NOVEL SPIRO[INDOLINE-3,2′THIAZOLO[5,4-*e*]PYRIMIDO[1,2-*a*]PYRIMIDINE] DERIVATIVES AS POSSIBLE ANTI-DERMATOPHYTIC & ANTI-CANDIDIASIS AGENT

G. Sharma[1], R. Sharma[2]*

[1]Department of Chemistry, MPS International, Jaipur, India
[2]Department of Microbiology, Mahatma Gandhi University of Medical Science & Technology, Jaipur, India; *e-mail: richa.phd.15@gmail.com

A novel series of 5′-benzylidene-3′-phenylspiro[indoline-3,2′-thiazolidine]-2,4′(1*H*)-diones **6a-d** and spiro[indoline-3,2′-thiazolo[5,4-*e*]pyrimido[1,2-*a*]pyrimidin]-2(1*H*)-one **9a-d** derivatives have been synthesized. All the newly synthesized compounds were evaluated for antifungal and anti-candidiasis activity by using Disc Diffusion and Modified Microdilution methods. The antimicrobial experiments have shown that the synthesized compounds demonstrated broad-spectrum antifungal activity *in vitro*. Among them, compounds **9a-9d** had stronger antifungal activity against *Trichophyton rubrum*, *Trichophyton mentagrophytes*, and *Candida albicans*; compounds **6a-d** also showed significant antifungal activity against selected fungal strains as compared to ketoconazole, the reference antifungal drug. The evaluation of antifungal activity against drug-resistant fungal variants showed that the designed compounds had significant antifungal activity against the tested variants. The combination of compounds (**6a-d**) and (**9a-d**) exhibited that the synthesized compounds had synergistic effects or additive effects. These results demonstrated that the synthesized compounds were putative chitin synthase inhibitors exhibiting broad spectrum antifungal activities. The present results indicate that novel spiro pyrimidine derivatives can be used as an active pharmaceutical ingredient for novel drug candidate for treatment of dermatophytosis and other fungal agents.

Key words: pyrimido-pyrimidine derivatives; dermatophytosis; fungal agents; combination

DOI: 10.18097/PBMC20247003180

INTRODUCTION

Emerging infectious diseases and the increasing number of multi-drug resistant microbial pathogens still make the treatment of infectious diseases an important and pressing global problem. Therefore, a substantial research for the discovery and synthesis of novel classes of antimicrobial agents is needed [1, 2]. It is reported that nearly a billion people have been affected by fungal infection ranging from superficial infections to potentially life-threatening invasive infections [3, 4]. In the face of the increasing number of population suffering HIV, tuberculosis, pneumonias, and cancer, the invasive fungal infection became the main cause of the mortality of these immunodeficiency or immunosuppressive patients (about 1.5 million deaths were reported annually); more than 80% of these deaths are occurring due to the invasive infections caused by *Candida*, *Aspergillus*, and *Cryptococcus* species [5]. There are only a few classes of systemic antifungal drugs used in clinical practice (azoles, polyenes and echinocandins) [6] and even the recent class (echinocandins) was discovered thirty years ago [7]. Furthermore, emergence of multidrug-resistant clinical fungal variants (against two or even three classes of antifungals) compromised the efficacy of current therapeutic methods [8, 9]. The scarcity of antifungal agents, coupled with the rapid spreading of drug resistance of fungi, highlights the urgent need for new drugs to cope with the increasingly serious problems of fungal infections.

Chitin, a polymer of β-(1,4)-N-acetyl-d-glucosamine (GlcNAc), is an essential polysaccharide of the fungal cell wall; it plays an important role in maintaining cell morphology and function. Chitin synthase (CHS) polymerizes GlcNAc into chitin from substrate UDP-GlcNAc. Inhibition of CHS interrupts chitin synthesis and leads to cell death.

Since CHS is absent in mammals inhibitors of this enzyme would not exhibit side-effects typical of pharmacological agents currently in clinical practice [10, 11], Furthermore, when the biosynthesis of β-(1,3)-glucan is inhibited by the antifungal echinocandins (semisynthetic lipopeptides), the fungal cells could survive due to increased formation of chitin, thus promoting the fungal resistance to echinocandins [12, 13]. Thus, besides the development of new antifungal drugs, inhibition of chitin synthesis would increase the sensitivity of the fungal cell to echinocandins during combined use of echinocandins with CHS inhibitors.

