Cl_2/AcOEt, 6:4); mp: 146-148 °C; ^{1}HNMR (300 MHz, DMSO-*d*$_6$): δ [ppm]= 3.90 (d, 4H, *J* = 23.4 Hz), 7.21-7.26 (m,10H), 13.46 (s, N*H*$_{triazole}$); elemental analysis: calcd for $C_{16}H_{15}N_3$: C 77.08, H 6.06, N 16.85; found: C 77.30, H 6.26, N 16.54.

3-Benzyl-5-(thiophen-2-yl)-1*H*-1,2,4-triazole (**26**): Column chromatography using $CHCl_3$, $CHCl_3$/AcOEt, 7:3 gave 91 mg of a white pearl solid (37%); R*f* 0.69 (CH_2Cl_2/AcOEt, 6:4); mp: 138-139 °C; ^{1}HNMR (300 MHz, DMSO-d_6): δ [ppm]= 4.06 (s, 2H, CH_2), 7.11-7.30 (m, 6H), 7.54 (s, 2H, $H_{thiophene}$), 13.87 (s, N$H_{triazole}$); elemental analysis: calcd for $C_{13}H_{11}N_3S$: C 64.71, H 4.59, N 17.41; found: C 64.99, H 4.78, N 17.71.

4-(3-benzyl-1*H*-1,2,4-triazol-5-yl)pyridine (**27**)[35]: Column chromatography using $CHCl_3$, $CHCl_3$/AcOEt, 7:3 gave 161 mg of a white powder solid (64%); R*f* 0.69 (AcOEt/MeOH, 9:1); mp: 197-201 °C; ^{1}HNMR (300 MHz, DMSO-d_6): δ [ppm]= 4.12 (s, 2H, CH_2),7.20-7.33 (m,1H), 7.25-7.29 (m, 4H), 7.44-7.48 (m,1H), 8.25 (d, 1H, *J* = 8.4 Hz), 8.59 (d, 1H, *J* = 4.8 Hz), 9.12 (t, 1H, *J* = 1.4 Hz), 14.0 (s, N$H_{triazole}$); elemental analysis: calcd for $C_{14}H_{12}N_4$: C 71.17, H 5.12, N 23.71; found: C 71.17, H 5.12, N 23.71.

3-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-5-(4-chlorophenyl)-1*H*-1,2,4-triazole (**28**): Column chromatography using $CHCl_3$, $CHCl_3$/AcOEt, 7:3 gave 157mg of a white solid (55%); R*f* 0.51 (AcOEt/CH_2Cl_2, 3:7); mp: 209-210 °C; ^{1}HNMR (300 MHz, DMSO-d_6): δ [ppm]= 3.99 (s, 2H, CH_2), 5.95 (s, 2H,C$H_{2benzdioxole}$), 6.76 (d, 1H, *J* = 1.5 Hz), 6.86 (t, 2H, *J* = 7.5 Hz) 7.51 (dd, 2H, *J* = 2.2 Hz), 7.48 (d, 2H, *J* = 1.8 Hz), 13.02 (s, N$H_{triazole}$); elemental analysis: calcd for $C_{16}H_{12}ClN_3O_2$: C 61.25, H 3.86, N 13.39; found: C 61.47, H 3.70, N 13.50.

4-((5-phenyl-1*H*-1,2,4-triazol-3-yl)methyl)aniline (**30**): Column chromatography using $CHCl_3$, $CHCl_3$/MeOH 9/1 as eluents gave 850 mg (90%) of an off-white solid; ^{1}H-NMR (300 MHz, $CDCl_3$): δ [ppm]= 4.06 (s, 2H, CH_2), 6.00 (br d, 2H, NH_2), 6.62 (d, 2H, *J* = 11.2 Hz, aromatic-H), 7.05 (d, 2H, *J* = 11.2 Hz, aromatic-H), 7.41 (complex m, 4H, aromatic-H), 8.03 (m, 1H, aromatic-H), 11.23 (br s, 1H, N*H*); elemental analysis: calcd for $C_{15}H_{14}N_4$: C 71.98, H 5.64, N 22.38; found: C 72.30, H 5.95, N 22.71.

