BMC Chemistry

RESEARCH

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Design, synthesis and evaluation of novel 1,2,4-triazole derivatives as promising anticancer agents

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Abstract

Herein, we reported the synthesis of nineteen novel 1,2,4-triazole derivatives including 1,3-diphenyl-2-(1H-1,2,4-triazol-1-yl) propan-1-ones (***7a-e***), 1-(1,3-diphenylpropan-2-yl)-1*H*-1,2,4-triazole (***8a-c***) and 1,4-diphenyl-2-(1H-1,2,4-triazol-1-yl) butane-1,4-diones (***10a-k***). The structures of these derivatives were confirmed by spectroscopic techniques like IR, ^{1}H-NMR, Mass spectroscopy and Elemental analysis. The cytotoxic activities of the synthesized compounds were evaluated against three human cancer cell lines including MCF-7, Hela and A549 using MTT assay. Compounds ***7d***, ***7e***, ***10a*** and ***10d*** showed a promising cytotoxic activity lower than 12 μM against Hela cell line. The safety of these compounds was also, evaluated on MRC-5 as a normal cell line and relieved that most of the synthesized compounds have proper selectivity against normal and cytotoxic cancerous cell lines. Finally, molecular docking studies were also, done to understand the mechanism and binding modes of these derivatives in the binding pocket of aromatase enzyme as a possible target.

Keywords: 1,2,4-Triazole, Anticancer, MTT assay, Molecular docking, ADME

Introduction

Cancer is characterized by the uncontrolled growth and proliferation of abnormal cells and is the second leading cause of morbidity and mortality in the world [1, 2]. According to the global cancer statistics, 9.6 million deaths and also, more than 18 million new cancer occurred in 2018 [3]. It is expected that the cancer mortality rate will rise dramatically in the future [3].

Various internal and external factors cause abnormal cell proliferation, leading to development of various cancers, including genetics, viruses, drugs, diet and smoking [4, 5]. Currently, three strategies including chemotherapy, radiotherapy, and surgery are used for the treatment of cancer. Chemotherapy is the most common treatment for cancer disease, in which various chemotherapeutic agents are utilized to kill the cancer cells with minimum harmful effect on normal cells [4, 6]. However, drug resistance, non-selectivity and toxicity of many anticancer drugs have limited their clinical uses [1, 7]. Hence, the discovery and development of more effective and potent anticancer agents is one of the most clinical challenges in modern medicinal chemistry [8].

Heterocyclic compounds containing nitrogen atoms, especially heterocyclic rings with three nitrogen atoms, like 1,2,4-triazole ring, are one of the most important active pharmaceutical scaffolds. These scaffolds are able to form hydrogen bonds with different targets, which leads to the improvement of pharmacokinetics, pharmacological, and toxicological properties of compounds

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[2–4, 9]. Among heterocyclic compounds, 1,2,4-triazole derivatives have attracted much attention because of their various biological activities such as antiviral [10], antibacterial [11], antifungal [12, 13], anti-tubercular [14–16], immunosuppressant [17], antihypertensive [18], anti-inflammatory [19, 20], anticonvulsant [21, 22], analgesic [23], hypoglycemic [24], antidepressant [25, 26] and anticancer [9, 27, 28] activities. Currently, Letrozole, Anastrozole, and Vorozole which are 1,2,4-triazole-based drugs, are widely used in the treatment of estrogen-dependent breast cancer [29, 30] (Fig. 1).

Some Clotrimazole derivatives have been reported as antifungal agents [2, 9, 31–33]. Song et al. synthesized a series of 4-N-nitrophenyl substituted amino-4H-1,2,4-triazole derivatives as promising aromatase inhibitors (Fig. 2, A) [34]. Moreover, Cevik et al. explored a new set of benzimidazole-triazolothiadiazine hybrids with potent aromatase inhibitory activities (Fig. 2, B) [35]. Hou et al. reported a series of 1,2,4-triazole derivatives with potent inhibitory activity against HepG2 cancer cell line (Fig. 2, C) [36]. In addition, X. Ouyang et al. showed that a set of 1,2,4-triazole derivatives, completely inhibited the

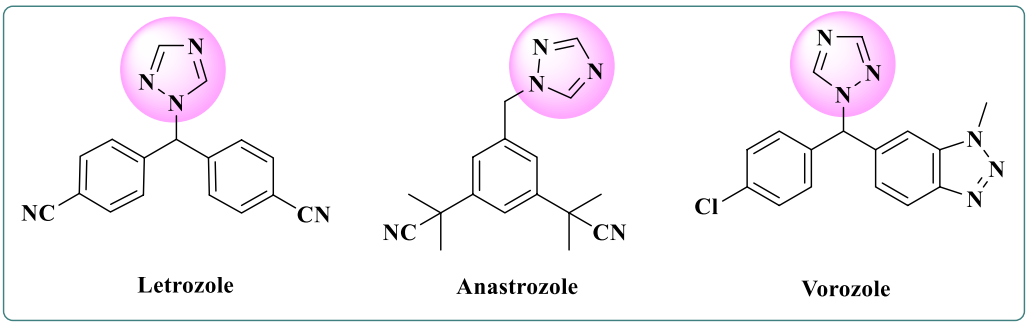

Fig. 1 Chemical structures of 1,2,4-triazole-based drugs

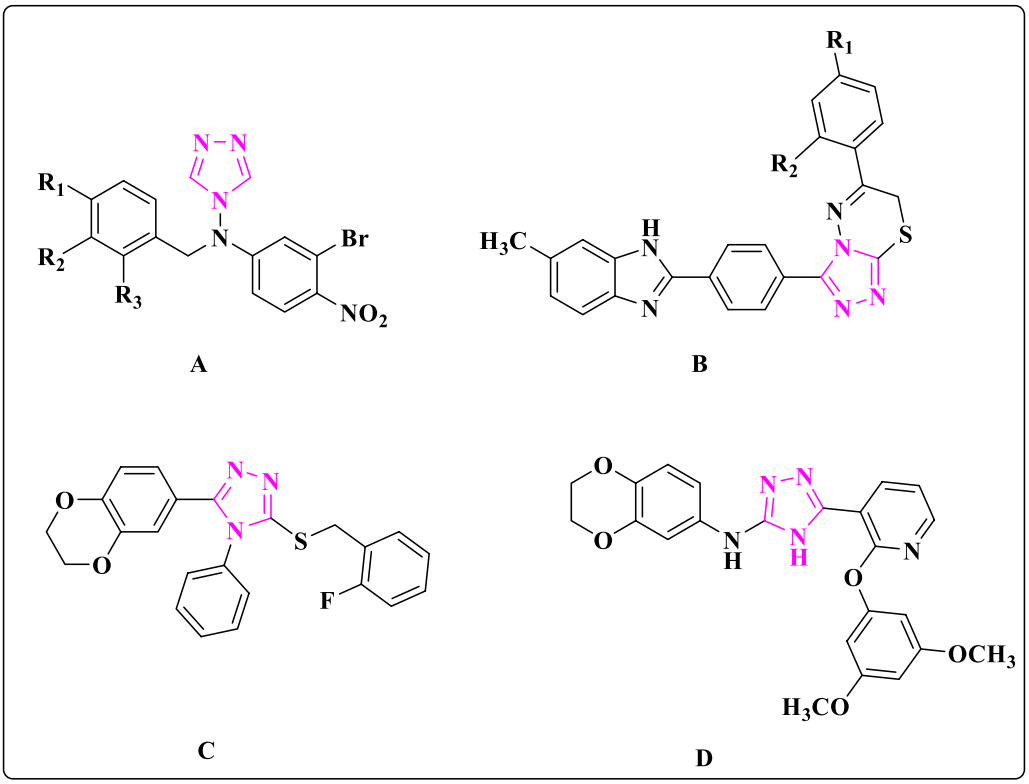

Fig. 2 Structure of 1,2,4-triazole derivatives with anticancer activity

tubulin polymerization by inducing cell cycle arrest at the G2/M phase of A431 cell line (Fig. 2, D) [37].

In the present study, three series of 1,2,4-triazole derivatives including 1,3-diphenyl-2-(1H-1,2,4-triazol-1-yl) propan-1-ones (***7a-e***), 1-(1,3-diphenylpropan-2-yl)-1*H*-1,2,4-triazole (***8a-c***) and 1,4-diphenyl-2-(1H-1,2,4-triazol-1-yl) butane-1,4-diones (***10a-k***) derivatives were designed, synthesized and evaluated for their anticancer activity against three human cancer cell lines (MCF-7, Hela and A549). The cytotoxic activity of all the synthesized compounds were assessed using the standard 3-(4,5-dimethylthiazol-yl)-2,5-diphenyl-tetrazolium bromide (MTT) assay. Furthermore, molecular docking study was carried out to find the possible interaction mode of these derivatives in the active site of aromatase enzyme as possible target.

Results and discussion

Design

The target 1,2,4-triazole derivatives were designed based on the chemical structures of Letrozole (**a**), Anastrozole (**b**) and 4-triazolylflavans (**c**) which act as aromatase inhibitors. Aromatase is a member of the cytochrome P450 superfamily that catalyzes the estrogen biosynthesis and can be considered as a therapeutic target due to its overexpression in breast cancer. Anastrozole and Letrozole are potent aromatase inhibitors that use in the treatment of ER-positive breast cancer. In addition, it has been previously reported that 4-triazolylflavans derivatives exhibited aromatase inhibitory effect [38, 39]. In these aromatase inhibitors, nitrogen atoms of 1,2,4-triazole ring bind to the iron in the heme moiety of CYP-450 and phenyl moieties have a key interaction in the active site of enzyme. Furthermore, carbonyl group is incorporated in the designed structures due to its ability to form hydrogen bonds. Therefore, 1,2,4-triazole moiety, phenyl rings and carbonyl groups were incorporated in the designed scaffolds (Fig. 3).