The aim of this study was to design and develop highly selective and efficacious antimicrobial agents of a novel series of pyrimido pyrimidine derivatives bearing different heterocyclic and aryl moieties. Prompted by the varied biological activities of pyrimido pyrimidine derivatives, we envisioned our approach towards the antimicrobial screening of a novel series of pyrimidine derivatives.

MATERIALS AND METHODS

Chemical Methods

All the chemical synthesis of 5′-benzylidene-3′-phenylspiro[indoline-3,2′-thiazolidine]-2,4′(1*H*)-diones **6a-d** and spiro[indoline-3,2′-thiazolo[5,4-*e*]pyrimido [1,2-*a*]pyrimidin]-2(1*H*)-one **9a-d** derivatives was carried as described in details in [14]. The scheme given below (Fig. 1) illustrates the main steps of the synthetic process. The purity of compounds was checked on thin layers of silica gel in various non-aqueous solvent systems, for example benzene:ethylacetate (9:1), benzene:dichloromethane (8:2). IR spectra (KBr) were recorded on a Magna FT IR-550 spectrophotometer and ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker DRX-300 using $CDCl_3$ at 300.15 and 75.46 respectively. Tetramethylsilane (TMS) was used as an internal reference. Mass spectrum of the representative compound was recorded on Kratos 50 mass spectrometer at 70 eV.

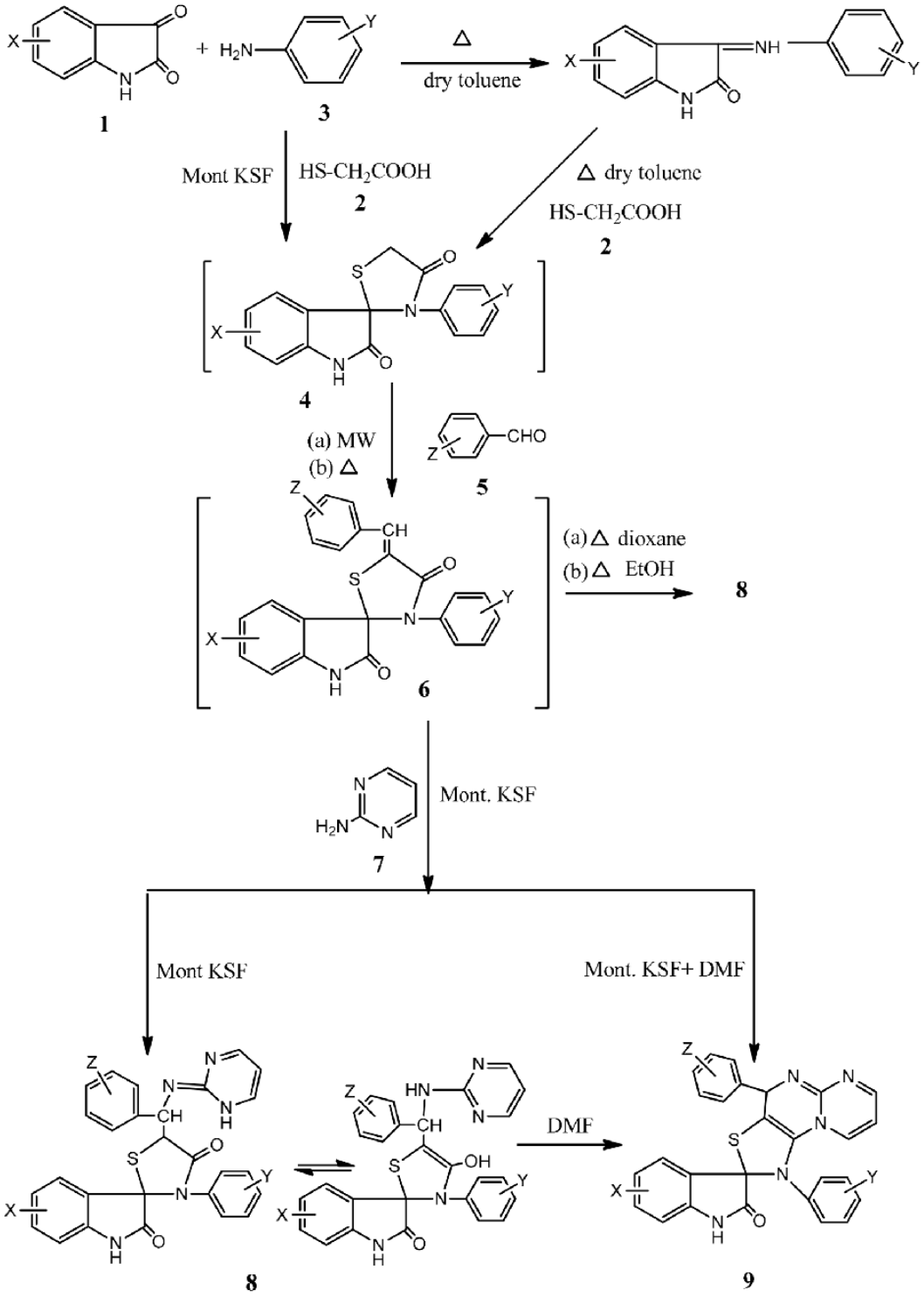

Figure 1. The scheme illustrating the main steps of the synthesis of desired compounds.