3-((5-(3-Chlorophenyl)-1*H*-1,2,4-triazol-3-yl)methyl)aniline (**31**): Column chromatography using $CHCl_3$, $CHCl_3$/MeOH 9/1 as eluents gave 207mg of a yellow oil (62%); R*f* 0.35 (AcOEt/ CH_2Cl_2,3:7); ^{1}HNMR ($CDCl_3$): δ [ppm]= 3.69 (s, 2H,NH_2), 4.06 (s,2H,CH_2), 6.54-6.66 (m, 3H), 7.10 (t, 2H, *J* = 7.7 Hz), 7.30-7.37 (m, 2H), 7.89-7.92 (m, 1H), 8.05 (s,1H, N*H*triazole); HRMS (*m/z*): $[M+H]^+$ calcd for $C_{15}H_{13}ClN_4$, 284.0829; found, 284.0838.

3-((5-(4-Chlorophenyl)-1*H*-1,2,4-triazol-3-yl)methyl)aniline (**32**): Column chromatography using $CHCl_3$, $CHCl_3$/MeOH 9/1 as eluents gave 207mg of a white powder (79%); $C_{15}H_{13}ClN_4$; R*f* 0.33 (AcOEt/CH_2Cl_2, 3:7); ^{1}H-NMR (300 MHz, $CDCl_3$): δ [ppm]= 4.09 (s, 2H, CH_2), 6.70-6.72 (m, 2H), 7.18-7.20 (m, 2H), 7.33 (d, 2H, *J* = 8.5), 7.97 (d, 2H, *J* = 8.5 Hz); NH, NH_2 not detectable; ESI-MS $(M-H)^-$ 282.8, 284.8 *m/z*; elemental analysis: calcd for $C_{15}H_{13}ClN_4$: C 63.27, H 4.60, N 19.68; found: C 63.07, H 4.98, N 19.89.

General procedure for the synthesis of triazole derivatives 11, 12, 16, 18, 19, 20 and 29.

The corresponding amine **30** / **31** / **32** / **9** (0.4 mmol) was dissolved in 5.5 mL of dry THF. The solution was cooled to 0 °C and three equivalents of DIPEA (1.2 mmol) were added. Then the benzoylchloride (0.4 mmol) was dissolved in 1.5 mL dry THF and added dropwise. The mixture was stirred in rt for 5 h (TLC monitoring). The solvents evaporated and the crude product was extracted with CH_2Cl_2 (3 x 20 mL), washed with water and brine (2 x 20 mL) and dried over Na_2SO_4. The residue was purified with column chromatography.

***N*-(4-((5-phenyl-1*H*-1,2,4-triazol-3-yl)methyl)phenyl)benzamide** (**11**)

Column chromatography using CH_2Cl_2, CH_2Cl_2/MeOH 10/1 as eluents gave 120 mg (86%) of a white solid;^{1}H-NMR (300 MHz, $CDCl_3$): δ [ppm]= 4.20 (s, 2H, CH_2), 7.32 (m, 2H, aromatic-H), 7.53 (complex m, 7H, aromatic-H), 7.87 (br d, 3H, *J* = 9.6 Hz, aromatic-H), 8.04 (br d, 2H, *J* = 10.8 Hz, aromatic-H); elemental analysis: calcd for $C_{22}H_{18}N_4O$: C 74.56, H 5.12, N 15.81; found: C 74.27, H 5.40, N 16.01.