Chemistry

The synthesis of the desired compounds (***7a-e, 8a-c, 10a-k***) was carried out according to the synthetic pathway illustrated in Fig. 4. The phenacyl chloride derivatives ***3a-f*** were prepared in high yield through Fridel Crafts acylation of mono or di-substituted benzene (***1a-f***) with chloroacetyl chloride (**2**) using aluminum trichloride ($AlCl_3$) as a strong Lewis acid catalyst [40, 41]. In the second step, intermediates ***5a-f*** were synthesized from the reaction of intermediates ***3a-f*** with 1,2,4-triazole (**4**) in the presence of sodium bicarbonate ($NaHCO_3$). Compounds ***7a-e*** were synthesized by treating benzyl bromide (***6a***) or benzhydryl bromide (***6b***) with intermediates ***5a-f*** in the presence of NaH as a strong base catalyst in acetonitrile. Subsequently, Huang Minlon reduction of compounds ***7a*** and ***7c-d*** in the presence of $N_2H_4.H_2O$ and KOH yielded compounds ***8a-c*** [42]. Compounds ***10a-k*** were prepared from the reaction

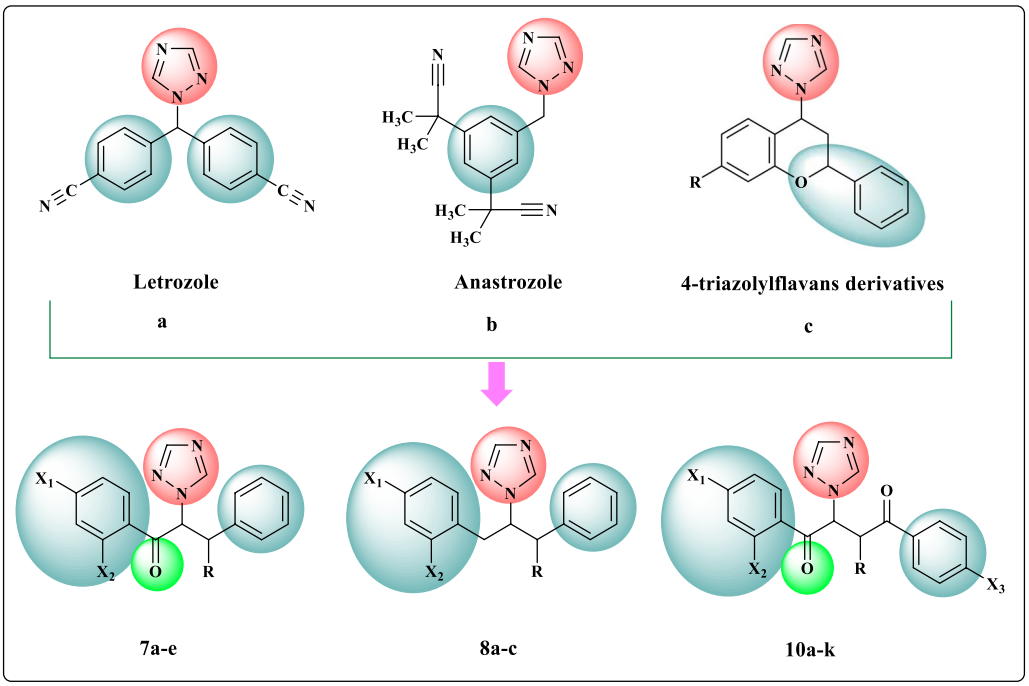

Fig. 3 Design of new 1,2,4-triazole derivatives

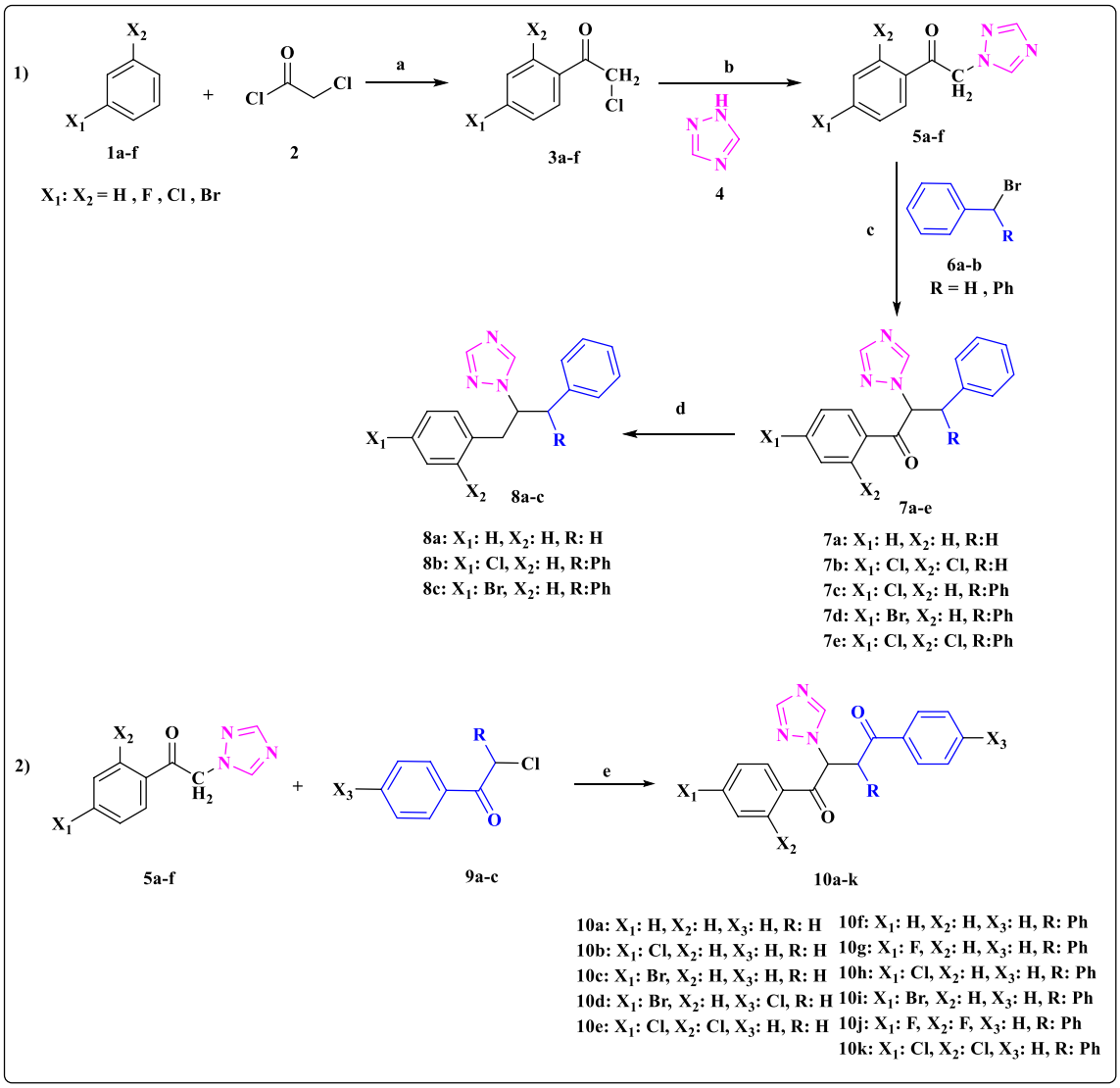

Fig. 4 Synthesis of target compounds ***7a-e, 8a-c*** and ***10a-k***. Reagents and conditions: a) $AlCl_3$, dichloromethane, r.t., 24 h, b) $NaHCO_3$, toluene, reflux, 20 h, c) NaH, CH_3CN, reflux, 24 h, d) $N_2H_4.H_2O$, KOH, Ethylene glycol,170 °C, 4 h, e) NaH, CH_3CN, reflux, 24 h

of 2-chloro-1,2-diphenylethanone (desyl chloride) or 2-chloro-1-phenylethanone derivatives with key intermediates ***5a-f*** utilizing NaH as base and in acetonitrile as solvent. The structures of the synthesized compounds were confirmed through ^{1}H-NMR, Mass and IR techniques. In the IR spectra of compounds ***7a-e,*** a signal for C=O group was observed at 1690–1723 cm^{-1}, while this signal was removed for compounds ***8a-c***. The IR absorption spectra of ***10a-k*** were characterized the presence of two signals for C=O groups at 1650–1712 cm^{-1}. ^{1}H-NMR spectrum of compounds ***7a-e*** showed two singlet peaks at 8.12–8.33 and 7.77–7.91 ppm assigned to the 1,2,4-triazole ring. In addition, in compounds ***7a*** and ***7b,*** the CH proton was observed at 6.17–6.24 ppm as a doublet of doublet peak and in compounds ***7c-e*** the CH proton was observed at 6.73–6.79 ppm as a doublet peak. ^{1}H-NMR spectrum of compounds ***8a-c*** showed two singlet peaks at 8.17–8.29 ppm and 7.78–7.85 ppm assigned to the 1,2,4-triazole ring and a multiplet peak at 4.59–4.67 ppm assigned to the CH proton. ^{1}H-NMR spectrum of compounds ***10a-k*** showed two singlet peaks at 7.97–8.35 ppm and 7.79–8.03 ppm assigned to the 1,2,4-triazole ring. Furthermore, in compounds ***10a-e*** with R=H, the CH proton appeared at 6.52–6.69 ppm as a triplet peak whereas in compounds ***10f-k*** with R=Ph, the CH proton appeared at 6.45–6.81 ppm as a doublet peak. All

the analytical data were documented in the Additional file 1: Data.

Evaluation of anticancer activity

All of the synthetic compounds (***7a-e, 8a-c*** and ***10a-k***) were screened for their in vitro cytotoxic effects against three human cancerous cell lines (MCF-7, Hela and A549) using MTT assay [43–45]. The biological results were expressed in terms of IC_{50} (Table 1). Generally, the best anticancer effect was seen on breast (MCF-7) and cervical (Hela) cell lines and less on lung cancer (A549) cell line. In this assay, *cis platin* was used as positive control [46–48]. As shown in Table 1, some of the compounds such as ***7b***, ***7d-7e***, ***10a*** and ***10c-d*** showed better antiproliferative activity compared to *cis platin* in all studied cancer cell lines. Assessments on propane-1-one derivatives (***7a-e***), compound ***7e*** bearing X_1:X_2 = Cl, R = Ph showed significant activity with IC_{50} = 4.7, 2.9 and 9.4 μM against MCF-7, Hela and A549 cell lines, respectively, followed by compound ***7d*** possessing X_1 = Br, X_2 = H, R = Ph with IC_{50} = 9.8, 12.1 and 43.4 μM. The obtained results indicated that the absence of electronegative groups at X position and also, the absence of phenyl ring at R position in analogue ***7a*** (unsubstituted one), dramatically decreased the cytotoxic effects against all studied cancer cell lines. On the other hand, propane-1-yl-derivatives (***8a-c***), showed less cytotoxicity effect compared to other studied compounds (***7a-e*** and ***10a-k***), which can be attributed to the reduction of carbonyl group at position 1 of propane chain. Further, a comparison of the cytotoxicity of compounds ***7a-e*** on Hela cell line showed that the anticancer activities of different substitutions on phenyl ring followed the order 2,4-di-Cl > 4-Br > 4-Cl > H, and interestingly, the relative order of the substitution effect on cytotoxicity for compounds ***8a-c*** was 4-Br > 4-Cl > H which was in line with above-mentioned results. In the case of butane-1,4-dione derivatives (***10a-k***), compound ***10a*** was found to have promising anticancer activity with IC_{50} = 6.43, 5.6 and 21.1 μM against MCF-7, Hela and A549 cell lines, respectively. The substitution of Br and Cl at X_1 and X_3 position produced appropriate derivative (***10d***) with IC_{50} values of 10.2, 9.8 and 16.5 μM. Besides, the cytotoxic activity of compounds ***10a-e*** on Hela cell line showed that the anticancer activities of different substitutions on the phenyl rings followed the order of H > 4Br > 2,4-di-Cl > 4-Cl. The incorporation of phenyl group at R position decreased cytotoxic activity. Among these compounds, ***10j*** bearing 2,4-diflouro group at the phenyl moiety demonstrated adequate cytotoxic effect. The safety of these compounds was also, evaluated on MRC-5 as normal cell line. The resulted indicated that most of the synthesized

Table 1 Cytotoxicity of the synthesized compounds against MCF-7, Hela and A549 cell lines [IC_{50} (μM)]