Biological Methods

(a) *In vitro* screening of the synthesized compounds using Disc Diffusion method. The synthesized compounds were screened for their antifungal activity against *Trichophyton rubrum*, *Trichophyton mentagrophytes*, and *Candida albicans* by the disc diffusion method [15]. Standard size Whatman no.1 filter paper discs, 6.0 mm in diameter, sterilized by dry heat at 140°C in an oven for one hour were used to determine the antifungal activity. SDA medium for disc diffusion test was prepared. After sterilization, it was poured into sterilized petriplates and allowed to solidify. A suspension that was just turbid by visual inspection was prepared by suspending in 0.9% NaCl solution and the homogeneous suspension was used for inoculation and test inoculum was maintained at $(1–5)\times10^6$ CFU/ml. The spore suspension of each of the fungi was prepared from 8 to 10-day-old cultures separately. The suspension was vortexed and 0.1 μl aliquots were spread over the respective agar medium plates. Sterilized filter paper discs were soaked in 50 mg/ml concentration of pure compounds. Similarly, two mixtures of compounds (one from **6a-6d** series and another one from **9a-9d** series) were also used in the same concentration (50 mg/ml) for comparison to the reference antifungal drug. The reference drug (Ketoconazole antibiotic) was used at the 50 mg/disc concentration impregnated in the filter-paper discs for evaluation of its antifungal activity. These discs were then placed over the plates preceded with respective microorganisms. The plates were incubated at 30°C for 48–72 h. Three replicates were kept in each case and average values were calculated. The diameter of the inhibition zones was measured in mm and the activity index was calculated on the basis of the size of the inhibition zone (IZ). The activity of compounds was evaluated using the following formula:

$$\textbf{Activity Index} = \frac{\text{Inhibition zone of Compound}}{\text{Inhibition zone of the reference drug}}.$$

Determination of Minimum Inhibitory Concentration by the Modified Microdilution Method [16]. The Minimum Inhibitory Concentrations (MIC) of a mixture of compounds against *T. rubrum*, *T. mentagrophytes,* and *C. albicans* were determined by the microdilution method with slight modification [16]. Sterilized Brain heart infusion semisolid agar media were poured into the sterilized culture tubes and allowed to solidify. Test inoculum was prepared in 0.9% NaCl solution, the suspension was vortexed properly. Different concentrations of the mixture of compounds were added in media containing culture tubes, afterwards a standard platinum loopful (~0.005 ml, Himedia, Flexiloop) of the innoculm suspension was inserted deep into each tube of medium containing a different concentration of compounds as well as compound free control. Different concentrations of compounds were added in media to find the lowest concentration at which no growth visually observed in media. The culture tubes were then incubated at 28°C for 48–72 h to determine the MIC. MIC was defined as the lowest concentration that did not yield visual growth after the incubation period. All experiments was performed in triplicates.

RESULTS AND DISCUSSION

There is a clear need in the development of new and effective antifungal agents, firstly, because of a limited repertoire of antifungal drugs and, secondly, emergence of fungal resistance to known antifungal agents. In this context, significant efforts are being undertaken to inhibit specific fungal enzymes involved in different biochemical pathways for the development of antifungal drugs. On the basis of previous published paper [14] a series of 5′-benzylidene-3′-phenylspiro [indoline-3,2′-thiazolidine]-2,4′(1*H*)-diones **6a-d** and spiro[indoline-3,2′-thiazolo[5,4-*e*]pyrimido[1,2-*a*] pyrimidin]-2(1*H*)-one **9a-d** derivatives have been synthesized (Table 1). In the present study, these compounds were screened for antidermatophytic and anti-candidiasis activity for the treatment of fungal infections.

