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Study of a Selected Series of 3- and 4-Arylcoumarins as Antifungal Agents against Dermatophytic Fungi: *T. rubrum* and *T. mentagrophytes*

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The main etiological agents in dermatophytosis of human skin and nails are Trichophyton, in particular *Trichophyton rubrum* (*T. rubrum*) and *Trichophyton mentagrophytes* (*T. mentagrophytes*). A new series of twenty-three 3- and 4-arylcoumarins was synthesized and the antifungal activities against clinical isolates of *T. rubrum* and *T. mentagrophytes* were evaluated. Sixteen out of twenty-three molecules exhibited antifungal activity against one or both fungi strains. In some cases, the activity against *T. rubrum* has been comparable to fluconazole, one of the standards, being 8-methoxy-3-(4′-nitrophenyl) coumarin (**16**) the best compound within this series (minimum inhibitory concentration, MIC = 6.25 μg/mL). The preliminary structure-activity relationship study showed that the antifungal activity depends on the position and nature of the substitution patterns. The cytotoxicity of eleven compounds on D-384 (astrocytoma), A-549 (lung cancer) and RKO (colorectal cancer) cell lines was also performed. With the aim of deeply understand the potential of these molecules as hits to develop new drugs, the theoretical absorption, distribution, metabolism and excretion (ADME) properties of the active compounds were calculated.

Introduction

The search and development of new compounds with antifungal potential are of great importance, due to the increase of fungal infections that affect between 20–25% of the world population.[1] The incidence of this affections represents a public health problem with a significant impact on medical care costs, as well as the appearance of primary and secondary antifungal resistance, which is attributed to multiple causes, from the immunodeficiency of patients, inadequate use of drugs, low bioavailability of antifungals or drug interactions.[2,3] The limitations of therapy are currently an increasingly worrying problem. Therefore, there is an urgent need to expand the therapeutic options, trying to reduce adverse effects.

In the period 1981–2010, twenty molecules with antifungal activity have been developed. However, only anidulafungin (a semisynthetic echinocandin) has been approved for its use in the United States of America, in 2006.[4] Then, in 2015 Food and Drug Administration (FDA) and the European Medicines Agency (EMA) approved cresemba® (isavuconazonium sulfate).[5] The latest synthetic antifungal drug approved by FDA is the recently approved brexafemme® (ibrexafungerp), a Scynexis antifungal drug for treating vaginal yeast infections. This drug represents the first new antifungal drug class in twenty years.[6]

According to Wei *et al*, active antifungal compounds could be classified in nine categories, according to their chemical structures: coumarins, lignans, terpenoids and sterol, saponins, quinones, alkaloids, flavonoids, phenyl derivatives and others.[7] Based on this classification, coumarins containing extra phenyl rings may be interesting scaffolds to explore.

Coumarins belong to a very broad group of phenolic compounds with the basic structure of C6–C3 units.[8] Coumarins and their derivatives have long been considered as bioactive agents, and due to the great diversity of molecules with a coumarin scaffold, many pharmacological properties are

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attributed to this bicyclic structure.[9] Amongst them, antibacterial and antifungal activities have been reported.[10,11,12]

Dermatophytosis and onychomycosis are an important health problem because they are related to local pain and paresthesia, limiting several daily activities.[13] There is a described cohort of patients presenting a chronic widespread dermatophytosis related to the presence of *Trichophyton rubrum* (*T. rubrum*), and this disease is usually recurrent and hard to control.[14] The main etiological agents of human skin and nails dermatophytosis are in fact Trichophyton, in particular *T. rubrum* and *Trichophyton mentagrophytes* (*T. mentagrophytes*) (Figure 1).[15] In addition, there is a described evidence from the seventies in which *T. mentagrophytes*, incubated with a medium enriched in coumarin, drastically reduced the growth rate.[16]

Our research group has been working on the development of small molecules with potential biological activity against different therapeutic targets. Among them, the potential of some coumarin derivatives against strains of bacteria and fungi has been studied.[17,18,19,20] Based on previous results from our research group and other groups,[21] a family of differently substituted 3- and 4-arylcoumarins has been designed to test their potential as antifungal agents against *T. rubrum* and *T. mentagrophytes*. Their cytotoxicity against three cell lines was also evaluated, and their theoretical properties as drug-like compounds were also calculated.

