Bull. Pharm. Sci., Assiut University, Vol. 45, Issue 1, 2022, pp. 191-199

Bulletin of Pharmaceutical Sciences
Assiut University
Website: http://bpsa.journals.ekb.eg/
e-mail: bullpharm@aun.edu.eg

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SYNTHESIS OF TWO NOVEL DERIVATIVES OF CYCLOSPORIN A AND EVALUATION OF THEIR ANTIPROLIFERATIVE EFFECT ON CANCER CELL LINES

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Two novel derivatives of cyclosporin A were designed and synthesized. Synthesis of target compounds has been performed using olefin metathesis chemistry. The structures of target compounds were confirmed using 1H and 13C NMR and high-resolution mass spectroscopy. The in vitro antiproliferative effect of the two compounds was tested over NCI-60 cancer cell lines of nine different cancer types. The piperidinedione derivative (compound 7) had an inhibitory effect higher than 80% over 13 cancer cell lines, and close to or higher than 100% over six cancer cell lines. Compound 7 showed also significantly higher inhibitory activity than cyclosporin A against non-small cell lung cancer NCI-H226 cell line. Moreover, compound 7 showed an overall moderate antiproliferative activity against the NCI-60 cancer cell lines with a mean value of 57.54 %. While, the pyrrolidindione derivative (compound 6) showed weak antiproliferative activity against the NCI-60 cancer cell lines with a mean value of 28.83%. Finally, the predicted pharmacokinetic properties of compounds 6 and 7 were better than that of cyclosporine A.

KEYWORDS: *Synthesis, Anti-proliferative effect, Cyclosporin A, olefin metathesis, pharmacokinetic.*

INTRODUCTION

Natural products (NPs) are secondary metabolites, produced by organisms (plants, fungi, bacteria, protozoans, insects and animals) in response to certain stimuli such as nutritional changes, infection and competition[1]. It is widely known that NPs are main sources of new drugs and therapeutic agents[2]. Among the famous examples of NPs used widely in today's medical health are lovastatin (anticholesterolemic agent), tacrolimus (immunosuppressive agent), paclitaxel and doxorubicin (antitumor agents), erythromycin (antibiotic), and amphotericin B (fungicidal agent)[1].

NPs are characterized by unique scaffold diversity and structural complexity. For example, they usually have a higher molecular mass, a larger number of sp^3 carbon atoms and oxygen atoms but fewer nitrogen and halogen atoms, higher numbers of H- bond acceptors and donors, and greater molecular rigidity compared with synthetic compound libraries[3]. The enormous structural diversity of NPs and their medicinal significance has led researchers to screen natural resources to find new 'lead' compounds. Molecular modifications of the functional groups of such lead compounds could produce novel structural analogs with greater pharmacological activity and fewer side effects[4].

Cyclosporine A (CsA), (Figure 1), is a well-known immunosuppressive cyclic undecapeptide, isolated from the fungus *Tolypocladium inflatum*[5]. CsA exerts its immunosuppressive action by first binding with high affinity to a cytosolic protein cyclophilin

Received in 15/12/2021 & Accepted in 21/1/2022

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A (CypA). The CsA-CypA complex binds to and inhibits the protein phosphatase activity of calcineurin, which is an essential mediator of calcium signaling in T cells[6].

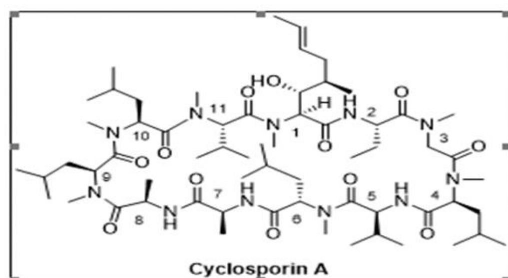


Fig. 1: Cyclosporin A structure

Cyclophilins, the principal CsA cellular target, are members of a protein family that catalyzes cis/trans isomerization of the peptidyl-prolyl bond. It has been reported that cyclophilins play significant roles in many biological processes, such as viral infections, cancer, neuroprotection, epithelial differentiation, and various inflammatory diseases[5]. Structural modification of CsA scaffold may result in new molecules that are less immunosuppressive but retain cyclophilin binding activity. It has been proposed that the non-immunosuppressive cyclophilin inhibitors may have potential utility for the treatment of many diseases such as viral infections, inflammation, cardiac failure, and cancer[7,8].
With the aim of improving the anticancer activity and decreasing the immunosuppressive activity of CsA, novel derivatives of CsA were designed, synthesized and tested over NCI-60 cancer cell lines.