Screening of compounds (Spiro **6a-d** and **9a-d** derivatives) using the disc diffusion and MIC (minimum inhibitory concentration) method against *T. rubrum*, *T. mentagrophytes*, and *C. albicans*. *T. rubrum* and *T. mentagrophytes* are known to be the main etiological agent of dermatophytosis and to date no antidermatophytic activity of novel series of 5′-benzylidene-3′-phenylspiro[indoline-3,2′-

Table 1. Synthesis of 5′-benzylidene-3′-phenylspiro[indoline-3,2′-thiazolidine]-2,4′(1*H*)-diones **6a-d** and spiro[indoline-3,2′-thiazolo[5,4-e]pyrimido[1,2-a]pyrimidin]-2(1H)-one **9a-d** derivatives [14]

Compound	X	Y	Z	Time (min)	Yield (%)	Temp (°C)
6a	H	4-Cl	4-$N(CH_3)_2$	6–8	88	243–245
6b	5-Br	4-CH_3	4-OCH_3	6–8	92	254–256
6c	5-CH_3	4-Cl	4-$N(CH_3)_2$	6–8	89	136–138
6d	H	4-F	4-$N(CH_3)_2$	6–8	87	183–185
9a	H	4-Cl	4-$N(CH_3)_2$	7–8	88	140–145
9b	5-Br	4-CH_3	4-OCH_3	7–8	89	213–215
9c	5-CH_3	4-Cl	4-$N(CH_3)_2$	7–8	83	203–205
9d	H	4-F	4-$N(CH_3)_2$	7–8	84	279–281

thiazolidine]-2,4′(1*H*)-diones **6a-d** and spiro[indoline-3,2′-thiazolo[5,4-*e*]pyrimido[1,2-*a*]pyrimidin]-2(1*H*)-one **9a-d** derivatives have been reported. This explains why the antimycotic studies have been performed using *T. rubrum*, *T. mentagrophytes*, and *C. albicans*. The results obtained showed the significant antifungal activity of compounds used alone and in combinations. Table 2 shows the results of the present work on the antifungal activity of compounds against *T. rubrum*, *T. mentagrophytes*, and *C. albicans* studied by two different methods. Most of the synthesized compounds exhibited excellent to good inhibition activities against all the fungal strains. In the present study, compound **9b** showed excellent antifungal activity against *T. rubrum*; other compounds **9c**, **9d**, **6a**, **6b**, **6d**, and **6c** were somewhat less active. Compound **9b** exhibited more potent activity than ketoconazole against *T. rubrum***,** *T. mentagrophytes*, and *C. albicans*. Other compounds were also more active than the reference drug and their inhibitory activity was comparable to the most potent compound (**9b**).

Table 3 shows results of evaluation of syngeristic and additive inhibitory activity of mixtures of compounds from **6a** to **6d** and from **9a** to **9d** (Fig. 2). These experiments were performed using *T. rubrum*, *T. mentagrophytes*, and *C. albicans* and compared with single compounds and the reference drug, ketokonazole. The mixtures of compounds showed excellent and synergistic antimycotic activity as compared to single compounds and the reference drug. The diameters of the inhibition zone (IZ) obtained from the mixture of compounds (**6a** to **6d**) at the total concentration 50 μg/ml were 86 mm, 88 mm, and 89 mm against *T. rubrum*, *T. mentagrophytes*, and *C. albicans*, respectively (Table 3). The results of determination of the MIC value have shown that the mixtures of compounds (**6a-d**) and (**9a-d**) exhibited inhibitory action against *T. rubrum* at the concentrations of 0.07 mg/ml to 0.09 mg/ml (Table 4). At 0.07 mg/ml, no growth of *T. rubrum* was observed after 6 days of incubation at 28°C. Similarly, MIC values of the mixture of compounds (**6a-d**) against

Table 2. Antifungal activity of synthesized novel spiro[indoline-3,2′-thiazolo[5,4-*e*]pyrimido[1,2-*a*]pyrimidine] derivatives against *T. rubrum*, *T. mentagrophytes*, and *C. albicans*

Compound	IZ of compounds (50 mg/ml) in mm		
	T. rubrum	*T. mentagrophytes*	*C. albicans*
6a	77	75	78
6b	75	74	72
6c	74	76	78
6d	73	72	76
9a	75	75	79
9b	85	78	75
9c	80	74	74
9d	76	82	85
Ketoconazole	48	45	40

Table 3. Antifungal activity of mixture of compounds (5′-benzylidene-3′-phenylspiro[indoline-3,2′-thiazolidine]-2,4′(1*H*)-diones **6a-d** and spiro[indoline-3,2′-thiazolo[5,4-*e*]pyrimido[1,2-*a*]pyrimidin]-2(1*H*)-one **9a-d**) derivatives against *T. rubrum*, *T. mentagrophytes*, and *C. albicans*