Compound	X_1	X_2	X_3	Y	R	IC_{50} (μM ± SEM)			
						MCF-7	Hela	A549	MRC-5
7a	H	H	–	C = O	H	154.2 ± 5.8	92.4 ± 7.3	149.6 ± 5.3	> 300
7b	Cl	Cl	–	C = O	H	23.4 ± 2.6	7.9 ± 3.1	75.8 ± 4.6	72.6 ± 3.4
7c	Cl	H	–	C = O	C_6H_5	60.0 ± 4.9	81.7 ± 6.3	177.3 ± 5.9	201.2 ± 9.5
7d	Br	H	–	C = O	C_6H_5	9.8 ± 0.9	12.1 ± 3.6	43.4 ± 4.5	35.6 ± 2.7
7e	Cl	Cl	–	C = O	C_6H_5	4.7 ± 1.4	2.9 ± 1.1	9.4 ± 1.8	27.8 ± 3.7
8a	H	H	–	CH_2	H	158.3 ± 3.5	141.5 ± 2.1	127.3 ± 4.9	279.1 ± 2.5
8b	Cl	H	–	CH_2	C_6H_5	178.5 ± 2.5	198.3 ± 5.5	124.1 ± 3.4	279.1 ± 2.8
8c	Br	H	–	CH_2	C_6H_5	52.8 ± 7.4	79.1 ± 2.5	104.5 ± 7.3	104.5 ± 7.3
10a	H	H	H	–	H	6.4 ± 1.7	5.6 ± 2.8	21.1 ± 4.2	21.7 ± 1.5
10b	Cl	H	H	–	H	62.6 ± 2.5	48.3 ± 4.1	110.5 ± 1.3	259.3 ± 8.3
10c	Br	H	H	–	H	17.3 ± 5.4	32.4 ± 6.9	103.7 ± 1.3	57.8 ± 1.7
10d	Br	H	Cl	–	H	10.2 ± 2.1	9.8 ± 1.7	16.5 ± 2.6	42.8 ± 2.1
10e	Cl	Cl	H	–	H	45.4 ± 6.5	31.6 ± 4.2	103.7 ± 5.9	104.5 ± 7.3
10f	H	H	H	–	C_6H_5	134.5 ± 4.5	82.7 ± 5.8	114.5 ± 7.6	289.1 ± 10.2
10 g	F	H	H	–	C_6H_5	93.0 ± 3.1	127.9 ± 6.1	149.8 ± 4.9	257.2 ± 4.3
10 h	Cl	H	H	–	C_6H_5	89.0 ± 5.2	172.3 ± 7.1	112.5 ± 10.8	249.3 ± 5.8
10i	Br	H	H	–	C_6H_5	72.2 ± 6.5	59.3 ± 2.7	134.8 ± 5.3	218 ± 3.2
10 J	F	F	H	–	C_6H_5	45.4 ± 3.2	12.3 ± 1.9	100.7 ± 1.8	101.2 ± 1.3
10 k	Cl	Cl	H	–	C_6H_5	44.1 ± 7.6	121.2 ± 6.8	102.5 ± 5.2	147.9 ± 6.1
Cis platin	–	–	–	–	–	36.5 ± 1.9	12.3 ± 3.3	14.8 ± 0.27	45.2 ± 2.5

compounds have proper selectivity against cancer cell lines (Fig. 5).

Molecular docking

The docking information of four 1,2,4-triazole derivatives possessing the highest (***10a*** and ***10d***) and lowest (***7c*** and ***8c***) cytotoxic activity were shown in Fig. 6 and Fig. 7. Redocking of 4-androstene-3–17-dione as co-crystal ligand, was done to assessment the docking results. The RMSD was obtained 0.40 Å in comparison to its coordination in the crystal structure. The all interaction and score binding of all studied compounds was shown in Table 2.

Compound ***10a*** through its carbonyl group interacted with Ser 478 via hydrogen bond and also, formed π-cation and π-π interactions with HEM. The phenyl ring of ***10a*** formed π-sigma bond with Leu 477 and also, some π-alkyl interactions with Val 373, Ile 133, Val 370 and Ala 306 residues were observed. In addition, hydrophobic interactions with Thr 310, Trp 224, Arg 115, Met 374, Phe 221, Leu 372, and Phe 134 residues were existence which led to desire affinity to aromatase enzyme. On the other hand, compound ***10d*** had same similarity interactions with ***10a*** as one of the best compound such as, π-π, π-sigma and π-alkyl with Leu 477, Val 370, Val 369, Phe 221, Leu 372, Met 374 and Ile 133 residues. Compound ***10d*** also, formed halogen bond and π-cation interaction with Ala 306 amino acid residue and HEM group, respectively. These interactions confirmed that compounds ***10a*** and ***10d*** were successfully bound to the aromatase enzyme via most of the previously binding interactions of co-crystal ligand of aromatase enzyme (3EQM) (natural substrate androstenedione (AD)), such as Phe134, Trp224, Val370, Val373, Met374 and HEM [49, 50].

Moreover, compound ***7c*** involved π-π and π-cation interactions with Tyr 424 and Lys 440 residues through its phenyl moiety. In addition, some π-alkyl interactions with Pro 429, Tyr 361, Val 422 and Phe 418 residues were observed. The groups of Glu 357, Phe 427, Phe 430, Met 444, Gln 428, Phe 432, Asn 421, Lys 354 and Tyr 441 residues involved to create a pocket around ***7c*** by van der Waals forces. As it was shown in Fig. 7, the most important residues in binding of ***8c*** was π-π and π-cation interactions between 1,2,4-triazole moiety and Tyr 424 and Lys 440 residues. Also, some π-π and π-alkyl interactions with Tyr 441, Val 422 and Met 444 residues were seen. A pocket of Phe 430, Phe 418, Phe 427, Asn 421, Gln 428 and Phe 432 residue were observed a round of ***8c*** with van der Waals forces.

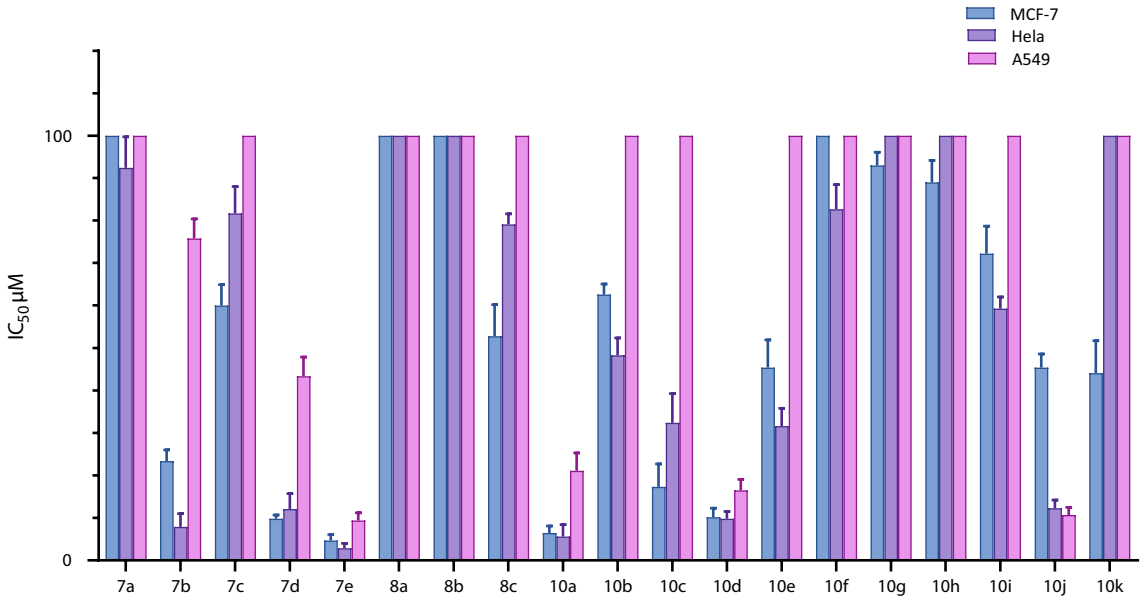

Fig. 5 Cytotoxic effect of compounds ***7a-e, 8a-c*** and ***10a-k*** on MCF-7, Hela and A549 cell lines Taken to gather, regarding the cytotoxic evaluations on ***7a***-***e*** and ***8a***-***c*** derivatives, it can be realizing that ***7e*** was the most potent derivative against all three tested cell lines. The structure activity relationship disclosed that electronegative substitution such as Cl and Br at para position of phenyl ring (X_1) and also, the presence of phenyl ring at R position could increase the inhibitory activity significantly in a ***7a-e*** series. Also, the presence of one-carbonyl group showed necessary for pharmacological effect. In addition, propane-1-yl-derivatives (***8a***-***c***) had least effect on cytotoxic activity. In the case of ***10a***-***k***, replacement of H with Ph moiety at R position led to decreased cytotoxic activity (***10f***-***k***) and also, no substituted analogue (***10a***) had favorable pharmacological effect on MCF-7 and Hela cell lines. The cytotoxicity of all synthesized compounds were shown in Table 1.

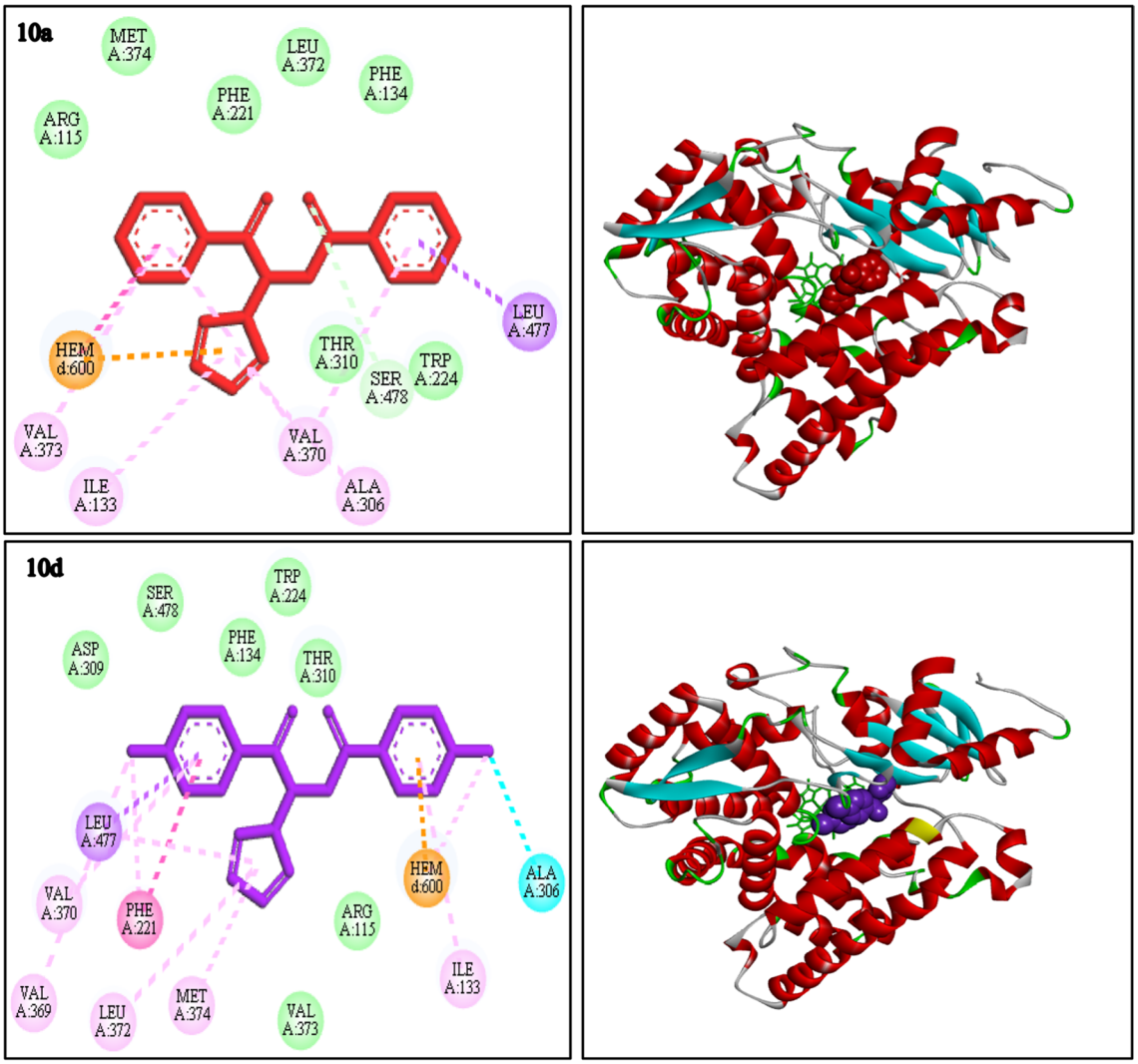

Fig. 6 2D interaction diagrams representing the docked conformation of compounds ***10a*** and ***10d*** in the human placental aromatase (3EQM). (Van der waals: green, dark pink: π-π, light pink: π-alkyl, purple: π-sigma, orange: π-cation, blue: halogen bond)

In silico ADME modeling study

ADME properties of the synthesized compounds were determined using SwissADME online software [51]. As depicted in Table 3, all of the compounds represented admissible molecular weight (MW < 500). They had desire lipophilicity (logP) values. In addition, the hydrogen bond properties including hydrogen bond donor (HBD), hydrogen bond acceptor (HBA) and rotatable bond (RB) are reasonable. According to rule of five, total polar surface area of all compounds are in accepted range ≤ 140 Å. Based on our results, all of the compounds indicated desire potential for oral bioavailability [52].

