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Novel potential anticancer agents

Izabela Jęśkowiak*, Stanisław Ryng

Department of Organic Chemistry, Faculty of Pharmacy,
Wroclaw Medical University, 211a Borowska Str., 50-556 Wrocław, Poland

*E-mail address: izabela.jeskowiak@student.umed.wroc.pl

ABSTRACT

Cancer is a widespread and lethal disease. It is considered as the first leading cause of deaths in economically developed countries. Nonetheless, the search for an effective treatment of cancer is still a major challenge. In this review, we analyzed the core structure of compounds and their impact on antitumor activity. Diversity of heterocyclic ring in the innovatory anticancer substances showed the potential in the design and development of new anticancer drugs.

***Keywords*:** anticancer agents, drug design, carcinoma cell lines

1. INTRODUCTION

Nowadays, we are confronted with the problem of low selectivity and resistance to anticancer drugs. In this review we want to show the tendency in receiving new synthetic potential oncologic medicines as well as to indicate in these substances the pharmacophore core scaffolds.

Anticancer properties of chemically synthesized compounds have continuously been optimized for better efficacy and selectivity. Derivatives of heterocyclic compounds are known to have a selective antiproliferative effect against many types of cancer [1-7].

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2. RESULT

Wang et al. synthesized four series of Sorafenib derivatives containing pyrazole scaffold. All of the target compounds were evaluated for cytotoxicity against human lung cancer A549, human liver cancer HepG2, human breast cancer MCF-7 and human prostatic cancer PC-3 cell lines. Most of the novel derivatives exhibited moderate to good antitumor activities. The best antitumor activity showed compound **8b** (Figure 1), which had cytotoxicity against A549, HepG2 and MCF-7 cell lines on the level equivalent to Sorafenib. The pyrazole scaffolds played an important role in the anticancer activity of this series of compounds. Various substitutions of the aryl group influenced the cytotoxicity of novel compounds. The group Br and Cl at C-3 position or none substituents enhanced antitumor activity of synthetized derivatives, but groups such as –CN, $–NO_2$ at C-4 position decreased the cytotoxicity of these substances [8].

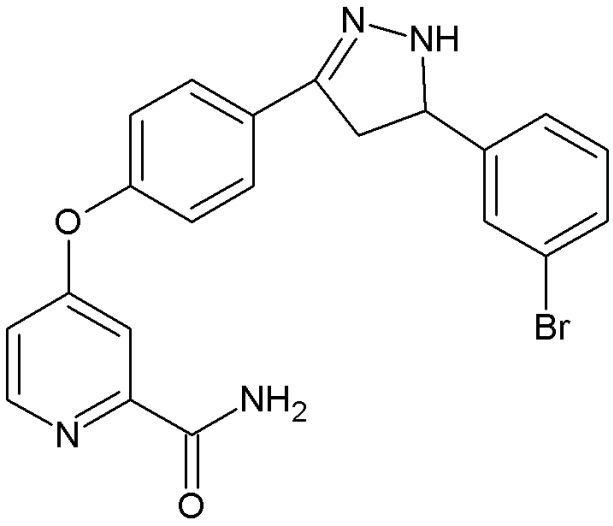


Figure 1. The compound **8b** obtained by Wang et al [8].

Ji et al. obtained a new class of spirotetrahydrothiopyran–oxindole p53–MDM2 inhibitors. The antitumor activity was evaluated against cell lines: HCT116 colon cancer cells, MCF-7 breast cancer cells and A549 lung cancer cells. Reference drugs were Nutlin-3, which is a representative p53-MDM2 inhibitor and the lead compound consists of a oxindolespirotetrahydropyran core scaffold. The compounds with large hydrophobic groups such as **B14** (Figure 2) were the most active against all the three cancer cell lines. Moreover, **B14** could effectively induce the apoptosis of A549 lung cancer cells by inhibiting p53–MDM2 protein-protein interaction. This study indicated the significance of a hydrofobic side chain and spiroindole–thiopyranopyridone on the tumor activity as well the impact of this core structure on potent MDM2 inhibitory [9].

