Arabian Journal of Chemistry (2022) **15**, 103782

King Saud University

Arabian Journal of Chemistry

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ORIGINAL ARTICLE

Fluorinated azole anticancer drugs: Synthesis, elaborated structure elucidation and docking studies

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Received 30 October 2021; accepted 8 February 2022
Available online 12 February 2022

KEYWORDS

Thiazoles;
Fluorinated compounds;
Hydrazonoyl chlorides;
Breast cancer;
Docking study

Abstract The present article deals with the synthesis of novel nano-sized fluorinated thiazoles and studying their anticancer potentiality. The targeted azoles could be accessed *via* trifluoromethylated thiosemicarbazone (**3**) prepared by reaction of with thiosemicarbazide in acidic solution of ethanol. The latter a fluorinated building block (**3**) have been reacted with appropriate derivatives of *a*-halo compounds namely, *N*-aryl 2-oxopropane-hydrazonoyl chlorides **4a-f** using dioxane containing TEA as base catalyst. Also, the reaction between *N*-(4-(1-(2-carbamothioylhydrazineyli dene)ethyl)phenyl)-2,2,2-trifluoroacetamide (**3**) and chloroacetonitrile **8** under the same experimental conditions furnished the corresponding amino thiazole derivative **11**. In the same manner the base catalyzed cyclocondensation reaction between *N*-(4-(1-(2-carbamothioylhydrazineylidene)ethyl)phenyl)-2, 2,2-trifluoroacetamide (**3**) and phenacyl bromide derivatives **12a-d** afforded the corresponding thiazoles **13a-d** in good yield**.** The structure of all synthesized thiazole derivatives as well as their mechanistic pathways were studied based on spectral data analysis and physical characteristics. The nanosized products were confirmed by using XRD analysis. Moreover, twelve samples were submitted for evaluation of their cytotoxicity activities against MDA-MB-231 (breast cancer cell) using colorimetric MTT assay, in comparison with Cisplatin standard drug. Two nano-sized thiosemicarbazone derivative **3** and the thiazole derivative **7c** showed potent activity with IC_{50} = 7.7 and 2.97 µg/ml, respectively in compared with the IC_{50} = 4.33 µg/ml of cisplatin. The nanosized thiazole derivative **7c** was more potent than cisplatin. Also, two thiazole derivatives **13b** and **7b** showed good activity with IC_{50} = 13.4 and 14.9 µg/ml. In addition, the molecular docking studies have been achieved using 4hy0, (X-chromosome-linked- inhibitor of apoptosis protein; (XIAP)).

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Peer review under responsibility of King Saud University.

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https://doi.org/10.1016/j.arabjc.2022.103782

1. Introduction

Cancers of all kinds are considered one of the most terrible diseases in the world, as they cause the death of more than 80% of patients annually. However, it causes many mental illnesses, especially in women with breast cancer after undergoing a mastectomy. To overcome the dangerous psychological symptoms of cancer, scientists are doing their best to design and manufacture new anti-cancer drugs, especially for breast cancer. Azole rings are known for their effectiveness against cancer (Al-Said et al., 2011; Mahmoud et al., 2020; Ahmad et al., 2018), bacteria (Al-Hussain et al., 2021; Muhammad et al., 2021), fungi (Ahmad et al., 2018) and many incurable diseases (Ahmad et al., 2018).

Among the azoles, thiazole ring has attracted significant attention in medicinal chemistry for the discovery and development of biologically active compounds (Ankali et al., 2021; Cordeiro and Kachroo, 2020; Mermer, 2020; Oliveira et al., 2020; Qazi et al., 2021), particularly, anticancer agents (Sunkari and Eppakayala, 2021; Ansari et al., 2020; Al-Hussain et al., 2020). It is found in many marine or naturally occurring compounds (Blunt et al., 2018; Li et al., 2018; Williamson et al., 1999) which has biological activity. The efficacy of derivatives containing thiazoles as antimicrobials (Eryılmaz et al., 2020), antineoplastic (Popsavin et al., 2007), anti-diabetes (Chen et al 2013), and others has been proven. Fig. 1 contains the structures of commercially available active drugs incorporated with the thiazole moiety. On the other hand, heterocyclic compounds combined with fluorine atoms have shown important and valuable results in the field of modern organic compound synthesis and the development of biologically relevant drugs used in the construction of pharmaceuticals. Furthermore, several fluorinated compounds have been synthesized as functional materials and spectroscopic methods have been used to investigate docking mechanisms in biological systems (Kirsch, 2013; Fluorine, 2014; Fluorinated, 2009; Reddy, 2015; Fluorine, 2009; Nosovaet al., 2018). By searching the literature, we found that more than 20% of the known drugs and 30% of the common agricultural chemicals on the market are with fluorine atoms (Liu et al., 2015). The trifluoromethyl moiety has bioisosteric characteristics of several groups and has a unique impact in its molecules as excellent metabolic stability, high electronegativity, and lipophilicity (Zhou et al., 2016; Fujiwara and O'Hagan, 2014). This group (CF3) can significantly alter the susceptibility of small molecules to lipids and increase their ability to penetrate the blood-brain barrier, which can lead to better absorption within the body and more desirable transport (Filler et al., 1993).

Moreover, nano-size-heterocyclic compounds characterized with effective biological activities due to their small size that allow to penetrate the cell membrane of the viruses or the microbes to DNA easily than the bulky groups. From our observation of all of the above and a complement to our research activities in field of synthesis bioactive heterocyclic compounds (Shaaban et al., 2022; Alhasani et al., 2022; Muhammad et al., 2019; Alsaedi et al., 2019; Dawood et al., 2019; Althagafi et al., 2019; Edrees and Farghaly, 2017; Muhammad et al., 2017), we focused herein to synthesis a series of nano-sized thiazoles carrying in its skeleton a trifluoromethyl group to investigate their activity against breast cancer. Additionally, a docking study of the most promising compounds will be conducted to predict their binding modes within the active site of 4hy0.

2. Results and discussion

2.1. Chemistry

One of the most common and versatile precursors in in heterocyclic synthesis are thiosemicarbazones, they are extensively used in in construction of valuable thiazole derivatives under mild reaction conditions (Mahmoud et al., 2020; Al-Soliemy et al., 2021). The required starting material *N*-(4-(1-(2-carba mothioylhydrazineylidene)ethyl)phenyl)-2,2,2-trifluoroaceta mide (**3**) was prepared *via* reaction of *N*-(4-acetylphenyl)-2,2,2-trifluoroacetamide **1** as a fluorinated building block with thiosemicarbazide **2** in ethanol under reflux in the presence of a catalytic amount of hydrochloric acid (Scheme 1). The structure of the thiosemicarbazone **3** was confirmed by all possible data from spectral and elemental analyses. For example, the ^{1}H NMR spectrum showed signals at δ 11.31, 10.19, 8.26, and 7.94 ppm attributed to four NH protons. In addition to one singlet signal with integration = 3H for methyl CH_3 group at δ 2.30 and two doublet signals in the rang of δ 7.68–7.97 for

