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Anticancer activity of some novel thieno [2, 3-d] pyrimidine derivatives.

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Abstract

As part of our search for searching for anticancer agents a novel series of thieno [2, 3-d] pyrimidine derivatives 9-14 were obtained via reaction of the strategic starting material ethyl 2-isothiocyanato-4, 5-dimethylthiophene-3- carboxylate 2 with sulfa-drugs namely, sulfanilamide, sulfa-thiazole, sulfa-diazine, sulfa-merazine, sulfa-dimethoxazine and sulfa-doxine, in dimethylformamide containing triethylamine as catalyst. The structures of the newly synthesized compounds were established by microanalysis, IR, 1H-NMR, 13C-NMR and mass spectral data. All the newly synthesized compounds were evaluated for their *in vitro* anticancer activity against human breast cancer cell line (MCF7). Most of the screened compounds exhibited higher anti-breast cancer activity compared with Doxorubicin as a reference drug. Compounds 14, 13, 9 and 12 (IC_{50} values 22.12, 22.52, 27.83 and 29.22 µM) showed higher anti-breast cancer activity than the Doxorubicin as a reference drug with (IC_{50} value 30.40 µM). In addition, compounds 10 and 11 with (IC_{50} values 34.64, 37.78 µM) are nearly as active as Doxorubicin as positive control.

Keywords: Design, Synthesis, Thieno [2, 3-d] pyrimidines, Anti-breast cancer activity.

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Introduction

According to WHO population-based data, cancer is a leading cause of mortality worldwide accounting for almost 13% of all death [1]. Among all types of cancer, lung, breast, colorectal, stomach, and prostate cancer is the underlying cause for the majority of cancer death. Hitherto, chemotherapy remains one of the therapeutic strategies adopted worldwide for the management of cancer either alone or in conjunction with surgery and/or radiotherapy. Currently in clinical use anticancer agents suffer from a number of drawbacks correlated to drugs' associated side effects and/or tumors' multi-drug resistance [2,3]. Hence, it obviously is still of interest to search for new bioactive molecules having anticancer activity. Thiophenes and thienopyrimidines have been reported to possess interesting biological and pharmacological activities where several derivatives are used as antibacterial [1-3], anti-inflammatory [4], anticancer [5,6], and antiviral agents [7].

From the chemical and structural point of view, literature survey showed that sulfonamide [4-8], bearing molecules play an important role in the anticancer activity. In addition, various compounds with a heterocyclic backbone scaffold demonstrated promising anticancer activity. For example, a number of thienopyrimidine derivatives were claimed to possess interesting anticancer activities [9,10]. Sulfonamides anticancer activity has been in many instances attributed to inhibition of carbonic anhydrase enzymes [4-6]. Carbonic anhydrases (CA, EC 4.2.1.1) represent a family of Zn based metallo enzymes that catalyzes the interconversion between carbon dioxide and bicarbonate with generation of protons. The carbonic anhydrase isozyme IX (CA IX) is reported to be associated with tumorogenesis being highly over expressed in hypoxic tumors and restrictedly expressed in normal tissues [11-14]. CA IX inhibitors have been shown to display promising anticancer activity in addition to having fewer side effects compared to other anticancer drugs. Many research endeavors have reported sulfonamide bearing molecules as promising anticancer agents acting through inhibition of carbonic anhydrase IX [11-14]. Most cancer patients are subjected to chemotherapy for the treatment of advanced cancers. However, most metastatic solid tumors eventually remain incurable even by treatment with recent anticancer drugs. Also, Cancer is a disease of striking significance in the world today. Although chemotherapy is the mainstay of cancer therapy, the use of available chemotherapeutic is often limited mainly due to undesirable side effects and a

limited choice of available anticancer drugs [15-17]. This clearly underlines the urgent need for developing novel chemotherapeutic agents with more potent anticancer activities. Many anticancer agents which act as tyrosine kinase inhibitors comprised the pyrimidine nucleus as a core moiety. This could be exemplified by different quinazoline derivatives such as gefitinib (IressaTM) [18] and tandutinib (MLN518) (phase II clinical trials [19] (Figure 1). In continuation of our work [20-24], it seemed of interest to design and synthesize a novel series of thienopyrimidines bearing biologically active sulfonamide moieties, analogues to gefitinib (IressaTM) and tandutinib (MLN518) to evaluate their anti-breast cancer activity.