Previous publications have reported that diphenylthiazole derivatives have anti-inflammatory and anticancer activities with a significant affinity for COX-2 enzyme. Abdelazeem A.H et al. obtained diphenylthiazole derivatives, in which antitumor activity was evaluated against MCF-7 human breast carcinoma, HT-29 human colorectal adenocarcinoma and A549 human lung carcinoma. The reference drug was Doxorubicin. The most active compounds were estimated in vitro for COX-1/COX-2 selectivity and inhibitory activity.

The present work suggests that the inhibition of COXs activity is associated with the strong anticancer effect, most notably with COX-2 selectivity. In addition, the most active antitumor compound **17b** (Figure 3) had greater in vivo anti-inflammatory activity compared to that of Indomethacin. The most active compounds **10b** and **17b** (Figure 3) were explored in terms of their inhibitory activity against three known anticancer targets, including BRAF, EGFR and tubulin. These compounds present outstanding activity against EGFR, good activity against BRAF, but weak activity in the tubulin polymerization assay. The multi-target mechanism of antitumor drugs is a desired property in chemotherapy [10].

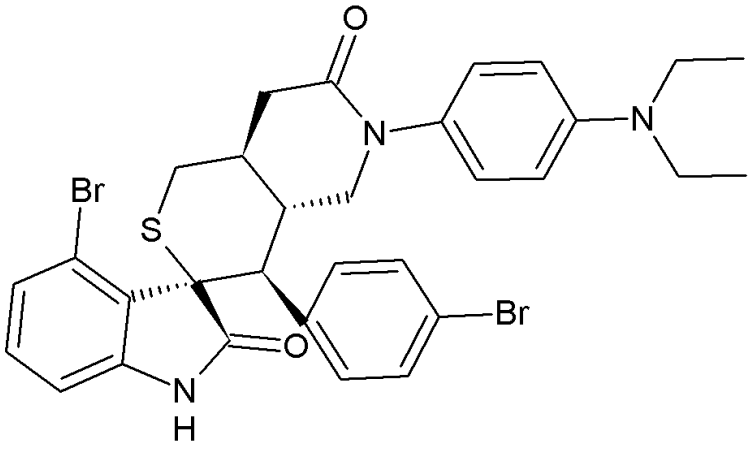


Figure 2. The compound **B14** obtained by Ji et al [9].