Experimental section

Chemistry

All reagents and solvents with analytical grade were purchased from commercial sources (Merck & Sigma Aldrich) and used without further purification. IR spectra (KBr, cm^{-1}) were recorded using a Perkin Elmer IR instrument. ^{1}H-NMR spectra were recorded in $CDCl_3$ on Bruker 500 MHz spectrophotometer using tetramethylsilane (TMS) as an internal standard. Chemical shift values were expressed in ppm scale (δ) and coupling constants were reported in hertz (Hz). An Agilent spectrometer was used for Mass spectra recordation. All melting points were measured with an Electro-thermal

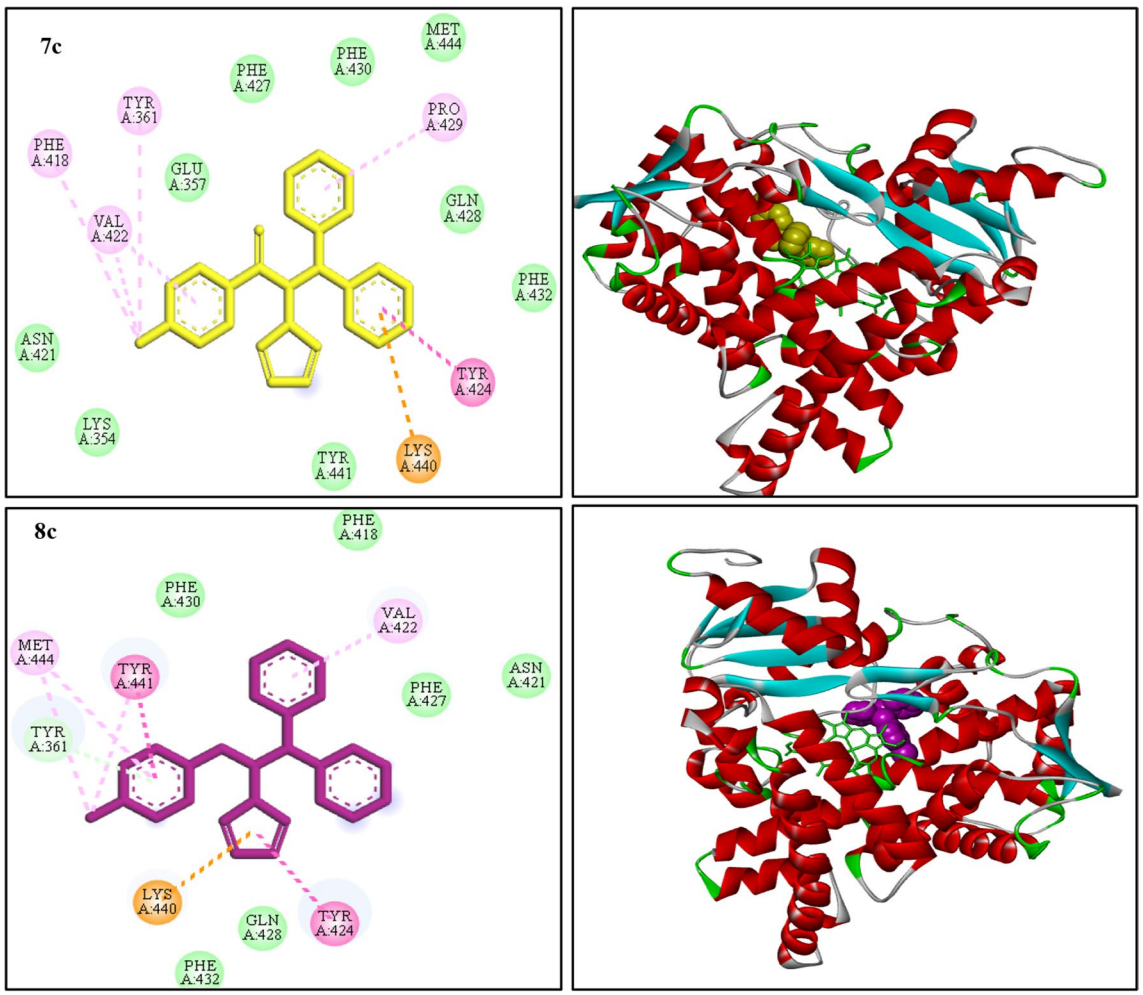

Fig. 7 2D interaction diagrams representing the docked conformation of compounds ***7c*** and ***8c*** in the human placental aromatase (3EQM). (Van der waals: green, dark pink: *π*-*π*, light pink: *π*-alkyl, purple: *π*-sigma, orange: *π*-cation, blue: halogen bond)

IA 9100 apparatus and were uncorrected. The progress of reactions was monitored using thin layer chromatography (TLC) sheets pre-coated with UV fluorescent silica gel Merck $60F_{254}$ and the spots were visualized using UV lamp. The purification of the synthesized compounds was performed by column chromatography.

General procedure for the synthesis of intermediates 3a-f

The appropriate $AlCl_3$ (60 mmol) was added to a stirred solution of phenyl halides (50 mmol) in dichloromethane (30 mL). After stirring for 30 min at room temperature, the mixture was cooled to 0 °C and a solution of chloroacetyl chloride (54 mmol) in dichloromethane (20 mL) was added dropwise to it. The resulting mixture was stirred at room temperature for 24 h. After this time, 50 mL of HCl solution (5%) was slowly added and the reaction mixture was extracted with dichloromethane (3 × 30 mL) and then washed with $NaHCO_3$ (20 mL), water (2 × 20 mL) and brine (20 mL), respectively. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under vacuum. Finally, the obtained precipitate was recrystallized from *n*-hexane to give intermediates **3a-f**.

General procedure for the synthesis of intermediates 5a-f

1,2,4-triazole (48 mmol) and $NaHCO_3$ (48 mmol) were added to a stirred solution of intermediates ***3a-f*** (40 mmol) in toluene. The reaction mixture was refluxed for 20 h. After this time, the reaction mixture was quenched with an ice bath and extracted with ethyl acetate (3 × 30 mL). Then, the organic phase was washed with water (2 × 20 mL) and brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuum. Finally, the residue was recrystallized from diethyl ether to afford the desired compounds ***5a-f***.

Table 2 The bonding energies (kcal/mol) and the detailed interactions of all synthesized compounds on 3EQM target using AutoDock Vina

Entry	Amino Acid	Ligand involved moiety	Type of interaction	B.E (kcal/mol)	Entry	Amino Acid	Ligand involved moiety	Type of interaction	B.E (kcal/mol)
7a	Met 374	benzyl	pi-sulfur	− 9.9	***10c***	HEM 600	benzoyl	pi-cation	− 9.2
	Leu 477, Ile 133, Ala 306, Val 370	1,2,4-triazole & benzoyl	pi-alkyl			Phe 134, Phe 221	1,2,4-triazole & benzoyl	pi-pi	
	HEM 600	benzoyl	pi-cation			Leu 372, Ser 478	1,2,4-triazole & C = O	Carbon hydrogen bond	
	Thr 310, Arg 115, Val 373, Phe 134, Leu 372, Phe 221, Ser 478, Trp 224	–	Vander waals			Ala 306, Ile 133, Val 370, Met 374	benzoyl & 1,2,4-triazole	pi-alkyl & alkyl	
7b	Val 370, Leu 477, Val 373, Ala 306, Ile 133, Ile 305, Phe 221, Trp 224	benzyl & benzoyl & 1,2,4-triazole	pi-alkyl & alkyl	− 10.5		Arg 115, Trp 224, Val 373, Thr 310, Leu 477, Asp 309	–	Vander waals	
	HEM 600	benzyl & benzoyl	pi-pi		***10d***	Ala 306	benzoyl	halogen	− 7.9
	Arg 115	benzyl	pi-cation			HEM 600	benzoyl	pi-cation	
	Glu 302, Ser 478, Phe 134, Met 374, Leu 372, Thr 310, Asp 309	–	Vander waals			Leu 477	benzoyl	pi-sigma	
7c	Tyr 424	di-phenyl	pi-pi	− 8.2		Phe 221	benzoyl	pi-pi	
	Lys 440	di-phenyl	pi-cation			Val 370, Val 369, Leu 372, Met 374, Ile 133, HEM 600, Phe 221	benzoyl & 1,2,4-triazole	alkyl & pi-alkyl	
	Phe 418, Val 422, Tyr 361, Pro 429	benzoyl & di-phenyl	pi-alkyl &| alkyl			Asp 309, Ser 478, Phe 134, Trp 224, Thr 310, Val 373, Arg 115	–	Vander waals	
	Asn 421, Lys 354, Glu 357, Phe 427, Phe 430, Met 444, Gln 428, Phe 432, Tyr 441	–	Vander waals		***10e***	Arg 115	1,2,4- triazole	Hydrogen bond	− 9.7
7d	Lys 440	di-phenyl	pi-alkyl	− 7.9		Ser 478	C = O	Carbon hydrogen bond	
	Tyr 424, Tyr 441	benzoyl & di-phenyl	pi-pi			HEM 600	benzoyl	pi-cation	
	Gln 428	C = O	Hydrogen bond			HEM 600	benzoyl	pi-sigma	
	Phe 432, Phe 430, Met 444, Tyr 361, Pro 429, Phe 427, Val 422, Phe 418	–	Vander waals			Ile 133, Phe 134, Ala 306, Val 370, Met 374, Val 373	benzoyl & 1,2,4-triazole	alkyl & pi-alkyl	
7e	Tyr 441, Phe 430, Met 444, Lys 440, Pro 429	1,2,4-triazole & benzoyl	pi-alkyl & alkyl	− 7.3		Leu 372, Leu 477, Phe 221, Asp 309, Trp 224, Thr 310	–	Vander waals	

Table 2 (continued)

