Journal of the Serbian Chemical Society
JSCS-info@shd.org.rs • www.shd.org.rs/JSCS
J. Serb. Chem. Soc. *84* (1) 1–10 (2019)
JSCS–5160
UDC 547.84'792'75'367+542.913:615.282
Original scientific paper

Synthesis and antimicrobial screening of novel 1,3-dioxolanes linked to N-5 of 5*H*-1,2,4-triazino[5,6-*b*]indole-3-thiol

EL SAYED RAMADAN*, HANAA A. RASHEED and EL SAYED H. EL ASHRY

Department of Chemistry, Faculty of Science, Alexandria University, Alexandria 21524, Egypt

(Received 27 November 2017, revised 26 July 2018, accepted 27 August 2018)

Abstract: Synthesis of 1-[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]-1*H*-indole-2,3-dione (**10**) was achieved by coupling 1*H*-indole-2,3-dione (**16**) with (*R*)-(2,2-dimethyl-1,3-dioxolan-4-yl)methyl 4-methylbenzenesulfonate (**15**) in the presence of sodium hydride in dry *N*,*N*-dimethylformamide at room temperature in a closed Erlenmeyer flask. Condensation of **10** with hydrazinecarbothioamide in water afforded the thiosemicarbazone derivative **17**; its subsequent cyclization with potassium carbonate in water gave the corresponding thione **18** in good yield. The 3-allylthio and 3-benzylthio derivatives **20** and **21** were also prepared by alkylating thiol **19** with alkyl halides in aqueous sodium hydroxide or coupling of 3-(allylthio/benzylthio)-5*H*-1,2,4-triazino[5,6-*b*]indoles (**23** and **24**) with compound **15** in NaH/DMF. Compound **20** was isomerized to a mixture of geometrical isomers (*E*/*Z*)-5-[(2,2-dimethyl-1,3-dioxolan-4-yl)-methyl]-3-(prop-1-en-1-ylthio)-5*H*-1,2,4-triazino[5,6-*b*]indoles (**25** and **26**), evidenced by their ^{1}H- and ^{13}C-NMR spectra taken in deuterodimethyl sulfoxide. Structural elucidation of the synthesized compounds was realized using FT-IR, ^{1}H-NMR, ^{13}C-NMR, mass spectrometry and elemental analysis. The newly synthesized compounds were found to possess moderate inhibitory activity against the fungus *Candida albicans* compared to clotrimazole as reference control. Compounds **10**, **17**, **19**, **20**, **21**, **23** and **24** had mean growth inhibition zones (*IZ*) and minimal inhibitory concentrations (*MIC*) in the range of 12–15 mm and 31.25–200 μg mL^{-1}, respectively, with inhibition levels in the range 70.58–88.23 %. Compound **19** exhibited moderate activity against Gram-positive bacteria *Staphylococcus aureus* relative to imipenem as the standard drug. All compounds were inactive against *Escherichia coli* and *Pseudomonas aeruginosa*.

Keywords: survey; alkylation; dioxolanes; 1*H*-indole-2,3-dione; *Candida albicans.*

* Corresponding author. E-mail: elsayedramadan2008@yahoo.com
https://doi.org/10.2298/JSC171127067R

INTRODUCTION

Isatin (1*H*-indole-2,3-dione) derivatives **1**–**4** (Fig. 1) were shown to possess biological and pharmacological properties.[1–4] In addition, the anti-poxviral drug isatin *β*-thiosemicarbazone and its derivatives (**5**) exhibited anti-HIV activity and induced the viral postreplicative transcription apparatus to synthesize longer than normal mRNAs in the treatment of wild-type vaccinia virus infected cells.[5,6] Moreover, 5-chloro-7-methylisatin *β*-thiosemicarbazone behaved as a potential ketone inhibitor of parasitic cysteine proteases identified in trypanosomes (cruzain and rhodesain) and malaria parasites.[7] The *N*-methylisatin derivative (SCH 16) was also found to completely inhibit *in vitro* and *in vivo* the Japanese encephalitis virus.[8] The cyclized derivative 2,4-dihydro-6,7-dimethyl-3*H*-1,2,4-triazino[5,6-*b*]-indole-3-thione showed a pronounced cytotoxicity against brine shrimp,[9] and a number of 3-(alkylthio)-5*H*-1,2,4-triazino[5,6-*b*]indoles (**6**) exhibited antihypoxic activity and protective action with respect to pulmonary edema.[10]