Compounds	**Test strain**	**IZ of mixture of compounds (50 mg/ml)**	**IZ of Ketoconazole (50 mg/ml)**	**AI**
Mixture of compounds (**6a-d**)	*T. rubrum*	86 mm	48 mm	1.79
	T. mentagrophytes	88 mm	45 mm	1.95
	C. albicans	89 mm	40 mm	2.22
Mixture of compounds (**9a-d**)	*T. rubrum*	84 mm	48 mm	1.75
	T. mentagrophytes	82 mm	45 mm	1.82
	C. albicans	87 mm	40 mm	2.17

Here, IZ = Inhibition zone (in mm) including the diameter of disc (6 mm), AI (Activity index).

Table 4. MIC of Mixture of compounds (5′-benzylidene-3′-phenylspiro[indoline-3,2′-thiazolidine]-2,4′(1*H*)-diones **6a-d** and spiro[indoline-3,2′-thiazolo[5,4-*e*]pyrimido[1,2-*a*]pyrimidin]-2(1*H*)-one) **9a-d**) derivatives against *T. rubrum*, *T. mentagrophytes*, and *C. albicans*

Mixture of Compounds	**Test Strain**	**MIC**
6a-d	*T. rubrum*	0.07 mg/ml
	T. mentagrophytes	0.08 mg/ml
	C. albicans	0.09 mg/ml
9a-d	*T. rubrum*	0.05 mg/ml
	T. mentagrophytes	0.04 mg/ml
	C. albicans	0.05 mg/ml

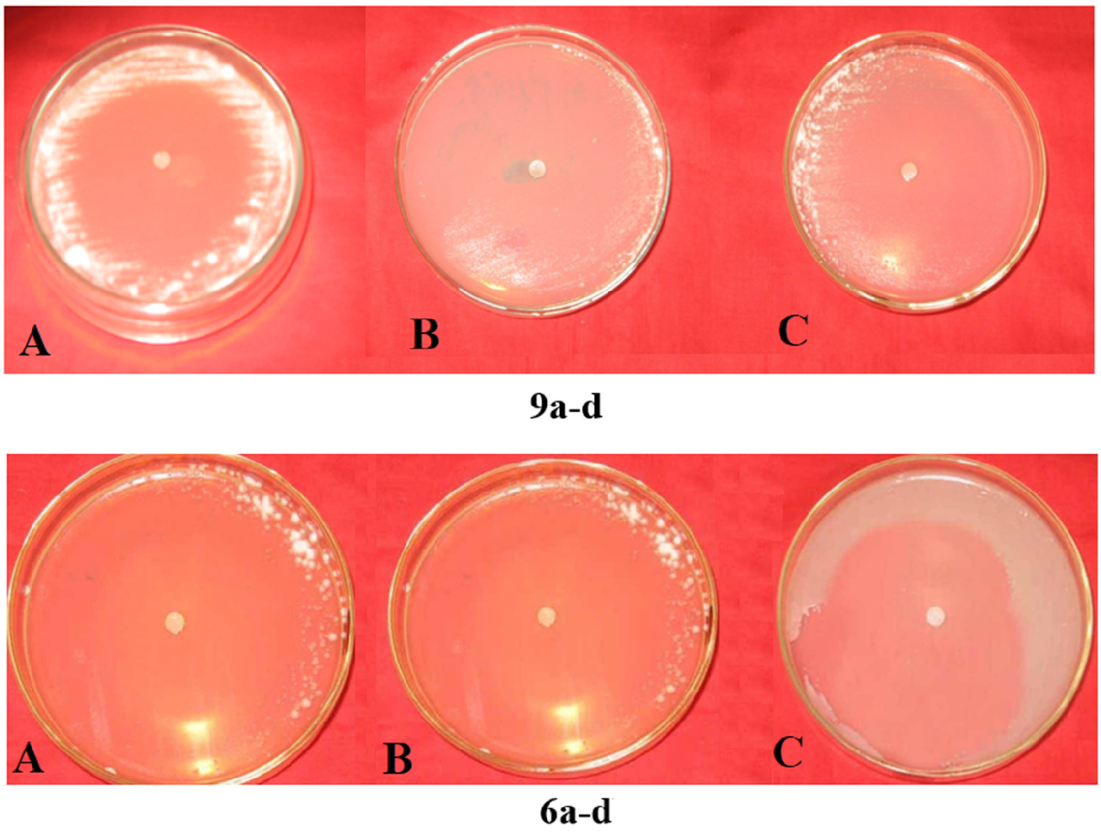

Figure 2. Antifungal activity of a mixture of compounds (**9a-d** and **6a-d**) against: (**A**) *T. rubrum*; (**B**) *T. mentagrophytes*; (**C**) *C. albicans*.

