Bioorganic Chemistry 92 (2019) 103218

Contents lists available at ScienceDirect

Bioorganic Chemistry

journal homepage: www.elsevier.com/locate/bioorg

New pyrimidine-benzoxazole/benzimidazole hybrids: Synthesis, antioxidant, cytotoxic activity, *in vitro* cyclooxygenase and phospholipase A2-V inhibition

Mohamed A. Abdelgawad[a,b,*], Rania B. Bakr[a,b], Waqas Ahmad[c], Mohammad M. Al-Sanea[a], Heba A.H. Elshemy[b]

[a] Pharmaceutical Chemistry Department, College of Pharmacy, Jouf University, Aljouf 2014, Saudi Arabia
[b] Pharmaceutical Organic Chemistry, Faculty of Pharmacy, Beni-Suef University, Beni-Suef 62514, Egypt
[c] School of Pharmaceutical Sciences, University Sains Malaysia, 11800 Pulau Pinang, Malaysia

ARTICLE INFO

Keywords:
Benzoxazole
Benzimidazole
Cytotoxicity
COXs
Antioxidant

ABSTRACT

To enhance the cytotoxicity of benzimidazole and/or benzoxazole core, the benzimidazole/benzoxazole azo-pyrimidine were synthesized through diazo-coupling of 3-aminophenybenzimidazole (**6a**) or 3-aminophenylbenzoxazole (**6b**) with diethyl malonate. The new azo-molanates **6a&b** mixed with urea in sodium ethoxide to afford the benzimidazolo/benzoxazolopyrimidine **7a&b**. The structure elucidation of new synthesized targets was proved using spectroscopic techniques NMR, IR and elemental analysis. The cytoxicity screening had been carried out against five cancer cell lines: prostate cancer (PC-3), lung cancer (A-549), breast cancer (MCF-7), pancreas cancer (PaCa-2) and colon cancer (HT-29). Furthermore, the antioxidant activity, phospholipase A2-V and cyclooxygenases inhibitory activities of the target compounds **7a&b** were evaluated and the new compounds showed potent activity (cytotoxicity IC_{50} range from 4.3 to 9.2 μm, antioxidant activity from 40% to 80%, COXs or LOX inhibitory activity from 1.92 μM to 8.21 μM). The docking of **7a&b** was made to confirm the mechanism of action.

1. Introduction

Cancer disease is the most dangerous disease coming after cardiovascular disease, and in 2018, it produced death of about 9.6 million deaths [1]. Although there is a great advance in treating cancer through targeting therapy, there is a need for process of anticancer drug discovery and development. So, efforts have been made for synthesis of potential anticancer drugs. As a result from that millions of variants organic or natural compounds have been synthesized and shown cytotoxic activity against different types of cancer cell [2]. Moreover, COX enzymes and phospholipase A2 had been reported to be highly found in solid tumors such as bladder and breast cancer [3–5].

Benzoxazole and benzimidazole scaffolds constitute many bioactive compounds possessing significant pharmacological activities for example antihistaminic [6], and antimicrobial [7,8], anti-inflammatory [9–11], antioxidant [12] and anticancer [7,13,14].

In 2017, the benzimidazol-2-yl-phenyl-hydrazono-pyrazol-3-one (**1**) (Fig. 1) had been prepared and was found to exhibit anticancer activity against A549 and MCF-7 and cell lines with IC_{50} = 8.46 and 6.42 μM, respectively [15]. In addition, benzimidazole derivative **2** (Fig. 1) was recorded to demonstrate cancer inhibitory effect against both HepG-2 and HCT-116 with IC_{50} = 2.10 and 1.25 μM [16]. Also, hybridizing benzoxazole ring with piperazine moiety produced compound **3** (Fig. 1) which showed anticancer activity towards MCF-7 cell lines with IC_{50} = 12 nM [17]. On the other hand, pyrimidine ring drawn much attention due to its biological importance as anti-inflammatory [18,19], antioxidant [20,21] and anticancer [22,23]. For example, the pyrimidotriazine-9-carbonitrile had been prepared by Fathalla et al. [24a] and was evaluated for its anticancer activity towards liver cancer cell line (HEPG-2). The result of evaluation detected that compound **4** (Fig. 1) had better anticancer activity (IC_{50} = 3.74 μg/ml) than the standard drug 5-fluorouracil (IC_{50} = 5 μg/ml).

COX-2 inhibitors could use it to prompt apoptosis is TRAIL receptor (cytokine that is normally secreted by all of our cells and could induce apoptosis in tumor cells). Another target for COX-2 inhibitors is PI3 Kinase; PI3 Kinase is a provocateur for Bad protein, the protein that has a major role in cancer development. COX-2 inhibitors stop the activity of Bcl-xL and induce the activity of Bcl-2 and by this, they restrain

* Corresponding author at: Pharmaceutical Chemistry Department, College of Pharmacy, Jouf University, Aljouf 2014, Saudi Arabia.
E-mail address: mhmdgwd@ju.edu.sa (M.A. Abdelgawad).

https://doi.org/10.1016/j.bioorg.2019.103218
Received 4 February 2019; Received in revised form 12 July 2019; Accepted 24 August 2019
Available online 26 August 2019
0045-2068/