Results and discussion

Twenty-three coumarins have been synthetized to explore how different chemical features on both 3- and 4-arylcoumarin scaffolds may affect the antifungal activity. Different substituents from the different quadrants of the Craig diagram (OCH_2COCH_3, $OCOCH_3$, OCH_2CH_3, OCH_3, CH_3, NH_2, NO_2, OH, Br and Cl) were introduced on the molecules, and structure-activity relationships were established. The synthetic procedures for obtaining the studied coumarin derivatives are represented in Scheme 1.

Acetoxy-3-arylcoumarins (**1**–**6**) were synthetized following the Perkin-Oglialoro protocol (Scheme 1). This methodology allows to, in a single step, acetoxylate free hydroxyl groups at the phenyl ring, and at the same time close the pyrone ring from the coumarin scaffold. Acetoxy-3-arylcoumarins were synthesized under anhydrous conditions, in the presence of anhydrous potassium acetate (CH_3CO_2K) and acetic anhydride (Ac_2O), the necessary hydroxysalicylaldehyde and the corresponding arylacetic acid, in reflux for sixteen hours. The product was purified by recrystallization in ethanol (EtOH). The appearance of the H-4 in the proton nuclear magnetic resonance (^{1}H NMR) of the final product corroborates the success of the reaction. The chemical shift of the H-4 is between 7.5 and 8.5 ppm.

Ether derivatives **7** and **8** were synthetized following the Williamson reaction protocol (Scheme 1). These ethers were obtained preparing a suspension of anhydrous potassium carbonate (K_2CO_3) and the corresponding hydroxycoumarin, in anhydrous acetone, adding chloroketone, at room temperature for sixteen hours. The final product was purified by flash column (hexane/ethyl acetate). The appearance of the methylene (CH_2) protons in the ^{1}H NMR of the final product corroborates the success of the reaction. The chemical shift of the CH_2 is around 4.6 ppm.

3-Arylcoumrins **9**–**18** were synthetized following a Perkin protocol (Scheme 1). 2-Hydroxybenzaldehyde and the corresponding arylacetic acid are mixed in the presence of dimethyl sulfoxide (DMSO) and the dehydrating agent *N,N′*-dicyclohexylcarbodiimide (DCC) at 110 °C for twenty-four hours. The final product was purified by flash column (hexane/ethyl acetate). The appearance of the H-4 in the ^{1}H NMR of the final product corroborates the success of the reaction. The chemical shift of the H-4 is between 7.5 and 8.5 ppm.

Finally, 4-arylcoumarins were synthetized following a direct coupling under Suzuki conditions (Scheme 1). For this reaction, the select halide was the 4-chloro-3-nitrocoumarin, mixed with the corresponding arylboronic acid, in a mixture one-to-one of dimethylformamide and water, with sodium carbonate (Na_2CO_3) and the catalyst *N,N′*-bis(salicylidene)-ethylenediamine-palladium (salen-Pd), heated to 110 °C for 120–180 minutes. The product obtained was purified by flash column (hexane/ethyl acetate) to give the desired 4-arylcoumarin. The symmetrical palladium(II) complex was obtained from the reaction of the Salen ligand with palladium acetate, for 20 hours, at room temperature. The appearance of the new aromatic signals in the ^{1}H NMR of the final product corrobo-