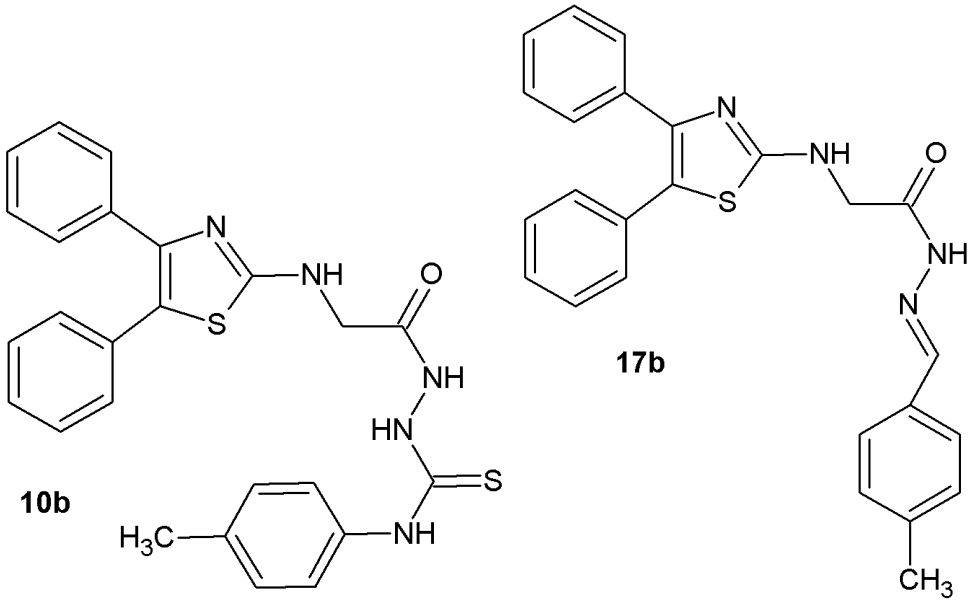


Figure 3. The compounds **10b** and **17b** obtained by Abdelazeem et al [10].

Yang C.J. et al. designed 7-substituted camptothecin derivatives with piperazinyl-sulfonylamidine moieties. All novel compounds presented cytotoxic activity against tested

cancer cell lines, i.e. KB nasopharyngeal carcinoma, A-549 lung carcinoma, MDA-MB-231 breast carcinoma, KB-VIN (MDR KB subline), MCF-7 breast adenocarcinoma and were more potent than irinotecan. Whereas irinotecan lost its effects completely against KB-VIN, the majority of compounds (especially **13r** and **13p** – Figure 4) from this series assessed cytotoxicity against the multidrug-resistant (MDR) KB-VIN and parental KB tumor cell lines. The 7-substituted camptothecin derivatives with piperazinyl-sulfonylamidine moieties are excellent candidates for treating MDR phenotype cancer [11].

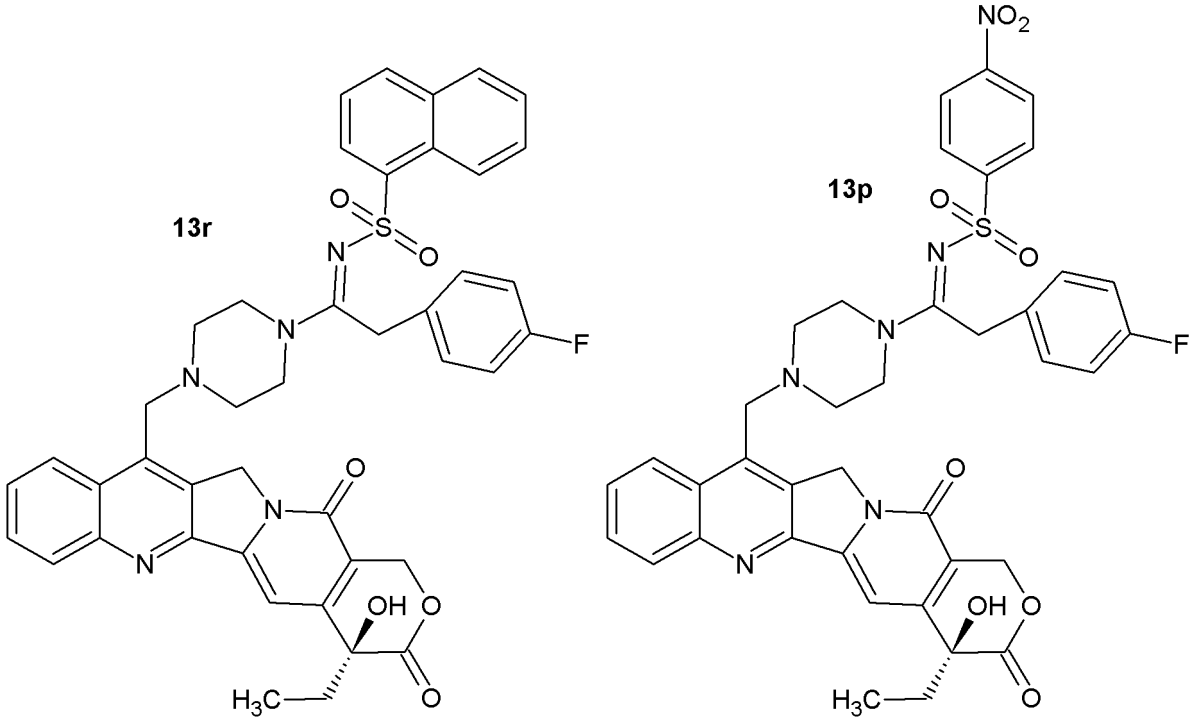


Figure 4. The compounds **13r** and **13p** obtained by Yang et al [11].