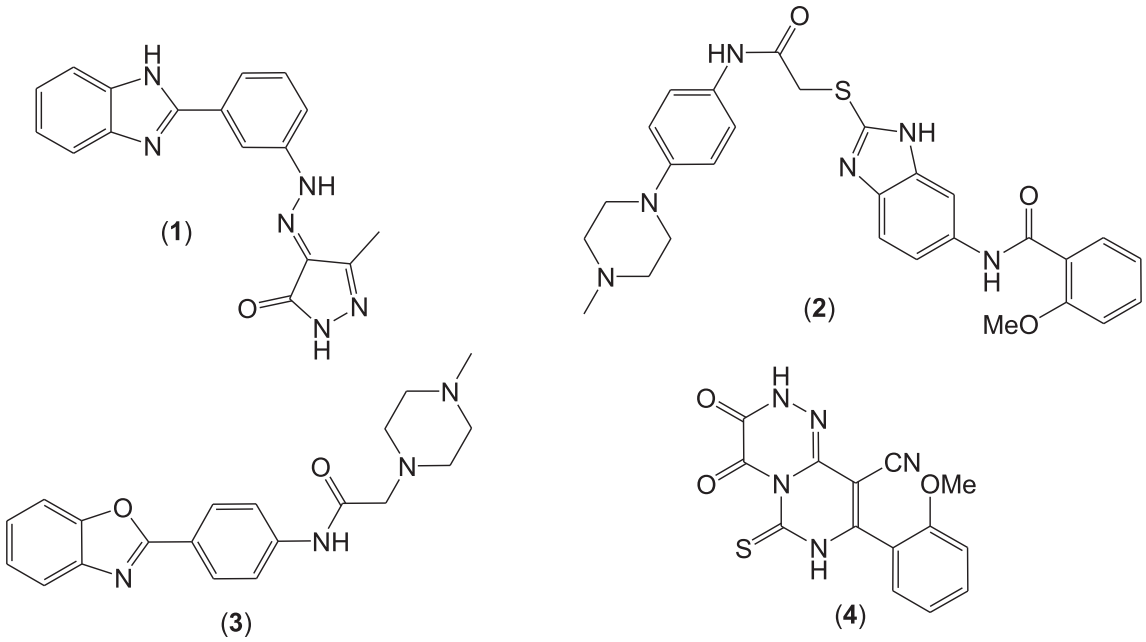


Fig.1. Chemical structures of some reported benzimidazole derivatives (**1, 2**), and benzoxazole derivative (**3**) and pyrimidine derivative (**4**) as anticancer agents.

apoptosis. Bcl-xL is a promoter for cell proliferation. COX-2 inhibitors activate procaspase-8 and convert it in to its active form (Caspase 8). This is a major step in the process of cell apoptosis [24b–24d].

Based on these studies and our research for preparing bioactive candidates with anticancer activity [25–27], we decided to synthesize novel benzimidazole and/or benzoxazole derivatives mixed with pyrimidine ring hoping that the new hybrids might exhibit anticancer activity with less side effects.

2. Results and discussion

2.1. Chemistry

The steps of compounds **6a&b** and **7a&b** preparations are displayed in Scheme 1. First, compounds **5a&b** were prepared as the reported procedures [4].

The new compounds were prepared following reported methods for diazocoupling of diazonium salts with active methylene in presence of sodium acetate [27]. The structure of azo-diethylmalonate **6a** and **6b** was elucidated from NMR spectra which showed aliphatic peaks at δ (m) 1.22 to 1.56 and (m) 4.20–4.46 indicating diethyl groups of ester. The azo-pyrimidinone derivatives **7a** and **7b** prepared as result of reaction of azo-compound **6a** and **6b** with urea or/and thiourea in basic solution of sodium ethoxide. The absence of aliphatic NMR peaks and presence of new NH peaks of azo-diethyl malonate **6a** and **6b** prove the cyclization and formation of new pyrimidinones **7a** and **7b**. The target compound structure was recognized by elemental and spectroscopic analyses.

2.2. Pharmacological screening

2.2.1. Screening of antioxidant activity using DPPH

Free radical scavenging effect of novel benzoxazole **7a** and benzimidazole **7b** had been evaluated using colorimetric test: DPPH (2,2-diphenyl-1-picrylhydrazyl) radical scavenging test using trolox as a standard. The results of inhibitory effects at different concentrations of the compounds **7a** and **7b** are explained in Fig. 2 this graph was plotted with the candidate concentration (μg/mL) on the x-axis and percentage scavenging effects on the y-axis. From this graph, both candidates exhibited good scavenger effect and the benzoxazole derivative **7b** demonstrated better scavenging activity against the DPPH radical than benzimidazole derivative **7a** at all the used concentrations.

