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Synthesis of Novel 2(3H)-Benzoxazolone Mannich Bases as Potential Agents for Future Studies of Cancer Treatment

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Author's contribution

The sole author designed, analysed, interpreted and prepared the manuscript.

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ABSTRACT

Aims: In this study, a series of new Mannich bases of 2(3H)-benzoxazolone derivatives containing substituted cyclic amine moieties with a potential to show cytotoxic activity have been prepared. In order to develop effective anticancer agents against various cancer cell lines, it is essential to study the structure activity relationship and the effect of different substituents on the activity of heterocyclic scaffolds which were known to have cytotoxic activities.
Study Design: *In silico* and experimental design.
Place and Duration of Study: Pharmaceutical Chemistry Department, Faculty of Pharmacy, Near East University, Nicosia, Cyprus, between January 2019- September 2020.
Methodology: In this work, 2(3H)-benzoxazolone derivatives were prepared by Mannich reaction. The synthesis and structural characterization of the compounds were performed experimentally by FT-IR, ^{1}H NMR, ^{13}C NMR spectra and elemental analysis. In silico prediction of cell line cytotoxicity with PASS based CLC-Pred tool was performed to predict cytotoxicity of the compounds against different tumor cell lines.
Results: *In silico* prediction results for the compounds showed that all benzoxazolone derivatives have cytotoxic activity against different cell lines and tumor types. It was clearly understood that the

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cytotoxicity of the compounds was affected by the substituents on their piperazine moieties and by the substituents on benzoxazolone core structure.
Conclusion: In conclusion, newly synthesized Mannich bases of benzoxazolone derivatives were reported for the first time which may have a potential to show anticancer activities at different cancer cell lines. The efficiency of new compounds against cancer could be found via PASS based CLC-Pred database and could be further investigated by *in vivo* experimental cytotoxicity studies in the future to design new anticancer drug candidates.

Keywords: 2(3H)-Benzoxazolone; piperazine; cytotoxicity; Mannich reaction; cancer; CLC-Pred database.

ABBREVIATIONS

NMR : Nuclear Magnetic Resonance
FT-IR : Fourier-Transform Infrared Spectro Scopy
PASS : Prediction of Activity Spectra for Subs Tances

1. INTRODUCTION

Heterocyclic compounds are useful pharmacophores in medicinal chemistry which play an important role to synthesize several chemical structures with different pharmacological activities [1]. Benzoxazolone derivatives with substituted piperazine moieties as cyclic amines were considered as privileged scaffolds in the design of new pharmacophores allowing several chemical modifications to take place for design and development of new drug candidates [2]. Some of the reported activities of 2(3H)-benzoxazolone derivatives includeanti microbial [3], analgesics [4-7] anti-inflam matory [8-11], anti-nociceptive [12], anticonvulsant [13], dopaminergic [14] and immu no-deficiency virus (HIV) reverse transcriptase inhibitory effects [15].

Mannich reaction is a useful procedure in order to synthesize natural and biologically active organic compounds. German chemist Carl Ulrich Franz Mannich gave his name to this reaction which he discovered in 1912 [16]. The Mannich reaction occurs by the condensation of amines mainly a primary or secondary amine into an aldehyde or usually a hydrochloride salt with a compound containing one or more active hydrogen atoms. The β-aminocarbonyl compound formed as a result of the reaction is called the Mannich base. In case of Mannich reaction, active hydrogen atoms are replaced with an aminomethyl group. Sometimes these aminomethyl groups can be found as substituted derivatives [17]. The popular application area to date has been in natural product synthesis and pharmaceutical chemistry [18,19]. Mannich base is a β-amino ketone which acts as an active agent as well as a crosslinker for the synthesis of very important pharmacophores or various natural products.The main mechanism of Mannich reaction has two steps; the first step is iminium ion formation shown in Fig. 1 and Fig. 2. The second step is the attack of iminium ion by benzoxazolone nucleus as a nucleophile. Mannich bases were preferred for use in the organic synthesis because of their reactivity in medicinal chemistry.

Second Step: Attack of iminium ion by the substrate and deprotonation of active hydrogen by nucleophile to give the target product as shown in Fig. 3.