Entry	Amino Acid	Ligand involved moiety	Type of interaction	B.E (kcal/mol)	Entry	Amino Acid	Ligand involved moiety	Type of interaction	B.E (kcal/mol)
	Tyr 424	di-phenyl	pi-pi		***10f***	Lys 440	C = O	Carbon hydrogen bond	− 8.9
	Lys 440	1,2,4-triazole	pi-cation			Tyr 361	benzoyl	pi-pi	
	Pro 429	1,2,4-triazole	Carbon hydrogen bond			Tyr 424	phenyl	pi-pi	
	Lys 440	1,2,4-triazole	Hydrogen bond			Pro 429	benzoyl	pi-alkyl	
	Phe 432, Gln 428, Phe 427	–	Vander waals			Val 422, Phe 427, Phe 432, Gln 428, Met 444, Phe 430, Tyr 441	–	Vander waals	
8a	Arg 115	benzyl	pi-cation	9.4	***10 g***	Tyr 424	phenyl	pi-pi	− 7.5
	HEM 600	benzyl	pi-pi			Pro 429	benzoyl	pi-alkyl	
	Met 374, Ala 306, Thr 310, Ile 133, Trp 224, Phe 221, Ser 478, Phe 134, Leu 372	–	Vander waals			Phe 418, Tyr 361, Tyr 441, Lys 440, Phe 430, Phe 432, Gln 428, Val 422, Phe 427	–	Vander waals	
	Val 373, Val 370, Leu 477	benzyl	pi-alkyl		***10 h***	Glu 357	benzoyl	pi-anion	-7.2
8b	Phe 432, Tyr 424, Pro 429, Met 444	benzyl & di-phenyl	pi-alky	− 7.8		Tyr 424, Tyr 361	benzoyl & phenyl	pi-pi	
	Tyr 424, Tyr 441	benzyl & di-phenyl	pi-pi			Val 422	benzoyl	pi-alkyl	
	Tyr 361	di-phenyl	pi-donor hydrogen bond			Phe 432, Tyr 441, Lys 440, Gln 428, Phe 430, Pro 429, Phe 427, Phe 418, Lys 354, Asn 421	–	Vander waals	
	Phe 427, Gln 428, Gly 433, Lys 440, Phe 430	–	Vander waals		***10i***	Tyr 244	1,2,4-triazole	Hydrogen bond	− 6.7
8c	Met 444, Val 422, Tyr 441	benzyl & di-phenyl	pi-alkyl & alkyl	− 7.8		Asp 476	phenyl	pi-anion	
	Tyr 441, Tyr 424	benzyl & 1,2,4-triazole	pi-pi			Ile 474	benzoyl	pi-sigma	
	Tyr 361	benzyl	pi-donor hydrogen bond			Ala 226, Ile 474	1,2,4-triazole & benzoyl	alkyl & pi-alkyl	
	Lys 440	1,2,4-triazole	pi-cation			His 475, Gln 225, Lys 230, Gly 69, Ile 229, Phe 65, Leu 66, Trp 67	–	Vander waals	
	Phe 430, Phe 418, Phe 427, Asn 421, Gln 428, Phe 432	–	Vander waals		***10j***	Lys 440, Gln 428	1,2,4-triazole & C = O	Hydrogen bond	− 7.8
10a	Ser 478	C = O	Carbon hydrogen bond	− 9.4		Lys 440	1,2,4-triazole	pi-cation	

Table 2 (continued)

Entry	Amino Acid	Ligand involved moiety	Type of interaction	B.E (kcal/mol)	Entry	Amino Acid	Ligand involved moiety	Type of interaction	B.E (kcal/mol)
	HEM 600	1,2,4-triazole	pi-cation			Tyr 361	phenyl	pi-donor hydrogen bond	
	Leu 477	benzoyl	pi-sigma			Tyr 424, Tyr 441	benzoyl & 1,2,4-triazole & phenyl	pi-pi	
	HEM 600	benzoyl	pi-pi			Pro 429, Met 444	Benzoyl & phenyl	pi-alkyl	
	Val 373, Ile 133, Val 370, Ala 306	1,2,4-triazole & benzoyl	pi-alkyl			Phe 432, Val 422, Phe 418, Phe 427, Phe 430,	----	Vander waals	
	Arg 115, Met 374, Phe 221, Leu 372, Phe 134, Thr 310, Trp 224	–	Vander waals		***10 k***	Asn 421	1,2,4-triazole	Hydrogen bond	− 7.3
10b	Met 374	benzoyl	pi-sulfur	− 9.3		Glu 357	phenyl	pi-anion	
	HEM 600	1,2,4-triazole	pi-cation			Tyr 361	phenyl	pi-pi	
	Phe 221, Val 370, Val 369, Ala 306, Ile 133	1,2,4-triazole & benzoyl	alkyl & pi-alkyl			Tyr 424, Lys 440, Tyr 441, Phe 430, Pro 429	benzoyl	alkyl & pi-alkyl	
	Thr 310, Asp 309, Ser 478, Trp 224, Leu 477, Phe 134, Arg 115, Val 373, Leu 372	–	Vander waals			Met 444, Lys 354, Phe 418, Gln 428, Phe 427, Val 422,	–	Vander waals	

Table 3 Physiochemical properties of the synthesized compounds ***7a-e***, ***8a-c*** and ***10a-k***

Entry	MW[a]	LogP[b]	HBD[c]	HBA[d]	TPSA (Å)[e]	RB[f]	Lipinski/Veber violation
7a	277.32	2.39	0	3	47.78	5	0
7b	346.21	3.40	0	3	47.78	5	0
7c	387.86	4.01	0	3	47.78	6	0
7d	432.31	4.11	0	3	47.78	6	0
7e	422.32	4.49	0	3	47.78	6	1
8a	263.34	3.32	0	2	30.71	5	0
8b	373.88	4.93	0	2	30.71	6	1
8c	418.33	5.04	0	2	30.71	6	1
10a	305.53	1.73	0	4	64.85	6	0
10b	339.78	2.23	0	4	64.85	6	0
10c	384.23	2.34	0	4	64.85	6	0
10d	418.67	2.84	0	4	64.85	6	0
10e	374.22	2.72	0	4	64.85	6	0
10f	381.43	2.84	0	4	64.85	7	0
10 g	399.42	3.22	0	5	64.85	7	0
10 h	415.87	3.32	0	4	64.85	7	0
10i	460.32	3.42	0	4	64.85	7	0
10j	417.41	3.59	0	6	64.85	7	0
10 k	450.32	3.79	0	4	64.85	7	0
Lipinski/Veber's Rules	≤ 500	≤ 5	≤ 5	≤ 10	≤ 140	≤ 10	≤ 1

[a] Molecular weight (MW). [b] Logarithm of partition coefficient between n-octanol and water (LogP). [c] Number of hydrogen bond donors (HBD). [d] Number of hydrogen bond acceptors (HBA). [e] Topological polar surface area (TPSA). [f] Number of rotatable bonds (RB)

General procedure for the synthesis of compounds 7a-e

A solution of intermediates ***5a-f*** (6 mmol) in acetonitrile (10 mL) was added to a suspension of NaH (8 mmol) in acetonitrile (30 mL) and the resulting mixture was stirred at room temperature for 1 h. Then, a solution of benzhydryl bromide or benzyle bromide (6 mmol) in 10 mL acetonitrile was added dropwise and the mixture was heated under reflux for 24 h. After cooling to room temperature, the solvent was evaporated in vacuum, 50 mL water was added and the mixture was extracted with dichloromethane (3×30 mL). In the following, the organic layers were dried over Na_2SO_4 and purified by column chromatography on silica gel eluting with ethyl acetate and petroleum ether (3:1) to afford desired products ***7a-e.***

1,3-diphenyl-2-(1H-1,2,4-triazol-1-yl) propan-1-one (7a) Yield: 46%. M. P.: 145–148 °C; IR (KBr, cm^{-1}): 3101 (C-H, aromatic), 2928.8 (C-H, aliphatic), 1690.0 (C = O, ketones), 1594.2 (C = N), 1283.7 (C–N stretch, aromatic).^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm): 8.28 (s, 1H, triazole), 7.92 (d, $J = 7.5$ Hz, 2H, Ar–H-CO), 7.91 (s, 1H, triazole), 7.59 (t, $J = 7.5$ Hz, 1H, Ar–H-CO), 7.46 (t, $J = 7.5$ Hz, 2H, Ar–H-CO), 7.18–7.24 (m, 3H, Ar–H), 7.01 (d, $J = 6.8$ Hz, 2H, Ar–H), 6.24 (dd, $J = 8.8$, 5.8 Hz, 1H, CH), 3.55 (dd, $J = 14.3$, 5.8 Hz, 1H, CH_2), 3.41 (dd, $J = 14.3$, 9.0 Hz, 1H, CH_2). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 193.8, 151.4, 143.6, 135.6, 134.8, 134.7, 129.5, 129.4, 129.3, 129.1, 127.9, 65.5, 39.0. MS m/z (%): 277.2 (5) [M^+], 208.1 (45), 105.2 (100), 91.0 (60), 77.1 (100), 51.0 (15). Elem. anal. calcd. For $C_{17}H_{15}N_3O$ (277.2); C, 73.63; H, 5.45; N, 15.15. Found: C, 73.60; H, 5.42; N, 15.12.

1-(2,4-dichlorophenyl)-3-phenyl-2-(1H-1,2,4-triazol-1-yl) propan-1-one (7b) Yield: 52%. M.P.: 121–123 °C; IR (KBr, cm^{-1}): 3133.7 (C–H stretch, aromatic), 2926.1 (C-H, aliphatic), 1723.8 (C = O, ketone), 1587.1 (C = N), 1294.1, 1248.1 (C–N stretch, aromatic), 1149.0 (Ar-Cl). ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm): 8.18 (s, 1H, triazole), 7.79 (s, 1H, triazole), 7.73 (d, $J = 8.6$ Hz, 1H, 2,4-diCl-Ar–H, H-6), 7.58 (s, 1H, 2,4-diCl-Ar–H, H-3), 7.38 (d, $J = 8.6$ Hz, 1H, 2,4-diCl-Ar–H, H-5), 7.18–7.23 (m, 3H, Ar–H), 6.98 (d, $J = 6.7$ Hz, 2H, Ar–H), 6.18 (dd, $J = 8.5$, 6.0 Hz, 1H, CH), 3.73 (dd, $J = 14.2$, 6.0 Hz, 1H, CH_2), 3.60 (dd, $J = 14.2$, 8.6 Hz, 1H, CH_2). MS m/z (%): 345.3 (4) [M^+], 279.9 (8), 189.9 (30), 144.9 (23), 173.0 (70), 109.0 (22), 91.1 (100), 74.0 (27), 63.1 (18), 50.1 (8). Elem. anal. calcd. For $C_{17}H_{13}Cl_2N_3O$ (345.3); C, 58.98; H, 3.78; N, 12.14. Found: C, 58.89; H, 3.72; N, 12.10.