Pyrazolone is one of the most important heterocyclic compounds with antitubercular, anti-inflammatory, antibacterial, antifungal and antitumor activity [12, 13]. Bakr E.A et al. have synthesized (E)-4-((2-hydroxyphenyl)diazenyl)-3-phenyl-1H-pyrazol-5(4H)-one, HL (Figure 5), and their Ni(II), Pd(II) and Pt(II) metal complexes, including the heterocyclic pyrazolone nucleus. The antitumor activity of these compounds were evaluated against four cell lines such as HePG-2 hepatocellular carcinoma, HCT116 colorectal carcinoma, PC-3 human prostate carcinoma and MCF-7 mammary gland breast carcinoma. The ligand HL presented a strong antitumor activity compared to reference drug (5-fluorouracil). For metal complexes, the order of activity was: Pd(II) > Ni(II) > Pt(II). The 5-fluorouracil had lower cytotoxic activity compared to the ligand HL and metal complexes against hepatocellular carcinoma and human prostate carcinoma. The antitumor activity of compounds may be similar to that of 5-fluorouracil which interferes with DNA replication. Moreover, the metal complexes showed much lower antioxidant activity than the free ligand HL. However, the complexes had higher antibacterial activity than the free ligand. This publication offered the use of ligand and their complexes in the novel oncology chemotherapy [14].

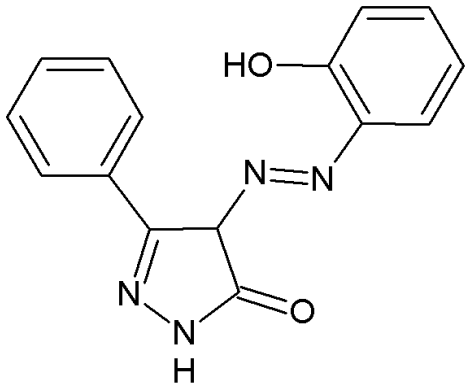


Figure 5. The ligand HL obtained by Bakr et al [14].

Many α-aminophosphonate derivatives containing a 2-oxoquinoline structure showed moderate to high levels of antitumor activities against the chosen cancer cell lines. The compounds received by Fang Y.L. et al. were examined for antitumor activities against the cancer cell lines: A549 (human lung adenocarcinoma cell), HeLa (human cervical carcinoma cell), MCF-7 (human breast cancer cell) and U2OS (human osteosarcoma cell). Most of these compounds exhibited more potent inhibitory activities comparable to 5-fluorouracil.

The mechanism of the representative compound **4u** (Figure 6) caused anticancer activity against human cervical carcinoma cells by inducting apoptosis and stopped the cell cycle at the S and G2 phases [15].

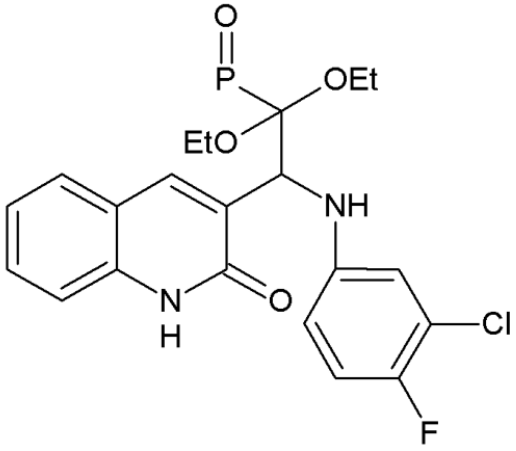


Figure 6. The compound **4u** obtained by Fang et al [15].