2.2.2. In vitro sPLA2-V and COXs inhibitory activity assay

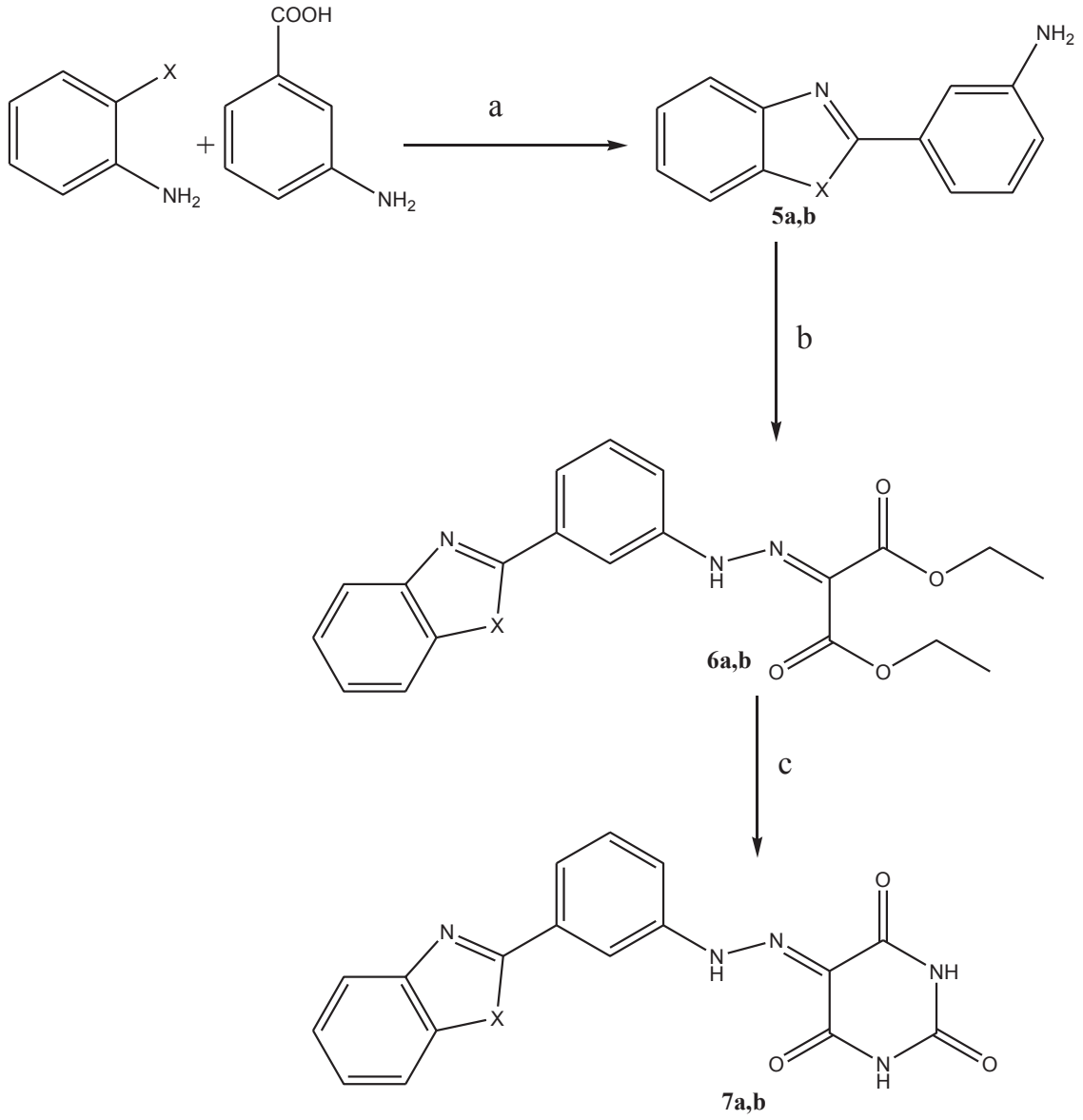
The potency of the newly prepared target compounds **7a** and **7b** as cyclooxygenase (COX) and phospholipase A2-V (sPLA2-V) inhibitors was determined as the concentration causing 50% inhibition (IC_{50}) for COX and *sPLA2-V* enzymes using an enzyme immunoassay (EIA) kit. The results showed that the target compounds (**7a** and **7b**) potent inhibitory activity against COX-1 (IC_{50} = 2.76, 1.92 μM), and moderate activity towards COX-2 (IC_{50} = 7.47, 8.21 μM), but both compounds have moderate inhibitory against secretory Phospholipase A2-V (sPLA2-V) (Table 1).

2.2.3. Cytotoxic activity

The cytotoxic activity of the newly target compounds was recorded using MTT assay against breast carcinoma (MCF-7), lung cancer (A549), human prostate cancer (PC-3), human pancreatic cancer (PaCa-2) and colorectal adenocarcinoma (HT-29) cell lines. From the obtained data, both the target compounds **7a** and **7b** showed moderate activity against all the tested cell lines (Table 2) with IC_{50} range = 4.3–8.8 μM. In addition, the benzimidazole derivative **7a** showed higher cytotoxic activity than the benzoxazole derivative **7b** against all the cell lines except non-small cell lung cancer (A549). Moreover, the target **7a** demonstrated comparable anticancer activity against colorectal adenocarcinoma (HT-29) cell lines (IC_{50} = 5.9 μM) to that showed by the standard drug doxorubicin (IC_{50} = 5.36 μM) (see Table 2).

2.3. Molecular docking study

The target compounds **7a&b** were exposed to molecular modeling study to explore modes of binding interactions with COX-2 enzyme by the use of MOE.2010 software (Molecular Operating Environment). The 3D crystal structure of COX-2 enzyme combined with the cocrystallized ligand (PDB code: 1CX2) was used for this study. Bromocelecoxib, S-58 binded with COX-2 isoform forming two hydrogen bonding interactions with His90 and Arg513 with binding affinity = −11.93 kcal/mol. Docking of compound **7a** within COX-2 binding site displayed that **7a** was good fitted with the receptor with three hydrogen bonding interactions with energy score = −11.50 kcal/mol (Table 3, Fig. 3).



Scheme 1. Reagent and reaction conditions; (a) PPA, reflux for 5h neutralization with Na2CO3, (b), HCl, sodium nitrite, DEM, sodium acetate, stirring for 2 h, (c) Sodium ethoxide, urea, ethanol, reflux for 4 h, water, HCl, cooling for 2 h.