1-(4-chlorophenyl)-3,3-diphenyl-2-(1H-1,2,4-triazol-1-yl) propan-1-one (7c) Yield: 63%. M.P.: 140–142 °C; IR (KBr, cm^{-1}): 3101.6 (C-H, aromatic), 2926.1 (C-H, aliphatic), 1691.4 (C=O, ketones), 1588.7 (C=N stretch, aromatic), 1275.4 (C–N stretch, aromatic), 1093.1 (Ar-Cl). ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm): 8.33 (s, 1H, triazole), 7.81 (d, *J*=8.2 Hz, 2H, Ar–H-CO, H-2 and H-6), 7.81 (s, 1H, triazole), 7.34 (d, *J*=8.3 Hz, 2H, Ar–H-CO, H-3 and H-5), 7.27 (d, *J*=7.5 Hz, 2H, Ar–H), 7.23–7.13 (m, 7H, Ar–H), 7.10 (t, *J*=7.3 Hz, 1H, Ar–H), 6.79 (d, *J*=11.6 Hz, 1H, CH–N), 5.09 (d, *J*=11.6 Hz, 1H, CH-$(Ph)_2$). MS m/z (%): 387.1 (12) [M^+], 317.1 (45), 242.1 (100), 178.1 (70), 167.3 (100), 152.0 (70), 141.0 (55), 111.0 (100), 91.0 (38), 75.1 (35), 51.1 (7). Elem. anal. calcd. For $C_{23}H_{18}ClN_3O$ (387.87); C, 71.22; H, 4.68; N, 10.83. Found: C, 71.20; H, 4.58; N, 10.80.

1-(4-bromophenyl)-3,3-diphenyl-2-(1H-1,2,4-triazol-1-yl) propan-1-one (7d) Yield: 58%. M.P.: 110–113 °C; IR (KBr, cm^{-1}): 3103.3 (C-H, aromatic), 2973.0 (C-H, aliphatic), 1692.8 (C=O, ketones), 1583.1 (C=N stretch, aromatic), 1287.8 (C–N stretch, aromatic), 1012.4 (Ar-Br). ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm): 8.13 (s, 1H, triazole), 7.77 (s, 1H, triazole), 7.71 (d, *J*=8.4 Hz, 2H, Ar–H-CO, H-2 and H-6), 7.51 (d, *J*=8.4 Hz, 2H, Ar–H-CO, H-3 and H-5), 7.26–7.11 (m, 10 H, Ar–H), 6.73 (d, *J*=11.6 Hz, 1H, CH–N), 5.07 (d, *J*=11.6 Hz, 1H, CH-$(Ph)_2$). MS m/z (%): 431.1 (5) [M^+], 363.0 (25), 248.1 (25), 207.0 (22), 184.9 (75), 167.3 (100), 152.0 (100), 128.0 (8), 91.0 (28), 76.1 (33), 51.0 (7). Elem. anal. calcd. For $C_{23}H_{18}BrN_3O$ (433.1); C, 63.90; H, 4.20; N, 9.72. Found: C, 63.85; H, 4.16; N, 9.68.

1-(2,4-dichlorophenyl)-3,3-diphenyl-2-(1H-1,2,4-triazol-1-yl) propan-1-one (7e) Yield: 48%. M.P.: 118–121°C. IR (KBr, cm^{-1}): 3130.3 (C–H stretch, aromatic), 2923.9 (C-H, aliphatic), 1700.1 (C=O, ketone), 1578.6 (C=N), 1276.3 (C–N stretch, aromatic), 1137.6 (Ar-Cl). ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm): 8.12 (s, 1H, triazole), 7.79 (s, 1H, triazole), 7.31 (d, *J*=1.8 Hz, 1H, 2,4-diCl-Ar–H, H-6), 7.30 (s, 1H, 2,4-diCl-Ar–H, H-3), 7.23–7.15 (m, 8H, Ar–H), 7.14 (d, *J*=1.8 Hz, 1H, 2,4-diCl-Ar–H, H-5), 7.13–7.10 (m, 2H, Ar–H), 6.74 (d, *J*=11.6 Hz, 1H, CH–N), 4.94 (d, *J*=11.6 Hz, 1H, CH-$(Ph)_2$). MS m/z (%): 421.2 (3) [M^+], 351.0 (15), 276.0 (68), 248.1 (45), 165.1 (100), 152.0 (52), 109.0 (20), 91.0 (33), 77.1 (12), 51.1 (5). Elem. anal. calcd. For $C_{23}H_{17}Cl_2N_3O$ (421.2); C, 65.41; H, 4.06; N, 9.95. Found: C, 65.38; H, 4.02; N, 9.92.

General procedure for the synthesis of compounds 8a-c

A mixture of compound ***7a*** or ***7c-d*** (1.6 mmol), hydrazine monohydrate (8 mmol) and potassium hydroxide (8 mmol) in ethylene glycol (50 mL) was heated at 170 °C for 4 h. Then, the reaction mixture was cooled to room temperature, quenched with water (500 mL) and acidified to pH=1 with concentrated hydrochloric acid and extracted with chloroform (3 × 30 mL). Afterwards, the organic layer was washed with brine and dried over Na_2SO_4. The crude product was purified by column chromatography on silica gel eluting with ethyl acetate and petroleum ether (1:1) to give pure compounds ***8a-c***.

1-(1,3-diphenylpropan-2-yl)-1H-1,2,4-triazole (8a) Yield: 39%. M.P.: 81–83 °C, IR (KBr, cm^{-1}): 3103.7 (C-H, aromatic), 2931.8 (C-H, aliphatic), 1598.8 (C=N), 1285.8 (C–N stretch, aromatic). ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm): 8.17 (s, 1H, triazole), 7.85 (s, 1H, triazole), 7.29–7.27 (m, 6H, Ar–H, H-2, H-4 and H-6), 7.13–7.11 (m, 4H, Ar–H, H-3 and H-5), 4.64 (m, 1H, CH), 3.70 (d, *J*=8.8 Hz, 4H, CH_2). MS m/z (%): 263.1 (10) [M^+], 201.1 (17), 172.0 (9) 105.2 (100), 91.0 (73), 77.1 (100), 63.1 (12), 51.1 (15). Elem. anal. calcd. For $C_{17}H_{17}N_3$ (263.1); C, 77.54; H, 6.51; N, 15.96. Found: C, 77.35; H, 6.49; N, 15.85.

1-(3-(4-chlorophenyl)-1,1-diphenyl-propan-2-yl)-1H-1,2,4-triazole (8b) Yield: 41%. M.P.: 93–96 °C; IR (KBr, cm^{-1}): 3103.4 (C-H, aromatic), 2959.5 (C-H, aliphatic), 1591.1 (C=N), 1278.6 (C–N stretch, aromatic). ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm): 8.29 (s, 1H, triazole), 7.78 (s, 1H, triazole), 7.46 (d, *c*=8.4 Hz, 2H, 4-Cl-Ar–H, H-2 and H-6), 7.28–7.26 (d, *J*=7.1 Hz, 2H, Ar–H), 7.24–7.08 (m, 8H, Ar–H), 7.05 (d, *J*=8.4 Hz, 2H, 4-Cl-Ar–H, H-3 and H-5), 4.67 (m, 1H, 4-Cl-Ar-CH_2-CH), 3.89 (d, *J*=11.2 Hz, 1H, Ar–CH), 3.42 (dd, *J*=14.2, 6.1 Hz, 1H, CH_2), 3.27 (dd, *J*=14.3, 8.5 Hz, 1H, CH_2). MS m/z (%): 373.1 (5) [M^+], 306.1 (8), 245.1 (15) 173.1 (35), 155.1 (30), 126.0 (100), 111.0 (45), 103.1 (33), 77.0 (25), 63.0 (4), 51.1 (7). Elem. anal. calcd. For $C_{23}H_{20}ClN_3$ (373.13); C, 73.89; H, 5.39; N, 11.24. Found: C, 73.80; H, 5.28; N, 11.19.

1-(3-(4-bromophenyl)-1,1-diphenyl-propan-2-yl)-1H-1,2,4-triazole (8c) Yield: 45%. M.P.: 88–91 °C; IR (KBr, cm^{-1}): 3105.1 (C-H, aromatic), 2970.5 (C-H, aliphatic), 1585.2 (C=N), 1288.1 (C–N stretch, aromatic). ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm): 8.18 (s, 1H, triazole), 7.81 (s, 1H, triazole), 7.57 (d, *J*=8.4 Hz, 2H, 4-Br-Ar–H, H-2 and H-6), 7.28–7.26 (d, *J*=7.0 Hz, 2H, Ar–H), 7.27–7.10 (m, 8H, Ar–H), 7.08 (d, *J*=8.5 Hz, 2H, 4-Br-Ar–H, H-3 and H-5), 4.59 (m, 1H, 4-Cl-Ar-CH_2-CH), 3.75 (d, *J*=11.5 Hz, 1H, Ar–CH), 3.50 (dd, *J*=14.2, 6.1 Hz, 1H, CH_2), 3.37 (dd, *J*=14.2, 8.5 Hz, 1H, CH_2). MS m/z (%): 417.0 (8) [M^+], 363.0 (10), 286.0 (15) 248.1 (25), 184.9 (55), 169.3 (100), 155.0 (48), 128.1 (15), 104.0 (15), 91.0 (23), 76.0 (43), 51.0 (7). Elem. anal. calcd. For $C_{23}H_{20}BrN_3$ (417.0); C, 66.04; H, 4.82; N, 10.04. Found: C, 66.01; H, 4.79; N, 10.02.

General procedure for the synthesis compounds 10a-k

A solution of intermediates ***5a-f*** (6 mmol) in acetonitrile (10 mL) was added to a suspension of NaH (8 mmol) in acetonitrile (30 mL) and the resulting mixture was stirred at room temperature for 1 h. Then, a solution of 2-chloro-2-phenyl acetophenone or halogenated phenacyl chloride (6 mmol) in 10 mL acetonitrile was added dropwise and the mixture was heated under reflux for 24 h. After cooling to room temperature, the solvent was evaporated in vacuum, 50 mL water was added and the mixture was extracted with dichloromethane (3 × 30 mL). In the following, the organic layers were dried over Na_2SO_4 and purified by column chromatography on silica gel eluting with ethyl acetate and petroleum ether (3:1) to afford desired products ***10a-k***.

4-diphenyl-2-(1H-1,2,4-triazol-1-yl) butane-1,4-dione (10a) Yield: 55%. M.P.: 115–118 °C, IR (KBr, cm^{-1}): 3093.5 (C–H stretch, aromatic), 2911.0 (C-H, aliphatic), 1691.0, 1668.8 (C=O, ketone), 1595.7 (C=N), 1271.3 (C–N stretch, aromatic). ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm): 8.29 (s, 1H, triazole), 7.96 (d, *J*=7.2 Hz, 4H, Ar–H-CO and Ar′-H–CO, H-2 and H-6), 7.90 (s, 1H, triazole), 7.58 (t, *J*=7.1 Hz, 2H, Ar–H-CO and Ar′-H–CO, H-4), 7.48 (d, 4H, Ar–H-CO and Ar′-H–CO, H-3 and H-5), 6.69 (t, *J*=6.0 Hz, 1H, CH), 4.15 (dd, *J*=18.0, 6.6 Hz, 1H, CH_2), 3.83 (dd, *J*=17.8, 5.9 Hz, 1H, CH_2). MS m/z (%): 305.3 (3) [M^+], 236.1 (10), 276.1 (100), 223.1 (80), 200.1 (35), 178.1 (10), 131.0 (8), 105.2 (98), 77.0 (100), 63.0 (5), 51.1 (20). Elem. anal. calcd. For $C_{18}H_{15}N_3O_2$ (305.12); C, 70.81; H, 4.95; N, 13.76. Found: C, 70.75; H, 4.92; N, 13.72.