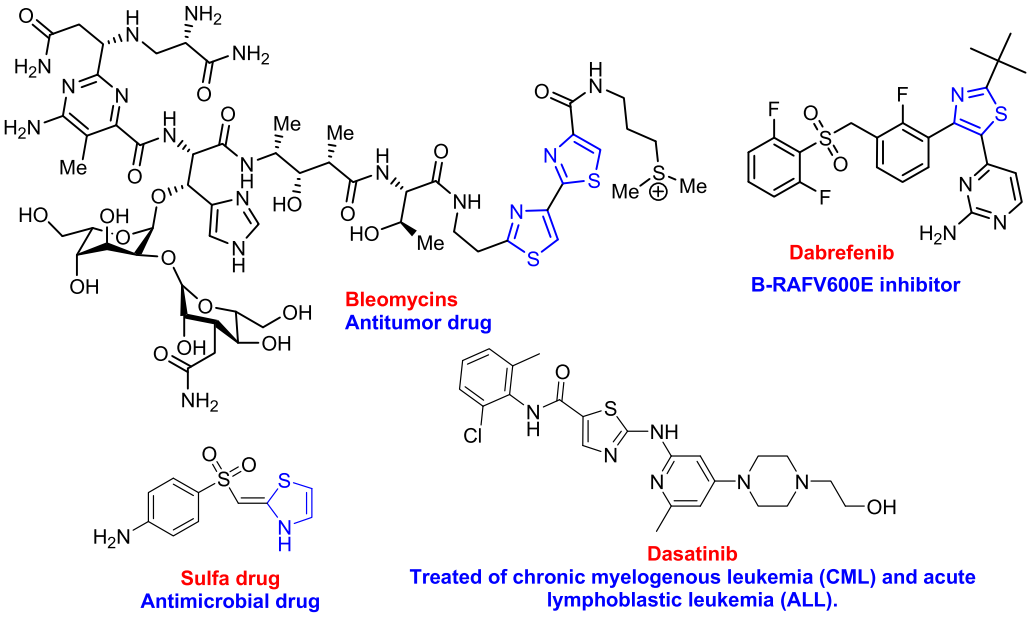
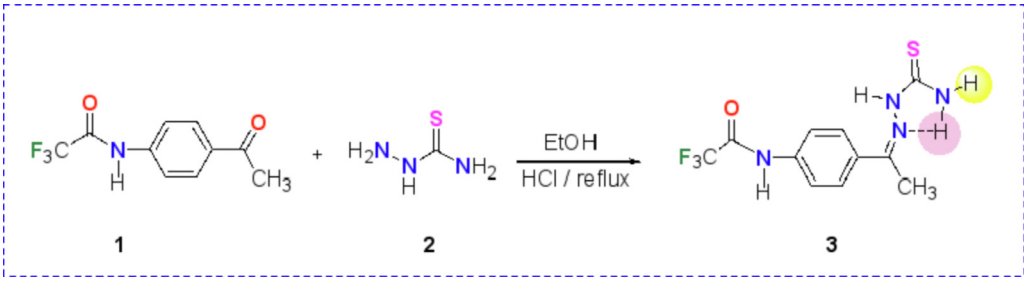


Fig. 1 Some commercial drugs containing thiazole ring.



Scheme 1 Synthesis of thiosemicarbazone derivative **3.**

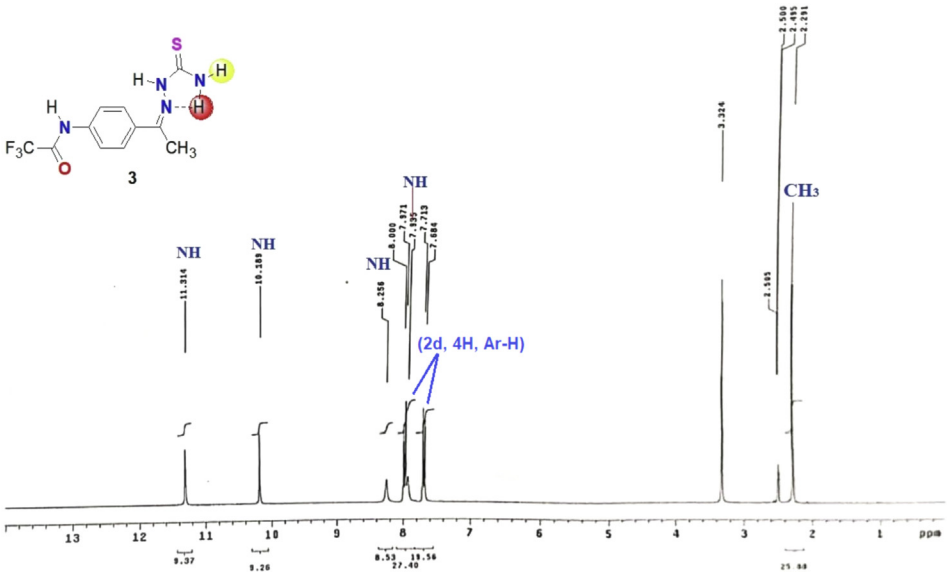


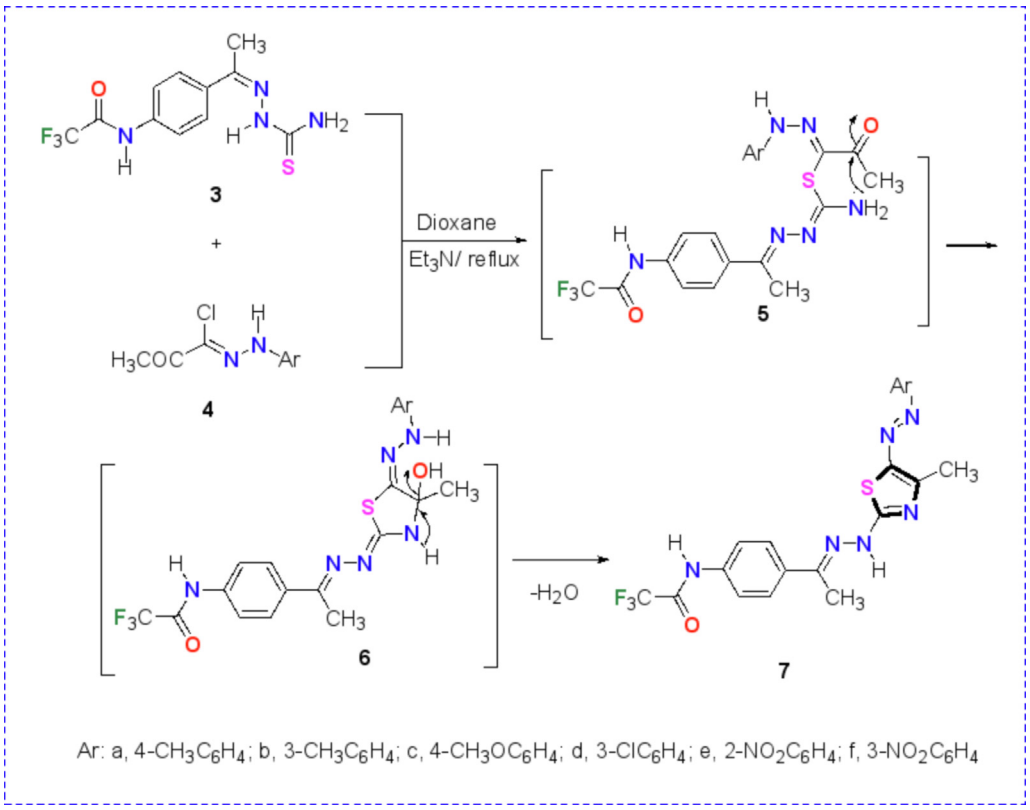
Fig. 2 The ^{1}H NMR spectrum of thiosemicarbazone derivative **3.**

the aromatic protons (Fig. 2). It is important to noted that the two protons of amino group are nonequivalent due to the intramolecular-H bond of one H with =N group (Zhang et al., 2009). Mass spectrum of the thiosemicarbazone derivative 3 showed the expected molecular ion peak at m/z = 304. In addition, the absorption bands for NH, NH_2, C=O and C=N were appeared in its IR spectrum at 3410, 3349, 3269, 1704, 1606 cm^{-1}, respectively. In addition to the other vibrational frequencies at 1537, 1183, 832 cm^{-1}.