Experimental

Melting points (°C, uncorrected) were determined in open capillaries on a Gallenkemp melting point apparatus (Sanyo Gallenkemp, Southborough, UK). Precoated silica gel plates (silica gel 0.25 mm, 60 G F 254; Merck, Germany) were used for thin layer chromatography, dichloromethane/methanol (9.5:0.5 ml) mixture was used as a developing solvent system and the spots were visualized by ultraviolet light and/or iodine. Infrared spectra were recorded on KBr discs using IR-470 Shimadzu spectrometer (Shimadzu, Tokyo, Japan). 1H-NMR spectra (in DMSO-d_6) were recorded on Bruker Ac-300 ultra-shield NMR spectrometer (Bruker, Flawil, Switzerland, δ ppm) at 300 MHz, using TMS as internal standard. Electron impact Mass Spectra were recorded on a, Shimadzu Gc-Ms-Qp 5000 instruments (Shimadzu, Tokyo, Japan). Elemental analyses were performed on Carlo Erba 1108 Elemental Analyzer (Heraeus, Hanau, Germany). All compounds were within ± 0.4% of the theoretical values.

Results

General Procedure for the synthesis of novel thienopyrimidine derivatives 9- 14.

A mixture of ethyl 2-isothiocyanato-4, 5-dimethylthiophene-3- carboxylate 2 (2.41 g, 0.01 mole), sulfa-drugs (0.012 mole) in dimethylformamide (20 ml) containing 3 drops of triethylamine was heated under reflux for 14 h. The reaction mixture was allowed to cool, filtered off the solid obtained and recrystallized from dioxane to give compounds 9-14, respectively.

Synthesis of 4-(5, 6-dimethyl-4-oxo-2-thioxo-1, 2-dihydrothieno[2, 3-d]pyrimidin-3(4H) yl)benzenesulfonamide(9).

Yield, 86%; m.p. 279.0°C; IR (KBr, cm^{-1}): at 3437, 3425, 3263 (NH, NH_2), 3100 (CH arom.), 2978, 2947(CH aliph.), 1674(C=O), 1338, 1161(SO_2), 1234 (C=S).1H-NMR (DMSO-d_6) δ: 2.2, 2.3 [2s, 6H, $2CH_3$], 7.3-8.2 [m, 6H, Ar-H + SO_2NH_2], 11.2 [s, 1H, NH, exchangeable with D_2O]. 13C-NMR (DMSO-d_6): 11.2, 12.4, 115.8, 120.4 (2), 128.8 (2), 130.7, 131.8, 133.9, 134.6, 148.2, 159.7, 180.1. MS m/z (%): 367 [M+] (20.18), 151 (100). Anal. Calcd. for $C_{14}H_{13}N_3O_3S_3$: C, 45.76; H, 3.57; N, 11.44. Found: C, 45.48; H, 3.25; N, 11.12.

Synthesis of 4-(5, 6-dimethyl-4-oxo-2-thioxo-1, 2-dihydrothieno[2, 3-d]pyrimidin-3(4H)-yl)-N-(thiazol-2-yl)benzenesulfonamide(10).

Yield, 90%; m.p. 205.1°C; IR (KBr, cm^{-1}): 3383, 3375 (NH), 3078 (CH arom.), 2978, 2947(CH aliph.), 1654 (C=O), 1593(C=N), 1388, 1141(SO_2), 1238 (C=S). 1H-NMR (DMSO-d_6) δ:2.1, 2.2 [2s, 6H, $2CH_3$], 6.8-8.2 [m, 6H, Ar-H], 8.7 [s, 1H, SO_2NH, exchangeable with D_2O], 11.1 [s, 1H, NH, exchangeable with D_2O]. 13C-NMR