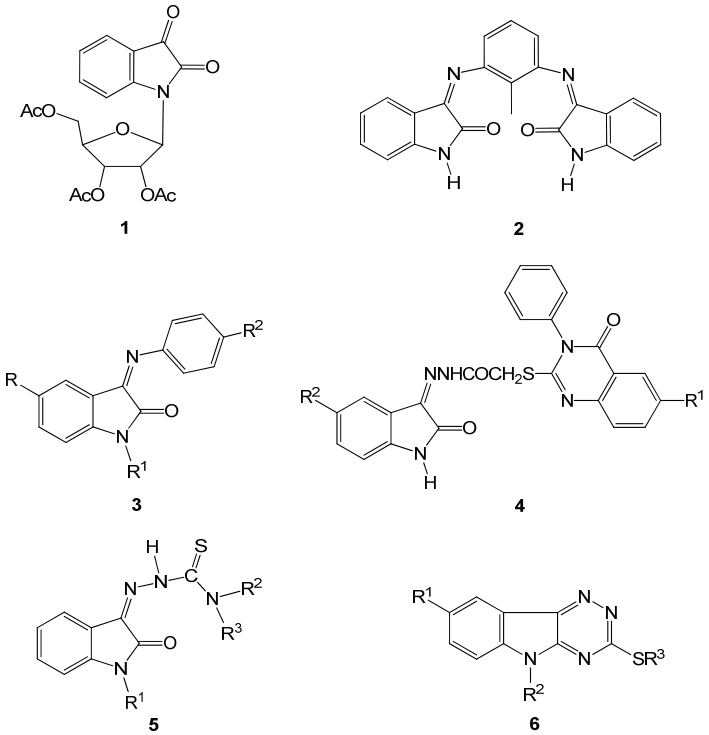


Fig. 1. Some biologically active isatin and 3-(alkylthio)-5*H*-1,2,4-triazino[5,6-*b*]indoles.

The discovery of 1,3-dioxolanes linked to thymidine (**7**), 5-substituted uracil (**8**) and cytosine (**9**),[11–15] as potential anti-HIV agents without acute cellular toxicity has attracted our attention to synthesize novel 1,3-dioxolanes linked to

different heterocyclic bases. In continuation of our work on triazino-indoles,[16–19] herein an efficient methodology is reported for the synthesis of some biologically active 1,3-dioxolanes bearing 1*H*-indole-2,3-dione (**10**), 5*H*-1,2,4-triazino[5,6-*b*]indole-3-thiol, and its 3-alkylthio derivatives (**11**, Fig. 2).

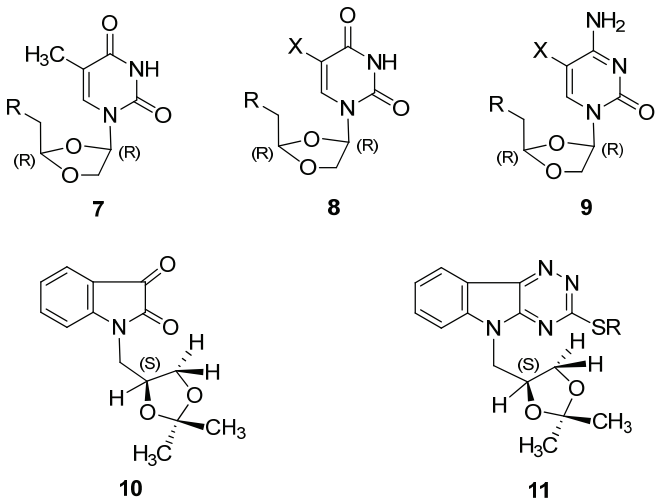


Fig. 2. Common 1,3-dioxolanes and the newly synthesized analogues.