Huang R. et al. introduced phosphoryl amino acid moiety into the parent alizatin core to create novel structures with strengthened antitumor activities and a potential apoptosis inducing effect.

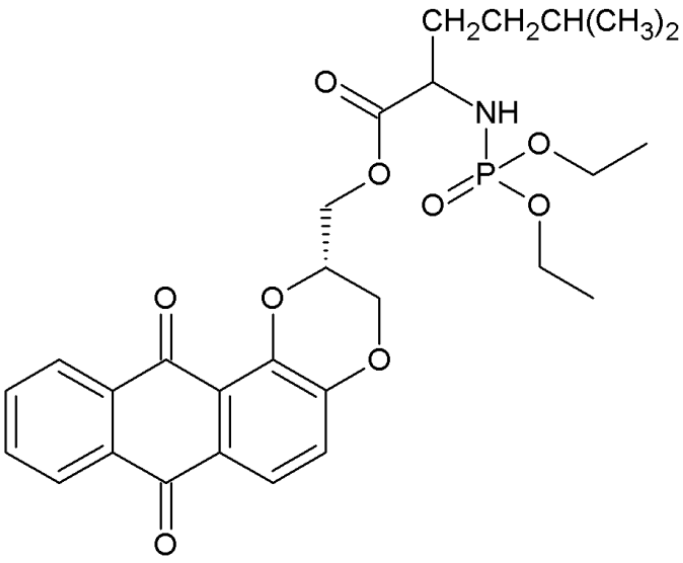


Figure 7. The compound **8d** obtained by Huang et al [16].

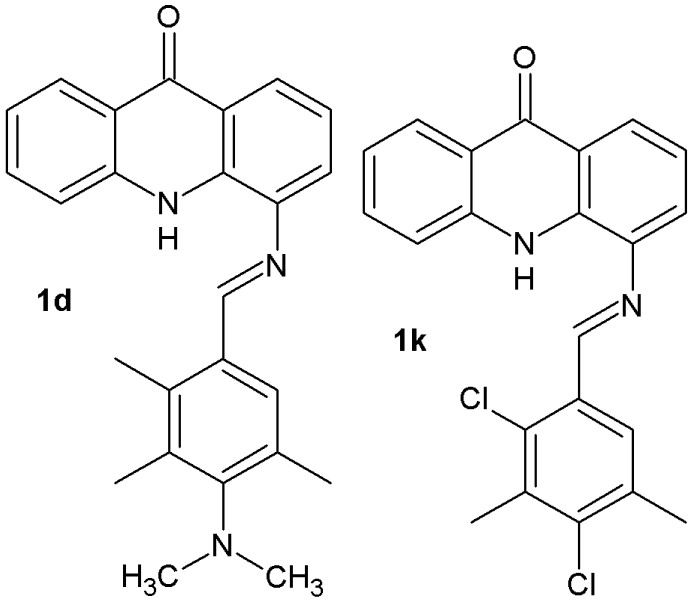


Figure 8. The compounds **1d** and **1k** obtained by Tian et al [17].