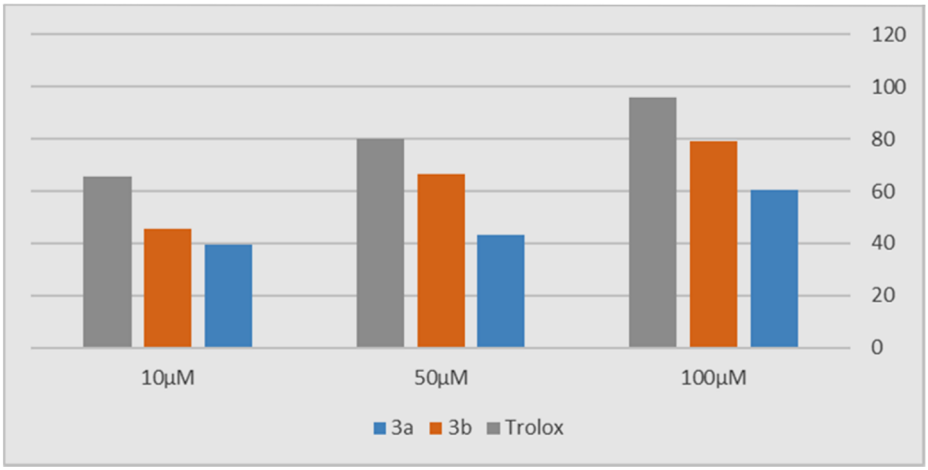


Fig. 2. DPPH radical scavenging effect of the target compounds **7a**, **7b** and torlox at different concentrations (10, 50 and 100 μM). SD = 0.23.

Table 1
Inhibition of secretory Phospholipase A2-V (sPLA2-V), COX-1, and COX-2 by tested compounds **7a** and **7b**.

Compound	$sPLA_2$-V[&&] IC_{50} (μM)	COX-1 IC_{50} (μM)	COX-2 IC_{50} (μM)
7a	7.51 ± 1.84	2.76 ± 0.5	7.47 ± 1.3
7b	5.72 ± 2.15	1.92 ± 0.9	8.21 ± 1.6
Dexamethasone	0.69 ± 0.01	ND*	ND*
Indomethacin*	ND*	0.29 ± 0.07	3.82 ± 0.08

ND* not done.

Moreover, docking of compound **7b** within COX-2 enzyme recorded that this compound showed docking score (S) = −11.50 kcal/mol. Furthermore, this compound **7b** showed two hydrogen bonding interactions; (i) C═O with Arg513 (2.51 Å), ii) C═O with Gln192 (2.79 Å) (Table 3, Fig. 4).

3. Material and methods

3.1. Chemistry

Thomas-Hoover apparatus was used for determination of melting points (uncorrected). The chemical structure of the prepared compounds was proved by NMR (using a BrukerAvance III 100 MHz for ^{13}C and 400 MHz for ^{1}H, Bruker AG, Switzerland). IR (by Nicolet 550 Series II Magna FT-IR), Mass (by Hewlett Packard 5988) spectroscopy and elemental analysis (.by Perkin-Elmer 2400 analyzer, Perkin-Elmer, Norwalk, CT, USA). Compounds **5a&b** were synthesized according to the literature procedure [4].

3.1.1. General methods for synthesis of 6a&b

To a cooled diazonium solution prepared from stirring compound **5a** or **5b** (0.01 mol) in (10%, 10 mL) hydrochloric acid and solution of sodium nitrite (0.01 mol, 5 mL water), a mixture of (0.01 mol) diethyl malonate and (0.01 mol) sodium acetate in (50%, 20 mL) aqueous ethanol was added and stirred for 4 h in ice bath. The product was filtered and crystallized from (95%) ethanol.

3.1.2. 2-{[3-(1H-Benzimidazol-2-yl)-phenyl]-hydrazono}-malonic acid diethyl ester (6a)

Yellowish white crystals in 90% yield; mp 145–147 °C; IR: 3445.6 (2NH), 3088.5 (CH, Aromatic), 2985.8 (CH, Aliphatic), 1701.4, 1666.3 (2C═O) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.22–1.56 (m, 6H, $CH_2\underline{CH_3}$), 4.20–4.40 (m, 4H, $\underline{\mathbf{CH_2}}CH_3$)7.04–7.20 (m, 3H, aminophenyl H-2,4,6), 7.38–7.64 (m, 4H, phenyl H-3, benzimidazole H-5, 6), 8.01–8.18 (m,2H, benzimidazole H-4,7), 12 (s, 1H, NH−N═); 13.80 (s,1H, imidazole NH), ^{13}C NMR (DMSO-d_6) δ 14.34, 14.59, 61.37, 61.84, 111.62, 115.87, 119.10, 122.06, 122.80, 123.16, 125.88, 128.19, 135.46, 143.92, 144.35, 151.48, 162.12, 162.80; Anal. Calcd for $C_{20}H_{20}N_4O4$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.20; H, 5.20; N, 14.70.

3.1.3. 2-{[3-(1H-Benzoxazol-2-yl)-phenyl]-hydrazono}-malonic acid diethyl ester (6b)

Yellowish white crystals in 85% yield; mp 158–160 °C; IR: 3200.5 (NH), 3000.3 (CH, Aromatic), 2900.4 (CH, Aliphatic), 1720.7, 1680.4 (2C═O) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.18–1.43 (m, 6H, $CH_2\underline{\mathbf{CH_3}}$), 4.21–4.49 (m, 4H, $\underline{\mathbf{CH_2}}CH_3$), 7.25–7.33 (m, 3H, aminophenyl H-2,4,6), 7.41–7.58 (m, 1H, phenyl H-3),7.69–7.78(m, 2H, benzoxazole H-5, 6), 8.22–8.36 (m,2H, benzoxazole H-4,7), 11.98 (s, 1H, NH−N═); ^{13}C NMR (DMSO-d_6) δ 14.32, 14.58, 61.47, 61.97, 111.23, 115.99, 119.99, 121.45, 124.48, 125.28, 125.65, 129.29, 142.15, 145.94, 150.62, 162.00, 162.67; Anal. Calcd for $C_{20}H_{19}N_3O_5$: C, 62.99; H, 5.02; N, 11.02. Found: C, 62.90; H, 5.10; N, 11.10

3.1.4. General procedure for synthesis of compound 7a&b

A mixture of **6a&b** (0.01 mol), urea (0.01 mol) in sodium ethoxide solution (0.03 mol sodium, 20 mL absolute ethanol) was heated under reflux for 4 h. (20 mL) Hot water was added to the mixture, and then sufficient quantity of hydrochloric acid was added till the mixture became acidic and then kept in the refrigerator for 5 h. The products 7A&b were filtered, and dried then crystallized from ethanol.