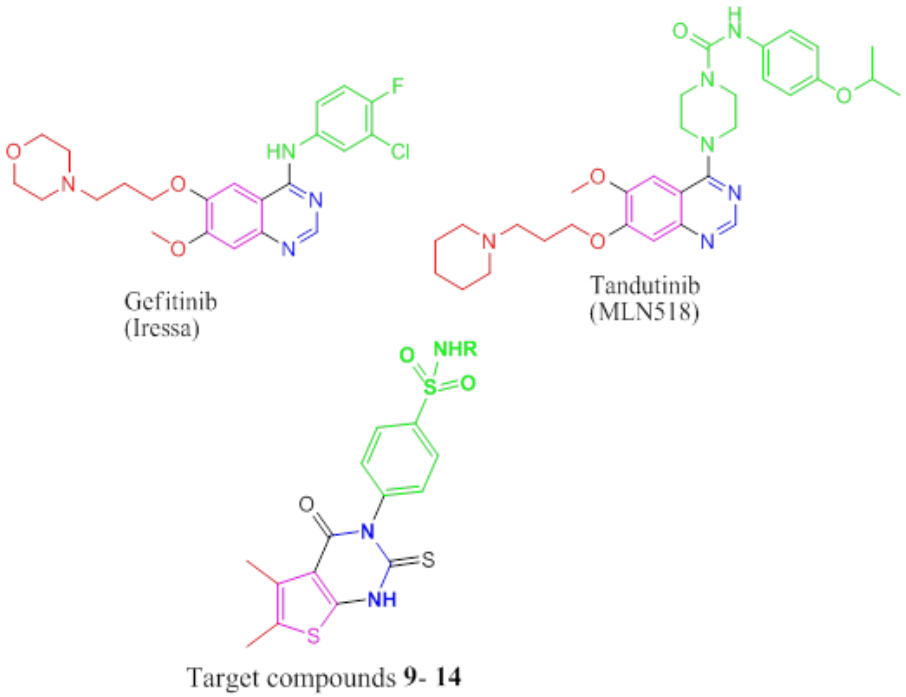


***Figure 1**: Biologically active (phase II clinical trials) and Target compounds 9-14*

(DMSO-d_6): 12.2, 13.1, 110.6, 115.8, 119.8 (2), 127.3 (2), 129.6, 130.8, 132.6, 133.2, 134.8, 150.2, 162.1, 169.7, 178.4. MS m/z (%): 450 [M+] (36.53), 93 (100). Anal. Calcd. for $C_{17}H_{14}N_4O_3S_4$: C, 45.32; H, 3.13; N, 12.43. Found: C, 45.68; H, 2.85; N, 11.15.

Synthesis of 4-(5, 6-dimethyl-4-oxo-2-thioxo-1, 2-dihydrothieno [2, 3-d] pyrimidin-3(4H)-yl)-N-(pyrimidin-2-yl) benzenesulfonamide(11).

Yield, 84%; m.p. 195.3°C; IR (KBr, cm^{-1}): 3425, 3124 (NH), 3109 (CH arom.), 2947, 2924 (CH aliph.), 1685 (C=O), 1577(C=N), 1342, 1161(SO_2), 1234 (C=S). 1H NMR (DMSO-d_6) δ:2.2, 2.3 [2s, 6H, $2CH_3$], 7.1-8.5 [m, 6H, Ar-H], 9.1 [s, 1H, SO2NH, exchangeable with D_2O], 11.3 [s, 1H, NH, exchangeable with D_2O]. 13C-NMR (DMSO-d_6): 10.8, 12.7, 114.3, 115.6, 120.4 (2), 129.6 (2), 130.3, 131.1, 133.2, 134.0, 151.2, 155.6 (2), 158.0, 167.4. 182.0. MS m/z (%): 445 [M+] (6.23), 156 (100). Anal. Calcd. for $C_{18}H_{15}N_5O_3S_3$: C, 48.52; H, 3.39; N, 15.72. Found: C, 48.26; H, 3.71; N, 15.44.

Synthesis of 4-(5, 6-dimethyl-4-oxo-2-thioxo-1, 2- dihydrothieno [2, 3-d] pyrimidin-3(4H)-yl)-N-(4, 6-dimethylpyrimidin-2-yl)benzenesulfonamide(12).