The antiproliferative activity of the compounds was characterized against five cancer cell lines MGC-803 (human gastric carcinoma), HepG2 (human liver carcinoma), T24 (human bladder cancer), SK-OV-3 (human ovarian cancer), NCI-H460 (human large cell lung cancer) and HL-7702 (human normal liver). Novel derivatives with an alizaryn core showed low cytotoxicity against normal HL-7702, but also exhibited relatively high cytotoxicity compared to alizaryn. The best cytotoxicity against SK-OV-3 cells had **8d** (Figure 7), which was slightly worse than Doxorubicin. This compound could act as a telomerase inhibitor and it stops the G2

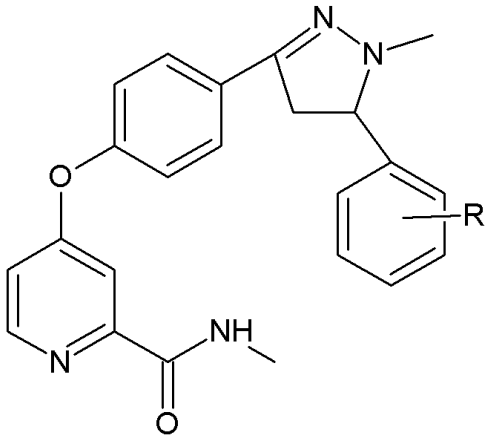
phase. The anticancer activity of this compound probably depended on the apoptosis of carcinoma cells via regulation of Bcl-2 family members as well as the activation of caspase-9 and caspase-3 [16].

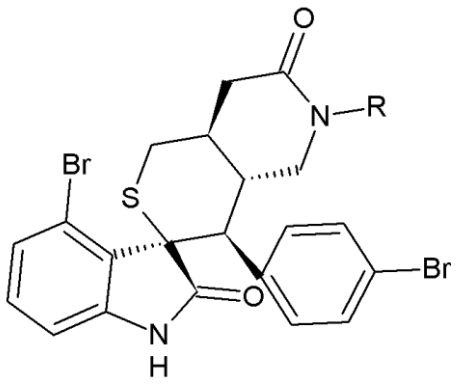
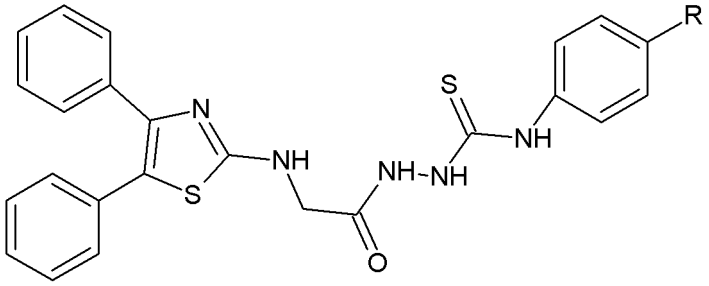
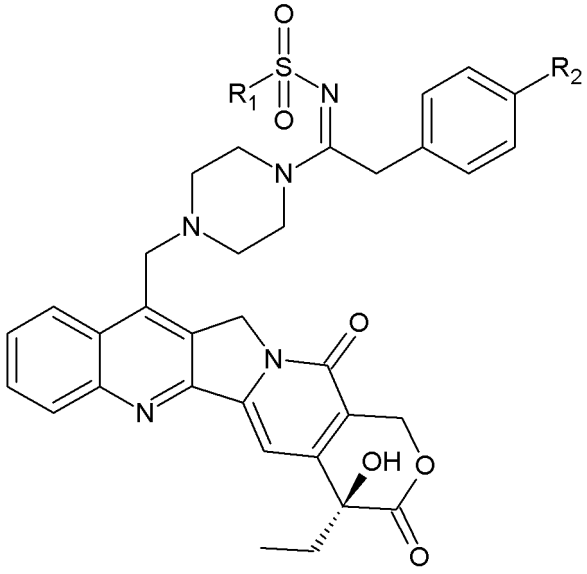
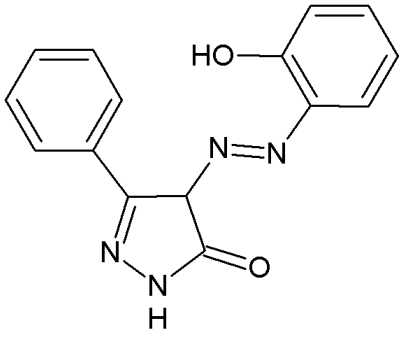
A series of 4-aminoacridone Schiff bases were screened for their antitumor activity against A549 human lung adenocarcinoma cells, HeLa human cervical carcinoma cells, SGC-7901 gastric cancer cell line and Raji cells (B-*cell* lymphoma line). These compounds showed cytotoxicity against the Raji cell and HeLa cell lines comparable to Cisplatin. Nevertheless, the implementation of a small electronegative group added to the 1.4-position or a large electropositive group at the 4-position of 4-aminoacridone caused an increase in the activity against Raji cells. Compounds **1d** and **1k** (Figure 8) possessed major potency and selectivity towards HeLa cells compared to any of the other cell lines. Docking analysis gave a proof that **1d** could act as a MDR inhibitor, because of its intense interactions with the P-glicoprotein transmembrane binding pocket comparable to its ATP binding site [17].