3.1.5. 5-{[3-(1H-Benzimidazol-2-yl)-phenyl]-hydrazono}-pyrimidinone-2,4,6-trione (7a)

Dark reddish crystals in 90% yield. mp 300 °C; IR: 3460, 3300, 3250, 3169 (4NH), 3043 (CH, Aromatic), 1720, 1687, 1681 (3C═O) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 7.20–7.37 (m, 2H, aminophenyl H-2,4), 7.5 (s, 1H, aminophenyl H-6), 7.65–7.67(m, 1H, aminophenyl H-3), 7.75–7.76(m, 2H, benzimidazole H-5, 6), 8.41–8.48 (m,2H, benzimidazole H-4,7), 11.39 (s, 1H, NH−N═),13.16 (s,1H, imidazole NH), 14.15 (s, 2H, NH, pyrimidinone); ^{13}C NMR (DMSO-d_6) δ 111.75, 117.46, 119.00, 119.24, 122.22, 123.05, 127.86, 128.29, 135.51, 142.93, 144.33, 150.29, 151.10; Anal. Calcd for $C_{17}H_{12}N_6O_3$: C, 58.62; H, 3.47; N, 24.13. Found: C, 58.60; H, 3.50; N, 24.10.

3.1.6. 5-{[3-(1H-Benzoxazol-2-yl)-phenyl]-hydrazono}-pyrimidinone-2,4,6-trione (7b). pale

Reddish crystals in 80% yield. mp 300 °C; IR: 3450, 3400, 3280 (3NH), 3040 (CH Aromatic), 1730, 1690, 1675 (3C═O) cm^{-1}; $^{1}HNMR$ (DMSO-d_6) δ 7.28–7.44 (m, 2H, aminophenyl H-2,4), 7.74–7.92 (m, 1H, aminophenyl H-3,6, benzimidazole-2-yl H-5, 6), 8.28–8.44 (m, 2H, benzimidazole-2-yl H-4,7), 11.30 (s, 1H, NH−N═), 11.61 (s, 1H, NH, pyrimidinone), 14.23 (s, 2H, NH, pyrimidinone); Anal. Calcd for $C_{17}H_{11}N_3O_4$: C, 58.62; H, 3.17; N, 20.05. Found: C, 58.70; H, 3.10; N, 20.10.

Table 3
Molecular modeling data for compounds **7a, 7b** and 5-SC during docking in the active site of COX-2 enzyme (PDB: 1CX2).

Compound No.	Affinity Kcal/mol	No.of hydrogen bonds	Distance (Å) from main residue		Functional group
7a	−11.50	3	2.88	Arg513	−C═O
			2.48	Tyr355	C═N
			2.78	Val523	Pyrazole NH
7b	−11.95	2	2.79	Gln192	−C═O
			2.51	Arg513	−C═O
5-SC	−11.93	2	2.30	Arg513	$-SO_2$
			2.41	His90	$-SO_2$

Table 2
Cytotoxicity activity of the target compounds **7a** and **7b.**

Comp.	Cell viability %	Cytotoxicity activity IC_{50} ± SEM (μM)				
		MCF-7	A-549	PC-3	PaCa-2	HT-29
7a	84	5.4 ± 1.2	9.2 ± 1.5	4.3 ± 0.8	4.5 ± 1.3	5.9 ± 1.4
7b	87	7.2 ± 2.3	8.4 ± 1.2	7.9 ± 1.6	8.8 ± 1.2	8.8 ± 2.2
Doxorubicin	–	2.01 ± 0.87	1.17 ± 0.35	0.91 ± 0.12	1.57 ± 0.02	5.36 ± 1.98