The synthetic utility of the thiosemicarbazone **3** have been explored in the synthesis of targeted thiazole derivatives containing trifluoroacetamido group *via* reaction between *N*-(4-(1-(2-carbamothioylhydrazineylidene)ethyl)phenyl)-2,2,2-trifluoroacetamide (**3**) and *N*-aryl 2-oxopropane-hydrazonoyl chlorides **4a-f** as depicted in Scheme 2**.** The thiazole derivatives **7a-f** were achieved through the substitution and cyclization reaction of thiosemicarbazone derivative **3** with 2-oxo-*N*-arylpropanehydrazonoyl chloride **4a-f** in dioxane under reflux and in the presence of TEA as a catalyst. The structure of these products **7a-f** were proved based on their spectral and elemental analyses. For example, the ^{1}H NMR spectrum of thiazole derivative **7b** (Fig. 3) showed the characteristic three methyl group singlet signals *at* δ = 2.29, 2.49 and 2.58 ppm in addition to two NH's singlet signals at δ = 10.47 and 11.42 ppm and the characteristic protons of the two aromatic rings as multiples in the range at δ = 6.78–7.78 with J = 8.7 *Hz*. Also, all IR spectra of derivatives **7a-f** were free from the characteristic carbonyl groups absorption bands of the starting hydrazonoyl halide substrate, as instance, the characteristic bands of **7b** appeared at ν_{max} 3285 (br. 2NH), 3050 (sp2 CH), 2922 (sp^3 C-H), 1727 (C=O), 1608 (C=N), 1493, 1290, 1188, 1159, 1017 cm^{-1}.

Two intermediates **5** and **6** are involved in this reaction through the initial *S*-alkylation of the thiosemicarbazone **3** by the hydrazonoyl chlorides **4a-f** followed by cyclization through nucleophilic condensation reaction as shown in Scheme 2.

The reactivity of carbothioamide **3** towards α-halo nitriles was examined to achieve the synthesis of novel amino thiazole derivative incorporated a trifluoroacetamido group as shown in Scheme 3**.** Thus, the reaction between *N*-(4-(1-(2-carbamothioylhydrazineylidene)ethyl)phenyl)-2,2,2-trifluoroacetamide (**3**) and chloroacetonitrile **8** in the presence of a basic catalyst (TEA) in refluxing dioxan furnished the corresponding amino thiazole derivative **11**. The structure of the synthesized amino thiazole has been elucidated *via* the recorded spectral δata and elemental analyses. ^{1}H NMR spectrum of amino-thiazole derivative **11** was recorded in DMSO d_6 and revealed four sin-



Scheme 2 Synthesis of thiazole derivatives **7a-f.**

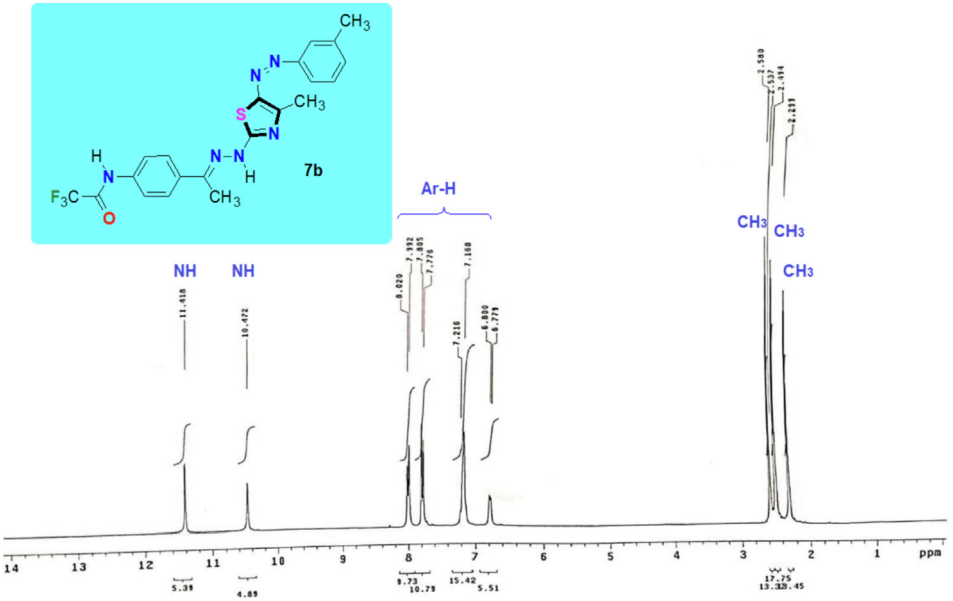
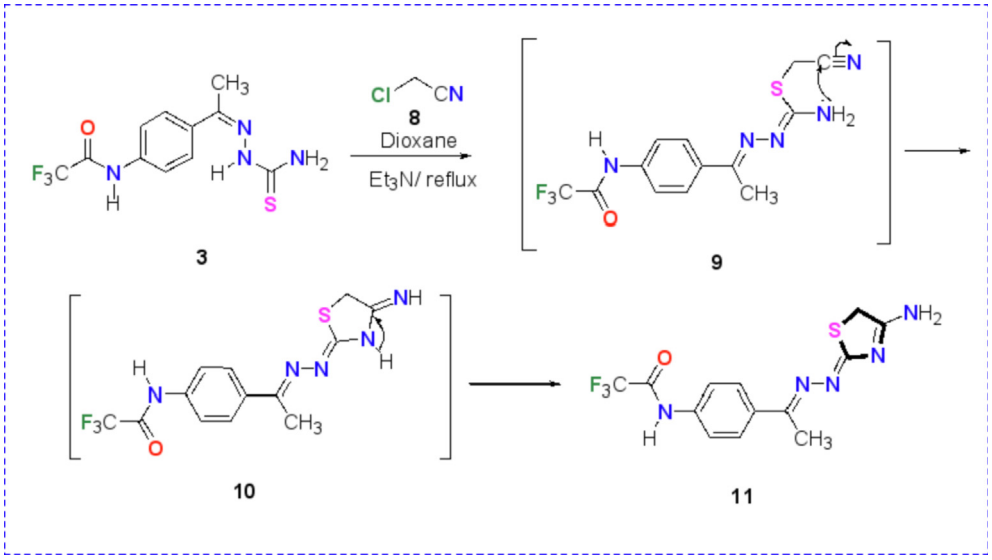