Experimental Chemistry

General

NMR spectra were recorded with a Bruker spectrometer, operating at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR. The multiplicities were abbreviated as s: singlet, d: doublet, t: triplet, m: multiplet, q: quartet. The coupling constants *J* are recorded in Hertz (Hz) and it's liable to a little difference because they used the intact values measured by spectrometer. The relative shift values of peak are recorded by ppm unit using tetramethylsilane (TMS) as standard material. High-resolution spectra were performed onWaters ACQUITY UPLC BEH C18 1.7µ Q-TOF SYNAPT G2-Si High Definition Mass Spectrometry. Thin layer chromatography (TLC) was performed using precoated plates (0.25 mm, Merck) of silica gel 60 F_{254} (230 ~ 400 mesh) for monitoring all reactions and under ultraviolet irradiation (254 nm). Column chromatography separations are performed using silica gel (230 ~ 400 mesh, Merck). All the commercially available reagent chemicals were obtained from Aldrich, TCI, Wako Pure Chemical, Acros and Dae-Jung Chemicals, and generally used without further purification.

Synthesis of 3,4-dimethyl-1-(4-vinylbenzyl)-1H-pyrrole-2,5-dione (4)

A mixture of 4-vinylbenzylamine (**1**) (0.11 g, 0.79 mmol) and 2,3-Dimethylmaleic anhydride (**2**) (0.1 g, 0.79 mmol) in DMF was stirred at 80 °C for 12 h. After cooling, the reaction mixture was partitioned between water and ethyl acetate. The ethyl acetate layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography using hexane/ethyl acetate (3:1) as mobile phase to afford the corresponding compound as sticky solid, yield (0.08 g, 42%), ^{1}H NMR ($CDCl_3$) δ 1.97 (s, 6H), 4.65 (s, 2H), 5.24 (dd, J = 0.8 Hz, 10.8 Hz, 1H), 5.74 (dd, J = 0.8 Hz, 17.6 Hz, 1H), 6.69 (dd, J = 10.8 Hz, 17.6 Hz, 1H), 7.33 (dd, J = 2.4 Hz, 6.4 Hz, 2H), 7.37 (dd, J = 2.4 Hz, 6.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 8.72, 41.24, 114.06, 126.44, 128.68, 136.24, 136.37, 137.07, 137.33, 171.82.

Synthesis of 1-(4-vinylbenzyl)piperidine-2,6-dione (5)

To a mixture of 4-vinylbenzylamine (**1**) (0.2 g, 1.5 mmol) and DMAP (0.55 g, 4.5 mmol) in dichloromethane, under nitrogen atmosphere, was added glutaryl chloride (**3**) (1.5 ml g, 12 mmol). The reaction mixture was stirred at room temperature overnight. The solvent was removed *in vacuo*, and the residue was partitioned between water and ethyl acetate. The ethyl acetate layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography using hexane/ethyl acetate (3:1) as mobile phase to afford the corresponding compound as sticky solid, yield (0.128 g, 37%), ^{1}H NMR ($CDCl_3$) δ 1.93

(pentet, J = 2.4, 6.4 Hz, 2H), 2.65 (t, J = 6.4 Hz, 4H), 4.94 (s, 2H), 5.23 (dd, J = 0.8 Hz, 10.8 Hz, 1H), 5.72 (dd, J = 0.8 Hz, 17.6 Hz, 1H), 6.69 (dd, J = 10.8 Hz, 17.6 Hz, 1H), 7.34-7.36 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 17.06, 32.86, 42.40, 113.87, 126.59, 129.05, 136.47, 136.76, 136.96, 172.44.