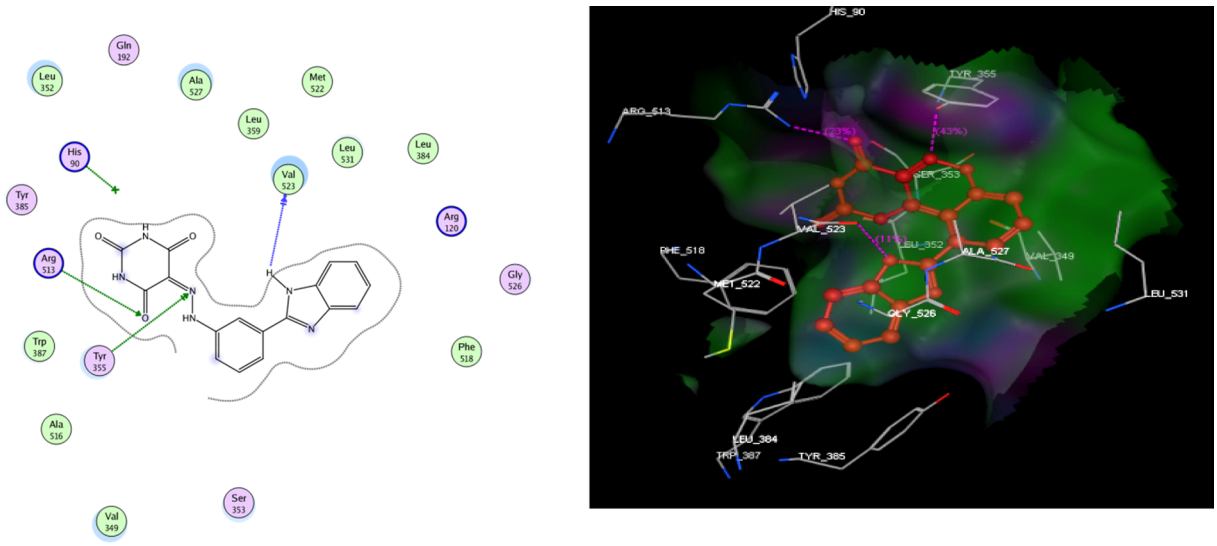


Fig. 3. Binding of the compound **7a** inside COX-2 active site. **(A)** The interactions of **7a**with COX-2 (using MOE site finder program), **(B)** 3D interactions of **7a** with Arg513, Val523 and Tyr355amino acids.

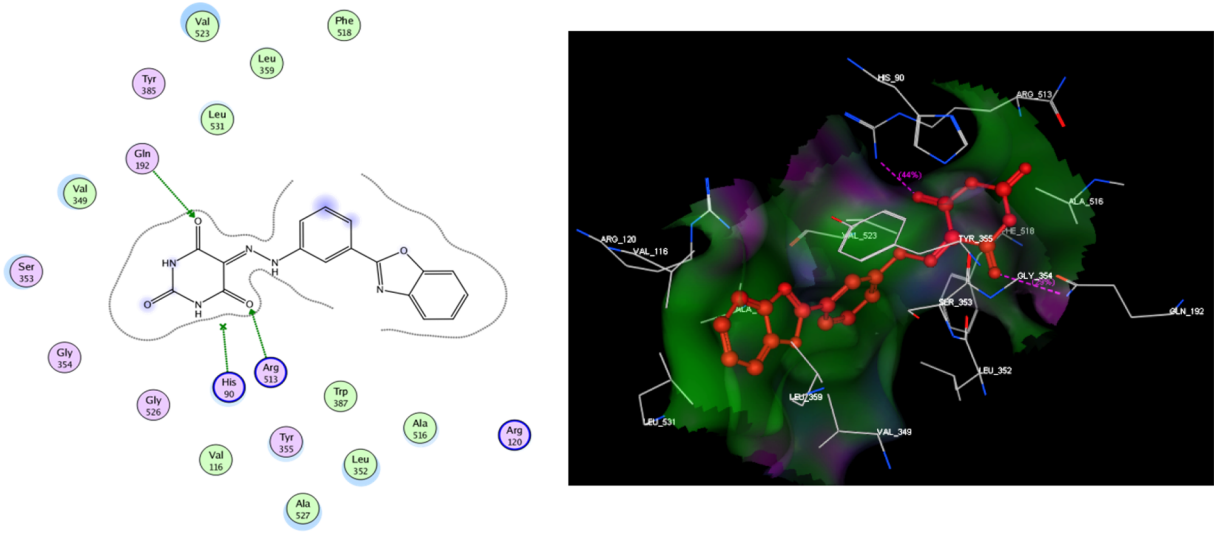


Fig. 4. Binding of the compound **7b** inside COX-2 active site. **(A)** The interactions of **7b** with COX-2 (using MOE site finder program), **(B)** 3D interactions of **7b** with Arg513 and Gln192 amino acids.

3.2. Pharmacological screening

3.2.1. DPPH radical scavenging activity

Scavenging DPPH assay was determined using of 1,1-diphenyl-2-picrylhydrazyl (DPPH) as reported [28]. 0.08 mL solution of the new compounds was mixed with a 1.92 mL 6 × 10–5 M solution of 1,1-diphenyl-2-picrylhydrazyl (DPPH) in ethanol and then absorbance reduction was calculated at λ = 515 nm over 3 min against a blank sample (containing methanol only). The ability of the tested samples to quench DPPH free radicals was determined according to the equation: scavenging % = [(AC − AA)/AC] × 100 where: AC—absorbance of the control at 0 min, AA—absorbance of the sample after 3 min. The antioxidant activity was expressed as μmol of Trolox per 100 g of fresh weight (FW) (TE—Trolox equivalent).

3.2.2. In vitro COX and sPLA2-V inhibition assay

The *in vitro* inhibition of ovine COX-1/COX-2 was calculated by enzyme immunoassay (EIA) kit as the reported procedure [29] and sPLA2-V inhibition was measured using Ellman's method [30].

3.2.3. Cytotoxic activity

Cytotoxic activity of the newly prepared targets was measured by (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) tetrazolium reduction assay as reported [31].

3.3. Molecular docking study

The crystal structures of COX-2 isoform was obtained from protein data bank at research collaboration for structural Bioinformatics (RSCB) (PDB:ID 1CX2) [32]. Docking of the co-crystallized ligand had been performed to estimate amino acid binding and root mean standard deviation (rmsd) which is equal to 0.87 Å. 3D structure of the tested compounds was designed by Molecular Operating Environment (MOE, Version 2005.06, Montreal, Canada). The 3D structures were protonated, energy minimized and docked within COX-2 active site.

4. Conclusion

Novel hybrid structures of benzoxazole and/or benzimidazole with pyrimidine scaffold **7a** and **7b** had been designed and synthesized.