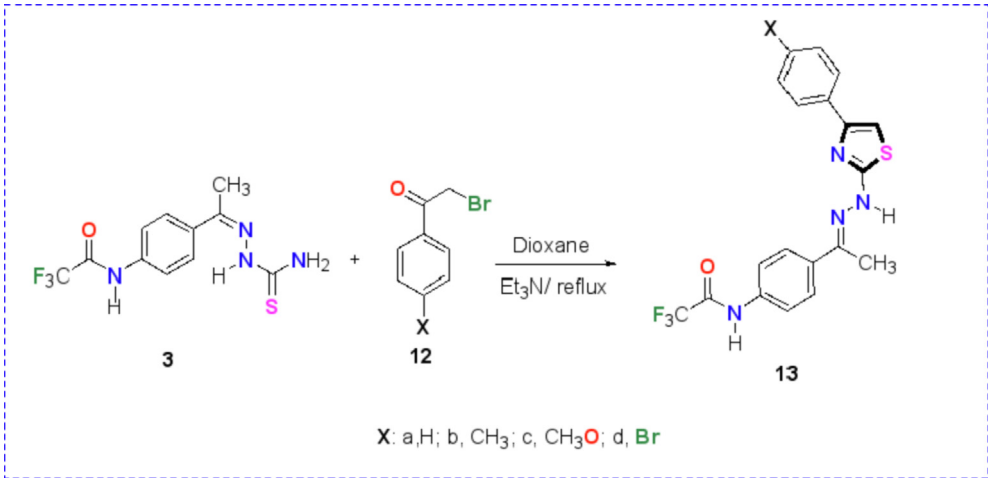
Fig. 3 The ^{1}H NMR spectrum of Thiazole derivatives **7b.**

glet signals for CH_3, NH_2, CH_2 and NH at δ = 2.55, 3.95, 4.45 and 10.18 ppm. The IR spectrum of amino-thiazole derivative **11** showed absorption bands at 3385, 3164 and 3112 cm^{-1} due to the NH_2 and NH groups.

In the same manner the base catalyzed cyclocondensation reaction between *N*-(4-(1-(2-carbamothioylhydrazineylidene)ethyl)phenyl)-2,2,2-trifluoroacetamide (**3**) and phenacyl bromide derivatives **12a-d** afforded the corresponding thiazoles



Scheme 3 Synthesis of amino-thiazole derivative **11.**



Scheme 4 Synthesis of thiazole derivatives **13a-d.**

13a-d as depicted in Scheme 4. The structures of the reaction products have been confirmed by spectroscopic data as well as elemental analysis.

2.2. X-Ray diffraction studies of the synthesized derivatives

XRD scanning was recorded for four selected derivatives **3**, **7c**, **11** and **13d** using Cu/Kα1 radiation-source at 2θ ranging from 0° to 90° (Fig. 4& Fig. 5). The starting thiosemicarbazone **3** and thiazole derivative **7c** found in crystalline feature while the other two thiazole derivatives **11** and **13d** are found as amorphous shape. Through FWHM method, the size of the crystals was estimated by Bragg and Scherrer equations (Cullity and Stock, 2001) for the two crystalline derivatives. The size of derivatives **3** and **7c** are in the nanometer range that equal 36.59 and 27.99 nm.

2.3. Biological screening of the novel thiazole derivatives

Twelve samples were submitted for evaluation of their cytotoxicity activities against MDA-MB-231 (breast cancer cell) using colorimetric MTT assay, in comparison with Cisplatin standard drug. All drug concentration were plotted against the cell viability to get the survival curve (cited in supplementary file). The 50% inhibitory concentration (IC_{50}) was obtained and the anti-proliferative activity was expressed as the mean IC_{50} of three independent experiments (μM) ± standard deviation from three replicates. The results were tabulated in Table 1. From the results of activity, we noted that the most active derivatives are the two nano-sized thiosemicarbazone derivative **3** and the thiazole derivative **7c** with IC_{50} = 7.7 and 2.97 μg/ml, respectively in compared with the IC_{50} = 4.33 μg/ml of cisplatin. In detailed, For the thiazole derivatives

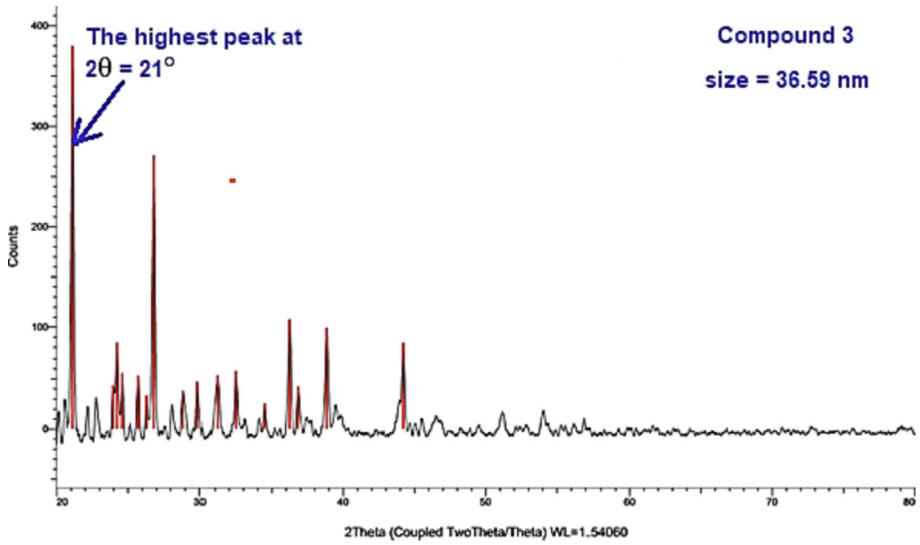


Fig. 4 XRD of compound **3.**

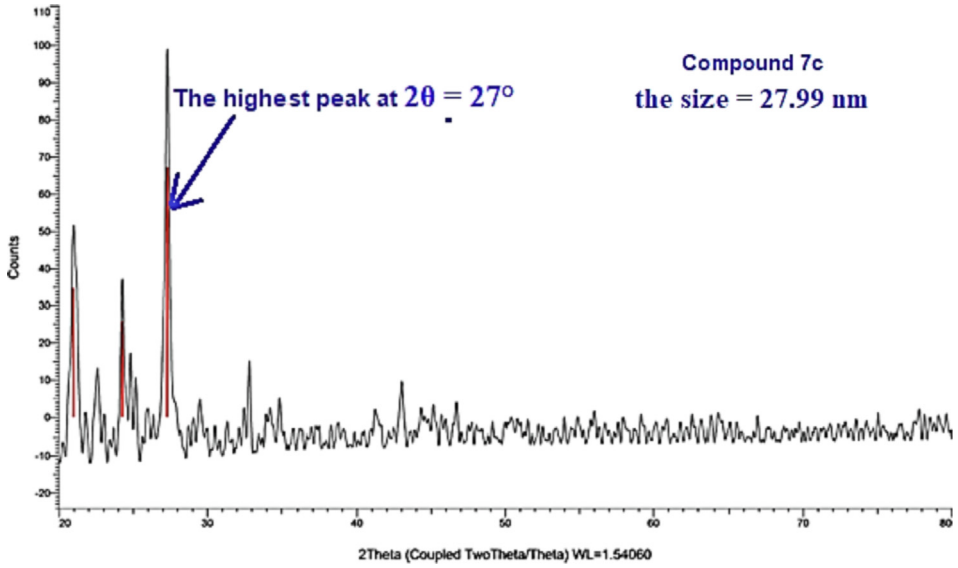


Fig. 5 XRD of compound **7c.**

Table 1 IC_{50} of the newly synthesized derivatives **3, 7a-f, 11** and **13a-d** against MDA-MB-231 cell line.