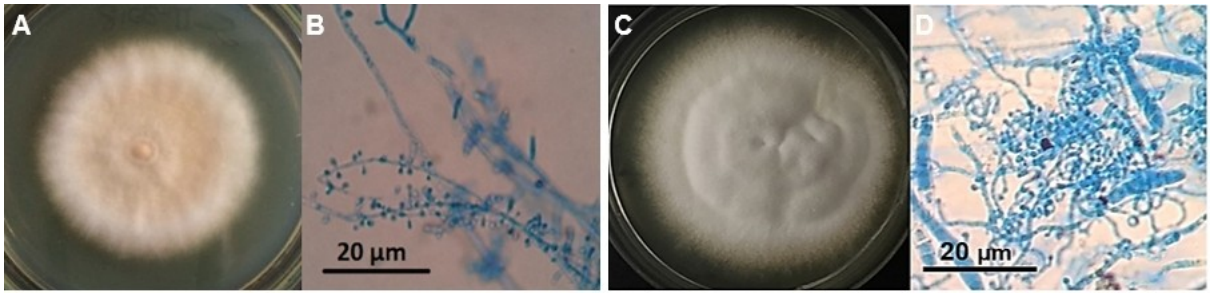
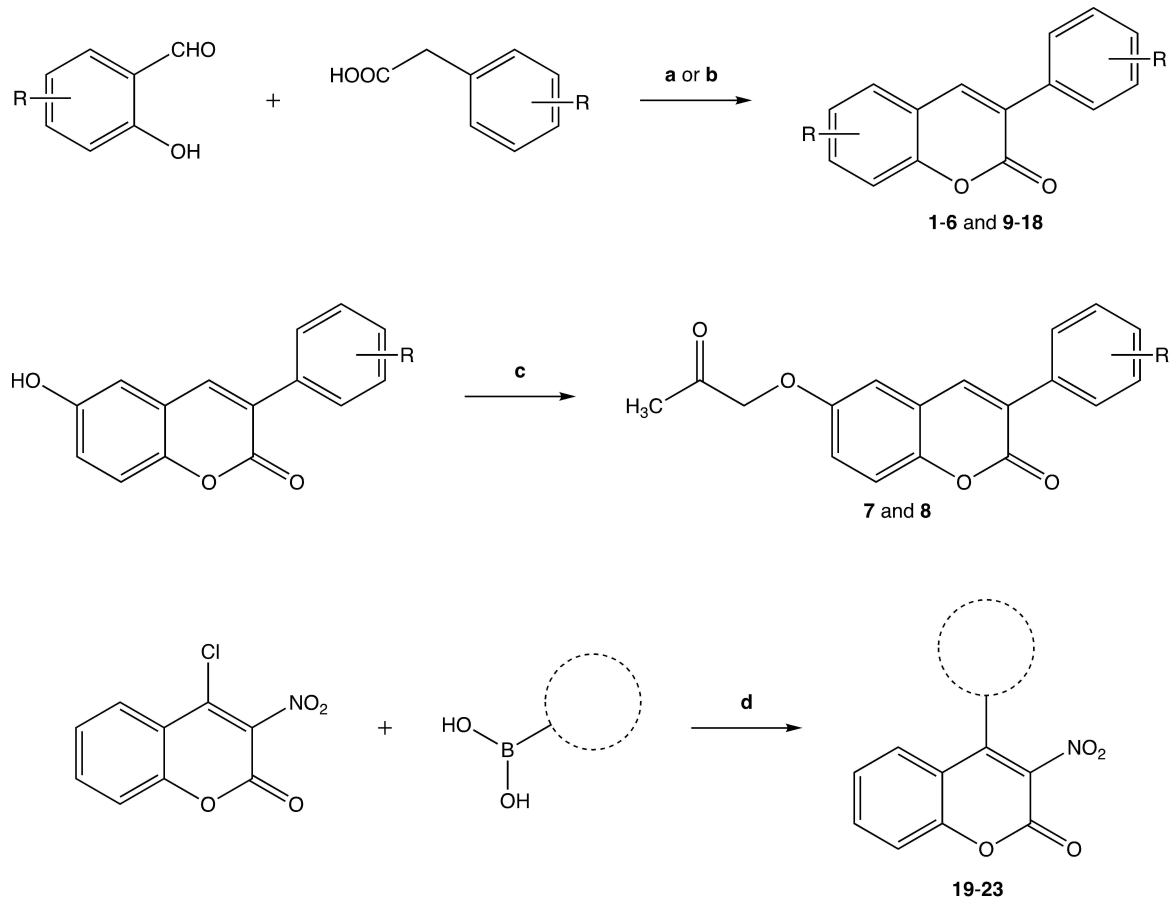