2,4-dichloro-*N*-(4-((5-phenyl-1*H*-1,2,4-triazol-3-yl)methyl)phenyl) benzamide (**12**): Column chromatography using CH_2Cl_2, CH_2Cl_2/MeOH 10/1 as eluents gave 114mg of a white solid (69%); R*f* 0.38 (CH_2Cl_2/AcOEt, 6:4); mp: 167-170 °C; ^{1}HNMR (300 MHz, DMSO-d_6): δ [ppm]= 4.06 (s, 2H, CH_2),7.27 (d, 2H, *J* = 8.4 Hz), 7.30-7.62 (m, 8H), 7.94 (d, 2H, *J* = 5.0 Hz), 10.68 (s, 1H, N*Hamid*), 13.8 (s, 1H, N*Htriazole*); elemental analysis: calcd for $C_{22}H_{16}Cl_2N_4O$: C 62.42, H 3.81, N 13.24; found: C 62.67, H 3.57, N 13.49.

(*N*-(4-((5-(4-chlorophenyl)-1*H*-1,2,4-triazol-3-yl)methyl)phenyl) benzamide (16): Column chromatography using CH_2Cl_2, CH_2Cl_2/MeOH 10/1 as eluents gave 39mg of a white solid (29%);R*f* 0.37, (CH_2Cl_2/AcOEt, 6:4); mp 237-238 °C; ^{1}HNMR (300 MHz, DMSO-d_6): δ [ppm]= 4.05-4.1 (m, 2H, CH_2), 7.25 (d, 2H, *J* = 8.3 Hz), 7.50-7.59 (m,5H), 7.69 (d, 2H, *J* = 8.3 Hz), 7.90 (d, 4H, *J* = 6.0 Hz), 10.2 (s, 1H, NH_{amid}),13.90 (s, N$H_{triazol}$); elemental analysis: calcd for $C_{22}H_{17}ClN_4$: C 67.95, H 4.41, N 14.41; found: C 68.25, H 4.67, N 14.70.

***N*-(4-((5-phenyl-1*H*-1,2,4-triazol-3-yl)methyl)phenyl)cyclohexane carboxamide** (**18**): Column chromatography using CH_2Cl_2, CH_2Cl_2/MeOH 10/1 as eluents gave 15mg of a yellow solid (10%); mp: 222-225 °C; ^{1}HNMR [300 MHz, $(CD_3)_2CO$]: δ [ppm]= 1.19-2.34 (m,10HcyHex), 4.25 (s, 2H, C*H2*), 7.29 (d, 2H, *J* = 8.8 Hz), 7.44-7.50 (m,3H), 7.62 (d,2H, *J* = 8.5 Hz), 8.05-8.32 (m, 2H), 9.00 (s,1H, N*H*); elemental analysis: calcd for $C_{22}H_{24}N_4O$: C 73.31, H 6.71, N 15.54; found: C 73.18, H 6.81, N 15.44.

***N*-(3-((5-(3-chlorophenyl)-1*H*-1,2,4-triazol-3-yl)methyl)phenyl) benzamide** (**19**): When **32** reacted with benzoylchloride under the same reaction conditions gave, after column chromatography of the residue using ethyl acetate/*n*-hexane 2:1 v/v as the eluent,120mg of an oily compound (61%); R*f* 0.30 (CH_2Cl_2/Hex,6:1). The latter was dissolved in HCl 1.25N in absolute ethanol to obtain its hydrochloride in pure form. White powder; mp: 200-202 °C (dec.). ^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]=4.10 (s, 2H), 6.03 (brs, 2H, exch. D_2O), 7.05 (d, 1H, *J* = 8.4 Hz), 7.29 (t, 1H, *J* = 8.4 Hz), 7.47-7.59 (m, 5H), 7.65-7.67 (m, 1H), 7.69 (s, 1H), 7.91 (d, 2H, *J* = 6.9 Hz), 7.97 (d, 2H, *J* = 8.4 Hz), 10.23 (s, 1H, exch. D_2O). IR (KBr film, cm^{-1}) 3256, 3061, 2567, 1651, 1618, 1537, 1315, 698. ESI-MS $(M+H)^+$ 389.0, 391.0; elemental analysis: calcd for $C_{22}H_{18}Cl_2N_4O$: C 62.13, H 4.27, N 13.17; found: C 62.42, H 4.11, N 13.33.