General procedure of synthesis of compounds 6 and 7

Cyclosporin A and Grubbs catalyst 2nd Generation (Benzylidene [1,3 –bis (2,4,6-trimethylphenyl) – 2 - imidazolidinylidene] dichloro (tricyclohexylphosphine)ruthenium) were dissolved in dry toluene. Then either compounds (**4**) or (**5**) was added and the reaction mixture was heated at 80 °C for 16 h. The resulting mixture was filtered through celite, concentrated in vacuo and flash chromatographed using dichloromethane / methanol (4 : 1) mobile phase to obtain the corresponding compounds **6** and **7**.

Pyrrolidinedione cyclosporin A (6)

The compound was obtained as a white solid with a yield (0.037 g, 79%); ^1H NMR ($CDCl_3$) δ 0.72 (d, J = 6.0 Hz, 3H), 0.81-0.99 (m, 30H), 1.06 (d, J = 6.8 Hz, 6H), 1.11 (s, 3H), 1.12 (s, 3H), 1.26-1.46 (m, 14H), 1.59-1.87 (m, 10H), 1.97 (s, 2H), 1.99-2.11 (m, 7H), 2.12-2.21 (m,2H), 2.31-2.42 (m, 2H), 2.71 (s, 3H), 2.75 (s, 3H), 3.12 (s, 3H), 3.14 (s, 3H), 3.29 (s, 3H), 3.43 (s, 3H), 3.56 (s, 3H), 3.78-3.82 (m, 1H), 4.56-4.58 (m, 1H), 4.64 (s, 2H), 4.70-4.72 (m, 1H), 4.75-4.79 (m, 1H), 4.84-4.87 (m, 1H), 4.94 (dd, J = 6.0 Hz, 10.0 Hz, 1H), 5.07-5.09 (m, 2H), 5.16 (d, J = 10.8 Hz, 1H), 5.34-5.39 (m, 2H), 5.59 (d, J = 5.2 Hz, 1H), 5.71-5.73 (m, 1H), 6.16 (dd, J = 7.6 Hz, 15.6 Hz, 1H), 6.31 (d, J = 15.6 Hz, 1H), 7.13 (d, J = 8.0 Hz, 1H), 7.28-7.32 (m, 4H), 7.53 (d, J = 8.0 Hz, 1H), 7.68 (d, J = 7.6 Hz, 1H), 8.04 (d, J = 9.6 Hz, 1H).

^{13}C NMR ($CDCl_3$) δ 8.69, 9.93, 14.12, 16.06, 16.83, 18.22, 18.41, 18.71, 19.94, 20.41, 21.12, 21.85, 22.70, 23.38, 23.49, 23.65, 23.72, 23.82, 24.33, 24.63, 24.76, 25.35, 27.23, 29.37, 29.71, 29.81, 31.14, 31.36, 31.61, 33.34, 34.23, 36.61, 37.56, 39.57, 40.41, 41.28, 45.15, 48.23, 48.53, 48.80, 50.38, 55.54, 57.63, 57.86, 75.28, 126.25, 128.63, 129.92, 130.89, 135.09, 137.27, 170.11, 170.19, 170.38, 170.60, 171.15, 171.46, 171.63, 171.85, 173.47, 173.74, 173.83, 174.00; MS [m/z + Na] 1424.9130.

Piperidinedione cyclosporin A (7)