Figure 1. *Trichophyton* genus: *T. rubrum*: A) colony in Sabouraud dextrose agar and B) Microscopy with lactophenol blue solution: tear-shaped hyphae and microconidia. *T. mentagrophytes*: C) colony in Sabouraud dextrose agar and D) Microscopy with lactophenol blue solution: Spiral and thrush hyphae; macroconidia and microconidia found in grape-like clusters.



Scheme 1. Scheme for the synthesis of coumarin derivatives. Reagents and conditions: a) CH_3CO_2K, Ac_2O, reflux, 16 h. b) DCC, DMSO, 110 °C, 24 h. c) K_2CO_3, Me_2CO, $ClCH_2COMe$, r.t., 16 h. d) Na_2CO_3, palladium complex (0.5 % in mole), DMF/H_2O (1 : 1), 110 °C, 120–180 min.

rates the success of the reaction. The chemical shifts of the aromatic protons are between 7.0 and 8.0 ppm.

Using these four versatile methodologies, twenty-three new compounds were prepared and characterized. All the details for the synthetic methodologies are included in the Supporting Information.

The antifungal activity of the twenty-three studied compounds was evaluated employing a broth microdilution test, using two synthetic triazoles as reference controls: fluconazole and voriconazole. Minimum inhibitory concentration (MIC) values were calculated for both *T. rubrum* and *T. mentagrophytes*. The results of the antifungal activity of all the synthesized coumarin derivatives are presented in Table 1.

From the series of 3-arylcoumarins, the most active compound against *T. rubrum* was the 8-methoxy-3-(4′-nitrophenyl)coumarin (**16**), with a MIC of 6.25 μg/mL. The activity of compound **16** is comparable to the reference drug fluconazole against *T. rubrum* (MIC = 1–4 μg/mL). Substituents at *para* position of the 3-phenyl ring and position 8 of the coumarin scaffold seems to be interesting for the desired activity.

From the series of acetoxy-3-arylcoumarins, the compounds with better activity against *T. rubrum* were compounds **3** (MIC = 12.5 μg/mL), **4** (MIC = 25 μg/mL) and **6** (MIC = 12.5 μg/mL). For *T. mentagrophytes*, compound **6** was the molecule with better activity (MIC = 25 μg/mL). Analyzing their structures, the three compounds maintained the acetoxy group at position 6 of the coumarin scaffold, having a bromine or an amino group at *para* or *meta* positions of the 3-phenyl ring. Chemically, the bromine is an electron withdrawing atom, weakly deactivating, and the amine is an electron donating group, strongly activating.

From the 4-aryl-3-nitrocoumarins series, compounds **19** (MIC = 12.5 μg/mL), **20** (MIC = 25 μg/mL), **21** (MIC = 25 μg/mL) and **22** (MIC = 25 μg/mL) presented the best activities against *T. rubrum*. Against *T. mentagrophytes*, all of the compounds from this series presented MICs higher than 50 μg/mL, proving to be selective against *T. rubrum*. From this series, the presence of the phenyl ring proved to be more interesting than the analog 2-chloropyridine. Regarding the position, both positions *meta* and *para* seems to be acceptable for the activity. Regarding the nature of the substituents, chlorine, methyl and methoxy seems to be acceptable. However, the non-substituted phenyl derivative (compound **19**) proved to be the best one within the series.

Of the compounds tested, eight have promising activities against *T. rubrum*, with an effective concentration between 6.25–25 μg/mL (Table 1). For *T. mentagrophytes*, only one compound presented effective activity: 6-Acetoxy-3-(4′-amino-

Table 1. Antifungal activity of 3- and 4-arylcoumarin derivatives against *T. rubrum* and *T. mentagrophytes*.