Yield, 88%; m.p. 227.8°C; IR (KBr, cm-1): 3425, 3120 (NH), 3100 (CH arom.), 2974, 2947 (CH aliph.), 1685 (C=O), 1597(C=N), 1381, 1161(SO_2), 1230 (C=S).1H NMR (DMSO-d_6) δ:2.1, 2.3 [2s, 6H, $2CH_3$], 2.4 [s, 6H, $2CH_3$ pyrimidine], 6.6-8.3 [m, 5H, Ar-H], 8.9 [s, 1H, SO_2NH, exchangeable with D_2O], 10.9 [s, 1H, NH, exchangeable with D_2O]. 13C-NMR (DMSO-d_6): 10.7, 12.3, 23.5 (2), 111.7, 115.0, 120.6 (2), 128.7 (2), 129.4, 130.6, 132.8, 133.7, 150.0, 159.6, 165.4 (2), 166.7. 181.8. MS m/z (%): 473 [M+] (2.63), 184 (100). Anal. Calcd. for $C_{20}H_{19}N_5O_3S_3$: C, 50.72; H, 4.04; N, 14.79. Found: C, 50.48; H, 3.69; N, 14.48.

Synthesis of N-(2, 6-dimethoxypyrimidin-4-yl)-4-(5, 6-dimethyl-4-oxo-2-thioxo-1, 2- dihydrothieno [2, 3-d] pyrimidin-3(4H)-yl)benzenesulfonamide(13).

Yield, 83%; m.p. 296.4°C; IR (KBr, cm^{-1}): 3340, 3186 (NH), 3055 (CH arom.), 2941, 2836 (CH aliph.), 1703 (C=O), 1618 (C=N), 1382, 1153 (SO_2), 1244 (C=S). 1H-NMR (DMSO-d_6) δ:2.2, 2.3 [2s, 6H, $2CH_3$], 3.8 [s, 6H, $2OCH_3$], 5.8 [s, 1H, CH pyrimidine], 7.0-8.0 [m, 4H, Ar-H], 8.9 [s, 1H, SO_2NH, exchangeable with D_2O], 10.6 [s, 1H, NH, exchangeable with D_2O]. 13C-NMR (DMSO-d_6): 11.2, 12.4, 55.2, 55.6, 81.7, 115.6, 120.2 (2), 127.0 (2), 129.6, 130.8, 132.9, 133.4, 151.0, 155.5, 158.7, 166.2, 169.8, 181.6. MS m/z (%): 505 [M+] (12.18), 153 (100). Anal. Calcd. for $C_{20}H_{19}N_5O_5S_3$: C, 47.51; H, 3.79; N, 13.85. Found: C, 47.25; H, 3.99; N, 14.17.

Synthesis of N-(5, 6-dimethoxypyrimidin-4-yl)-4-(5, 6-dimethyl-4-oxo-2-thioxo-1, 2- dihydrothieno [2, 3-d] pyrimidin-3(4H)-yl) benzenesulfonamide(14).

Yield, 79%; m.p. 130.6°C; IR (KBr, cm^{-1}): 3110 (NH), 3012 (CH arom.), 2981, 2945, 2868(CH aliph.), 1656(C=O), 1583(C=N), 1377, 1163(SO_2), 1240 (C=S). 1H-NMR (DMSO-d_6) δ:2.1, 2.2 [2s, 6H, $2CH_3$], 3.8, 3.9 [2s, 6H, $2OCH_3$], 7.1-8.5 [m, 5H, Ar-H], 9.1 [s, 1H, SO_2NH, exchangeable with D_2O], 11.0 [s, 1H, NH, exchangeable with D_2O]. 13C-NMR (DMSO-d_6): 10.6, 12.4, 54.0, 55.6, 115.4, 119.7 (2), 128.3 (2), 129.7, 129.9, 131.0, 132.8, 133.4, 150.1, 151.8, 152.6, 157.7, 162.0, 182.6. MS m/z (%): 505 [M+] (7.56), 138 (100). Anal. Calcd. for $C_{20}H_{19}N_5O_5S_3$: C, 47.51; H, 3.79; N, 13.85. Found: C, 47.84; H, 3.54; N, 13.51.