The compound was obtained as a white solid with a yield (0.045 g, 75%); ^1H NMR ($CDCl_3$) δ 0.71 (d, J = 6.0 Hz, 3H), 0.83-0.99 (m, 30H), 1.06 (d, J = 6.8 Hz, 6H), 1.10 (s, 3H), 1.12 (s, 3H), 1.27-1.46 (m, 14H), 1.59-1.84 (m, 10H), 2.03-2.20 (m, 9H), 2.29-2.40 (m, 2H), 2.67-2.69 (m, 10H), 3.11 (s, 3H), 3.12 (s, 3H), 3.29 (s, 3H), 3.44 (s, 3H), 3.56 (s, 3H), 3.77-3.79 (m, 1H), 4.57-4.59 (m, 1H), 4.69-4.72 (m, 1H), 4.77 (d, J = 14.0 Hz, 1H), 4.83-4.87 (m, 1H), 4.91-4.93 (m, 1H), 4.94 (s, 2H), 5.05-5.10 (m, 2H), 5.16 (d, J = 10.8 Hz, 1H), 5.33-5.37 (m, 2H), 5.59 (d, J = 5.6 Hz, 1H), 5.72 (dd, J = 4.4 Hz, 11.2 Hz, 1H), 6.13-6.20 (m, 1H), 6.31 (d, J = 15.6 Hz, 1H), 7.13 (d, J = 8.0 Hz, 1H), 7.19-7.34 (m, 4H), 7.53 (d, J = 8.4 Hz, 1H), 7.68 (d, J = 7.6 Hz, 1H), 8.04 (d, J = 10.0 Hz, 1H).

^{13}C NMR ($CDCl_3$) δ 9.94, 16.07, 16.82, 17.09, 18.23, 18.41, 18.72, 19.97, 20.43, 21.12, 21.85, 23.39, 23.52, 23.66, 23.73, 23.85, 24.32, 24.62, 24.88, 25.38, 29.27, 29.53, 29.71, 29.81, 31.16, 31.37, 31.62, 32.93, 34.28, 36.03, 36.69, 37.01, 37.56, 38.96, 39.60, 40.41, 42.42, 45.15, 48,21, 48.53, 48.78, 55.51, 57.64, 57.83, 59.02, 75.33, 126.02, 128.06, 128.79, 129.05, 129.69, 130.99, 135.76, 137.14, 170.10, 170.18, 170.35, 170.62, 171.14, 171.42, 171.64, 172.35, 173.46, 173.75, 173.84, 174.03; MS [m/z + H] 1389.9253, [m/z + Na] 1411.9055.

Biological Evaluation

Screening against a panel of 60 cancer cell lines was carried out at the National Cancer Institute (NCI), Bethesda, Maryland, USA, applying the standard protocol of the NCI[9].

Computational pharmacokinetic study

The pharmacokinetic properties of compounds 6, 7 and CsA was anticipated with the assistance of ADMETlab server. The compounds' structures were drawn by ChemDraw Ultra, saved as (.sdf) file, and then uploaded to ADMETlab server[10], which predicts the physicochemical descriptors and pharmacokinetic properties using certain algorithms.

RESULTS AND DISCUSSION

Rational design

In designing the novel CsA analogs, we considered the binding mode in CypA–CsA–CaN complex. The crystal structure of the CypA–CsA–CaN showed that CsA residues 9, 10, 11, 1, 2 and 3 are inserted into the nonpolar pocket of the CypA active site, while CsA residues Sar-3 to d-Ala-8 binds to the surface of CaN [11, 12]. Therefore, we thought that a modification in the part of CsA that binds to CypA would produce new derivatives that are less immunosuppressive but retain cyclophilin binding activity; we aimed to shift the affinity to cancer related cyclophilins. We have chosen nitrogen heterocyclic moieties, to be attached to CsA, due to their similarity to some other peptidyl prolyl cis-trans isomerase inhibitors [13]. For example, PiB (Figure 2) is peptidyl prolyl cis-trans isomerase inhibitor that was identified through Library screening. PiB inhibited Pin1 with IC50 of ~ 1.5 µM [14]. Pin1 is peptidyl prolyl cis-trans isomerase that has important roles in transcription regulation, cell cycle progression, apoptosis and protein degradation and it influences various oncogenic signaling pathways[15]. Another study by Uchida and co-workers has identified another Pin1 inhibitor, the phenyl-isothiazolone TME-001 (Figure 2) with IC_{50} of 6.1 µM [16]. Therefore, we designed two new derivatives that might be considered as a combination/hybrid of CsA and nitrogen heterocyclic moieties of the small molecules peptidyl prolyl cis-trans isomerase inhibitors.