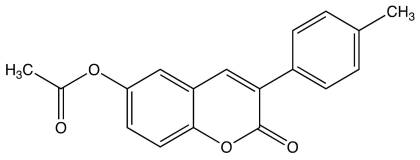
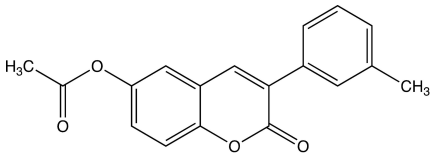
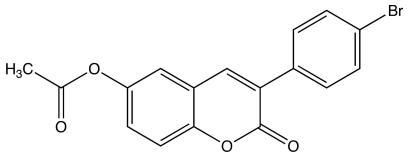
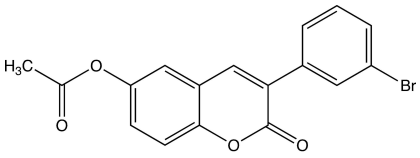
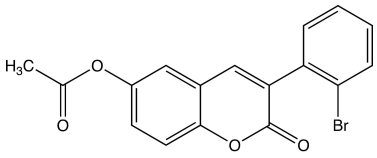
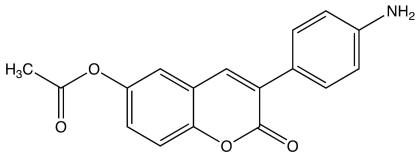
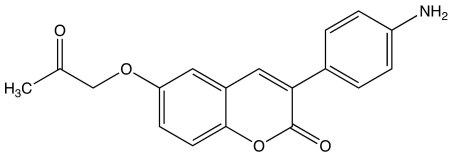
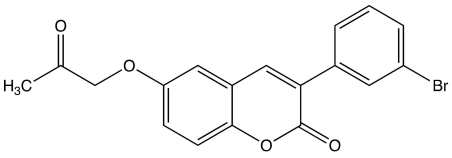
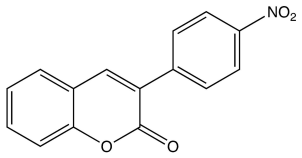
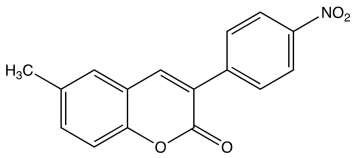
Compound	Chemical structure	*T. rubrum* MIC (μg/mL)	*T. mentagrophyte* MIC (μg/mL)
1		50	> 50 *
2		83.33	50
3		12.5	62.5
4		25	62.5
5		> 50 *	> 50 *
6		12.5	25
7		41.66	50
8		> 50 *	> 50 *
9		50	> 50 *
10		50	> 50 *