Sample Code	IC_{50} values (μg/ml)
	MDA-MB-231
3	7.7 ± 0.41
7a	97.1 ± 4.9
7b	14.9 ± 0.97
7c	2.97 ± 0.32
7d	27.2 ± 1.7
7e	51.8 ± 3.4
7f	366 ± 21.4
11	45.8 ± 2.8
13a	28.8 ± 1.9
13b	13.4 ± 0.85
13c	55.8 ± 3.8
13d	408 ± 19.8
Cisplatin	4.33 ± 0.12

7a-f, the methoxy derivative **7c** revealed good anticancer activity. The thiazole derivative carrying Cl at position 3 of aromatic ring **7d** showed moderate activity with IC_{50} value of 27.2 μg/ml. On the other hand, compounds **7a** and **7f** were the least active derivatives in this series showing IC_{50} of 97.1 and 366 μg/ml, respectively. Concerning the other thiazole series **13a-d**, derivative **13b** showed good activity. While thiazoles **13a** and **13c** displayed moderate cytotoxicity (IC_{50} = 28.8 and 55.8 μg/ml, respectively). The bromo-thiazole derivatives **13d** exhibited weak activity with IC_{50} value of 408 μg/ml. Finally. the nanosized thiazole derivative **7c** was more potent than cisplatin. Also, two thiazole derivatives **13b** and **7b** showed good activity with IC_{50} = 13.4 and 14.9 μg/ml.

2.4. Docking study for selected derivatives

The use of theoretical programs to predict the biological activity of compounds before starting to synthesize is considered a

scientific trend that benefits the drug manufacturing system. As it reduces time and effort and helps design drugs with functional groups of high efficiency. One of those programs is molecular docking, which has become a widespread tool for drug discovery (Gümüş et al, 2022; Mahmudov et al., 2022). To foretell the binding mode of thiosemicarbazone derivative **3** and the thiazole derivatives **7b**, **7c**, **7d**, **11**, **13a** and **13b** into the active site of the tumor cell MDA-MB-231, a docking study of these selected derivatives was executed using MOE (2014.0901) (Molecular Operating Environment software). The molecular docking studies have been achieved using 4hy0, (X-chromosome-linked- inhibitor of apoptosis protein; (XIAP)). XIAP is a member of IAP family which has important role in blocking cell death. Its inhibitor leads to apoptosis induction and thus can be used as a target in cancer treatment. The results are presented in Table 2 and Figs. 6-9. Redocking of the co-crystallized ligand (3S,7R,8AR)-2-{(2S)-2-(4,4-difluorocyclohexyl)-2-[(N-methyl-L-alanyl)amino]acetyl}-N-[(4R)-3,4-dihydro-2H-chromen-4-YL]-7-ethoxyocta-hydropyrrolo[1,2-a]pyrazine-3-carboxamide) was first done for validation. It

Table 2 Docking results of the selected thiazole derivatives **3**, **7b**, **7c**, **7d**, **11**, **13a** and **13b** with the receptors of (4hy0).

Compd.	Ligand moiety	Receptor site	Interacting residues (Type of interaction)	Distance (°A)	E (kcal/mol)	Docking score (kcal/mol)
3	N 11	O THR 271 (A)	H-donor	2.99	−6.0	−4.2056
7b	N 2	O GLY 273 (A)	H-donor	3.30	−1.3	−5.0713
	6-ring	CA THR 271 (A)	pi-H	4.02	−0.6	
	6-ring	N GLY 295 (A)	pi-H	4.45	−0.9	
7c	F 50	NZ LYS 299 (A)	H-acceptor	2.97	−1.3	−5.6099
	5-ring	CA THR 271 (A)	pi-H	4.02	−0.7	
7d	–	–	–	–	–	−5.0313
11	N 20	N GLY 273 (A)	H-acceptor	3.35	−1.2	−4.6352
	O 31	N GLY 295 (A)	H-acceptor	3.35	−0.9	
13a	O 29	N GLY 295 (A)	H-acceptor	3.34	−0.6	−5.0236
13b	–	–	–	–	–	−5.0880

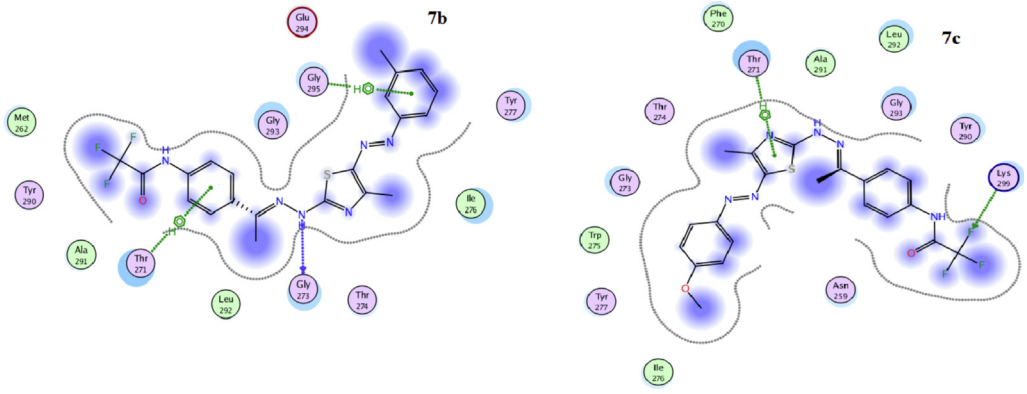


Fig. 6 The 2D docked model of compounds **7b** and **7c** into the active site of 4hy0.

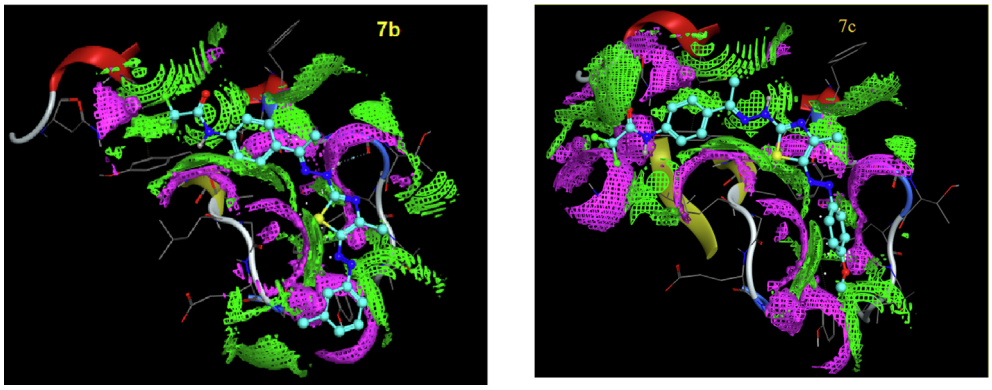


Fig. 7 The contact performance of compounds **7b** and **7c** into the active site of 4hy0, respectively.