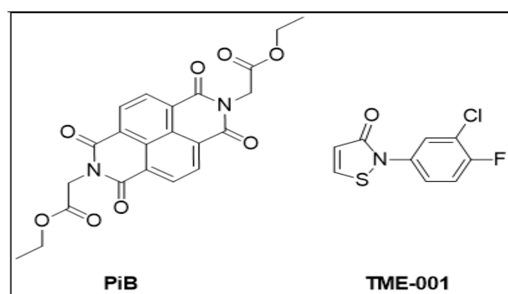
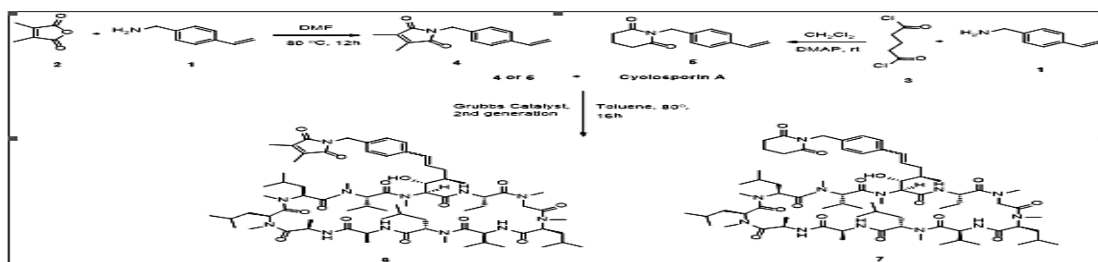


Fig. 2: Structure of PiB and TME-001

Chemistry

we used a simple synthetic strategy to obtain the target compounds **6** and **7** as illustrated in Scheme 1. Treatment of 4-vinylbenzylamine **1** with 2,3-Dimethylmaleic anhydride **2** led to the formation of the imide **4** in a typical reaction of a cyclic anhydride and a primary amine. While the imide **5** resulted from reaction of glutaryl chloride **3** with 4-vinylbenzylamine **1** in presence of DMAP. This reaction is thought to proceed in two steps, first a nucleophilic substitution of amine on one of the two acyl chloride moieties, followed by another nucleophilic substitution of the amide and the other acyl chloride moiety to form the cyclic imide **5**. Then compounds **4** and **5** were coupled to CsA using Grubbs catalyst 2nd generation having the chemical name (Benzylidene[1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro(tricyclohexylphosphine) ruthenium) to give the target compounds **6** and **7** in good yields. The (4*R*)-4-[(*E*)-butenyl]-4,*N*-dimethyl-L-threonine residue of CsA (MeBmt, residue 1) was used for the synthesis of the new analogues for two reasons. First, the double bond in MeBmt residue is easily accessible through olefin metathesis. Second, substitution at the double bond in MeBmt residue will keep the main skeleton of CsA unchanged giving an opportunity to study the effect of changing in MeBmt residue only.

NMR and mass spectroscopy confirmed the structures of the synthesized compounds. ^{1}H-NMR spectroscopy of compounds **6** and **7** showed four protons of the phenyl ring around 7.2 ppm, and singlet peak of two benzylic protons around 4.6 and 4.9 ppm in compounds **6** and **7** respectively. In addition, the characteristic vinyl protons of compounds **4** and **5** disappeared in compounds **6** and **7**, and the two olefenic protons appeared. ^{13}C-NMR of compounds **6** and **7** showed the aromatic carbon peaks between 126 to 137 ppm. In addition, the characteristic vinyl carbon peak of compounds **4** and **5**, at about 114 ppm, disappeared in compounds **6** and **7**. For a good comparison, we have taken NMR of CsA on the same instrument; the ^{1}H NMR spectral range from 6 to 8.5 ppm of CsA, compounds **6** and **7** are shown in (Figure 3), and the ^{13}C NMR of compounds **5**, **7** and CsA are shown in (Figure 4). The detailed ^{1}H and ^{13}C NMR charts are shown in the supplementary data.



Scheme 1: Synthesis of the target CsA derivatives.