Table 1. continued

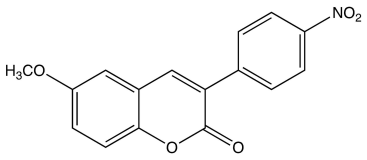
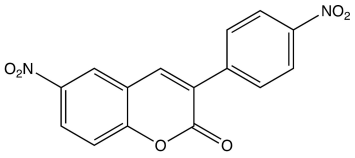
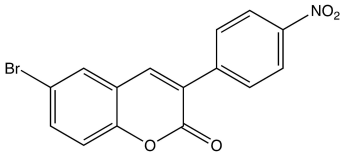
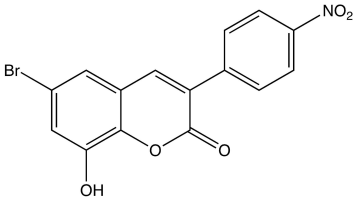
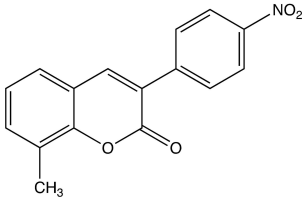
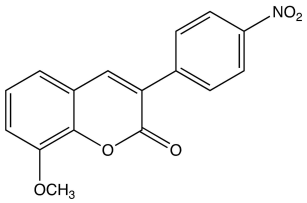
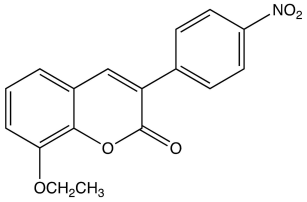
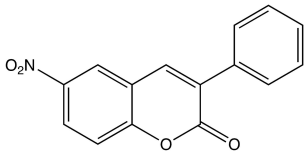
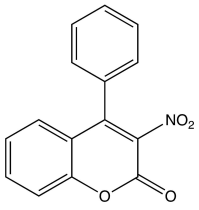
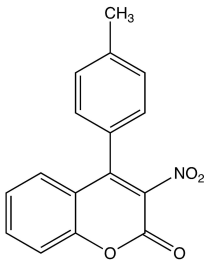
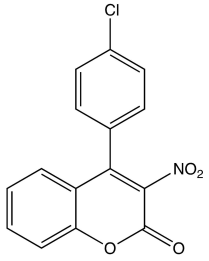
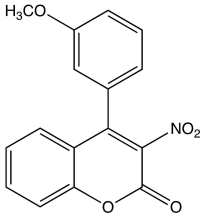
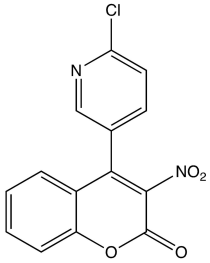
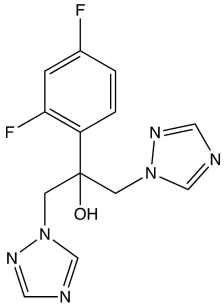
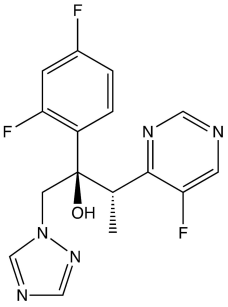
Compound	Chemical structure	*T. rubrum* MIC (μg/mL)	*T. mentagrophyte* MIC (μg/mL)
11		50	> 50 *
12		50	> 50 *
13		41.66	62.5
14		> 50 *	> 50 *
15		> 50 *	> 50 *
16		6.25	62.5
17		> 50 *	> 50 *
18		> 50 *	> 50 *
19		12.5	125

Table 1. continued

Compound	Chemical structure	*T. rubrum* MIC (μg/mL)	*T. mentagrophyte* MIC (μg/mL)
20		25	125
21		25	62.5
22		25	62.5
23		> 50 *	> 50 *
Fluconazole		1–4	13–20
Voriconazole		0.0078–0.0150	0.0315–0.0625

* 50 μg/mL – higher concentration studied for these compounds (at higher concentrations the solutions presented some turbidity or precipitation).

phenyl)coumarin (**6**, MIC = 25 μg/mL). With a MIC of 50 μg/mL, 6-acetoxy-3-(3′-methylphenyl)coumarin (**2**) and 3-(4′-aminophenyl)-6-(2-oxopropoxy)coumarin (**7**) may also be the inspiration for further studies. As observed, most of the studied compounds are selective against the main etiological agent of human skin and nails dermatophytosis: *T. rubrum*. Because the mechanism of action of these compounds is not known, it is too early to conclusively establish the reasons for this selectivity. We can only speculate based on the structural evidence. The increase of the functional group at position 6 of the coumarin scaffold and specially the presence of an amine group at *para* position of the 3-phenyl ring seems to be interesting when looking for agents with activity against *T. mentagrophytes*.

6-Methoxy-3-(4′-nitrophenyl)coumarin (**11**) and 6-nitro-3-(4′-nitrophenyl)coumarin (**12**) were previously studied for their potential as antibacterial agents, against clinical isolates of *Staphylococcus aureus* (Gram-positive) and *Escherichia coli* (Gram-negative).[19] Compound **12** proved to be active against *S. aureus*, presenting a MIC of 128 μg/mL.