These new compounds had been evaluated for their antioxidant and anticancer activities. From the results, both candidates **7a** and **7b** exhibited good scavenger effect and the benzoxazole derivative **7b** demonstrated better scavenging activity than benzimidazole derivative **7a**. For their anticancer activity, both compounds **7a** and **7b** revealed moderate activity against breast carcinoma (MCF-7), non-small cell lung cancer (A549), human prostate cancer (PC-3), human pancreatic cancer (PaCa-2) and colorectal adenocarcinoma (HT-29) cell lines with IC_{50} range = 4.3–8.8 μM. Furthermore, the inhibitory activity of the targets **7a** and **7b** against COX and phospholipase A2-V enzymes was measured as postulated mechanism for their cytotoxic activity. The obtained data revealed that both compounds exhibited moderate inhibitory towards secretory Phospholipase A2-V and COX-2 enzymes. In conclusion, this study showed the activity of the designed compounds **7a** and **7b** as leads for further development in the field of anticancer agents.

Acknowledgement

Authors would like to appreciate the support of Jouf university and the help of Mr. Saife M. Alshmardal, and Mr. Saeed A. Almohammadi for this work.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bioorg.2019.103218.

References

[1] L.P. Freedman, D. Maine, Women's Mortality: A Legacy of Neglect, The Health Of Women, Routledge, 2018, pp. 147–170.
[2] F.E. Koehn, G.T. Carter, The evolving role of natural products in drug discovery, Nat. Rev. Drug Discov. 4 (2005) 206.
[3] M.A. Abdelgawad, R.B. Bakr, H.A. Omar, Design, synthesis and biological evaluation of some novel benzothiazole/benzoxazole and/or benzimidazole derivatives incorporating a pyrazole scaffold as antiproliferative agents, Bioorgan. Chem. 74 (2017) 82–90.
[4] K.F. Scott, G.G. Graham, K.J. Bryant, Secreted phospholipase A2 enzymes as therapeutic targets, Exp. Opin. Therap. Targets 7 (2003) 427–440.
[5] S. Nyegaard, V.A. Novakovic, J.T. Rasmussen, G.E. Gilbert, Lactadherin inhibits secretory phospholipase A2 activity on pre-apoptotic leukemia cells, PloS One 8 (2013) e77143.
[6] J. Yu, M. Lu, [C12mim] Br: a temperature-dependent phase transfer catalyst and its application for aerobic oxidative synthesis of 2-aryl benzimidazoles, benzoxazoles or benzothiozoles catalyzed by TEMPO based ionic liquid, J. Chin. Chem. Soc. 61 (2014) 578–582.
[7] D. Seenaiah, P.R. Reddy, G.M. Reddy, A. Padmaja, V. Padmavathi, Synthesis, antimicrobial and cytotoxic activities of pyrimidinyl benzoxazole, benzothiazole and benzimidazole, Eur. J. Med. Chem. 77 (2014) 1–7.
[8] E. Oksuzoglu, B. Tekiner-Gulbas, S. Alper, O. Temiz-Arpaci, T. Ertan, I. Yildiz, et al., Some benzoxazoles and benzimidazoles as DNA topoisomerase I and II inhibitors, J. Enzyme Inhibition Med. Chem. 23 (2008) 37–42.
[9] S.M. Sondhi, N. Singh, A. Kumar, O. Lozach, L. Meijer, Synthesis, anti-inflammatory, analgesic and kinase (CDK-1, CDK-5 and GSK-3) inhibition activity evaluation of benzimidazole/benzoxazole derivatives and some Schiff's bases, Bioorgan. Med. Chem. 14 (2006) 3758–3765.
[10] P.A. Thakurdesai, S.G. Wadodkar, C.T. Chopade, Synthesis and anti-inflammatory activity of some benzimidazole-2-carboxylic acids, Pharmacologyonline 1 (2007) 314–329.
[11] M. Gaba, D. Singh, S. Singh, V. Sharma, P. Gaba, Synthesis and pharmacological evaluation of novel 5-substituted-1-(phenylsulfonyl)-2-methylbenzimidazole derivatives as anti-inflammatory and analgesic agents, Eur. J. Med. Chem. 45 (2010) 2245–2249.
[12] S. Durgamma, A. Muralikrishna, V. Padmavathi, A. Padmaja, Synthesis and antioxidant activity of amido-linked benzoxazolyl/benzothiazolyl/benzimidazolyl-pyrroles and pyrazoles, Med. Chem. Res. 23 (2014) 2916–2929.
[13] S.-T. Huang, I.-J. Hsei, C. Chen, Synthesis and anticancer evaluation of bis (benzimidazoles), bis (benzoxazoles), and benzothiazoles, Bioorgan. Med. Chem. 14 (2006) 6106–6119.
[14] M. Hranjec, M. Kralj, I. Piantanida, M. Sedić, L. Šuman, K. Pavelić, et al., Novel cyano-and amidino-substituted derivatives of styryl-2-benzimidazoles and benzimidazo [1, 2-a] quinolines. Synthesis, photochemical synthesis, DNA binding, and antitumor evaluation, part 3, J. Med. Chem. 50 (2007) 5696–5711.
[15] M.A. Abdelgawad, R.B. Bakr, A.O. El-Gendy, G.M. Kamel, A.A. Azouz, S.N.A. Bukhari, Discovery of a COX-2 selective inhibitor hit with anti-inflammatory activity and gastric ulcer protective effect, Future Med. Chem. 9 (2017) 1899–1912.