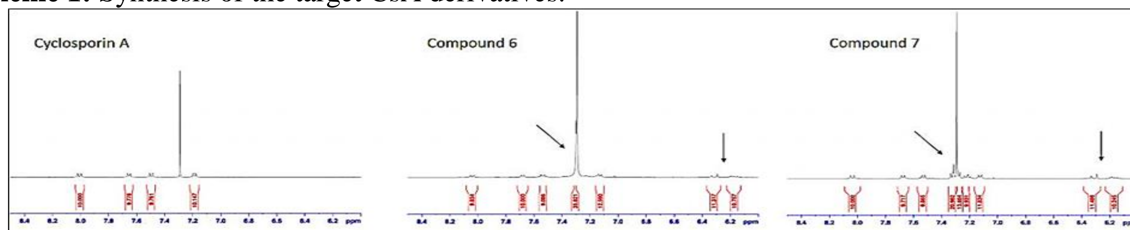


Fig. 3: ^{1}H-NMR of compounds 6, 7 and CsA (from 6 to 8.5 ppm)

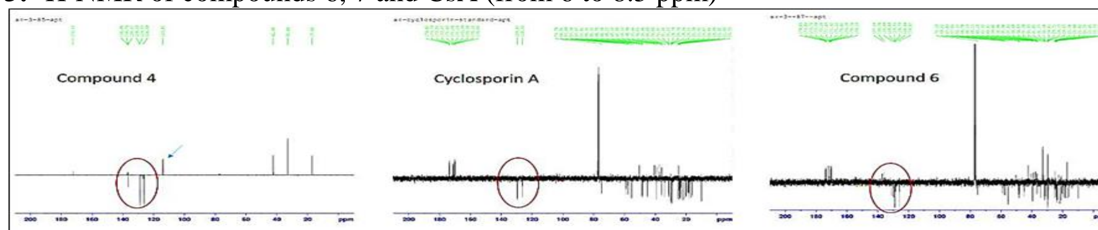


Fig. 4: ^{13}C-NMR of compounds 4, 6 and CsA

Biological evaluation

To test the effect of chemical modifications in CsA derivatives on antiproliferative activity; the target compounds were tested for their *in vitro* antiproliferative activity against tumor cells in a full panel of 60 cell lines taken from nine different tissues (blood, lung, colon, CNS, skin, ovary, kidney, prostate, and breast) by national cancer institute (NCI), Bethesda, Maryland, USA[9]. The compounds were tested at a single-dose concentration of 10 Mm, and the results were compared with the recorded results of CsA against NCI cell lines. Compound **7** showed also an overall moderate antiproliferative activity with a mean value of 57.54 %. While, compound **6** showed an overall weak antiproliferative activity with a mean value of 28.83%. The maximum inhibitory effect of compound **6** was against PC-3 prostate cell line with a value of 60.22% (Figure 5). Compound **7** had an inhibitory effect higher than 80% over 13 cancer cell lines, and close to or higher than 100% over six cancer cell lines (Figure 6). More importantly, the piperidinedione derivative **7** showed comparable activity to CsA against these cell lines; SR, HCT-15, LOX IMVI, T-47D (Table 1, and Figures 6 and7). Moreover, compound **7** showed significantly higher inhibition than CsA against NCI-H226 cell line.

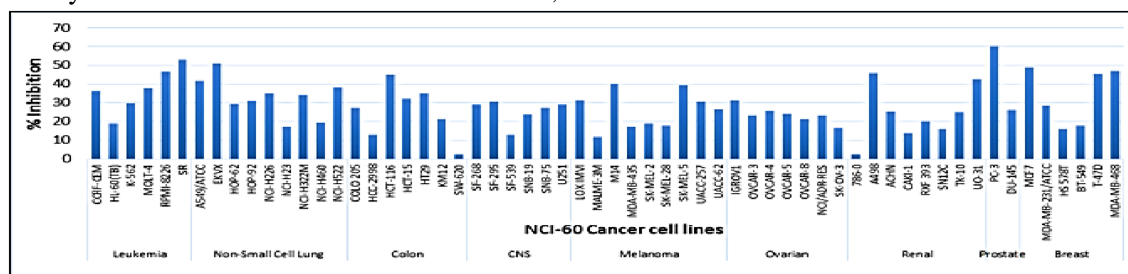


Fig. 5: % Inhibition expressed by compound **6** at a single-dose concentration of 10 μM over the NCI-60 cancer cell lines