EXPERIMENTAL

General

The starting chemicals and reagents used in this study were purchased from Sigma–Aldrich. Melting points were determined with a Mel-Temp apparatus and are uncorrected. Thin-layer chromatography (TLC) was performed on Baker–Flex silica gel 1B-F plates using ethyl acetate/petroleum ether (4:1 volume ratio, b.p: 60–80 °C) as eluent and the compounds were detected by UV light absorption. FT-IR spectra were measured on a Shimadzu 8400 S spectrometer. ^{1}H-NMR spectra were recorded on a Bruker Avance AV 300 spectrometer (300 MHz) and Varian Gemini spectrometer (200 MHz). ^{13}C-NMR spectra were measured on a JEOL ECA-500 spectrometer at 125 MHz. The chemical shifts (δ) are given in parts per million (ppm) relative to TMS as an internal standard. The coupling constant values (J) are reported in Hz. Mass spectrometry was realized using electron ionization (EI) on a Finnigan MAT 312 spectrometer and fast atom bombardment (FAB) on a Karatos MS 50 spectrometer. Microanalysis was performed on a Vario elementar EL III analyzer.

Analytical and spectral data of the synthesized compounds are given in Supplementary material to this paper.

The antimicrobial tests were performed in the Pharmaceutical Microbiology Department, Faculty of Pharmacy, Alexandria University. Column chromatography was performed using silica gel (200–400 mesh, Merck) and anhydrous sodium sulfate was employed as a drying agent.

Syntheses

*1-[(2,2-Dimethyl-1,3-dioxolan-4-yl)methyl]-1*H-*indole-2,3-dione (**10**)*. Compound **15** (2.86 g, 10 mmol) was added to a stirred solution of 1*H*-indole-2,3-dione (**16**, 1.47 g, 10 mmol) and sodium hydride (0.56 g, 10 mmol, 60 % in mineral oil) in 20 mL of dry DMF in a 50 mL closed Erlenmeyer flask. The reaction mixture was stirred at room temperature for an additional 24 h. The product was extracted with ethyl acetate (3×20 mL); the organic layers were combined, dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue was purified by silica gel column chromatography using a gradient ethyl acetate/*n*-hexane (1:10 volume ratio). Yield: 69 %.

*2-[1,2-Dihydro-1-{(2,2-dimethyl-1,3-dioxolan-4-yl)methyl}-2-oxo-3*H-*indol-3-ylidene]-hydrazinecarbothioamide (**17**)*. To a solution of compound **10** (1.30 g, 5 mmol) in water (20 mL) was added a solution of hydrazinecarbothioamide (0.455 g, 5 mmol) in water (5 mL) and two drops of glacial acetic acid. The reaction mixture was heated under reflux for 2 h. The product that separated out on cooling was filtered and recrystallized from ethanol. Yield: 84 %.

*5-[(2,2-Dimethyl-1,3-dioxolan-4-yl)methyl]-5*H-*1,2,4-triazino[5,6-*b*]indole-3-thiol (**19**)*. *Method a*: a mixture of compound **17** (1.67 g, 5 mmol) and anhydrous potassium carbonate (0.69 g, 5 mmol) in water (20 mL) was heated under reflux for 7 h. On cooling, the mixture was filtered and the filtrate was acidified with dilute acetic acid. The separated product was filtered off, washed with water and recrystallized from ethanol. Yield: 75 %. *Method b*: a mixture of compound **10** (0.261 g, 1.0 mmol), hydrazinecarbothioamide (0.091 g, 1.0 mmol) and anhydrous potassium carbonate (0.138 g, 1.0 mmol) in water (10 mL) was heated under reflux for 10 h. The reaction mixture was processed as before to give a product identical with that obtained from method a. Yield: 82 %.

*Alkylation of 5*H-*1,2,4-triazino[5,6-*b*]indole-3-thiol (**22**)*. Compound **22** (2.02 g, 10 mmol) in a solution of sodium hydroxide (0.40 g, 10 mmol) in water (25 mL) was stirred for 10 min until complete dissolution. The required alkyl halide (10 mmol) was then added during 10 min and the mixture was stirred for a further 30 min. The separated solid was filtered off, washed with water and recrystallized from ethanol to give compounds **23** and **24**.

*Synthesis of 1,3-dioxolane analogues **20** and **21**. Method a*: compound **19** (1.58 g, 5 mmol) in a solution of sodium hydroxide (0.20 g, 5 mmol) in water (10 mL) was stirred for 10 min until dissolution. The required allyl/benzyl halide (5 mmol) was then added dropwise and stirring was continued for a further 30 min. The separated solid was filtered, washed with water and recrystallized from ethanol. *Method b*: a stirred solution of compounds **23** or **24** (5 mmol) in dry DMF (10 mL) was treated with NaH (0.28 g, 5 mmol, 60 % in mineral oil) in a 50 mL closed Erlenmeyer flask and compound **15** (1.43 g, 5 mmol) was added under stirring for 24 h. The reaction mixture was processed as before to give products that were found to be identical with those obtained from method a.