T. mentagrophytes and *C. albicans* were found to be 0.08 mg/ml and 0.09 mg/ml respectively. Another mixture of compounds (**9a** to **9d**) also showed significant inhibitory activity against *T. rubrum*, *T. mentagrophytes*, and *C. albicans.* The MIC values of the mixture of compounds of this series against *T. rubrum*, *T. mentagrophytes*, and *C. albicans* were found to be 0.05 mg/ml, 0.04 mg/ml, and 0.05 mg/ml respectively (Table 4). These results were observed after 6 days, 12 days, 18 days, and 24 days; no growth was observed up to 30 days at that low concentration. Control was taken without addition of the mixtures of compounds showed 100% growth of *T. rubrum*, *T. mentagrophytes*, and *C. albicans*. These results coincide with data by Hu et al., who reported the antifungal activity of novel spiro-quinolinone derivatives against *C. neoformans*, *A. fumigatus*, and *A. flavus* as high as fluconazole [17]. These results are also in agreement with data by Rani and Kunta, who reported that pyrrolo[2,1-b]benzothiazole derivatives **9a-e** could effectively inhibit the growth of the tested bacteria strains [18]. Pyrido[2,3-d] pyrimidine ring systems have assorted biological and pharmacological activities such as analgesic, anti-inflammatory, antitubercular [19], antimicrobial [20, 21], antiviral [22]; they also demonstrate antioxidant properties and can act as inhibitors of dihydrofolate reductase and glucosidase [23]. Our present findings suggest that both mixtures of compounds are to be more additive, syngeristic, and effective in inhibiting the growth of *T. rubrum*, *T. mentagrophytes*, and *C. albicans* as compared to the reference drug. These results indicate that the mixtures of compounds as well as single compounds can be used as antifungal agents against *T. rubrum*, *T. mentagrophytes*, and *C. albicans*. They also could be considered as an active pharmaceutical drug active ingredient (in various compositions) to combat the fungal resistance in dermatophytosis (ringworm) and candidiasis patients.

CONCLUSIONS

In summary, the synthesized 5′-benzylidene-3′-phenylspiro[indoline-3,2′-thiazolidine]-2,4′(1*H*)-diones and spiro[indoline-3,2′-thiazolo[5,4-*e*]pyrimido[1,2-*a*] pyrimidin]-2(1*H*)-one derivatives exhibit promising antifungal activity against dermatophytes and *Candida*. Among the synthesized compounds, compound **9b** showed more potent inhibitory activity than standard antifungal drug, ketoconazole and a mixture of compounds (**9a-d**) exhibited excellent activity as compared to single compounds and ketoconazole against tested strains. Hence it is concluded that there is enough scope for further study in the developing these as good lead compounds. Moreover, this preliminary study is encouraging to further explore their broad spectrum pharmacological activities particularly enzyme inhibition.

FUNDING

The author(s) received no financial support for the research, authorship, and/or publication of this article.

COMPLIANCE WITH ETHICAL STANDARDS

This article does not contain any research involving humans or the use of animals as objects.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