Cancer is the most prominent, complex and lethal disease which became a serious concern of today's medical science. It poses a great challenge to medical scientific community for development of drugs, medicines and procedures for safer treatment and cure of cancer disease [20,21]. The results of previous anticancer studies clearly indicate that molecules bearing benzoxazolone scaffold have strong cytotoxic effects on cancer cells [22-24]. It is well understood from these results that effect of substituents on the anticancer activity of benzoxazolone Mannich bases has become important for the development of new drug molecules for future studies [22]. Ivanova and co-workers studied benzoxazolone derivatives having chalcone like structures for anticancer activity against BV-173, a human pre-B-cell leukemia cell line, with molarities ranging between 4,7- 18,4 μM and the IC_{50} values were measured showing moderate activity [22]. Similarly, Ognyan *et al* studied possible anticancer activities of benzoxazolone derivatives with trimethoxyphenyl propenoyl group at position 6 of the core structure [23]. The compounds were evaluated for their cytotoxicity against several cell lines such as BV-173, HL-60, SKW-3, MDA-MB-231 and K-562. These derivatives were found to have highest chemosensitivity in BV- 173 but they were

moderately active in SKW-3 cell lines. Earlier in 2020, Erdag *et al* investigated similar benzoxazolone derivatives having different piperazine group at the third position of the core structure which were screened for their cytotoxicity toward MCF-7 cancer cell line via MTT assay [24]. It was reported that compounds having 2,5 xxx-dimethylphenyl piperazine substituents at the 3-position of benzoxazolone were effective in non-metastatic MCF-7 cell line and they were found to induce apoptosis via different pathways according to the immunocytochemical evaluations [24].

Further studies involving cytotoxic activities of benzoxazolones appear promising in the development of effective novel large series of benzoxazolone analogues which will be subjected to cytotoxicity testing for different tumor cell lines in view of defining prospective lead compounds. Nowadays, especially anticancer agents are in the group of essential

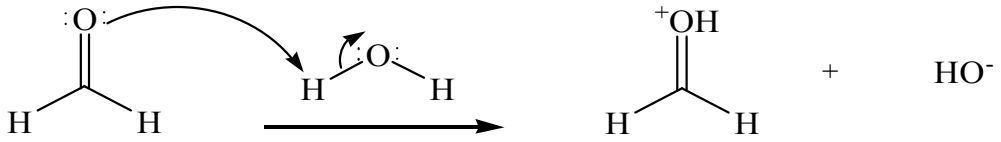

Fig. 1. Formation of iminiumion

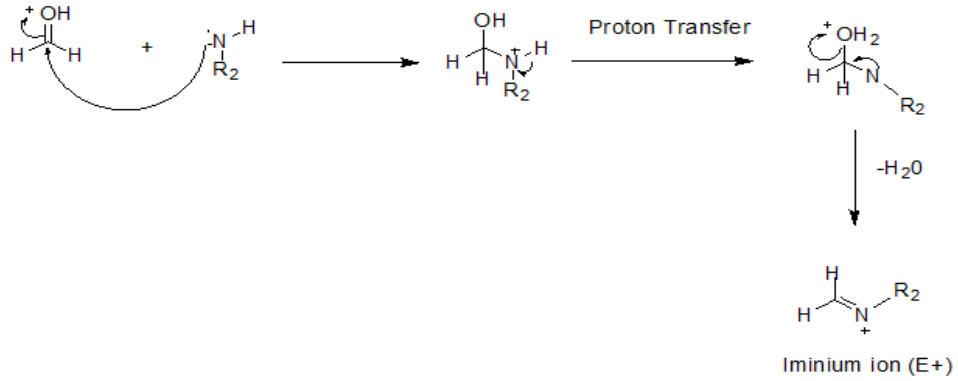

Fig. 2. Mannich reaction mechanism of benzoxazolone derivatives (first step)