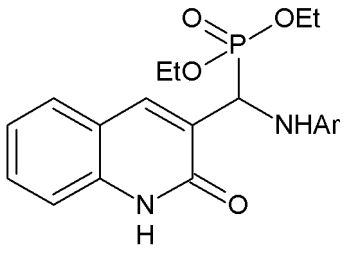
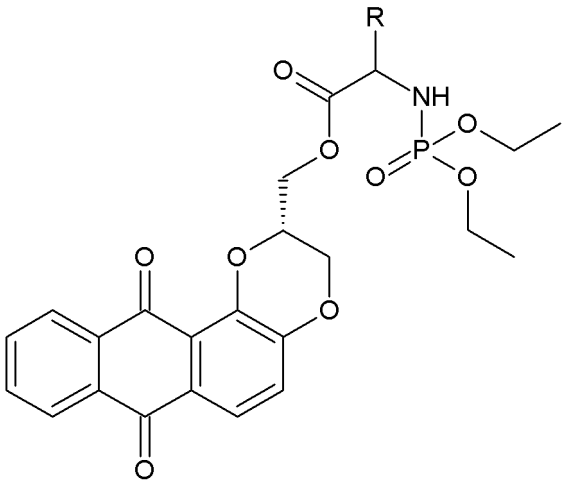
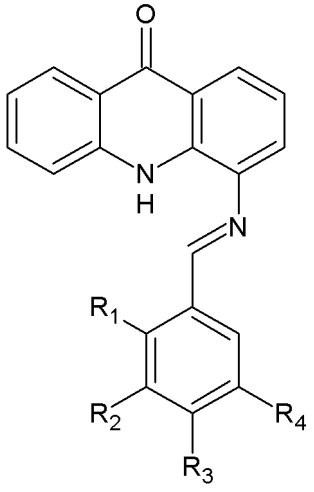
3. CONCLUSIONS

The results showed that these core structure scaffolds (Table 1) play a key role in anticancer activity. There are many different types of basic structures, which could have an influence on various carcinoma cell lines. The majority of research concerns the antitumor activity against human breast cancer cells and human lung cancer cells. Most of the compounds showed activity against the tested cell lines, but only one study examined the influence of new compounds in the normal human cell lines. The lack of cytotoxicity towards healthy cells is an important feature of potential medicine. Furthermore, this property also proved the selectivity of substances in the treatment of certain types of cancer. It is interesting that the most potent anticancer diphenylthiazole derivatives had anti-inflammatory activity.

Table1. Core scaffolds of novel potential anticancer compounds.

Researcher's group	**Core scaffold**
Wang M. et al.	

Ji C. et al.	
Abdelazeem A.H. et al.	
Yang C.J. et al.	
Bakr E.A et al.	

Fang Y.L. et al.	
Huang R. et al.	
Tian L. et al.	