REFERENCES

1. *Holla B.S., Mahalinga M., Karthikeyan M.S., Akberali P.M., Shetty N.S.* (2006) Synthesis of some novel pyrazolo[3,4-d] pyrimidine derivatives as potential antimicrobial agents. Bioorg. Med. Chem., **14**(6), 2040–2047. DOI: 10.1016/j.bmc.2005.10.053
2. *Kaplancikli Z.A., Turan-Zitouni G., Ozdemir A., Revial G.* (2008) New triazole and triazolothiadiazine derivatives as possible antimicrobial agents. Eur. J. Med. Chem., **43**(1), 155–159. DOI: 10.1016/j.ejmech.2007.03.019
3. *Pathakumari B., Liang G., Liu W.* (2020) Immune defence to invasive fungal infections: A comprehensive review. Biomed. Pharmacother., **130**, 1105. DOI: 10.1016/j.biopha.2020.110550
4. *Pristov K.E., Ghannoum M.A.* (2019) Resistance of *Candida* to azoles and echinocandins worldwide. Clin. Microbiol. Infect., **25**(7), 792–798. DOI: 10.1016/j.cmi.2019.03.028
5. *Cortés J.C.G., Curto M.Á., Carvalho V.S.D., Pérez P., Ribas J.C.* (2019) The fungal cell wall as a target for the development of new antifungal therapies. Biotechnol. Adv., **37**(6), 10735. DOI: 10.1016/j.biotechadv.2019.02.008
6. *Lenardon M.D., Munro C.A., Gow N.E.R.* (2010) Chitin synthesis and fungal pathogenesis. Curr. Opin. Microbiol., **13**(4), 416–423. DOI: 10.1016/j.mib.2010.05.002
7. *Curto M.Á., Butassi E., Ribas J.C., Svetaz L.A., Cortés J.C.G.* (2021) Natural products targeting the synthesis of β(1,3)-D-glucan and chitin of the fungal cell wall. Existing drugs and recent findings. Phytomedicine, **88**, 153556. DOI: 10.1016/j.phymed.2021.153556
8. *Noureldin N.A., Kothayer H., Lashine E.M., Baraka M.M., Huang Y., Li B., Ji Q.* (2018) Design, synthesis and biological evaluation of novel quinazoline-2,4-diones conjugated with different amino acids as potential chitin synthase inhibitors. Eur. J. Med. Chem., **152**, 560–569. DOI: 10.1016/j.ejmech.2018.05.001
9. *Masubuchi K., Tangiguchi M., Umeda M., Hattori I., Suda K., Kohchi H., Isshik Y., Sakai T., Kochchi M., Shirai M.* (2022) Synthesis and structure-activity relationships of novel fungal chitin synthase inhibitors. Bioorg. Med. Chem. Lett., **10**(13), 1459–1462. DOI: 10.1016/s0960-894x(00)00257-2
10. *Bongomin F., Gago S., Oladel R.O.* (2017) Global and multi-national prevalence of fungal diseases — estimate precision. J. Fungi (Basel), **3**(4), 57. DOI: 10.3390/jof3040057
11. *Limper A.H., Adenis A., Le T., Harrison T.S.* (2017) Fungal infections in HIV/AIDS. Lancet Infect. Dis., **17**(11), 334–343. DOI: 10.1016/S1473-3099(17)30303-1
12. *Robbins N., Wright G.D., Cowen L.D.* (2016) Antifungal drugs: The current armamentarium and development of new agents. Microbiol. Spectr., **4**(5), DOI: 10.1128/microbiolspec.FUNK-0002-2016
13. *Mroczyńska M, Brillowska-Dąbrowska A.* (2022) Review on current status of echinocandins use. Antibiotics (Basel), **9**(5), 227. DOI: 10.3390/antibiotics9050227
14. *Dandia A., Sharma G., Singh R., Laxkar A.* (2009) A new strategy for the synthesis of novel spiro [indoline-3,2′-thiazolo [5, 4-e] pyrimido [1, 2-a] pyrimidine] derivatives. Arkivoc, **14**, 100–108.
15. *Gould J.C., Bowie J.H.* (1952) The determination of bacterial sensitivity to antibiotics. Edinburgh Med. J., **59**(4), 178–199.
16. *Provine H., Hadley S.* (2000) Preliminary evaluation of a semisolid agar antifungal susceptibility test for yeasts and molds. J Clin. Microbiol., **38**(2), 537–541. DOI: 10.1128/jcm.38.2.537-541.2000
17. *Wu H., Du C., Xu Y., Liu L., Zhou X., Ji Q.* (2022) Design, synthesis, and biological evaluation of novel spiro[pyrrolidine-2,3′-quinolin]-2′-one derivatives as potential chitin synthase inhibitors and antifungal agents. Eur. J. Med. Chem., **233**, 114208. DOI: 10.1016/j.ejmech.2022.114208
18. *Rani N.V., Kunta R.* (2021) PEG-400 promoted a simple, efficient and eco-friendly synthesis of functionalized novel isoxazolyl pyrido[2,3-d]pyrimidines and their antimicrobial and anti-inflammatory activity. Synthetic Communications, **51**(8), 1171–1183. DOI: 10.1080/00397911.2021.1871759
19. *Rajesh S.M., Kumar R.S., Libertsen L.A., Perumal S., Yogeeswari P., Sriram D.* (2011) An atomefficient, solvent-free, green synthesis and antimycobacterial evaluation of 2-amino-6-methyl-4-aryl-8-[(e)-arylmethylidene]-5,6,7,8-tetrahydro-4h-pyrano[3,2-c]pyridine-3-carbonitriles. Bioorg. Med. Chem. Lett., **21**(10), 3012–3016. DOI: 10.1016/j.bmcl.2011.03.045
20. *Abdelhameed R.M., Darwesh O.M. El-Shahat M.* (2020) Synthesis of arylidene hydrazinylpyrido[2,3-*d*]pyrimidin-4-ones as potent anti-microbial agents. Heliyon, **6**(9), e04956. DOI: 10.1016/j.heliyon.2020.e04956
21. *Elsaedany S.K., AbdEllatif zein M., AbdElRehim E.M., Keshk R.M.* (2021) Synthesis and biological activity studies of novel pyrido[2,3-d]pyrimidines and pyrido[2,3-d]triazines. Russ. J. Bioorg. Chem., **47**(2), 552–560. DOI: 10.1134/S1068162021020114
22. *de Goey D.A., Betebenner D.A., Grampovnik D.J., Liu D., Pratt J.K., Tufano M.D., He W., Krishnan P., Pilot-Matias T.J., Marsh K.C., Molla A., Kempf D.J., Maring C.J.* (2013) Discovery of pyrido[2,3-d]pyrimidine-based inhibitors of HCV NS5A. Bioorg. Med. Chem. Lett., **23**(12), 3627–3630. DOI: 10.1016/j.bmcl.2013.04.009
23. *Wang M., Yang J., Yuan M., Xue L., Li H., Tian C., Wang X., Liu J., Zhang Z.* (2017) Synthesis and antiproliferative activity of a series of novel 6-substituted pyrido[3,2-d]pyrimidines as potential nonclassical lipophilic antifolates targeting dihydrofolate reductase. Eur. J. Med. Chem., **128**, 88–97. DOI: 10.1016/j.ejmech.2017.01.033