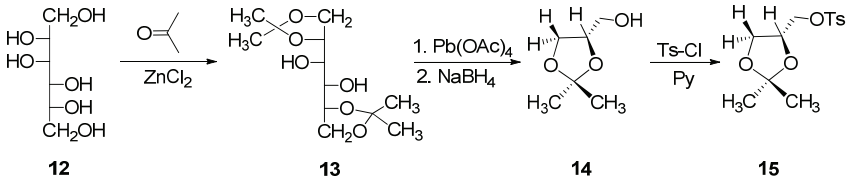
Antimicrobial testing

The synthesized 1,3-dioxolanes were screened for their antibacterial activity against Gram-positive bacteria *Staphylococcus aureus* (ATCC 6538P) and Gram-negative bacteria *Escherichia coli* (ATCC 8739), *Pseudomonas aeruginosa* (ATCC 9027) and their antifungal activity against *Candida albicans* (ATCC 2091) by the agar well-diffusion technique,[20] using a 1 mg per 1 mL solution in ethanol. Each tested organism was cultured in 3 mL of sterile nutrient broth and incubated for 18 h at 37 °C. Aseptically, 0.4 mL was taken with a glass pipette from resultant microbial growth and transferred into 40 mL of warm agar in one sterile flask for each organism. The seeded agar was poured into sterile Petri dishes (≈15 cm in diameter) onto a level surface to obtain a layer of about 4 mm thickness and the plates were then left to

solidify. Cups of 8 mm in diameter were made using a cork borer, the sample size for all the compounds was fixed at 65 μL and the plates were then incubated at 37 °C for 24 h. The diameter of each resultant growth inhibition zone (*IZ*) in mm was accurately measured in three different directions and its mean was calculated. The minimal inhibitory concentration (*MIC*) was evaluated in μg mL^{-1} by a broth dilution method.[21] Clotrimazole (0.01 g mL^{-1}) and imipenem (10 mcg per disc) were used as standard drugs.

RESULTS AND DISCUSSION

The reactions required for the synthesis of the target compounds are outlined in Schemes 1 and 2. Thus, (*R*)-(2,2-dimethyl-1,3-dioxolan-4-yl)methyl 4-methylbenzenesulfonate (**15**) was prepared in three steps starting from D-mannitol (**12**) (Scheme 1). Isopropylidenation of **12** with acetone in the presence of anhydrous zinc chloride gave 1,2:5,6-di-*O*-isopropylidene-D-mannitol (**13**), which was converted into isopropylideneglycerol **14** by oxidative cleavage with $Pb(OAc)_4$, followed by $NaBH_4$ reduction. Its reaction with tosyl chloride in pyridine afforded **15** in good yield.[22,23]