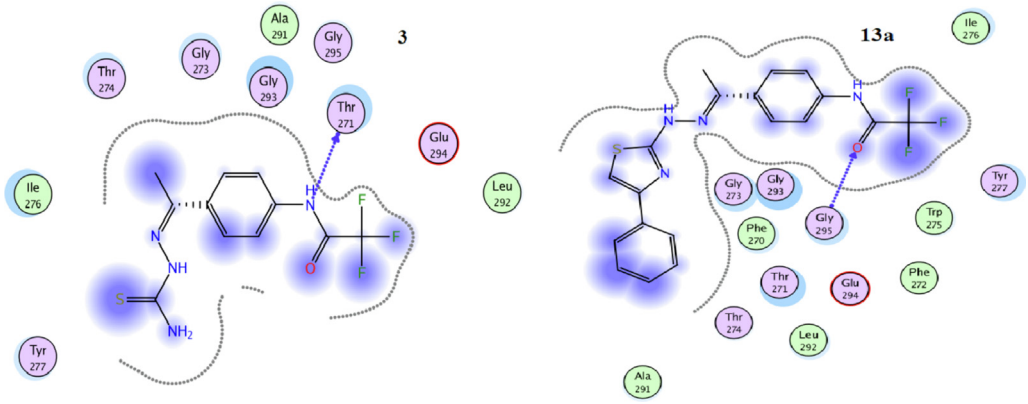


Fig. 8 The 2D docked model of compounds **3** and **13a** into the active site of 4hy0.

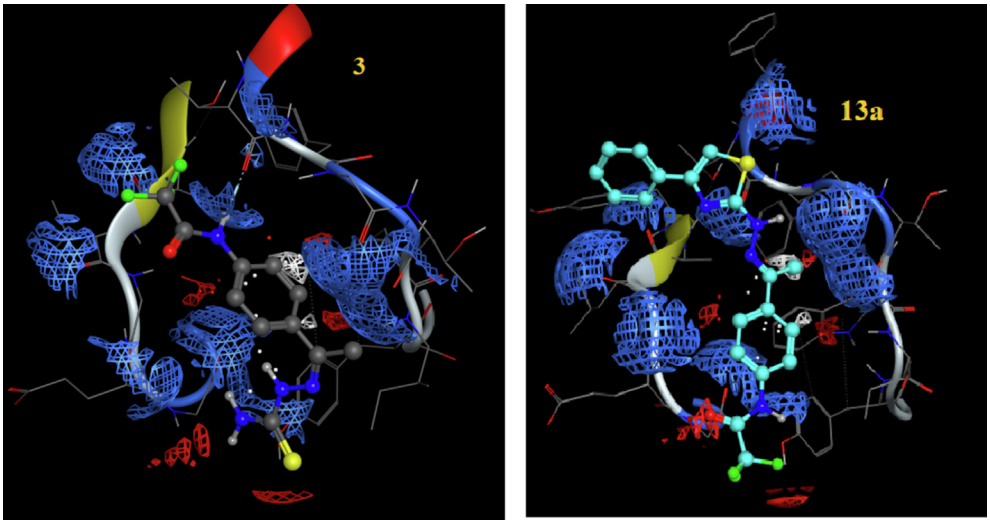


Fig. 9 The electrostatic map of compounds **3 and 13a** into the active site of 4hy0, respectively.

revealed docking score = -5.2142 kcal/mol. Noticeably, all tested derivatives were involved in interactions with 4hy0-protein with docking score ranging from −5.6099 to −4.2056 kcal/mol. The most reactive derivative **7c** showed the highest docking score −5.6099 kcal/mol; this result was coincident with the in vitro experimental results. Table 2 and Fig. 7 and Fig. 8 indicated that there are several types of interaction as H-acceptor, H-donor pi-H. The essential part for the interaction in derivative **7c** were the thiazole ring and the trifluoromethyl groups which involved in the interaction with the 4hy0-protein THR271 and LYS299 residue, respectively. The docking score for compound **7c** is larger than that for the co-crystallized ligand. The low value of docking score of thiosemicarbazide **3** in compared with all tested thiazole derivatives **7b**, **7c**, **7d**, **11**, **13a** and **13b** can be attributed to the lack of the thiazole ring.

3. Conclusion

In conclusion, it is evident that this study has shown a convenient pathway to access novel nano-sized fluorinated thiazoles using a mild reaction condition. Thus, the trifluoro-methylated thiosemicarbazone (**3**) have been reacted with appropriate derivatives of *a*-halo compounds namely, *N*-aryl 2-oxopropane-hydrazonoyl chlorides **4a-f**, chloroacetonitrile **8** and phenacyl bromide derivatives **12a-d** in dioxane containing catalytic amount of triethylamine afforded the corresponding thiazoles **13a-d** in good yield**.** The structure elucidation of the targeted compounds could be achieved by spectral data analysis and physical tools. Evaluation of the cytotoxicity activities of the synthesized products against MDA-MB-231 (breast cancer cell) using colorimetric MTT assay, in comparison with Cisplatin standard drug have been established. Some nano-sized products showed a fruitful antitumor activity specially when compared with the reference drug. The molecular docking studies have concluded the obtained biological results efficiently.

4. Experimental

4.1. Chemistry

The supplementary file contains all characterization and pictures for each device that have been utilized to record the spectral data for the new synthesized derivatives (S1).

4.1.1. Synthesis of N-(4-(1-(2-carbamothioylhydrazineylidene) ethyl)phenyl)-2,2,2-trifluoroacetamide (3)

Previously [20,23], we described the synthesis of related thiosemicarbazone derivatives as follows: condensation reaction under reflux of acetyl derivative **1** (0.005 mol) with thiosemicarbazide **2** (0.005 mol) in 20 mL ethanol after the solution was boiled, drops of conc. HCl was added. Through the reflux of the reaction, the yellow solid of the thiosemicarbazone derivative **3** was precipitated after ten min., then the reflux was completed for one hour. The yellow solid was collected and crystallized from ethanol as white solid, (84% yield), mp 210–212 °C; IR (KBr) ν_{max} 3410, 3349, 3269 (NH and NH_2), 3181 (sp^2 C-H), 1704 (C = O), 1606 (C = N), 1537, 1183, 832 cm^{-1}; ^1H NMR (DMSO d_6) δ 2.30 (s, 3H, CH_3), 7.68 (d, J = 9 Hz, 2H, Ar-H), 7.94 (s, 1H, NH), 7.97 (d, J = 9 Hz, 2H, Ar-H), 8.26 (s, 1H, NH), 10.19 (s, 1H, NH), 11.31 (s, 1H, NH); MS m/z (%) 304 (M^+, 11), 298 (39), 256 (25), 255 (31), 235 (73), 205 (21), 167 (38), 135 (34), 101 (28), 97 (62), 82 (26), 78 (34), 77 (20). Anal. Calcd. for $C_{11}H_{11}F_3N_4OS$ (304.29): C, 43.42; H, 3.64; N, 18.41. Found: C, 43.38; H, 3.47; N, 18.31%.