Table 1: % inhibition of compounds **7** against most sensitive cancer cell lines in comparison with CsA

Cell line/Cancer type	% Inhibition at 10 µM	
	Compound 7	CsA (ref. 9)
SR/Leukemia	102.57	100
NCI-H226/Non-small lung cancer	122.85	94.2
HCT-15/Colon	80.53	81
HT29/Colon	124.80	137.2
LOX IMVI/Melanoma	98.99	99.6
A498/Renal	95.46	105.7
RXF 393/Renal	82.67	No available data
MCF7/Breast	74.74	81.3
T-47D/Breast	74.72	76.2

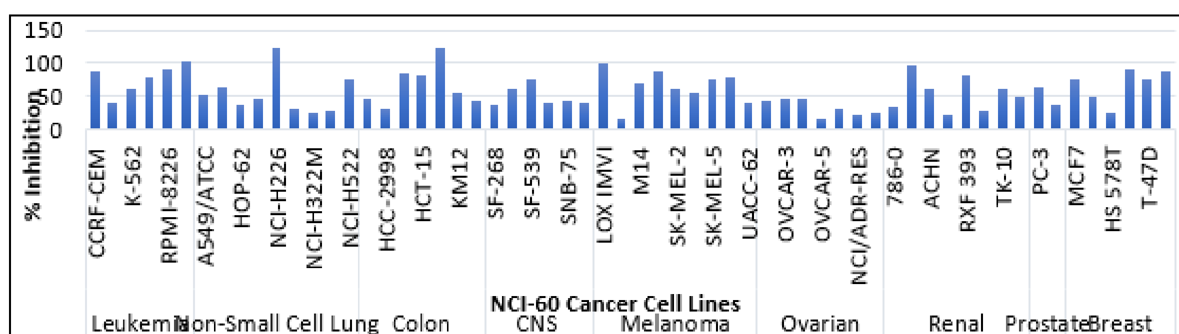


Fig. 6: % Inhibition expressed by compound **7** at a single-dose concentration of 10 µM over the NCI-60 cancer cell lines

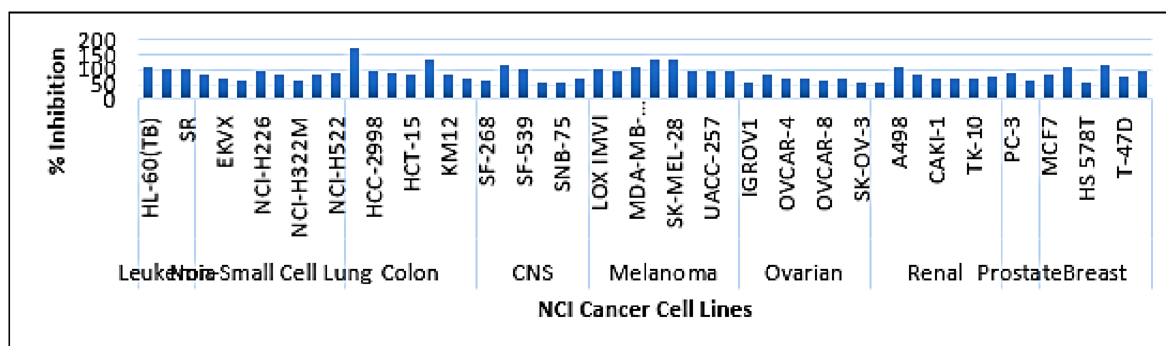


Fig. 7: % Inhibition expressed by CsA at a single-dose concentration of 10 µM over the NCI cancer cell lines

Table 2: predicted pharmacokinetic properties of compounds 6, 7 and CsA

Compound	(LogS) Solubility (mol/L)	(LogD) Distribution Coefficient D at PH=7.4	Human Intestinal Absorption	Plasma Protein Binding (%)
6	**-4.640**	**3.496**	**0.288**	**74.441**
7	**-4.671**	**3.474**	**0.242**	**78.715**
CsA	**-4.095**	**3.299**	**0.222**	**92.113**