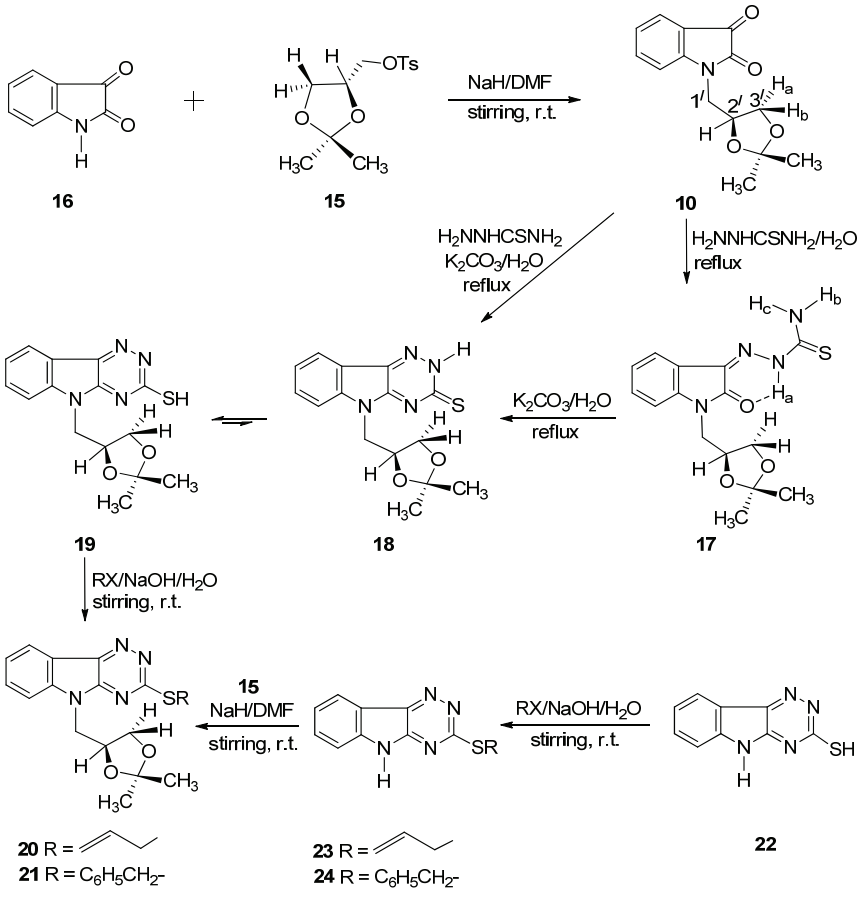


12 **13** **14** **15**

Scheme 1. Synthesis of (*R*)-(2,2-dimethyl-1,3-dioxolan-4-yl)methyl 4-methylbenzene sulfonate.

Eco-friendly coupling reaction of 1*H*-indole-2,3-dione (**16**) with **15** was performed in anhydrous *N,N*-dimethylformamide in the presence of sodium hydride in a closed Erlenmeyer flask at room temperature to give 1-[(2,2-dimethyl-1,3--dioxolan-4-yl)methyl]-1*H*-indole-2,3-dione (**10**) as a red syrup (Scheme 2). Subsequent condensation with hydrazinecarbothioamide in water and a few drops of glacial acetic acid gave 2-[1,2-dihydro-{(2,2-dimethyl-1,3-dioxolan-4--yl)methyl}-2-oxo-3*H*-indol-3-ylidene]hydrazinecarbothioamide (**17**) in 84 % yield. The IR spectrum of **17** showed bands at 3359.77, 3245.97 and 3151.47 cm^{-1}, characteristics for the NH and NH_2 groups, and two bands at 1691.46 and 1228.57 cm^{-1} due to C=O and C=S stretching vibrations, respectively. No SH band was observed at 2500–2600 cm^{-1}, the range in which the SH stretching vibrations are most likely to appear. This clearly shows that no thione–thiol tautomerism occurred in this compound in the solid state. Its ^{1}H-NMR spectrum in DMSO-d_6 showed also the presence of three downfield singlet peaks at δ 12.35, 9.08, and 8.73 ppm corresponding to NH_a, NH_b and NH_c, respectively (Scheme 2). The configuration about imine linkage (C=N) in **17** was assigned as *Z* due to the existence of intramolecular hydrogen bonding between the ketonic oxygen at C-2 of the indole ring and H_a of thiosemicarbazone moiety.[24]

A green synthesis of the cyclized compound 5-[(2,2-dimethyl-1,3-dioxolan--4-yl)methyl]-2,5-dihydro-3*H*-1,2,4]-triazino[5,6-*b*]indole-3-thione (**18**) was achieved by the dehydrative cyclization of **17** in aqueous potassium carbonate. The reaction was completed in 7 h at reflux and the yield reached 75 %. However, it was obtained in one pot by refluxing **10** with hydrazinecarbothioamide in aqueous potassium carbonate for 10 h, but the yield was improved to 82 %. The ^{1}H-NMR spectrum of compound **18** in DMSO-d_6 showed a D_2O-exchangeable singlet at δ 14.62 ppm due to SH proton, evidencing its existence in solution in the thiol form **19** in which the aromatic ring character (14-π electrons) is preserved.



Scheme 2. Eco-friendly synthesis of novel 1,3-dioxolane analogues.

Alkylation of thiol **19** with allyl bromide or benzyl chloride was performed in a solution of sodium hydroxide in water at room temperature to give 3-(allylthio/benzylthio)-5-[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]-5*H*-1,2,4-triazino[5,6--*b*]indoles (**20** and **21**) in good yields. An unequivocal synthesis of **20** and **21** was

realized by alkylating 5*H*-[1,2,4]-triazino[5,6-*b*]indole-3-thiol (**22**) with allyl bromide or benzyl chloride to give the corresponding *S*-alkylated derivatives **23** and **24**, followed by their coupling with **15** in the presence of NaH/DMF. The advantages of these eco-friendly reactions are the ease of reactions work-up and excellent yields of the products.