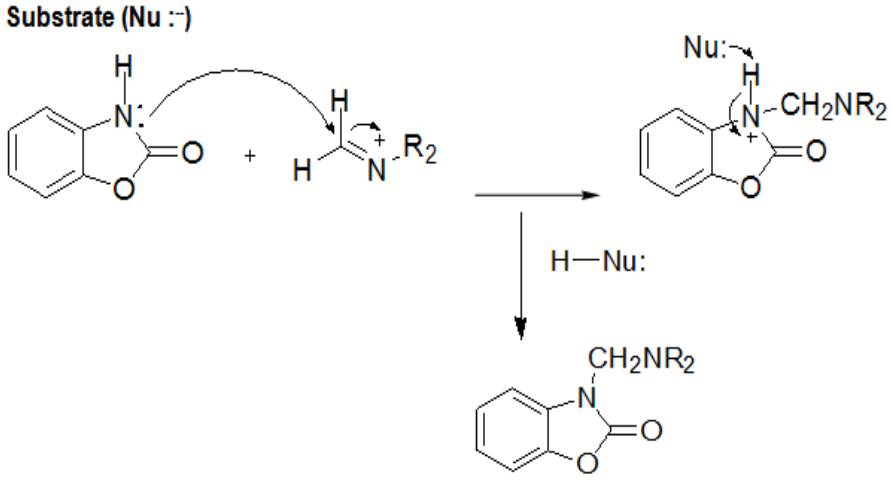

Fig. 3. Mannich reaction mechanism of benzoxazolone derivatives (second step)

drug molecules and the need of designing selective anti-cancer drugs has become important. In this work, in silico research study on cytotoxicity potential of novel benzoxazolone derivatives against different cell lines is aimed to be helpful in drug discovery and to encourage new cytotoxicity studies to be carried out *in vivo* environment for further evaluations in the future.

2. MATERIALS AND METHODS

2.1 Materials

All chemicals were obtained from Sigma Aldrich Chemical Co. and were used without further purification. Melting point of the compounds was recorded on the Mettler Toledo FP 900 Thermo System Digital apparatus.The FT-IR spectra of the compounds were recorded on a Perkin Elmer Spectrum 100 spectrophotometer with attenuated total reflection (ATR) (in wave numbers) in cm^{-1}. The ^{1}H and ^{13}C NMR spectra of the compounds were recorded on a Mercury Varian 400 MHz NMR Spectrometer using deuterated chloroform ($CDCl_3$) and dimethylsulfoxide (DMSO-d_6) as solvents.

Chemical shift (δ) values were reported in parts per million (ppm). Elemental analyses (C, H, N) were performed on Leco CHNS 932 analyzer. The purity of the compounds was assessed by thin layer chromatography (TLC).

2.2 General Synthesis Method

Synthesis was carried out similar to the previously published procedure [24]. In the synthesis, equal molar concentrations of 2(3H)-benzoxazolone or 5-chloro-2(3H)-benzoxazolone and appropriate piperazine derivatives were dissolved separately in methanol and mixed after addition of appropriate amount of formalin (35% w/v) into the reaction mixture followed by heating under reflux conditions for 1 hour. The reaction mixture was put into an ice bath after reflux and solid precipitate was dried after vacuum filtration and then purified by recrystallization using ethanol as a solvent.

2.3 *In silico* Prediction of Cell Line Cytotoxicity

CLC-Pred Tool was performed to predict cytotoxicity of synthesized compounds for different tumor cell lines. CLC- Pred method is based on structure-cell line cytotoxicity relationships designed by PASS (Prediction of Activity Spectra for Substances), a database which gives the significant bioactivities of chemical compounds as Pa (Probable activity) and Pi (Probable inactivity) values to mention the compounds, whether they are active or inactive. The accuracy of in silico prediction results significantly matches with the results of *in vivo* experimental (about 96%). The efficiency of compounds against cancer could be determined and optimized using this PASS based CLC-Pred database in the future to develop potential anticancer drugs. Predicted cytotoxicity gives results against various human cell lines represented with Pa values if Pa value is >0.5 the probability of action is considerably high and whereas Pi value indicates inactivity.

5-chloro-3-(1-piperonylpiperazin-1-ylmethyl) benzoxazol-2-one (**1**)

White solid (51, yield %); mp 162.2 ºC. IR (cm^{-1}) 2800-3050 (C-H), 1765 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 7.4-6.8 (m, 6H, Ar-CH), 4.7 (s, 2H, CH_2), 4.1 (s, 2H, piperonyl-O-CH_2-O) 3.9 (s, 2H, CH_2), 2.9 (t, 4H, pip-CH_2 H^2, H^6), 2.8 (t, 4H, pip-CH_2 H^3, H^5).^{13}C NMR (100 MHz, $CDCl_3$) δ 181.3 (C=O),155.1,150.9,142.5,141.1, 136.1,133.8, 132.8, 130.9, 129.4,127.3,125.7, 124.1 (Ar-C), 65.1 (CH_2), 62.3 (CH_2), 60.9 (CH_2), 53.0, 50.5 (pip-C). Anal.Calc. for $C_{20}H_{20}ClN_3O_4$ C, 59.78; H, 5.02; N, 10.46; Found C, 58.63; H, 4.85; N, 10.21.