4.1.2. Synthesis of thiazole derivatives 7a-f, 11 and 13a-d

A mixture of *N*-(4-(1-(2-carbamothioylhydrazineylidene)ethyl) phenyl)-2,2,2-trifluoroacetamide (**3**) and α-haloketones **4a-f** or **12a-d** or chloro-acetonitrile **8** (0.0025 mol of each) in 100 mL round flask dissolved on hot in dioxane (20 mL). Then, Et_3N (0.35 mL) was added and the whole mixture was refluxed for 5 h. After the reactions were completed *via* monitoring with TLC, the colored solids were collected and purified through crystallization from dioxane to give thiazole derivatives **7a-f, 13a-d** and **11**, respectively.

4.1.2.1. 2,2,2-Trifluoro-N-(4-{1-[(4-methyl-5-p-tolylazo-thiazol-2-yl)-hydrazono]-ethyl}-phenyl)-acetamide (7a). Red solid, (86% yield), mp 238–240 °C; IR (KBr) ν_{max} 3400, 3307 (2NH), 2938 (sp^3 C-H), 1704 (C = O), 1599 (C=N), 1536, 1503, 1375, 1298, 1236, 1181, 1034, 830 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.36 (s, 3H, CH_3), 2.52 (s, 3H, CH_3), 2.68 (s, 3H, CH_3), 7.17–8.12 (m, 8H, Ar-H), 10.42 (s, 1H, NH), 11.21 (s, 1H, NH); MS m/z (%) 460 (M^+, 43), 434 (23), 390 (39), 382 (53), 368 (55), 360 (52), 344 (56), 334 (60), 319 (70), 299 (64), 229 (52), 168 (100), 128 (32), 96 (33), 76 (29). Anal. Calcd. for $C_{21}H_{19}F_3N_6OS$ (460.48): C, 54.77; H, 4.16; N, 18.25. Found: C, 54.59; H, 4.02; N, 18.09%.

4.1.2.2. 2,2,2-Trifluoro-N-(4-{1-[(4-methyl-5-m-tolylazo-thiazol-2-yl)-hydrazono]-ethyl}-phenyl)-acetamide (7b). Orange solid, (83% yield), mp 212–214 °C; IR (KBr) ν_{max} 3285 (br. 2NH), 3050 (sp^2 CH), 2922 (sp^3 C-H), 1727 (C=O), 1608 (C=N), 1493, 1290, 1188, 1159, 1017 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.29 (s, 3H, CH_3), 2.49 (s, 3H, CH_3), 2.58 (s, 3H, CH_3), 6.78–7.22 (m, 4H, Ar-H),7.78 (d, J = 8.7 *Hz*, 2H, Ar-H), 7.99 (d, J = 8.7 *Hz*, 2H, Ar-H), 10.47 (s, 1H, NH), 11.42 (s, 1H, NH); MS m/z (%) 460 (M^+, 26), 447 (91), 426 (47), 423 (100), 408 (41), 361 (54), 334 (66), 223 (44), 172 (51), 90 (15). Anal. Calcd. for $C_{21}H_{19}F_3N_6OS$ (460.48): C, 54.77; H, 4.16; N, 18.25. Found: C, 54.65; H, 4.02; N, 18.19%.

4.1.2.3. 2,2,2-Trifluoro-N-[4-(1-{[5-(4-methoxy-phenylazo)-4-methyl-thiazol-2-yl]-hydrazono}-ethyl)-phenyl]-acetamide (7c). Red crystals, (82% yield), mp 203–204 °C; IR (KBr) ν_{max} 3441 (br. 2NH), 1708 (C=O), 1599 (C=N), 1374, 1293, 1265, 1192, 1161 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.47 (s, 3H, CH_3), 2.57 (s, 3H, CH_3), 3.75 (s, 3H, OCH_3), 6.93 (d, J = 7.8 *Hz*, 2H, Ar-H), 7.34 (d, J = 7.8 *Hz*, 2H, Ar-H), 7.77 (d, J = 8.7 *Hz*, 2H, Ar-H), 7.97 (d, J = 8.7 *Hz*, 2H, Ar-H), 10.0 (s, 1H, NH), 11.44 (s, 1H, NH); MS m/z (%) 476 (M^+, 15), 469 (81), 459 (50), 442 (51), 416 (58), 404 (40), 369 (23), 347 (50), 328 (47), 320 (100), 314 (77), 290 (42), 274 (60), 269 (57), 154 (36), 76 (35). Anal. Calcd. for $C_{21}H_{19}F_3N_6O_2S$ (476.47): C, 52.94; H, 4.02; N, 17.64. Found: C, 52.86; H, 3.97; N, 17.48%.

4.1.2.4. N-[4-(1-{[5-(3-Chloro-phenylazo)-4-methyl-thiazol-2-yl]-hydrazono}-ethyl)-phenyl]-2,2,2-trifluoro-acetamide (7d). Orange solid, (86% yield), mp 237–238 °C; IR (KBr) ν_{max} 3410, 3287 (2NH), 1706 (C=O), 1595 (C=N), 1595, 1511, 1244, 1169 cm^{-1}; ^1H NMR (DMS-d_6) δ 2.50 (s, 3H, CH_3), 2.59 (s, 3H, CH_3), 6.98–7.35 (m, 4H, Ar-H), 7.78 (d, J = 8.7 *Hz*, 2H, Ar-H), 8.0 (d, J = 8.7 *Hz*, 2H, Ar-H), 10.61 (s, 1H, NH), 11.44 (s, 1H, NH); MS m/z (%) 480 (M^+, 48), 475 (53), 449 (39), 432 (40), 424 (100), 376 (47), 328 (39), 271 (29), 198 (38), 150 (37), 131 (43), 77 (18). Anal. Calcd. for $C_{20}H_{16}F_3N_6OS$ (480.89): C, 49.95; H, 3.35; N, 17.48. Found: C, 49.83; H, 3.26; N, 17.35%.

4.1.2.5. 2,2,2-Trifluoro-N-[4-(1-{[4-methyl-5-(2-nitro-phenylazo)-thiazol-2-yl]-hydrazono}-ethyl)-phenyl]-acetamide (7e). Red solid, (80% yield), mp 212–214 °C; IR (KBr) ν_{max} 3287 (br. 2NH), 1703 (C=O), 1609 (C=N), 1535, 1350, 1248, 1162 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.59 (s, 3H, CH_3), 2.70 (s, 3H, CH_3), 7.02–8.22 (m, 8H, Ar-H), 10.65 (s, 1H, NH), 11.80 (s, 1H, NH); MS m/z (%) 491 (M^+, 34), 455 (57), 424 (100), 390 (68), 371 (57), 306 (66), 276 (50), 108 (66), 104 (70). Anal. Calcd. for $C_{20}H_{16}F_3N_7O_3S$ (491.45): C, 48.88; H, 3.28; N, 19.95. Found: C, 48.74; H, 3.16; N, 19.87%.