The ^{13}C-NMR spectrum of compound **20** in deuterodimethyl sulfoxide indicated that a facile allylic rearrangement occurred to give geometrical isomers (*E*/*Z*)-5-[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]-3-(prop-1-en-1-ylthio)-5*H*-1,2,4--triazino[5,6-*b*]indoles **25** and **26** (Fig. 3). This result was evidenced by the appearance of two signals at δ 18.59 and 15.09 ppm for the terminal methyl group of the *E* and *Z* isomers and two signals at δ 44.27 and 44.31 ppm for two N–CH_2 groups with the absence of any signal for an S–CH_2 carbon atom. Moreover, four ^{13}C signals appeared at δ 25.09, 25.16, 26.47 and 26.49 ppm due to the methyl groups of 1,3-dioxolane ring. The presence of signals for Ar–C, CH=CH and quaternary carbon of the C–Me_2 group in the range of δ 109.10––166.19 ppm also confirmed such an observation. The ^{1}H-NMR spectrum of compound **20** in DMSO-d_6 was in agreement with the proposed structures **25** and **26**. The ethylenic proton geminal to the terminal methyl group resonated as a multiplet at δ 5.94–6.14 ppm, while two doublet peaks for the ethylenic proton neighbors to sulfur appeared at δ 6.84 ppm (J = 15.0 Hz, *E*-isomer) and 7.08 ppm (J = 9.6 Hz, *Z*-isomer) with an *E*:*Z* ratio of 2:3, respectively. An allylic rearrangement of compound **20** was not detected in deuterochloroform (Supplementary material).

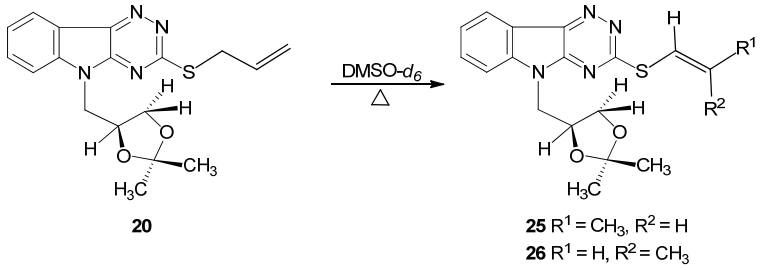


Fig. 3. Allylic rearrangement of compound **20** in deuterodimethyl sulfoxide.

Antimicrobial results

The results of the antimicrobial studies presented in Table I revealed that the synthesized compounds showed moderate antimicrobial activity against the fungus *C. albicans* with growth inhibition zones (*IZ*) in the range of 12–15 mm relative to clotrimazole as antifungal medication (*IZ* = 17 mm). However, they were inactive against the Gram-positive bacteria *S. aureus* and Gram-negative strains *E. coli* and *P. aeruginosa*, except 5-[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]-

-5*H*-1,2,4-triazino[5,6-*b*]indole-3-thiol (**19**), which showed low activity against *S. aureus* (*IZ* = 12 mm and inhibition level = 40 %) as compared to the broad spectrum antibiotic imipenem (*IZ* = 30 mm and inhibition level = 100 %).

TABLE I. *In vitro* antimicrobial activity of the synthesized compounds against *C. albicans*; *IZ*: mean growth inhibition zones; errors: ±5 %; *MIC*: minimal inhibitory concentration; inhibition level, % = 100(*IZ* of compound/*IZ* of reference drug)

Compound	*IZ* / mm	Inhibition level, %	*MIC* / μg mL^{-1}
10	13	76.47	125
17	15	88.23	125
19	13	76.47	> 200
20	13	76.47	62.50
21	14	82.35	31.25
23	12	70.58	> 200
24	12	70.58	> 200
Clotrimazole	17	–	–