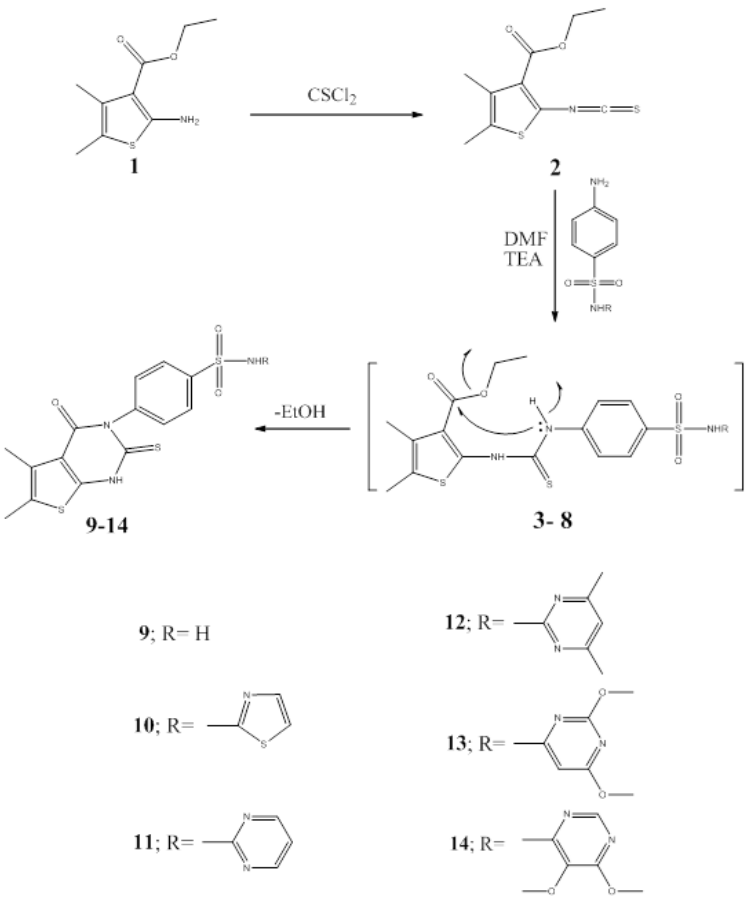
(Scheme 1)

In vitro Anticancer Activity

The cytotoxic activity was measured *in vitro* for the newly synthesized compounds using the SulfoRhodamine-B stain (SRB) assay using the Skehan et al. [25]. The *in vitro* anticancer screening was done at the Pharmacology Unit, the National Cancer Institute, Cairo University. Cells were plated in 96-multiwall microliter plate (104-cells/well) for 24h before treatment with the compound(s) to allow attachment of cell to the wall of the plate. Test compounds were dissolved in DMSO and diluted with saline to the appropriate volume. Different concentrations of the compound under test (10, 25, 50 and 100 μM) were added to the cell monolayer. Triplicate wells were prepared for each individual dose. Monolayer cells were incubated with the compound (s) for 48 h at 37°C and in atmosphere of 5% CO_2. After 48 h, cells were fixed, washed, and stained for 30 min with 0.4% (W/V) with SRB dissolved in 1% acetic acid. Excess unbound dye was removed by four washes with 1% acetic acid and attached stain was recovered with Tris-EDTA buffer. Color intensity was measured in an enzyme- linked immunosorbent assay ELISA reader. The relation between surviving fraction and drug concentration is plotted to get the survival curve for breast tumor cell line after the specified time [25]. The molar concentration required for 50% inhibition of cell viability (IC_{50}) was calculated and the results are given in (Table 1).The relationship between surviving fraction and drug concentration was plotted to obtain the survival curve of breast cancer cell line (MCF7). The response parameter calculated was IC_{50} value, which corresponds to the concentration required for 50% inhibition of cell viability.

In vitro Anti-Breast Cancer Activity

The newly synthesized compounds were evaluated for their *in vitro* anticancer activity against human breast cancer cell line, MCF7. Doxorubicin, which is one of the most effective anticancer agents, was used as the reference drug in this study. The relationship between surviving fraction and drug concentration was plotted to obtain the survival curve of breast cancer cell line (MCF7). The response parameter calculated was the IC_{50} value, which corresponds to the concentration required for 50% inhibition of cell viability. Table 1 shows the *in vitro* cytotoxic activity of the newly synthesized compounds. Most of the tested



Scheme 1: *Formation of compounds 9-14.*

Table 1*: In-vitro anticancer screening of the newly synthesized compounds against human breast cancer cell line (MCF-7)*