Computational pharmacokinetic study

CsA has poor solubility, weak absorption and variable bioavailability[17] . The structural modifications in the new analogs, in addition to their impact on the CsA pharmacodynamics, may also affect the pharmacokinetic properties. Therefore, we did comparative computational studies between CsA and the new analogs (compounds **6** and **7**) using pharmacokinetic

predictive tool (ADMETlab server)[10]. We found that the new derivatives (compounds **6** and **7**) have better predicted solubility, absorption, distribution, and less plasma protein binding than the parent compound (CsA) (Table 2).

Conclusion

Synthesis of new analogs of approved drugs is a well-known strategy in drug discovery research. New analogs are usually designed with the aim of improving activity, enhancing pharmacokinetic properties, increasing selectivity, overcoming drug resistance, or getting a clearer picture about structure activity relationship. In this line; we have designed, synthesized and screened two CsA derivatives with the aim of improving antiproliferative activity. The pyrrolidinone analog (compound **6**) showed weak activity, while the piperidinedione analog (compound **7**) showed comparable activity to the parent compound (CsA) against four cell lines. Moreover, compound **7** showed significantly higher inhibition than CsA against NCI-H226 cell line (non-small cell lung cancer). It can be concluded that a little difference in structure between compounds **6** and **7** has resulted in dramatic difference in antiproliferative activity; this is an important aim of analog design and study. Finally, both compounds **6** and **7** showed better-predicted pharmacokinetic properties than CsA.

Formatting of funding sources

This research was supported by Korea Institute of Science and Technology, Seoul, Republic of Korea

Acknowledgement

We would like to express our gratitude and thanks to the National Cancer Institute (NCI), Bethesda Maryland, USA for performing the anticancer testing of new compounds. We also would like to express our gratitude and thank to Prof. Hyun-Mee Park at Advanced Analysis Center, Korea Institute of Science and Technology, Seoul, Korea, for carrying out the mass spectroscopic analyses.

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Bull. Pharm. Sci., Assiut University, Vol. 45, Issue 1, 2022, pp. 191-199.

نشـرة العلـوم الصيدليـــــة
جامعة أسيوط

تشييد مشتقين جديدين من السيكلوسبورين أ وتقييم تأثيرهم المضاد لتكاثر الخلايا السرطانية

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في هذا البحث تم تصميم وتشييد مشتقين جديدين من السيكلوسبورين أ. وقد تم تشييد المركبات المستهدفة باستخدام كيمياء الإبدال الأوليفينية olefin metathesis. وقد تم التأكد من الصيغة البنائية للمركبات المستهدفة بواسطة تقنية الرنين النووي المغناطيسي لعنصري الهيدروجين والكربون، بالإضافة لمضياف الكتلة عالي الدقة. وتم اختبار الفاعلية البيولوجية للمركبات المشيدة كمضادات للسرطان ضد ستين نوعا من الخلايا السرطانية في المعهد الوطني للسرطان بالولايات المتحدة الأمريكية. وقد أظهر المركب رقم ٧ تأثيرا مثبطا لنمو الخلايا السرطانية بنسبة تزيد عن ٨٠% في ثلاثة عشر نوعا من الخلايا السرطانية، وأظهر نفس المركب أيضا تأثيرا مثبطا لنمو الخلايا السرطانية بنسبة تقترب من أو تزيد عن ١٠٠% في ستة أنواع من الخلايا السرطانية. ومن أهم النتائج أن مركب رقم ٧ أظهر تثبيطا لنمو خلايا سرطان الرئة من نوع NCI-H226 يفوق بكثير التثبيط الناتج عن المركب الأصل (السيكلوسبورين أ). أخيرا، فقد أظهرت بعضُ حسابات المحاكاة والنمذجة حركية دوائية متوقعة للمركبين ٦ و٧ أفضل من تلك المتوقعة للسيكلوسبورين أ.