It is clear that compounds **10**, **17**, **19**, **20**, **21**, **23** and **24** possessed comparable *IZ* values against *C. albicans*. Thus, they were further screened to determine their minimal inhibitory concentrations (*MIC*) values. The most active compounds against *C. albicans* were 3-(allylthio)- and 3-benzylthio)-5-[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]-5*H*-1,2,4-triazino[5,6-*b*]indoles **20** and **21**, their *MIC* values were 62.50 and 31.25 μg mL^{-1}, respectively. Compound **21** possessing benzyl group at the sulfur atom at position 3 of the triazino-indole ring system revealed the highest degree of potency against this strain. On the other hand, the *MIC* values for dioxolane **10** and its thiosemicarbzone **17** were found to be 125 μg mL^{-1}, while compound **19** and 3-(allylthio/benzylthio)-5*H*-1,2,4-triazino[5,6-*b*]indoles **23** and **24** have *MIC* values of more than 200 μg mL^{-1}. These findings indicated that the combination of 1,3-dioxolane ring at N-5 and allyl/benzyl group at S-3 with the 5*H*-1,2,4-triazino[5,6-*b*]indole-3-thiol ring system enhanced their antimicrobial activity against *C. albicans*. The inhibition level of the synthesized compounds ranged in 70.58–88.23 %.

CONCLUSIONS

In conclusion, an eco-friendly synthesis of some novel 1,3-dioxolanes linked to 1*H*-indole-2,3-dione and 5*H*-1,2,4-triazino[5,6-*b*]indole-3-thiol was achieved by their coupling reactions with (*R*)-(2,2-dimethyl-1,3-dioxolan-4-yl)methyl-4-methylbenzensulfonate in the presence of NaH/DMF in a closed Erlenmeyer flask at room temperature. 3-(Allylthio/benzylthio)-5-[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]-5*H*-1,2,4-triazino[5,6-*b*]indoles were also prepared by different routes. All the compounds were tested *in vitro* for their antimicrobial activity against certain microorganisms and some compounds showed significant activity against *C. albicans*. Clean reactions and good yields of products were observed.

SUPPLEMENTARY MATERIAL

Spectral and analytical data are available electronically at the pages of journal website: http://www.shd.org.rs/JSCS/, or from the corresponding author on request.

ИЗВОД

СИНТЕЗА И АНТИМИКРОБНА АКТИВНОСТ НОВИХ 1,3-ДИОКСОЛАНА ВЕЗАНИХ ЗА N-5 АТОМ 5*H*-1,2,4-ТРИАЗИНО[5,6-*b*]ИНДОЛ-3-ТИОЛА

EL SAYED RAMADAN, HANAA A. RASHEED и EL SAYED H. EL ASHRY

Department of Chemistry, Faculty of Science, Alexandria University, Alexandria 21524, Egypt

Синтеза 1-[(2,2-диметил-1,3-диоксолан-4-ил)метил]-1*H*-индол-2,3-диона (**10**) постигнута је куповањем 1*H*-индол-2,3-диона (**16**) са (*R*)-(2,2-диметил-1,3-диоксолан-4-ил)--метил-4-метилбензенсулфонатом (**15**) у присуству натријум-хидрида у сувом *N*,*N*--диметилформамиду на собној температури у затвореном ерленмајеру. Кондензацијом **10** са хидразинкарботиоамидом у води добијен је тиосемикарбазонски дериват **17**; даљом циклизацијом уз калијум-карбонат у води добијен је одговарајући тион **18**, у добром приносу. Алкиловањем тиола **19** халогеналканима у присуству воденог раствора натријум-хидроксида добијени су 3-алилтио и 3-бензилтио деривати **20** и **21**, редом. Исти деривати добијени су куповањем 3-(алилтио/бензилтио)-5*H*-1,2,4-триазино[5,6-*b*]индола **23** односно **24** са једињењем **15** уз NaH у DMF-у. Једињење **20** се изомеризује у смешу геометријских изомера (*E*/*Z*)-5-[(2,2-диметил-1,3-диоксолан-4-ил)метил]-3-(проп-1-ен-1-илтио)-5*H*-1,2,4--триазино[5,6-*b*]индола **25** и **26** током снимања ^{1}H- и ^{13}C-NMR спектара у деутеро-диметил-сулфоксиду. Одређивање структуре је извршено помоћу FT-IR, ^{1}H- NMR, ^{13}C-NMR, масеном спектрометријом и елементалном анализом. Нова једињења показују умерену инхибиторну активност против гљивице *Candida albicans*, у поређењу са клотримазолом као контролом. Једињења **10**, **17**, **19**, **20**, **21**, **23** и показују средњу вредност зоне инхибиције (*IZ*) 12–15 mm и минималну инхибиторну активност (*MIC*) 31,25–200 μg mL^{-1}, са нивоом инхибиције од 70,58–88,23 %. У поређењу са стандардом, једињење **19** показује умерену активност према Грам-позитивној бактерији *Staphylococcus aureus*. Према *Escherichia coli* and *Pseudomonas aeruginosa* тестирана једињења нису показала активност.