[16] P. Xiang, T. Zhou, L. Wang, C.-Y. Sun, J. Hu, Y.-L. Zhao, et al., Novel benzothiazole, benzimidazole and benzoxazole derivatives as potential antitumor agents: synthesis and preliminary in vitro biological evaluation, Molecules 17 (2012) 873–883.
[17] M.A. Abdelgawad, A. Belal, H.A. Omar, L. Hegazy, M.E. Rateb, Synthesis, anti-breast cancer activity, and molecular modeling of some benzothiazole and benzoxazole derivatives, Archiv der Pharmazie 346 (2013) 534–541.
[18] M.A. Abdelgawad, R.B. Bakr, A.A. Azouz, Novel pyrimidine-pyridine hybrids: synthesis, cyclooxygenase inhibition, anti-inflammatory activity and ulcerogenic liability, Bioorgan. Chem. 77 (2018) 339–348.
[19] A.P. Keche, G.D. Hatnapure, R.H. Tale, A.H. Rodge, S.S. Birajdar, V.M. Kamble, A novel pyrimidine derivatives with aryl urea, thiourea and sulfonamide moieties: synthesis, anti-inflammatory and antimicrobial evaluation, Bioorgan. Med. Chem. Lett. 22 (2012) 3445–3448.
[20] S. Panda, P. Chowdary, Synthesis of novel indolyl-pyrimidine antiinflammatory, antioxidant and antibacterial agents, Indian J. Pharmaceut. Sci. 70 (2008) 208.
[21] C.M. Bhalgat, M.I. Ali, B. Ramesh, G. Ramu, Novel pyrimidine and its triazole fused derivatives: synthesis and investigation of antioxidant and anti-inflammatory activity, Arab. J. Chem. 7 (2014) 986–993.
[22] K. Abdellatif, E. Abdelall, M.A. Abdelgawad, R.R. Ahmed, R.B. Bakr, Synthesis, docking study and antitumor evaluation of certain newly synthesized pyrazolo [3, 4-d] pyrimidine derivatives, Organ. Chem. Indian J. 10 (2014) 157–167.
[23] K.R. Abdellatif, E.K. Abdelall, M.A. Abdelgawad, R.R. Ahmed, R.B. Bakr, Synthesis and anticancer activity of some new pyrazolo [3, 4-d] pyrimidin-4-one derivatives, Molecules 19 (2014) 3297–3309.
[24] (a) O. Fathalla, I. Zeid, M. Haiba, A. Soliman, S.I. Abd-Elmoez, W. El-Serwy, Synthesis, antibacterial and anticancer evaluation of some pyrimidine derivatives, World J. Chem. 4 (2009) 127–132;
(b) G. Steinbach, P.M. Lynch, R.K. Phillips, M.H. Wallace, E. Hawk, G.B. Gordon, et al., The effect of celecoxib, a cyclooxygenase-2 inhibitor, in familial adenomatous polyposis, New Engl. J. Med. 342 (26) (2000) 1946–1952;
(c) S. Perwez Hussain, C.C. Harris, Inflammation and cancer: an ancient link with novel potentials, Int. J. Cancer 121 (11) (2007) 2373–2380;
(d) C. Sobolewski, C. Cerella, M. Dicato, L. Ghibelli, M. Diederich, The role of cyclooxygenase-2 in cell proliferation and cell death in human malignancies, Int. J. Cell Biol. 2010 (2010).
[25] M.A. Abdelgawad, R.B. Bakr, O.A. Alkhoja, W.R. Mohamed, Design, synthesis and antitumor activity of novel pyrazolo [3, 4-d] pyrimidine derivatives as EGFR-TK inhibitors, Bioorgan. Chem. 66 (2016) 88–96.
[26] R.B. Bakr, A.B.M. Mehany, K.R.A. Abdellatif, E.G.F.R. Synthesis, Inhibition and anticancer activity of new 3, 6-dimethyl-1-phenyl-4-(substituted-methoxy) pyrazolo [3, 4-d] pyrimidine derivatives, anti-cancer agents in medicinal, Chem. (Formerly Curr. Med. Chem.-Anti-Cancer Agents) 17 (2017) 1389–1400.
[27] A. Belal, M.A. Abdelgawad, New benzothiazole/benzoxazole-pyrazole hybrids with potential as COX inhibitors: design, synthesis and anticancer activity evaluation, Res. Chem. Intermed. 43 (2017) 3859–3872.
[28] U. Szymanowska, B. Baraniak, A. Bogucka-Kocka, Antioxidant, anti-inflammatory, and postulated cytotoxic activity of phenolic and anthocyanin-rich fractions from Polana Raspberry (Rubus idaeus L.) Fruit and Juice—In Vitro Study, Molecules 23 (2018) 1812.
[29] R.J. Kulmacz, W.E. Lands, Requirements for hydroperoxide by the cyclooxygenase and peroxidase activities of prostaglandin H synthase, Prostaglandins 25 (1983) 531–540.
[30] W. Ahmad, E. Kumolosasi, I. Jantan, S.N. Bukhari, M. Jasamai, Effects of novel diarylpentanoid analogues of curcumin on secretory phospholipase A2, cyclooxygenases, lipo-oxygenase, and microsomal prostaglandin E synthase-1, Chem. Biol. Drug Des. 83 (2014) 670–681.
[31] M.C. Alley, D.A. Scudiero, A. Monks, M.L. Hursey, M.J. Czerwinski, D.L. Fine, et al., Feasibility of drug screening with panels of human tumor cell lines using a microculture tetrazolium assay, Cancer Res. 48 (1988) 589–601.
[32] R.G. Kurumbail, A.M. Stevens, J.K. Gierse, J.J. McDonald, R.A. Stegeman, J.Y. Pak, et al., Structural basis for selective inhibition of cyclooxygenase-2 by anti-inflammatory agents, Nature 384 (1996) 644–648.