3-[4- (2-ethylbenzyl) piperazin-1-ylmethyl] benzoxazol-2-one (**2**)

Brown solid (54, yield %); mp 182.3 ºC. IR (cm^{-1}) 2800-3065 (C-H), 1760 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 7.4-6.7 (m, 8H, Ar-CH), 4.7 (s, 2H, CH_2),3.5 (s, 2H, CH_2), 2.9 (t, 4H, pip-CH_2 H^2, H^6), 2.8 (t, 4H, pip-CH_2 H^3, H^5), 2.4 (q, 2H, CH_2), 2.3 (t, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.1 (C=O)155.3,142.5, 136.2,130.2, 129.7,127.0,125.4, 124.5, 123.7, 122.5, 109.9, 109.3 (Ar-C), 64.5 (CH_2), 60.6 (CH_2), 52.8, 50.6 (pip-C), 19.4 (CH_2), 19.1 (CH_3). Anal.Calc. for $C_{21}H_{25}N_3O_2$ C, 71.77; H, 7.17; N, 11.96; Found C, 70.84; H, 7.02; N, 10.79.

5-chloro-3-[4- (2- ethylbenzyl), piperazin-1-ylmethyl] benzoxazol-2-one (**3**)

White solid (47, yield %); mp 191.5 ºC. IR (cm^{-1}) 2800-3065 (C-H), 1760 (C=O).). ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 7.4-6.7 (m, 8H, Ar-CH), 4.7 (s, 2H, CH_2),3.5 (s, 2H, CH_2), 2.9 (t, 4H, pip-CH_2 H^2, H^6), 2.8 (t, 4H, pip-CH_2 H^3, H^5), 2.4 (q,

2H, CH_2), 2.3 (t, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.6 (C=O), 155.3, 142.5, 136.2, 130.2, 127.0, 125.4, 124.5, 123.7, 122.5, 109.9, 109.3 (Ar-C), 64.5 (CH_2), 60.6 (CH_2), 52.8, 50.6 (pip-C), 19.4 (CH_2), 19.1 (CH_3). Anal.Calc. for $C_{21}H_{24}ClN_3O_2$ C, 65.36; H, 6.27; N, 10.89; Found C, 64.74; H, 6.14; N, 10.30.

5-chloro-3-[4-(4 - hydroxyphenyl) piperazin-1-ylmethyl] benzoxazol-2-one (4)

White solid (36, yield %); mp 189.3 ºC. IR (cm^{-1}) 2800-3065 (C-H), 1760 (C=O). ^1H NMR (400 MHz, $CDCl_3$), δ (ppm): 7.8-6.8 (m, 7H, Ar-CH), 5.3 (br, 1H, OH), 4.7 (s, 2H, CH_2), 2.9 (t, 4H, pip-CH_2 H^2, H^6), 3.4 (t, 4H, pip-CH_2 H^3, H^5), 2.5 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.5 (C=O), 154.9, 153.8, 141.0, 132.5, 130.3, 129.4, 127.9, 123.9,122.7, 113.6, 110.9, 109.8 (Ar-C), 64.4 (CH_2), 50.1, 47.2 (pip-C). Anal. Calc. for $C_{18}H_{18}ClN_3O_3$ C, 60.09; H, 5.04; N, 11.68; Found C, 59.66; H, 4.82; N, 11.06.

3-(4-cyclopropylpiperazin-1-ylmethyl)benzoxazol-2-one (5)

Brown solid (47, yield %); mp 166.5 ºC. IR (cm^{-1}) 2800-3060 (C-H), 1765 (C=O). ^1H NMR (400 MHz, $CDCl_3$), δ (ppm): 7.3-7.1 (m, 4H, Ar-CH), 4.7 (s, 2H, CH_2), 2.7 (t, 4H, pip-CH_2 H^2, H^6), 2.5 (t, 4H, pip-CH_2 H^3, H^5), 2.2 (m, 1H, cyclopropyl-CH H^1), 1.8 (q, 2H, cyclopropyl-CH_2 H^2), 1.2 (q, 2H, cyclopropyl-CH_2 H^3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.5 (C=O) 155.3, 142.5, 132.0,123.7, 122.5, 109.9 (Ar-C), 64.4 (CH_2), 50.9, 48.6 (pip-C), 43.3 (cyclopropyl-CH), 26.2, 25.8 (cyclopropyl- CH_2). Anal.Calc. for $C_{15}H_{19}N_3O_2$ C, 65.91; H, 7.01; N, 15.37; Found C, 65.54; H, 6.86; N, 15.27.