(Примљено 27. новембра 2017, ревидирано 26. јула, прихваћено 27. августа 2018)

REFERENCES

1. S. E. Kassab, G. H. Hegazy, N. M. Eid, K. M. Amin, A. A. El-Gendy, *Nucleosides, Nucleotides Nucleic Acids* **29** (2010) 72
2. A. Jarrahpour, D. Khalili, E. De Clercq, C. Salmi, J. M. Brunel, *Molecules* **12** (2007) 1720
3. M. Verma, S. N. Pandeya, K. N. Singh, J. P. Stables, *Acta Pharm.* **54** (2004) 49
4. A. Gürsoy, N. Karalı, *Eur. J. Med. Chem.* **38** (2003) 633
5. T. R. Bal, B. Anand, P. Yogesswari, D. Sriram, *Bioorg. Med. Chem. Lett.* **15** (2005) 4451
6. S. G. Cresawn, C. Prins, D. R. Latner, R. C. Condit, *Virology* **363** (2007) 319
7. I. Chiyanzu, E. Hansell, J. Gut, P. J. Rosenthal, J. H. Mckerrow, K. Chibale, *Bioorg. Med. Chem. Lett.* **13** (2003) 3527
8. L. Sebastian, A. Desai, M. N. Shampur, Y. Perumal, D. Sriram, R. Vasanthapuram, *Virol. J.* **5** (2008) 64
9. M. M. Hossain, N. Islam, R. Khan, M. R. Islam, *Bangladesh J. Pharmacol.* **2** (2007) 66
10. A. B. Tomchin, A. V. Kropotov, *Pharm. Chem. J.* **32** (1998) 22

11. L. J. Wilson, W. B. Choi, T. Spurling, D. C. Liotta, R. F. Schinazi, D. Cannon, G. R. Painter, M. S. Clair, P. A. Furman, *Bioorg. Med. Chem. Lett.* **3** (1993) 169
12. D. W. Norbeck, S. Spanton, S. Broder, H. Mitsuya, *Tetrahedron Lett.* **30** (1989) 6263
13. W. B. Choi, L. J. Wilson, S. Yeola, D. C. Liotta, R. F. Schinazi, *J. Am. Chem. Soc.* **113** (1991) 9377
14. C. K. Chu, S. K. Ahn, H. O. Kim, J. W. Beach, A. J. Alves, L. S. Jeong, Q. Islam, P. Van Roey, R. F. Schinazi, *Tetrahedron Lett.* **32** (1991) 3791
15. E. V. Efimtseva, S. N. Mikhailov, S. V. Meshkov, H. Lonnberg, *Acta Chem. Scand.* **46** (1992) 1122
16. A. Mousaad, N. Rashed, E. Ramadan, E. S. H. El Ashry, *Spectrosc. Lett.* **27** (1994) 677
17. E. S. H. El Ashry, N. Rashed, H. Abdel Hamid, E. Ramadan, *Z. Naturforsch., B* **52** (1997) 873
18. N. Rashed, H. Abdel Hamid, E. Ramadan, E. S. H. El Ashry, *Nucleosides Nucleotides* **17** (1998) 1373
19. E. S. H. El Ashry, H. Abdel Hamid, A. Mousaad, E. Ramadan, *J. Chem. Res., Miniprint* (2002) 752
20. S. R. Jain, A. Kar, *Planta Med*. **20** (1971) 118
21. H. M. Ericsson, J. C. Sherris, *Acta Pathol. Microbiol. Scand., B: Microbiol. Immunol.* **217** (1971) Suppl 217:1+
22. B. B. Lohray, B. M. Rajesh, V. Bhushan, *Indian J. Chem., B* **41** (2002) 586
23. K. Yamada, Y. Yoshiazwa, K. Oh, *Molecules* **17** (2012) 4460
24. E. Kohli, R. Arora, R. Kakkar, *Can. Chem. Trans*. **2** (2014) 327.