4.1.2.6. 2,2,2-Trifluoro-N-[4-(1-{[4-methyl-5-(3-nitro-phenylazo)-thiazol-2-yl]-hydrazono}-ethyl)-phenyl]-acetamide (7f). Red solid, (78% yield), mp 210–212 °C; IR (KBr) ν_{max} 3353 (br. 2NH), 3058 (sp^2 C-H), 1713 (C=O), 1598 (C=N), 1514, 1439, 1321, 1157 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.29 (s, 3H, CH_3), 2.63 (s, 3H, CH_3), 6.66–7.83 (m, 8H, Ar-H), 10.76 (s, 1H, NH), 11.24 (s, 1H, NH); MS m/z (%) 491 (M^+, 26), 451 (66), 366 (41), 280 (54), 266 (100), 247 (87), 190 (56), 171 (33), 124 (99), 109 (69), 76 (21). Anal. Calcd. for $C_{20}H_{16}F_3N_7O_3S$ (491.45): C, 48.88; H, 3.28; N, 19.95. Found: C, 48.69; H, 3.09; N, 19.78%.

4.1.2.7. N-(4-{1-[(4-Amino-5H-thiazol-2-ylidene)-hydrazono]-ethyl}-phenyl)-2,2,2-trifluoro-acetamide (11). Buff solid, (88% yield), mp 190–192 °C; IR (KBr) ν_{max} 3385, 3164, 3112 (NH_2, NH), 1649 (C=O), 1600 (C=N), 1530, 1485, 1441, 1247, 1188, 1155, 1031 cm^{-1}; ^1H NMR (DMS-d_6) δ 2.55 (s, 3H, CH_3), 3.95 (s, 2H, NH_2), 4.45 (s, 2H, CH_2), 7.69–8.30 (m, 4H, Ar-H), 10.18 (s, 1H, NH); MS m/z (%) 343 (M^+, 36), 335 (70), 315 (45), 300 (99), 283 (71), 267 (64), 192 (44), 144 (100), 122 (31), 88 (50), 75 (42). Anal. Calcd. for $C_{13}H_{12}F_3N_5OS$

(343.33): C, 45.48; H, 3.52; N, 20.40. Found: C, 45.31; H, 3.43; N, 20.28%.

4.1.2.8. 2,2,2-Trifluoro-N-(4-{1-[(4-phenyl-thiazol-2-yl)-hydrazono]-ethyl}-phenyl)-acetamide (13a). White solid, (83% yield), mp 270–272 °C; IR (KBr) ν_{max} 3459, 3113 (2NH), 3072 (sp^2 CH), 1702 (C = O), 1619, 1587 (C = N), 1514, 1414, 1367, 1291, 1255, 1208, 1159 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.45 (s, 3H, CH_3), 7.37–8.33 (m, 10H, Ar-H and Thiazole-H), 11.01 (s, 1H, NH), 11.40 (s, 1H, NH); MS *m/z* (%) 404 (M^+, 20), 391 (21), 355 (34), 319 (57), 284 (48), 260 (46), 240 (74), 1227 (100), 109 (36). Anal. Calcd. for $C_{19}H_{15}F_3N_4OS$ (404.41): C, 56.43; H, 3.74; N, 13.85. Found: C, 56.28; H, 3.69; N, 13.77%.

4.1.2.9. 2,2,2-Trifluoro-N-(4-{1-[(4-p-tolyl-thiazol-2-yl)-hydrazono]-ethyl}-phenyl)-acetamide (13b). White solid, (86% yield), mp 255–256 °C; IR (KBr) ν_{max} 3391, 3310 (2NH), 2924 (sp3 CH), 1708 (C = O), 1607 (C = N), 1544, 1287, 1157 cm^{-1}; MS *m/z* (%) 418 (M^+, 61), 392 (61), 382 (53), 347 (38), 278 (38), 243 (100), 202 (35), 182 (38), 166 (51), 133 (42), 127 (61), 81 (37). Anal. Calcd. for $C_{20}H_{17}F_3N_4OS$ (418.44): C, 57.41; H, 4.10; N, 13.39. Found: C, 57.39; H, 4.01; N, 13.28%.

4.1.2.10. 2,2,2-Trifluoro-N-[4-(1-{[4-(4-methoxy-phenyl)-thiazol-2-yl]-hydrazono}-ethyl)-phenyl]-acetamide (13c). White solid, (80% yield), mp 240–242 °C; IR (KBr) ν_{max} 3400 (br. 2NH), 1714 (C = O), 1612 (C = N), 1541 1252, 1157, 1090 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.36 (s, 3H, CH_3), 3.93 (s, 3H, OCH_3), 6.86–8.10 (m, 8H, Ar-H), 7.44 (s, 1H, Thiazole-H), 11.34 (s, 1H, NH), 11.91 (s, 1H, NH); MS *m/z* (%) 434 (M^+, 27), 427 (68), 416 (46), 390 (37), 340 (22), 304 (30), 282 (100), 227 (54), 150 (43), 128 (41), 86 (30), 80 (32). Anal. Calcd. for $C_{20}H_{17}F_3N_4O_2S$ (434.43): C, 55.29; H, 3.94; N, 12.90. Found: C, 55.17; H, 3.79; N, 12.82%.

4.1.2.11. N-[4-(1-{[4-(4-Bromo-phenyl)-thiazol-2-yl]-hydrazono}-ethyl)-phenyl]-2,2,2-trifluoro-acetamide (13d). Pale yellow solid, (88% yield), mp 232–234 °C; IR (KBr) ν_{max} 3444 (br. 2NH), 3005 (sp2 CH), 1716 (C = O), 1597 (C = N), 1510, 1337, 1246, 1154, 1111 cm^{-1}; MS *m/z* (%) 482 (M^+, 21), 389 (27), 359 (21), 262 (58), 241 (30), 174 (48), 161 (100), 136 (41), 103 (36), 99 (60), 85 (32), 77 (32). Anal. Calcd. for $C_{19}H_{14}BrF_3N_4OS$ (483.30): C, 47.22; H, 2.92; N, 11.59. Found: C, 47.07; H, 2.83; N, 11.41%.

4.1.3. Antitumor assay

MDA-MB-231 (breast cancer cell) was obtained VACSERA Tissue Culture Unit. and the used chemicals as DMSO, crystal violet and trypan blue dye were supplied from Sigma Aldrich company (St. Louis, Mo., USA). The detailed method used for the propagation and evaluation the cytotoxicity was followed the reported procedure (Mosmann, 1983).

4.1.4. Molecular docking studies

Molecular docking analysis was done by using MOE-Dock 2014 software (Molecular, 2014). Chemical structures of the thiosemicarbazone **3** and thiazole derivatives **7b**, **7c**, **7d**, **11**, **13a** and **13b** were drawn by MOE-builder and minimized through the program force field MMFF94x. Then, the protein was prepared, hydrogen atoms were added and undesirable water molecules were removed. After that, docking of the 3D conformers was done; using rescoring 1(London dG) and rescoring 2 (GBVI/WSA dG). "Ligand Interactions" tool was utilized for the visualization of the 2D protein-ligand interactions showing the different formed interactions.

Ethics approval and consent to participate

Not applicable.

Human and animal rights

No Animals/Humans were used for studies that are the basis of this research.

Availability of data and materials

The data supporting the findings of the article is available at the corresponding author.

Funding

The study was funded by the Deanship scientific research, Taif University, KSA, [Research project number: 1-441-144].

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

All authors would like to thank Deanship of Scientific Research at Taif University for the financial support to this research [Research project number: 1-441-144].

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.arabjc.2022.103782.

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