5-chloro-3-(4-cyclopropylpiperazin-1-ylmethyl) benzoxazol-2-one (6)

White solid (42, yield %); mp 172.1 ºC. IR (cm^{-1}) 2800-3060 (C-H), 1765 (C=O). ^1H NMR (400 MHz, $CDCl_3$), δ (ppm): 7.3-7.1 (m, 3H, Ar-CH), 4.7 (s, 2H, CH_2), 2.7 (t, 4H, pip-CH_2 H^2, H^6), 2.5 (t, 4H, pip-CH_2 H^3, H^5), 2.2 (m, 1H, cyclopropyl-CH H^1), 1.8 (q, 2H, cyclopropyl-CH_2 H^2), 1.2 (q, 2H, cyclopropyl-CH_2 H^3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.5 (C=O) 155.3, 142.5, 132.0,123.7, 122.5, 109.9 (Ar-C), 64.4 (CH_2), 50.9, 48.6 (pip-C), 43.3 (cyclopropyl-CH), 26.2, 25.8 (cyclopropyl- CH_2). Anal.Calc. for $C_{15}H_{18}ClN_3O_2$ C, 58.54; H, 5.89; N, 13.65; Found C, 57.85; H, 5.71; N, 13.54.

3-[4- (2-bromophenyl) piperazin-1-ylmethyl] benzoxazol-2-one (**7**)

Brown solid (52, yield %); mp 178.2 ºC. IR (cm^{-1}) 2800-3060 (C-H), 1765 (C=O). ^1H NMR (400 MHz, DMSO-d_6), δ (ppm): 7.4-6.8 (m, 8H, Ar-CH), 4.7 (s, 2H, CH_2), 3.2 (t, 4H, pip-CH_2 H^2, H^6), 2.5 (t, 4H, pip-CH_2 H^3, H^5). ^{13}C NMR (100 MHz, DMSO-d_6) δ 155.0, 150.5, 149.3, 131.9, 122.9, 121.5, 117.9, 112.4, 110.6, 110.0, 109.7, 109.0 (Ar-C), 64.2 (CH_2), 50.2, 48.3 (pip-C). Anal.Calc. for $C_{18}H_{18}BrN_3O_2$ C, 55.63; H, 4.63; N, 10.81; Found C, 55.49; H, 4.36; N, 10.77.

5-chloro-3-[4- (2-bromophenyl) piperazin-1-ylmethyl] benzoxazol-2-one (**8**)

White solid (57, yield %); mp 186.2 ºC. IR (cm^{-1}) 2800-3060 (C-H), 1765 (C=O). ^1H NMR (400 MHz, DMSO-d_6), δ (ppm): 7.4-6.8 (m, 7H, Ar-CH), 4.7 (s, 2H, CH_2), 3.2 (t, 4H, pip-CH_2 H^2, H^6), 2.5 (t, 4H, pip-CH_2 H^3, H^5). ^{13}C NMR (100 MHz, DMSO-d_6) δ 155.0, 150.5, 149.3, 131.9, 122.9, 121.5, 117.9, 112.4, 110.6, 110.0,109.7, 109.0 (Ar-C), 64.2 (CH_2), 50.2, 48.3 (pip-C). Anal. Calc. for $C_{18}H_{17}BrClN_3O_2$ C, 51.10; H, 4.02; N, 9.93; Found C, 51.15; H, 3.82; N, 9.89.

3. RESULTS AND DISCUSSION

In Mannich reaction between benzoxazolone derivatives and appropriate piperazine derivatives, there is a condensation between active hydrogen of benzoxazolone ring at 3rd position and the active hydrogen of piperazine ring in presence of formalin (35% w/v) and a methylene bridge is formed between these two structures. The general structure of compounds is shown in Fig. 4. and the types of substituents as R groups are listed in Table 1.

These newly synthesized derivatives contain different R groups on their piperazine moieties than other structurally similar compounds synthesized before with this method [24]. The results of in silico prediction of cytotoxicity for the compounds are summarized in Table 1.