***N*-(3-((5-(3-chlorophenyl)-1*H*-1,2,4-triazol-3-yl)methyl)phenyl) benzamide** (**20**): When **31** reacted with benzoylchloride under the same reaction conditions gave, after column chromatography of the residue using CH_2Cl_2, CH_2Cl_2/MeOH 10/1, 120mg of a white foamy solid (63%); R*f* 0.30 (CH_2Cl_2/Hex, 6:1); mp 59-61 °C; ^{1}HNMR (300 MHz, $CDCl_3$): δ [ppm]= 4.06 (s, 2H, CH_2), 6.54-6.66 (m, 6H), 7.10 (t, 2H, *J* = 7.7 Hz), 7.30-7.37 (m, 3H), 7.89-7.92 (m,2H),10.2 (s, 1H, N*Hamid*). ESI-MS $(M+H)^+$ 389.0, 391.0; HRMS (*m/z*): $[M+H]^+$ calcd for $C_{22}H_{17}ClN_4O$, 388.1091; found, 388.1086.

4-Methyl-*N*-(4-((5-phenyl-1*H*-1,2,4-triazol-3-yl)methyl)phenyl) benzenesulfonamide (**29**): When **30** reacted with tosyl chloride under the same reaction conditions gave, after column chromatography of the residue using CH_2Cl_2, CH_2Cl_2/MeOH 10/1, 102mg of a white solid (66%); R*f* 0.32 (CH_2Cl_2/AcOEt, 6:4); mp: 208-212 °C; ^{1}HNMR (300 MHz, DMSO-d_6): δ [ppm]= 2.29 (s, 3H, CH_3), 3.96 (s, 2H, CH_2), 6.98 (d, 2H, *J* = 8.7 Hz), 7.12 (d, 2H, *J* = 8.7 Hz), 7.28 (d, 2H, *J* = 7.6 Hz), 7.40-7.42 (m, 3H), 7.61 (d, 2H, *J* = 8.0 Hz), 7.90 (d, 2H, *J* = 6.5 Hz), 10.14 (s, 1H, N$H_{sulphamid}$), 13.77 (s, N*Htriazol*); elemental analysis: calcd for $C_{22}H_{20}N_4O_2S$: C 65.33, H 4.98, N 13.85; found: C 65.33, H 4.98, N 13.85.

General procedure for the synthesis of triazole derivatives 13, 14, 15 and 17

Equal amount of amine **30** (1eq) and the corresponding chlorobenzoic acid (1eq), 2eq of *N*-methyl morpholine and 1.2eq of HOBt were dissolved in dry THF and cooled to 0 °C in ice-bath and then 1.2eq of EDC was added. The reaction was warmed to room temperature and stirred under argon

flow overnight. The reaction mixture was extracted 3 times with brine and CH_2Cl_2. Organic phases were combined and dried under sodium sulphate, filtrated, and evaporated to dryness. The crude product was purified with column chromatography.

3-Chloro-*N*-(4-((5-phenyl-1*H*-1,2,4-triazol-3-yl)methyl)phenyl) benzamide (**13**): Column chromatography using CH_2Cl_2/AcOEt, 7:3 gave 84mg of a white solid (60%); R*f* 0.62 (CH_2Cl_2/AcOEt, 6:4); mp: 235-236 °C ^{1}HNMR (300 MHz, DMSO-d_6): δ [ppm]= 4.01 (s, 2H, CH_2), 7.22-7.30 (m, 6H), 7.40-7.52 (m, 5H), 7.95 (d, 2H, *J* = 1.5 Hz), 10.11 (s, 1H, NH_{amid}),13.85 (s, N$H_{triazol}$); elemental analysis: calcd for $C_{22}H_{17}ClN_4O$: C 67.95, H 4.41, N 14.41; found: C 67.66, H 4.09, N 14.58.