Received: 12. 03. 2024.
Revised: 06. 06. 2024.
Accepted: 10. 06. 2024.

НОВЫЕ ПРОИЗВОДНЫЕ СПИРО[ИНДОЛИН-3,2′ТИАЗОЛО[5,4-*e*]ПИРИМИДО[1,2-*a*]ПИРИМИДИНА] КАК ВОЗМОЖНОЕ АНТИДЕРМАТОФИТНОЕ И АНТИКАНДИДОЗНОЕ СРЕДСТВО

Г. Шарма[1], Р. Шарма[2]*

[1]Department of Chemistry, MPS International, Jaipur, India
[2]Department of Microbiology, Mahatma Gandhi University of Medical Science & Technology, Jaipur, India; *e-mail: richa.phd.15@gmail.com

Синтезирована новая серия производных 5′-бензилиден-3′-фенилспиро[индолин-3,2′-тиазолидин]-2,4′(1*H*)-дионов **6a-d** и спиро[индолин-3,2′-тиазоло[5,4-*e*]пиримидо[1,2-*a*]пиримидин]-2(1*H*)-она **9a-d**. Все синтезированные соединения были исследованы на противодерматофитную и противокандидозную активность с использованием диско-диффузного метода и модифицированного метода микроразведения. Эксперименты показали, что *in vitro* синтезированные соединения проявляют противогрибковую активность широкого спектра. Соединения **9a-d** обладали более сильной противогрибковой активностью против *Trichophyton rubrum*, *Trichophyton mentagrophytes* и *Candida albicans*; соединения **6a-d** также показали значительную противогрибковую активность против отдельных штаммов грибов по сравнению с противогрибковым препаратом сравнения кетоконазолом. Оценка противогрибковой активности против лекарственно-устойчивых вариантов грибов показала, что разработанные соединения обладают значительной противогрибковой активность. Комбинация соединений (**6a-d**) и (**9a-d**) показала, что синтезированные соединения обладают синергическим или аддитивным действием. Синтезированные соединения проявляют противогрибковую активность широкого спектра, возможно, действуя в качестве ингибитора хитинсинтазы. Полученные результаты свидетельствуют о том, что новые спиропиримидиновые производные могут быть использованы в качестве активного фармацевтического ингредиента для создания новых лекарственных препаратов для лечения дерматофитии и других грибковых заболеваний.

Полный текст статьи на русском языке доступен на сайте журнала (http://pbmc.ibmc.msk.ru).

Ключевые слова: дерматофития; пиримидо-пиримидиновые производные; грибковые агенты; комбинация

Финансирование. Авторы не получали финансовой поддержки для проведения исследований, авторства и/или публикации данной статьи.

Поступила в редакцию: 12.03.2024; после доработки: 06.06.2024; принята к печати: 10.06.2024.