In the FT-IR spectra, the N-H band of benzoxazolone and piperazine derivatives at 3100-3450 cm^{-1} has disappeared for all compounds. This absence of the absorption band confirms that the reaction took place between the nitrogen atom of the benzoxazolone ring and nitrogen atom of piperazine moeity. For all molecules, the (C=O) stretching band of the lactam ring appear at 1760-1765 cm^{-1}.

In the ^{1}H NMR spectra of all compounds in general, the hydrogen atoms of the methylene bridge between benzoxazolone nitrogen and piperazine nitrogen was appeared as a singlet at 4.7 ppm on the ^{1}H NMR spectra which is the evidence of formation of Mannich reaction.The piperazine protons (H^{6} and H^{2}) and (H^{3} and H^{5}) appeared as triplets at 2.9-2.3 ppm range for all compounds.The aromatic hydrogens appeared as multiplets between 6.7 to 7.8 ppm on ^{1}H-NMR spectra as expected for all compounds. The integral values of the aromatic protons match to the proposed structures.

From Table 1, it is clear that all synthesized compounds showed Pa values 0.5 or higher than 0.5, indicating that these compounds would be active and their Pi values indicate that their possibilities of being inactive in experimental study is very low. Compounds which contain same R groups have high Pa values for the same cancer cell lines and changing the R group on the piperazine moieties for all compounds result in the change of compounds' possible effects on different tumor types. Interestingly, compounds with chlorine substituent (-Cl) at position 5 of the benzoxazolone core structure have Pa values slightly higher than the compounds without having the chlorine substituent. These results clearly indicate that changing the nature of R group on the piperazine moiety as aromatic or aliphatic substituents as well as presence of chlorine substituent at position 5 are two possible modifications that can be done in order to adjust the possible cytotoxic activity of benzoxazolone derivatives for different cancer cell lines.

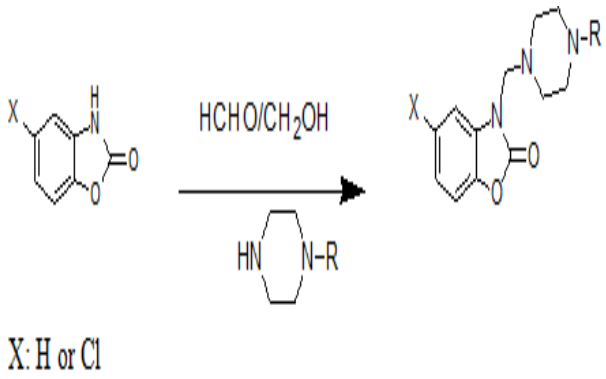

Fig. 4. Synthesis pathway of benzoxazolone mannich bases

Table 1. *In silico* CLC-Pred cell line cytotoxicity prediction of synthesized compounds

Compound Name	X	R	Pa	Pi	Cell Line	Tumor Type
Compound 1	-Cl	1-piperonyl-	0.754	0.004	RKO	Colon carcinoma
Compound 2	-H	2-ethylbenzyl-	0.502	0.003	SNU-398	Renal carcinoma
Compound 3	-Cl	2-ethylbenzyl-	0.504	0.043	SNU-398	Hepatocellular carcinoma
Compound 4	-Cl	4-hydroxyphenyl-	0.802	0.003	PC-9	Lung adenocarcinoma
Compound 5	-H	-cyclopropyl-	0.529	0.018	NCI-H1975	Bronchoalveolar carcinoma
Compound 6	-Cl	-cyclopropyl-	0.695	0.015	NCI-H1975	Bronchoalveolar carcinoma
Compound 7	-H	2-bromophenyl-	0.539	0.017	MKN-74	Stomach Adenocarcinoma
Compound 8	-Cl	2-bromophenyl-	0.575	0.014	MKN-74	Stomach Adenocarcinoma

4. CONCLUSION

In conclusion, newly synthesized Mannich bases of benzoxazolone derivatives were reported for the first time which may have a potential to show anticancer activities at different tumor cell lines as investigated using PASS based in silico CLC-Pred tool. It will be worthwhile to do a systematic experimental study on the effect of the type of substituents on all possible cancer cell lines for the related derivatives of these compounds to help future drug design and development for the treatment of cancer diseases.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Author has declared that no competing interests exist.

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