Comparing our results with some previous works describing the antifungal potential of coumarins, for example the study with coumarins reported by Mercer *et al.*, the antifungal activity of our derivatives is remarkable.[22] In that work, the best derivatives from a synthetic group of simple coumarins (esculin, esculin, daphnetine, fraxin and fraxetine) presented MICs between 11.13–356.28 μg/mL. Similar MIC concentrations were obtained by Navarro-García *et al.* for daphnoretin, umbelliferone and scopoletin against different fungi, among those *T. rubrum* and *T. mentagrophytes*, for which scopoletin exhibited a MIC = 12.5 μg/mL.[23]

Eleven selected coumarins, among which are included eight with the best antifungal activities (MICs < 25 μg/mL), were evaluated against tumor cells, obtaining the results expressed in Figure 2. The percentages of inhibition of the proliferation of the D-384 (astrocytoma), A-549 (lung cancer) and RKO (colorectal cancer) cell lines, incubated with 100 μM of each derivative, are represented in Figure 2.

As observed, most of the compounds do not have any inhibitory effect on cell proliferation. Compounds **19**, **21** and **22** presented a slightly decrease in the cell growth for the RKO cell line in the case of the compounds **19** and **21**, and for D-384 cell line in the case of compound **22**.

In order to assess the possible *in vivo* activity of the studied compounds, theoretical physicochemical properties of the 3- and 4-arylcoumarins **1**–**23** were calculated. These parameters are good indicators of the capacity to cross cellular membranes and therefore of their ADME (absorption, distribution, metabolism and excretion) properties. Molinspiration cheminformatics software was used to calculate the octanol/water partition coefficient (LogP), the polar surface area (TPSA), the number of atoms and molecular weight (MW), the number of H-bond acceptors (n ON) and H-bond donors (n OHNH), as well as the volume (V) and the number of rotatable links (n rotb).[24] All the results, together with the prediction of the violations of Lipinski rules (n viol), are included in Table 2.

Analyzing the data, theoretically all the 3- and 4-arylcoumarins **1**–**23** possess the desirable physicochemical properties for a good bioavailability, and none of the compounds violate the Lipinski rule of five (Table 2). 8-Methoxy-3-(4′-nitrophenyl) coumarin (**16**) has a high value of LogP, combined with a low TPSA, desirable characteristics to develop a new drug.

Conclusions

This report describes the activity of twenty-three compounds against two important agents responsible for dermatophytosis: *T. rubrum* and *T. mentagrophytes*. 8-Methoxy-3-(4′-nitrophenyl) coumarin (**16**) presents the best MIC against *T. rubrum* within the studied series (6.25 μg/mL), and 6-acetoxy-3-(4′-aminophenyl)coumarin (**6**) presents the best MIC against *T. mentagrophytes* (25 μg/mL). The compounds proved to be non-