2-Phenyl-*N*-(4-((5-phenyl-1*H*-1,2,4-triazol-3-yl)methyl)phenyl) acetamide (**14**): Column chromatography using CH_2Cl_2/AcOEt, 7:3 gave 64mg of a white solid (44%); R*f* 0.32 (CH_2Cl_2/AcOEt, 6:4); mp: 233-236 °C^{1}HNMR (300 MHz, DMSO-d_6): δ [ppm]= 4.06 (s, 4H, CH_2), 7.29 (d, 3H, *J* = 8.4 Hz), 7.38-7.44 (m, 4H), 7.46-7.65 (m, 3H), 7.96 (dd, 4H, *J* = 4.1 Hz),10.30 (s, 1H, NH_{amid}), 13.81 (s, N$H_{triazol}$); elemental analysis: calcd for $C_{23}H_{20}N_4O$: C 74.98, H 5.47, N 15.21; found: C 75.30, H 5.79, N 15.55.

2-(Naphthalen-2-yl)-*N*-(4-((5-phenyl-1*H*-1,2,4-triazol-3-yl)methyl) phenyl)acetamide (15): Column chromatography using CH_2Cl_2/AcOEt, 7:3 gave 120mg of yellow solid (72%); R*f* 0.23 (CH_2Cl_2/AcOEt, 6:4); mp: 233-236°C; ^{1}HNMR (300 MHz, DMSO-d_6): δ [ppm]= 3.78 (s, 2H, CH_2), 4.02 (s, 2H, CH_2), 7.23-7.30 (s, 2H, *J* = 8.2 Hz), 7.37-7.48 (m, 8H), 7.83-7.95 (m, 6H), 10.19 (s,1H,NH_{amid}),13.85 (s, N$H_{triazol}$); elemental analysis: calcd for $C_{27}H_{22}N_4O$: C 77.49, H 5.30, N 13.39; found: C 77.77, H 5.11, N 13.08.

3-phenyl-N-(4-((5-phenyl-1H-1,2,4-triazol-3-yl)methyl)phenyl) propanamide (**17**): Column chromatography using CH_2Cl_2/AcOEt, 7:3 gave 145mg of a white solid (63%); R*f* 0.54 (CH_2Cl_2/AcOEt, 7:3); mp: 198-200 °C^{1}HNMR (300 MHz, DMSO-d_6): δ [ppm]= 2.57 (t, 2H, PhCH_2CH_2-CO, *J* = 8.0 Hz), 2.87 (t, 2H, PhCH_2CH$_2$-CO, *J* = 8.1 Hz), 3.94 (s, 1H, CH_A), 3.99 (s, 1H, CH_B), 7.12-7.27 (m, 7H), 7.38-7.51 (m, 5H), 7.94 (d, 2H, *J* = 6.9 Hz) ,9.86 (s,1H, NH_{amid}),13.78 (s, N$H_{triazol}$); elemental analysis: calcd for $C_{24}H_{22}N_4O$: C 75.37, H 5.80, N 14.65; found: C 75.72, H 5.49, N 14.93.

General procedure for the synthesis of triazole derivatives 21, 22, 23 and 24

The corresponding amine **30** / **32** (0.4 mmol) was dissolved in 3 mL of dry THF. The solution was cooled to 0 °C and triethylamine (0.4 mmol) was added. Then the corresponding phenylisocyanate (0.4 mmol) was dissolved in 3 mL dry THF and added dropwise. The mixture was stirred in rt for 48 h (TLC monitoring). The mixture was quenched with water and extracted with AcOEt (3x20 mL), washed with water and brine (2x20 mL) and dried over Na_2SO_4. The residue was purified with column chromatography.