Perhaps the use of metal complexes to the most active compounds, which did not undergo clinical research or current anticancer medicines, would decrease the range of adverse effect. Some 7-substituted camptothecin derivatives with piperazinyl-sulfonylamidine moieties, deserve particular attention, because of their characteristic cytotoxicity against multi-drug resistance nasopharyngeal carcinoma cell lines.

The main aim of synthesizing new anticancer compounds is to produce a substance that would destroy only cancerous cells, saving healthy cells of the organism, a substance that would also be characterized by a substantial effectiveness and good tolerance. For this reason, there is

ongoing research devoted to obtaining compounds with such desired features, but learning about more pharmacophore could increase the success of this process.

References

[1] A.M. Saleh, M.O. Taha, M.A. Aziz, M.A. Al-Qudah, R.F. AbuTayeh, S.A. Rizvi, *Cancer Letters* 375 (2016) 199-208.

[2] B. Zhang, W. Shi, J. Li, C. Liao, L. Yang, W. Huang, H. Qian, *ChemBiol Drug Des.* (2017) 1-9.

[3] A.H. Abdelazeem, M.T. El-Saadi, E.G. Said, B.G.M. Youssif, H.A. Omar, S.M. El-Moghazy, *Bioorganic Chemistry* 75 (2017) 127-138.

[4] K.W. Pratz, S.M. Luger, *Curr. Opin. Hematol.* 21(2014) 72-78.

[5] Sudhindra, C.C. Smith, *Hematol. Malig. Rep.* 9 (2014) 174-185.

[6] D. Micozzi, F.M. Carpi, S. Pucciarelli, V. Polzonetti, P. Polidori, S. Vilar, B. Williams, S. Costanzi, S. Vincenzetti, *Int. J. Biol. Macromol.* 63 (2014) 64-74.

[7] P.D. Eckford, F.J. Sharom, *Chem. Rev.* 109 (2009) 2989-3011.

[8] M. Wang, M. Wang, S. Xu, H. Lei, C. Wang, Z. Xiao, S. Jia, J.Zhi, P. Zheng, W. Zhu, *Bioorganic & Medicinal Chemistry* 25 (2017) 5754-5763.

[9] C.Ji, S. Wang, S. Chen, S. He, Y. Jiang, Z. Miao, J. Li, C. Sheng, *Bioorganic & Medicinal Chemistry* 25 (2017) 5268-5277.

[10] C.J. Yang, Z.L. Song, M. Goto, Y.Q. Liu, K.Y. Hsieh,S.L. Morris-Natschke, Y.L. Zhao, J.X. Zhang, K.H. Lee, *Bioorganic & Medicinal Chemistry Letters* 27 (2017) 3959-3968.

[11] E.A. Bakr, G.B. Al-Hefnawy, M.K. Awad, H.H. Abd-Elatty, M.S. Youssef, *Appl.Organometal. Chem*. (2017) e4104-e4122.

[12] J. Lu, L. Zhang, L. Liu, G. Liu, D. Jia, D. Wu, G. Xu, *Spectrochim. Acta* 71 (2008) 1036-1041.

[13] A.A.S. Al-Hamdani, W. Al-Zoubi, *Spectrochim. Acta Part A: Mole and Biomol. Spect.* 137 (2015) 75-89.

[14] Y.L. Fang, Z.L. Wu, M.W. Xiao, Y.T. Tang, K.M. Li, J. Ye, J.N. Xiang, A.X. Hu, *Int. J. Mol. Sci*. 17 (2016) 653-668.

[15] R. Huang, L. J,G. Yao, W. Dai, X. Huang,Z.X. Liao, H. Wang, *Med. Chem. Res*.26 (2017) 2363-2374.

[16] L. Tian, C.J. Feng, T.X. Li, Z. Li, W.H. Yang, X.E. Han, *Med. Chem. Res*. 26 (2017) 2538-2546.

[17] A.H. Abdelazeem, A.M. Gouda, H.A. Omar, M.F. Tolba, *Bioorg. Chem*. 57 (2014) 132-141