Compound no.	Compound concentration (µM)				IC_{50} (µM)
	10 (µM)	25 (µM)	50 (µM)	100 (µM)	
	Surviving fraction (mean ± SE)#				
Doxorubicin	0.7211 ± 0.06	0.5463 ± 0.02	0.4614 ± 0.03	0.4942 ± 0.06	30.40
9	0.8425 ± 0.07	0.5324 ± 0.06	0.2731 ± 0.01	0.2284 ± 0.03	27.83
10	0.9294 ± 0.09	0.6825 ± 0.05	0.2583 ± 0.07	0.3387 ± 0.05	34.64
11	0.9128 ± 0.08	0.6316 ± 0.09	0.3658 ± 0.04	0.2245 ± 0.07	37.78
12	0.8334 ± 0.08	0.6153 ± 0.05	0.1349 ± 0.06	0.1502 ± 0.05	29.22
13	0.7656 ± 0.06	0.4462 ± 0.06	0.3136 ± 0.08	0.1544 ± 0.04	22.52
14	0.7474 ± 0.05	0.4813 ± 0.07	0.1916 ± 0.07	0.0992 ± 0.03	22.12

compounds exhibited significant activity compared to the Doxorubicin as reference drug. From the results of Table 1, it was found that thienopyrimidine containing biologically active sulfa-doxine at 3-position with thione moiety at 2-position 14, sulfa-dimethoxazine at 3-position, with thione moiety at 2-position 13, sulfanilamide at 3-position with thione moiety at 2-position 9, and sulfa-merazine at 3-position with thione moiety at 2-position 12 with IC_{50} values (22.12, 22.52, 27.83, and 29.22 µM) exhibited more potent anti-breast cancer activity than the reference drug with IC_{50} value (30.40 µM). Farther, thienopyrimidine bearing the biologically active sulfa-thiazole at 3-position with thione moiety at 2-position 10 and sulfa-diazine at 3-position with thione moiety at 2-position 11 with IC_{50} values (34.64, 37.78 µm) are nearly as active as Doxorubicin as positive control.

Discussion

The compounds were designed in the aim of exploring their anti-breast cancer activity. The sequence of reaction followed in the synthesis of the target compounds is illustrated in (Scheme 1). As a part of a program aimed at the synthesis of novel thieno [2, 3-d]pyrimidine derivatives having the biologically active sulfonamide moieties 9-14, namely sulfanilamide 9, sulfa- thiazole10, sulfa-diazine11, sulfa- merazine12, sulfa- dimethoxazine13 and sulfa- doxine14, which could be useful for biological screening, we have investigated the possible utility of 2-isothiocyanatothiophene 2 [26] to react with sulfa- drugs in dimethylformamide in the presence of trimethylamine as catalyst to give novel thienopyrimidine derivatives 9-14 in high yield (Scheme 1). Thus, treatment of 2 with sulfa-drugs in refluxing dimethylformamide in presence