1-Phenyl-3-(4-((5-phenyl-1*H*-1,2,4-triazol-3-yl)methyl)phenyl)urea (**21**): Column chromatography using CH_2Cl_2, CH_2Cl_2/MeOH 10/1 as eluents gave 120 mg (86%) of a white solid; ^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]=4.11 (s, 2H, CH_2), 6.98-7.03 (m, 1H), 7.19-7.29 (m, 5H), 7.36-7.44 (m, 5H), 7.68 (s,1H), 7.94 (dd, 2H, *J* = 6.3 Hz), 8.82 (s, 1H, exch. D_2O, NH_{amid}), 8.93 (s, 1H, exch. D_2O, NH_{amid}), 13.81 (s, 1H, N$H_{triazole}$); elemental analysis: calcd for $C_{22}H_{19}N_5O$: C 71.53, H 5.18, N 18.96; found: C 71.15, H 5.00, N 19.30.

1-(4-Chlorophenyl)-3-(4-((5-phenyl-1H-1,2,4-triazol-3-yl)methyl) phenyl)urea (**22**): Column chromatography using CH_2Cl_2, CH_2Cl_2/MeOH 10/1 as eluents gave 100mg of a yellow solid (80%)'; R*f* 0.46 (MeOH/ CH_2Cl_2,1:9); mp: 205-209 °C; ^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 4.01 (s, 2H, CH_2), 6.98-7.03 (m, 1H), 7.19-7.29 (m, 5H), 7.36-7.44 (m, 4H), 7.68 (s,1H), 7.94 (dd, 2H, *J* = 6.3 Hz), 8.82 (s, 1H, exch. D_2O, NH_{amid}), 8.93 (s, 1H, exch. D_2O, NH_{amid}), 13.81 (s, 1H, N$H_{triazole}$); elemental analysis: calcd for $C_{22}H_{18}ClN_5O$: C 65.43, H 4.49, N 17.34; found: C 65.80, H 4.21, N 17.54.

***N*-(3-Chlorophenyl)-*N*^{1}-[3-(5-(3-chlorophenyl)-1*H*-1,2,4-triazol-3-yl) methyl]phenylurea (23):** Column chromatography using ethyl acetate/*n*-hexane 1:1 as eluents gave 48 mg of a white powder (53%); mp: 198-200 °C; ^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 4.08 (s, 2H), 6.92 (d, 1H, *J* = 7.5 Hz), 6.98 (d, 1H, *J* = 7.5 Hz), 7.19-7.51 (m, 7H), 7.68 (s, 1H), 7.92-7.94 (m, 1H), 7.96 (s, 1H), 8.86 (s, 1H, exch. D_2O), 8.97 (s, 1H, exch. D_2O); NH not detectable. IR (KBr film, cm^{-1}) 3292, 3063, 1642, 1591, 1554, 1226, 780. ESI-MS (M+H)$^+$ 438.0, 440.0, 442.0; elemental analysis: calcd for $C_{22}H_{17}Cl_2N_5O$: C 60.29, H 3.91, N 15.98; found: C 60.24, H 3.93, N 15.62.

***N*-(3-Chlorophenyl)-*N*^{1}-[3-(5-(4-chlorophenyl)-4*H*-1,2,4-triazol-3-yl) methyl]phenylurea (24):** Column chromatography using ethyl acetate/*n*-hexane 1:1 as eluents gave 50mg of a white powder, yield (53%); mp: 203-205 °C. ^{1}H-NMR (300 MHz, methanol-d_4): δ [ppm]= 4.16 (s, 2H), 6.98-7.03 (m, 2H), 7.20-7.39 (m, 7H), 7.46 (d, 2H, *J* = 9.0 Hz), 7.62 (s, 1H), 7.96 (s, 1H, exch. D_2O), 7.99 (s, 1H, exch. D_2O); NH not detectable. IR (KBr film, cm^{-1}) 3276, 1651, 1591, 1556, 1222. ESI-MS (M-H)$^-$ 435.8, 437.8, 439.9; elemental analysis: calcd for $C_{22}H_{17}Cl_2N_5O$: C 60.29, H 3.91, N 15.98;found: C 59.98, H 4.01, N 15.71.