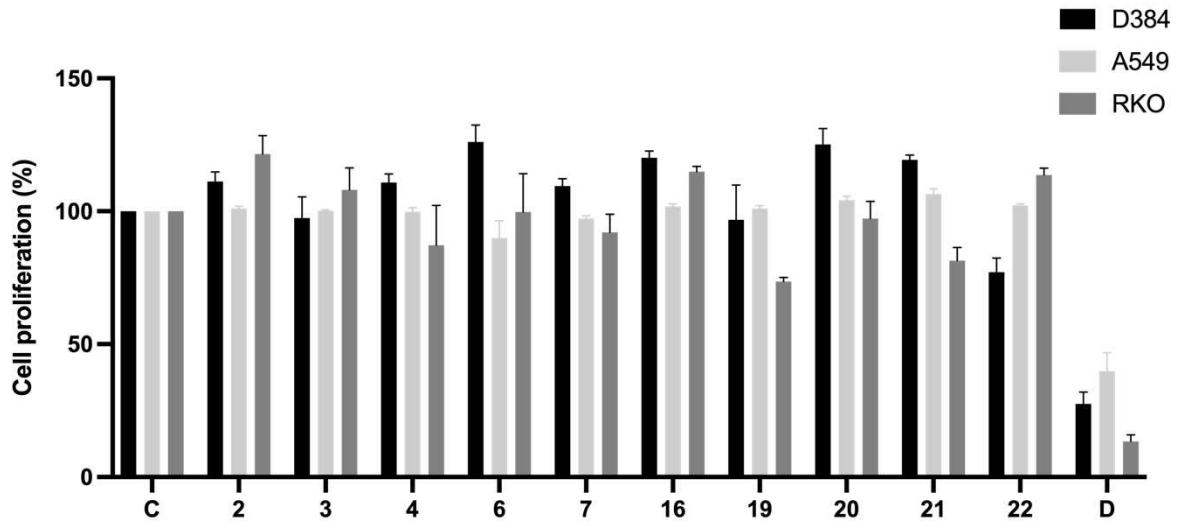


Figure 2. Cell proliferative assay (MTS). Cell lines D-384, A-549 and RKO were exposed to 100 μM of each derivative. Doxorubicin was used as reference drug. C = control. D = doxorubicin at 0.5 μg/mL.

Table 2. Molecular properties of 3- and 4-arylcoumarins **1**–**23** calculated using the Molinspiration software.

Compound	LogP[a]	TPSA[b]	*n* atoms	MW (g/mol)[c]	*n* ON[d]	*n* OHNH[e]	*n* rotb[f]	V (Å^3)[g]	*n* viol[h]
1	3.71	56.52	22	294.31	4	0	3	261.08	0
2	3.69	56.52	22	294.31	4	0	3	261.08	0
3	4.07	56.52	22	359.18	4	0	3	262.41	0
4	4.07	56.52	22	359.18	4	0	3	262.41	0
5	4.07	56.52	22	359.18	4	0	3	262.41	0
6	2.34	82.54	22	295.29	5	2	3	255.81	0
7	2.39	82.54	23	309.32	5	2	4	272.62	0
8	4.10	56.52	23	373.20	4	0	4	279.21	0
9	3.70	76.03	20	267.24	5	0	2	223.33	0
10	4.12	76.03	21	282.27	5	0	2	239.89	0
11	3.73	85.27	22	297.27	6	0	3	248.88	0
12	3.63	121.86	23	312.24	8	0	3	246.66	0
13	4.48	76.03	21	346.14	5	0	2	241.22	0
14	4.19	96.26	22	362.13	6	1	0	249.23	0
15	4.12	76.03	21	282.27	5	0	2	239.89	0
16	3.73	85.27	22	297.27	6	0	3	248.88	0
17	4.08	85.27	23	311.29	6	0	4	265.68	0
18	3.70	76.03	20	267.24	5	0	2	223.33	0
19	3.62	76.03	20	267.24	5	0	2	223.33	0
20	4.07	76.03	21	281.27	5	0	2	239.89	0
21	4.30	76.03	21	301.69	5	0	2	236.87	0
22	3.66	85.27	22	297.27	6	0	3	248.88	0
23	3.57	88.93	21	302.67	6	0	2	232.71	0

[a] LogP – octanol/water partition coefficient;[b] TPSA – polar surface area;[c] MW – number of atoms and molecular weight;[d] *n* ON – number of H-bond acceptors; [e] *n* OHNH – H-bond donors;[f] V – volume;[g] *n* rotb – number of rotatable links;[h] *n* viol – number of violations of Lipinski rules.

cytotoxic for D-384 (astrocytoma), A-549 (lung cancer) and RKO (colorectal cancer) cell lines, at concentrations of 100 μM. Finally, all the compounds present adequate theoretical ADME properties to be drug-like molecules. This initial screening may open new doors for the development of an antifungal agent based on the coumarin scaffold.

Supporting Information summary

All the general methodologies for the synthesis of the compounds, the characterization of the new compounds, and the methodologies for the antifungal activity and cytotoxicity are detailed in the supporting information.

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Conflict of Interest

The authors declare no conflict of interest.

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