1-(4-chlorophenyl)-4-phenyl-2-(1H-1,2,4-triazol-1-yl) butane-1,4-dione (10b) Yield: 67%. M.P.: 131–133 °C; IR (KBr, cm^{-1}): 3092.8 (C–H stretch, aromatic), 2920.3 (C-H, aliphatic), 1692.6, 1655.5 (C=O, ketone), 1586.3 (C=N), 1272.1 (C–N stretch, aromatic), 1090.4 (Ar-Cl). ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm): 8.25 (s, 1H, triazole), 7.96 (d, *J*=7.2 Hz, 2H, Ar–H-CO, H-2 and H-6), 7.90 (s, 1H, triazole), 7.83 (d, *J*=8.5 Hz, 2H, 4-Cl-Ar–H-CO, H-2 and H-6), 7.44 (t, *J*=7.1 Hz, 1H, Ar–H-CO, H-4), 7.39 (d, *J*=8.5 Hz, 2H, 4-Cl-Ar–H-CO, H-3 and H-5), 7.30 (d, *J*=7.1 Hz, 2H, Ar–H-CO, H-3 and H-5), 6.65 (t, *J*=6.2 Hz, 1H, CH), 4.13 (dd, *J*=18.0, 6.6 Hz, 1H, CH_2), 3.80 (dd, *J*=17.9, 5.9 Hz, 1H, CH_2). MS m/z (%): 339.1 (8) [M^+], 287.1 (13), 263.0 (25), 178.1 (10), 170.0 (18), 139.1 (100), 105.1 (100), 77.0 (83), 51.1 (13). Elem. anal. calcd. For $C_{10}H_{14}ClN_3O_2$ (339.1); C, 63.63; H, 4.15; N, 12.37. Found: C, 63.59; H, 4.10; N, 12.35.

1-(4-bromophenyl)-4-phenyl-2-(1H-1,2,4-triazol-1-yl) butane-1,4-dione (10c) Yield: 44%. M.P.: 149–151 °C. IR (KBr, cm^{-1}): 3073.7 (C–H stretch, aromatic), 2925.4 (C-H, aliphatic), 1697.1, 1659.5 (C=O, ketone), 1589.5 (C=N), 1279.1 (C–N stretch, aromatic), 1009.6 (Ar-Br).^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm): 8.34 (s, 1H, triazole), 7.96 (d, *J*=7.1 Hz, 2H, Ar–H-CO, H-2 and H-6), 7.92 (s, 1H, triazole), 7.74 (d, *J*=8.3 Hz, 2H, 4-Br-Ar–H-CO, H-2 and H-6), 7.56 (d, *J*=8.3 Hz, 2H, 4-Br-Ar–H-CO, H-3 and H-5), 7.43 (t, *J*=7.1 Hz, 1H, Ar–H-CO, H-4), 7.30 (d, *J*=7.1 Hz, 2H, Ar–H-CO, H-3 and H-5), 6.69 (t, *J*=6.4 Hz, 1H, CH), 4.15 (dd, *J*=18.0, 6.7 Hz, 1H, CH_2), 3.82 (dd, *J*=18.0, 6.1 Hz, 1H, CH_2). MS m/z (%): 383.0 (3) [M^+], 303.0 (12), 236.1 (15), 200.1 (17), 183.0 (17), 154.9 (10), 105.1 (98), 77.1 (100), 51.1 (18). Elem. anal. calcd. For $C_{18}H_{14}BrN_3O_2$ (383.0); C, 56.27; H, 3.67; N, 10.94. Found: C, 56.20; H, 6.60; N, 10.92.

1-(4-bromophenyl)-4-(4-chlorophenyl)-2-(1H-1,2,4-triazol-1-yl) butane-1,4-dione (10d) Yield: 46%. M.P.: 162–165 °C, IR (KBr, cm^{-1}): 3069.2 (C–H stretch, aromatic), 2922.3 (C-H, aliphatic), 1689.7 (C=O, ketone), 1590.7 (C=N), 1279.3 (C–N stretch, aromatic), 1093.4 (Ar-Cl), 1012.4 (Ar-Br). ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm): 8.35 (s, 1H, triazole), 8.04 (d, *J*=8.4 Hz, 2H, 4-Cl-Ar–H-CO, H-2 and H-6), 7.94 (s, 1H, triazole), 7.88 (d, *J*=8.4 Hz, 2H, 4-Br-Ar–H-CO, H-2 and H-6), 7.40 (d, *J*=8.4 Hz, 2H, 4-Br-Ar–H-CO, H-3 and H-5), 7.30 (d, *J*=8.4 Hz, 2H, 4-Cl-Ar–H-CO, H-3 and H-5), 6.68 (t, *J*=6.0 Hz, 1H, CH), 4.15 (dd, *J*=17.9, 6.8 Hz, 1H, CH_2), 3.82 (dd, *J*=18.0, 6.2 Hz, 1H, CH_2). MS m/z (%): 416.9 (3) [M^+], 335.0 (100), 291.0 (23), 212.0 (30), 182.9 (50), 156.9 (18), 139.10 (100), 111.0 (100), 75.1 (47), 63.0 (10). Elem. anal. calcd. For $C_{18}H_{13}BrClN_3O_2$ (416.9); C, 51.64; H, 3.13; N, 10.04. Found: C, 51.60; H, 3.09; N, 10.01.

1-(2,4-dichlorophenyl)-4-phenyl-2-(1H-1,2,4-triazol-1-yl) butane-1,4-dione (10e) Yield: 52%. M.P.: 153–156 °C, IR (KBr, cm^{-1}): 3098.2 (C–H stretch, aromatic), 2929.0 (C-H, aliphatic), 1710.5, 1673.5 (C=O, ketone), 1581.3 (C=N), 1272.1 (C–N stretch, aromatic), 1137.6 (Ar-Cl). ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm): 8.31 (s, 1H, triazole), 7.94 (s, 1H, triazole), 7.92 (d, *J*=7.2 Hz, 2H, Ar–H-CO, H-2 and H-6), 7.65 (d, *J*=8.3 Hz, 1H, 2,4-diCl-Ar–H-CO, H-2), 7.46 (t, *J*=7.2 Hz, 1H, Ar–H-CO, H-4), 7.22 (s, 1H, 2,4-diCl-Ar–H, H-5), 7.14 (t, *J*=7.1 Hz, 2H, Ar–H-CO, H-3 and H-5), 7.06 (d, *J*=8.4 Hz, 1H, 2,4-diCl-Ar–H-CO, H-3), 6.52 (t, *J*=6.0 Hz, 1H, CH), 4.12 (dd, *J*=18.2, 5.1 Hz, 1H, CH_2), 3.79 (dd, *J*=18.2, 7.0 Hz, 1H, CH_2. MS m/z (%): 373.2 (4) [M^+], 338.1 (25), 268.0 (18), 240.0 (5), 172.9 (75), 145.0 (28), 105.2 (100), 91.0 (20), 77.0 (73), 51.0 (13). Elem. anal. calcd. For $C_{18}H_{13}Cl_2N_3O_2$ (373.2); C, 57.77; H, 3.50; N, 18.95. Found: C, 57.75; H, 3.48; N, 18.91.

4-triphenyl-3-(1H-1,2,4-triazol-1-yl) butane-1,4-dione (10f) Yield: 64%. M.P.: 185–188 °C; IR (KBr, cm^{-1}):

3068.6 (C–H stretch, aromatic), 2924.0 (C-H, aliphatic), 1698.1, 1663.7 (C=O, ketone), 1596.3 (C=N), 1276.8 (C–N stretch, aromatic). ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm): 8.15 (s, 1H, triazole), 7.99 (d, *J*=7.7 Hz, 2H, Ar–H-CO-CHN, H-2 and H-6), 7.90 (d, *J*=7.7 Hz, 2H, Ar–H-CO–CH-Ar, H-2 and H-6), 7.87 (s, 1H, triazole), 7.55–7.46 (m, 2H, 2Ar-H–CO, H-4), 7.40 (t, *J*=7.4 Hz, 4H, 2Ar-H–CO, H-3 and H-5), 7.23–7.18 (m, 3H, Ar–H, H-3, H-4 and H-5), 7.13 (d, *J*=6.5 Hz, 2H, Ar–H, H-2 and H-6), 6.66 (d, *J*=10.5 Hz, 1H, CH–N), 5.69 (d, *J*=10.5 Hz, 1H, CH-Ph). MS m/z (%): 381.2 (8) [M^+], 312.1 (6), 276.1 (100), 209.1 (35), 170.1 (45), 131.0 (18), 104.8 (100), 90.0 (40), 76.9 (100), 63.1 (7), 51.1 (40). Elem. anal. calcd. For $C_{24}H_{19}N_3O_2$ (381.4); C, 75.57; H, 5.02; N, 11.02. Found: C, 75.52; H, 5.01; N, 11.02.

1-(4-fluorophenyl)-3,4-diphenyl-2-(1H-1,2,4-triazol-1-yl) butane-1,4-dione (10 g) Yield: 34%. M.P.: 154–157 °C; IR (KBr, cm^{-1}): 3094.9 (C–H stretch, aromatic), 2918.0 (C-H, aliphatic), 1695.9, 1658.5 (C=O, ketone), 1598.2 (C=N), 1240.9 (C–N stretch, aromatic), 1275.5 (Ar-F). ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm): 8.28 (s, 1H, triazole), 7.92 (dd, *J*=8.7, 5.3 Hz, 2H, 4-F-Ar–H-CO, H-3 and H-5), 7.79 (s, 1H, triazole), 7.55 (d, *J*=7.5 Hz, 2H, Ar–H-CO, H-2 and H-6), 7.23–7.13 (m, 7H, Ar–H and Ar–H-CO, H-3 and H-5), 7.09 (t, *J*=7.5 Hz, 1H, Ar–H-CO, H-4), 7.04 (t, *J*=8.6 Hz, 2H, 4-F-Ar–H-CO, H-2 and H-6), 6.81 (d, *J*=11.6 Hz, 1H, CH–N), 5.09 (d, *J*=11.6 Hz, 1H, CH-Ph). MS m/z (%): 399.2 (5) [M^+], 365.4 (4), 332.4 (10), 305.3 (22), 295.1 (10), 226.1 (75), 197.2 (10), 172.0 (18), 149.0 (25), 123.2 (100), 95.1 (100), 75.0 (38), 63.1 (22), 51 (9). Elem. anal. calcd. For $C_{24}H_{18}FN_3O_2$ (399.2); C, 72.17; H, 4.54; N, 4.76. Found: C, 72.15; H, 4.51; N, 4.75.

1-(4-chlorophenyl)-3,4-diphenyl-2-(1H-1,2,4-triazol-1-yl) butane-1,4-dione (10 h) Yield: 40%. M.P.: 174–176 °C; IR (KBr, cm^{-1}): 3100.4 (C–H stretch, aromatic), 2979.5 (C-H, aliphatic), 1696.4, 1659.6 (C=O, ketone), 1588.8 (C=N), 1275.8 (C–N stretch, aromatic), 1092.2 (Ar-Cl). ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm): 8.11 (s, 1H, triazole), 7.94 (d, *J*=7.4 Hz, 2H, Ar–H-CO, H-2 and H-6), 7.89 (d, *J*=8.4 Hz, 2H 4-Cl-Ar–H-CO, H-2 and H-6), 7.84 (s, 1H, triazole), 7.57 (d, *J*=8.5 Hz, 2H 4-Cl-Ar–H-CO, H-3 and H-5), 7.53 (t, *J*=7.4 Hz, 1H, Ar–H-CO, H-4), 7.541 (t, *J*=7.4 Hz, 2H, Ar–H-CO, H-3 and H-5), 7.22–21 (m, 3H, Ar–H), 7.12–10 (m, 2H, Ar–H), 6.60 (d, *J*=10.1 Hz, 1H, CH–N), 5.66 (d, *J*=10.0 Hz, 1H, CH-Ph). MS m/z (%): 415.1 (4) [M^+], 397.1 (5), 346.1 (5), 310.1 (15), 276.1 (30), 242.0 (60), 207.0 (25), 197.2 (10), 170.0 (20), 139.1 (100), 104.9 (100), 90.0 (18), 77.1 (100), 63.0 (3), 51.1 (12). Elem. anal. calcd. For $C_{24}H_{18}ClN_3O_2$ (415.1); C, 69.31; H, 4.36; N, 10.10. Found: C, 69.29; H, 4.32; N, 10.09.