Antifungal activity evaluation

Strains *C. albicans* 475/15, *C. albicans* 10/15 and *C. krusei* H1/16 were isolated from oral cavities of patients at Ear, nose and throat clinic, Clinical hospital center, Zvezdana Serbia. They were identified on CHROMagar plates and maintained on Sabouraud Dextrose Agar. Reference strains *C. albicans* ATCC 10231 and *A. fumigates* ATCC 9197 were also used in this study. Minimal inhibitory (MIC) and minimal fungicidal (MFC) concentrations were determined according to Smiljkovic *et al*.[36] The MIC values were considered as the lowest concentrations without microscopically observed fungal growth after 24 h incubation at 37 °C for *Candida* strains and 72 h at 28 °C for *A. fumigatus*. Following the serial subcultivations of 10 µL into microtiter plates containing 100 µL of broth per well, as well as subsequent incubation at 37 °C for 24 h (*Candida* sp.) and 28°C for 72 h (*A. fumigatus*), the lowest concentrations with no visible growth were defined as the MFC values, indicating 99.5 % killing of the original inoculum.

Molecular descriptors calculations and Quantitative structure-activity relation (QSAR) modeling

The 29 tested triazole derivatives (**Table 1**) were sketched in 2D form and then were converted in 3D form and prepared in pH 7.0 ± 0.5 using LigPrep[37] program of MAESTRO software.[38] The cheminformatics program Canvas[39] was carried out to build a pool of molecular descriptors, including physicochemical, constitutional and topological descriptors. Totally, 100 descriptors were calculated and were utilized as the dependent parameters of the QSAR modeling. The observed MIC and MFC values (**Table 2**) indicated that the examined derivatives possessed higher antifungal activity against *Aspergillus fumigatus* ATCC9197 strain, in comparison to the other 4 strains. Therefore, the MIC values of this strain were selected as the dependent variable for the QSAR models development. In the present study, the Multiple Linear Regression (MLR) analysis was implemented, using Canvas program,[36] to quantify the relationship between linear combinations of the dependent variable MIC and the statistical significance molecular descriptors. The validation of the derived QSAR models is necessary in order to identify and evaluate their predictive ability. The synthesized compounds, comprising the dataset of the present study, are divided randomly into training set (70%) responsible for model construction and test set (30%) responsible for model validation. For the assessment of statistical quality of all QSAR derived models several validation parameters were employed. Especially, in QSAR model summary, N is the number of compounds, R^2 is the squared correlation coefficient (goodness of fit), Q^2 is the predictability coefficient, F-value is

the Fischer ration between the variances of calculated and observed activities and RMSE is the root mean square error.

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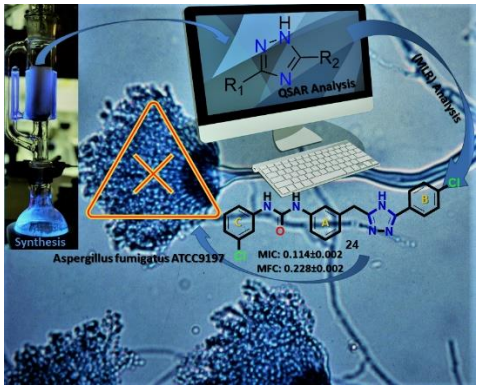

Triazole, the magic ring: The present work has extended the structure‑activity relationships of substituted 1,2,4-triazole derivatives in determining *in vitro* inhibitory and fungicidal activity. Our studies demonstrate that the antifungal activity of this class of compounds is greatly dependent upon the substitution on either the aromatic ring A or C. Multiple linear regression (MLR) analysis revealed three critical descriptors that contribute on the activity.