of triethylamine as catalyst furnished the corresponding sulfonamide derivatives 9-14, through the formation of intermidiates 3-8. The structures of the later products were assigned on the basis of their analytical and spectral data. The IR spectra of the reaction products showed in each case three absorption bands corresponding to NH functions in the region 3425-3110 cm^{-1}, in addition to a carbonyl absorption band in the region 1703-1654 cm^{-1},absorption bands assigned to C=S function in the region 1244- 1230 cm^{-1}, absorption bands due to SO_2 functions in the region 1388-1141 cm^{-1}. IR spectrum of compound 9 revealed the absence of N=C=S group and presence of characteristic bands at 3437, 3425, 3263 cm^{-1} (NH, NH2), 3100 cm^{-1} (CH arom.), 2978, 2947 cm^{-1} (CH aliph.), 1674 cm^{-1} (C=O), 1338, 1161 cm^{-1} (SO_2), 1234 cm^{-1} (C=S). ^{1}H-NMR spectrum of 9 in (DMSO-d_6) revealed singlet at 11.2 ppm assigned to NH group, ^{13}C-NMR spectrum of compound 9 exhibited singlet at 180.1 ppm attributed to C=S group. Compound 10 was established on the basis of elemental analysis and spectral data. IR spectrum of compound 10 showed the absence of N=C=S group and presence of characteristic bands at 3383, 3375 cm^{-1} (NH), 3078 cm^{-1} (CH arom.), 2978, 2947 cm^{-1} (CH aliph.), 1654 cm^{-1} (C=O), 1593 cm^{-1} (C=N), 1388, 1141 cm^{-1} (SO_2), 1238 cm^{-1} (C=S). ^{1}H-NMR spectrum of 10 in (DMSO-d_6) revealed signals at 8.7, 11.1 ppm due to SO_2NH and NH groups. ^{13}C-NMR spectrum of 10 showed singlet at 178.4 ppm for C=S group. Compound 11 was proved on the basis of elemental analysis and spectral data. IR spectrum of compound 11 exhibited the absence of N=C=S group and presence of characteristic bands at 3425, 3124 cm^{-1} (NH), 3109 cm^{-1} (CH arom.), 2947, 2924 cm^{-1} (CH aliph.), 1685 cm^{-1} (C=O), 1577 cm^{-1} (C=N), 1342, 1161 cm^{-1} (SO_2), 1234 cm^{-1} (C=S). ^{1}H-NMR spectrum of 11 in (DMSO-d_6) showed signals at 9.1, 11.3 ppm due to SO_2NH and NH groups. ^{13}C-NMR spectrum of 11 exhibited singlet at 182.0 ppm assigned C=S group. Compound 12 was established on the basis of elemental analysis and spectral data. IR spectrum of compound 12 showed the absence of N=C=S group and presence of characteristic bands at 3425, 3120 cm^{-1} (NH), 3100 cm^{-1} (CH arom.), 2974, 2947 cm^{-1} (CH aliph.), 1685 cm^{-1} (C=O), 1597 cm^{-1} (C=N), 1381, 1161 cm^{-1}1 (SO_2), 1230 cm^{-1} (C=S). ^{1}H-NMR spectrum of 12 in (DMSO-d_6) revealed singlet at 2.4 ppm attributed to CH_3 group for pyrimidine ring. ^{13}C-NMR spectrum of 12 revealed singlet at 181.8 ppm according to C=S group. Compound 13 was elucidated on the basis of elemental analysis and spectral data. IR spectrum of compound 13 revealed the absence of N=C=S group and presence of characteristic bands at 3340, 3186 cm^{-1} (NH), 3055 cm^{-1} (CH arom.), 2941, 2836 cm^{-1} (CH aliph.), 1703 cm^{-1} (C=O), 1618 cm^{-1} (C=N), 1382, 1153 cm^{-1} (SO_2), 1244 cm^{-1} (C=S). ^{1}H-NMR spectrum of 13 in (DMSO-d_6) showed singlet at 3.8 ppm assigned to 2OCH_3 groups. ^{13}C-NMR spectrum of 13 showed signals at 55.2, 55.6 ppm attributed to 2OCH_3 groups. Compound 14 was proved on the basis of elemental analysis and spectral data. IR spectrum of compound 14 exhibited the absence of N=C=S group and presence of characteristic bands at 3110 cm^{-1} (NH), 3012 cm^{-1} (CH arom.), 2981, 2945, 2868 cm^{-1} (CH aliph.), 1656 cm^{-1} (C=O), 1583 cm^{-1} (C=N), 1377, 1163 cm^{-1} (SO_2), 1240 cm^{-1} (C=S). ^{1}H-NMR spectrum of 14 in (DMSO-d_6) showed signals at 3.8, 3.9 ppm assigned to 2OCH_3 groups, while its ^{13}C-NMR spectrum exhibited singlet at 182.6 ppm according to C=S group.

Conclusion

The objective of the present study was to synthesize and investigate the anti-breast cancer activity of some novel thieno [2,3-d] pyrimidine derivatives carrying the biologically active benzenesulfonamide moieties at 3-position and thione moiety at 2-position. Compounds 14 bearing sulfa-doxine at 3-position, thione moiety at 2-position, 13 having sulfa-dimethoxazine, 9 carrying the corresponding sulfanilamide and 12 incorporating sulfa-merazine with IC_{50} values (22.12, 22.52, 27.83, 29.22 μM) were found the most active compounds compared with Doxorubicin as reference drug, while compounds 10 and 11 with IC_{50} values (34.64, 37.78 μM) are nearly as active as Doxorubicin as positive control.

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