1-(4-bromophenyl)-3,4-diphenyl-2-(1H-1,2,4-triazol-1-yl) butane-1,4-dione (10i) Yield: 48%. M.P.: 168–171 °C; IR (KBr, cm^{-1}): 3069.2 (C–H stretch, aromatic), 2922.4 (C-H, aliphatic), 1696.7, 1657.8 (C=O, ketone), 1584.4 (C=N), 1277.1 (C–N stretch, aromatic), 1007.3 (Ar-Br). ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm): 8.16 (s, 1H, triazole), 7.98 (d, *J*=7.4 Hz, 2H, Ar–H-CO, H-2 and H-6), 7.79 (s, 1H, triazole), 7.76 (d, *J*=8.5 Hz, 2H, 4-Br-Ar–H-CO, H-2 and H-6), 7.55 (d, *J*=8.5 Hz, 2H, 4-Br-Ar–H-CO, H-3 and H-5), 7.52 (t, *J*=7.4 Hz, 1H, Ar–H-CO, H-4), 7.40 (t, *J*=7.4 Hz, 2H, Ar–H-CO, H-3 and H-5), 7.22–21 (m, 3H, Ar–H), 7.11–10 (m, 2H, Ar–H), 6.57 (d, *J*=10.4 Hz, 1H, CH–N), 5.64 (d, *J*=10.4 Hz, 1H, CH-Ph). MS m/z (%): 459.1 (2) [M^+], 390.0 (3), 354.1 (7), 286.0 (35), 276.1 (25), 207.1 (18), 182.9 (60), 154.9 (30), 105.1 (100), 91.1 (18), 77.1 (85), 51.1 (10). Elem. anal. calcd. For $C_{24}H_{18}BrN_3O_2$ (459.1); C, 62.62; H, 3.94; N, 9.13. Found: C, 62.60; H, 3.90; N, 9.09.

1-(2,4-difluorophenyl)-3,4-diphenyl-2-(1H-1,2,4-triazol-1-yl) butane-1,4-dione (10j)
Yield: 45%. M.P.: 114–117 °C; IR (KBr, cm^{-1}): 3062.4 (C–H stretch, aromatic), 2922.7 (C-H, aliphatic), 1676.7 (C=O, ketone), 1611.8 (C=N), 1271.9 (Ar-F). ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm): 8.21 (s, 1H, triazole), 8.03 (s, 1H, triazole), 7.98 (d, *J*=7.3 Hz, 2H, Ar–H-CO, H-2 and H-6), 7.90 (dt, *J*=17.1, 9.5 Hz, 1H, 4-F-Ar–H-CO, H-6), 7.71 (t, *J*=7.3 Hz, 1H, Ar–H-CO, H-4), 7.46 (t, *J*=7.4 Hz, 2H, Ar–H-CO, H-3 and H-5), 7.18–7.14 (m, 3H, Ar–H), 7.08–7.06 (m, 2H, Ar–H), 6.89 (td, *J*=8.4, 2.1 Hz, 1H, 4-F-Ar–H-CO, H-3), 6.73 (ddd, *J*=10.1, 10.0, 2.2 Hz, 1H, 4-F-Ar–H-CO, H-5), 6.45 (d, *J*=10.4 Hz, 1H, CH–N), 5.61 (d, *J*=10.3 Hz, 1H, CH-Ph). MS m/z (%): 417.2 (7) [M^+], 342.1 (15), 310.1 (15), 276.1 (50), 244.2 (100), 214.0 (35), 191.1 (10), 176.1 (33), 141.2 (100), 105.2 (100), 90.1 (25), 76.9 (100), 63.0 (43), 51.1 (33). Elem. anal. calcd. For $C_{24}H_{17}F_2N_3O_2$ (417.2); C, 69.06; H, 4.11; N, 10.07. Found: C, 69.05; H, 4.10; N, 10.02.

1-(2,4-dichlorophenyl)-3,4-diphenyl-2-(1H-1,2,4-triazol-1-yl) butane-1,4-dione (10 k)
Yield: 39%. M.P.: 178–181 °C; IR (KBr, cm^{-1}): 3102.8 (C–H stretch, aromatic), 2931.3 (C-H, aliphatic), 1712.0, 1676.4 (C=O, ketone), 1584.3 (C=N), 1276.0 (C–N stretch, aromatic), 1135.7 (Ar-Cl). ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm): 7.97 (s, 1H, triazole), 7.88 (s, 1H, triazole), 7.65 (d, *J*=8.5 Hz, 1H, 2,4-diCl-Ar–H, H-6), 7.52 (t, 1H, Ar–H-CO, H-4), 7.49 (d, 2H, Ar–H-CO, H-2 and H-6), 7.42 (t, 2H, Ar–H-CO, H-3 and H-5), 7.32 (d, *J*=1.7 Hz, 1H, 2,4-diCl-Ar–H, H-3), 7.22 (dd, *J*=8.4, 1.7 Hz, 1H, 2,4-diCl-Ar–H, H-5), 7.18–7.16 (m, 3H, Ar–H), 7.12–7.09 (m, 2H, Ar–H), 6.70 (d, *J*=10.3 Hz, 1H, CH–N), 5.57 (d, *J*=10.3 Hz, 1H, CH-Ph). MS m/z

(%): 449.1 (7) [M^+], 344.0 (10), 276.0 (85), 241.1 (5), 172.9 (80), 145.0 (35), 105.2 (100), 90.0 (20), 77.0 (100), 51.1 (12). Elem. anal. calcd. For $C_{24}H_{17}Cl_2N_3O_2$ (449.1); C, 64.01; H, 3.81; N, 9.33. Found: C, 63.98; H, 3.78; N, 9.26.

In vitro cytotoxic assay

Chemicals

Fetal bovine serum (FBS) and RPMI-1640 medium were purchased from Gibco Invitrogen Co. (Scotland, UK) and sigma Aldrich, respectively. Dimethyl sulfoxide (DMSO), doxorubicin, penicillin, streptomycin was also purchased from Sigma Aldrich.

Cell cultures

Cell cultures were obtained from the human lung cancer cell line (A549), human cervical cancer cell line (Hela), human breast cancer cell line (MCF-7) and Normal cells isolated from human lung tissue (MRC-5) taken from the National Cell Bank of Iran (NCBI, Pasteur Institute, Tehran, Iran). All cells were cultured in RPMI-1640 medium supplemented with 10% FBS, antibiotics (penicillin 100 U/mL, streptomycin 100 lg/mL), at 37 ˚C in a humidified atmosphere containing 5% CO_2.

MTT assay

Cytotoxic activities of all the synthesized compounds were assessed by standard 3-(4,5-dimethylthiazol-yl)-2,5-diphenyl-tetrazolium bromide (MTT) assay [53]. The assay was performed according to a known protocol [54–56]. The cells were seeded and plated in 96-well microplates at a density of 1×10^4 cells per well in 180 µL complete culture media. After 24 h incubation, the cells were treated with 100 mL of different concentrations of synthesized compounds ranging from 1×10^{-4} to 1×10^{-7} M at identical conditions in triplicates. After 72 h, media were replaced with 150 µL media containing 0.5 mg/mL of MTT solution [57]. The plates were incubated at 37 °C for additional four hours. Then, media containing MTT were discarded and 150 µL dimethylsulfoxide (DMSO, > 99%) was added to each well to dissolve the formazan crystals. The absorbance in each well was determined at 570 nm by a BioRad microplate reader (Model 680) and then the IC_{50} values were calculated and demonstrated as mean ± SEM [58].

Molecular docking study

Molecular docking studies were performed by AutoDock 4.2 program and AutoDock Tools 1.5.4 to investigate the binding mode of derivative in the active site of receptor [59]. The X-ray crystallographic structures of aromatase (PDB: 3EQM) (39) were obtained from the protein data bank (http://www.rcsb.org). Then, all water molecules and co-crystallized ligand were removed and hydrogen atoms were added to the protein and finally saved as pdbqt format. In the following, 3D structures of ligands were drawn and minimized under Molecular Mechanics MM^+ and semi-empirical AM1 methods, using HyperChem software and saved as pdbqt format. The box dimensions were set at $65 \times 65 \times 65$ with 0.375 Å grid spacing. Docking validation was done by re-docking the original ligand into the active site of receptor. Finally, conformations with the lowest free energies of binding were selected for analysis.

Conclusion

In summary, we have designed and synthesized nineteen new 1,2,4-triazole-based derivatives starting from different phenyl halide analogues through three or four different steps. Their chemical structures were fully confirmed by IR, ^{1}H-NMR, Mass spectra and elemental analysis. In vitro cytotoxic activity of the synthesized compounds were evaluated against three human cancer cell lines including MCF-7, Hela and A549, using MTT assay. The obtained results indicated that the synthesized compounds possessed relatively high to moderate antiproliferative activities against MCF-7 and Hela cancer cell lines. Compounds ***7d***, ***7e***, ***10a*** and ***10d*** were the most potent ones against three tested cell lines. Based on structure activity relationship (SAR) studies, it was found that the presence of electronegative substituents on the phenyl ring, as well as the presence of one-carbonyl group, resulted in a relative increase in the cytotoxic activity of the synthesized compounds. The outcome results relived that these active derivatives can be considered as a lead compound for anticancer treatments.

Abbreviations

ADME: Adsorption Distribution, Metabolism and Discretion; RMSD: Root Mean Square Deviation; TPSA: Total polar surface area; MTT: (3-(4, 5 dimethylthiazol-yl)-2,5-diphenyl-tetrazolium bromide).

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13065-022-00887-x.

Additional file 1: Figures S1–S58

Acknowledgements

Not applicable.

Author contributions

LE write the biological section and performed docking study. SS prepared the manuscript, and write the synthesize section. AM contributed to the synthesis of compounds. SKh contributed to the preparation of the manuscript. AS supervise the computational study. HS edit the manuscript. ZF performed the biological study. MF supervised the biological study ZR contributed to the

preparation of the manuscript and supervised the study. All authors read and approved the final manuscript.

Funding
Financial assistance from the Shiraz University of Medical Sciences by way of grant number 16388 is gratefully acknowledged.

Availability of data and materials
The data sets used and analyzed during the current study are available from the corresponding author on reasonable request. We have presented all data in the form of Tables and Figure. The PDB code (3EQM) was retrieved from protein data bank (www.rcsb.org). https://www.rcsb.org/structure/3EQM. A549 cells (ATCC No. CCL-185 human lung cancer cell line), Hela cells (ATCC No. CCL-2 human cervical cancer cell line), MCF-7 cells (ATCC No. HTB-22 human breast cancer cell line), MRC-5 cells (ATCC No. CCL-171 human lung tissue),. All the cell lines were purchased from the National Cell Bank of Iran (NCBI, Pasteur Institute, Tehran, Iran).

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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Received: 10 September 2022 Accepted: 29 October 2022
Published online: 12 November 2022

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