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SYNTHESIS OF SULFONAMIDES CONTAINING PYRROLE AND IMIDAZO[2,1-b][1,3,4]THIADIAZOLE MOIETIES AS ANTICANCER AGENTS

Jalal H. Abdullah[1], Tawfeek A. Yahya[1]*, Mokhtar ABD-Hafiz AL-Ghorafi[1]

Medicinal, Pharmaceutical Organic and Analytical Chemistry Department, Faculty of Pharmacy, Sana'a University, Sana'a 18084, Yemen.

***Corresponding Author: Tawfeek A. Yahya**

Medicinal, Pharmaceutical Organic and Analytical Chemistry Department, Faculty of Pharmacy, Sana'a University, Sana'a 18084, Yemen.

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ABSTRACT

Series of sulfonamides containing pyrrole and imidazo[2,1-b][1,3,4]thiadiazole moieties were synthesized. The in vitro cytotoxicity of these compounds was evaluated against MCF-7. The tested compounds showed moderate to good cytotoxic activities to doxorubicin (IC_{50}= 0.82 µM) with IC_{50} ranges1.23-5.01 µM. the compound 4a was the best one among the series with IC_{50} value of 1.23 µM.

KEYWORDS: Imidazo[2,1-b][1,3,4]thiadiazole, Sulfonamide, Pyrrole, MCF-7, Cytotoxic Activity.

INTRODUCTION

Cancer is a notably complex, widespread and lethal disease accounting for 7.6 million deaths (around 13% of all deaths) in 2008, that are projected to continue rising, with an estimated 13.1 million deaths in 2030.[1] Cancer can affect almost every tissue lineage in the human body and poses great challenges to medical science. Most cancers are characterized by uncontrolled cell proliferation, lack of cell differentiation and loss of contact inhibition, which confers upon the tumor cell a capability to invade local tissues and metastasize.[2,3] Nearly all cancers are caused by abnormalities in the genetic material of the transformed cells and involve deregulation of essential enzymes and other proteins controlling cell division and proliferation.[4] Several lines of evidence support the view that chemotherapy has become one of the most significant treatment modalities in cancer management. However, the non-selectivity and acute toxicity of many antitumor agents beside the development of cellular drug resistance have been the major deterrent in their usage for treating human cancer, prompting the search for new antitumor agents with improved tumor selectivity, efficiency, and safety.[5-7]

Several pyrrole and fused pyrrole derivatives have been reported as biologically active compounds with variant activities[8-12] especially anticancer activity.[14-15] On the other hand, sulfonamides constitute an important class of drugs with several types of pharmacological activities[16], including anticancer activity[17], anti-inflammatory[18], antimicrobial[19] and antibacterial.[20] On the other hands, some imidazo[2,1-b]-1,3,4-thiadiazole derivatives showed anticancer[21], antitubercular[22], antibacterial[23,24], antifungal[25], anticonvulsant and analgesic[26], antisercetory[27], antiapoptotic[28], anti-inflammatory[29], cardiotonic[30], diuretic[31] activities.

In the design of new drugs, the hybridization and bioisosterism approaches might allow obtaining molecules with improved the biological activity with respect to the corresponding lead compounds. Thus, adopting these approaches, two series of sulfonamide-heterocyclic hybrids comprising two types of heterocyclic patterns; one containing pyrrole **(4 a-j)** and the others with imidazo[2,1-b][1,3,4]thiadiazole **(5 a, b)** were synthesized as potential antitumor agents.

RESULTS AND DISCUSSION

Chemistry

The synthesis of the target compounds in this study is depicted in schemes 1. Reaction of 2-bromo-1-(substitutedphenyl)ethanone **(1a, b)** with sulfanilamide yielded the corresponding 4-(2-(substitutedphenyl)-2-oxoethylamino)benzenesulfonamide **(2a, b)**,[32] which upon reaction with malononitrile in absolute ethanol in presence of sodium ethoxide afforded the pyrrole derivatives **(3a, b)**.[33]

The reaction of compounds **(3a, b)** with various aryl isothiocyanates in refluxing absolute ethanol generates the corresponding thiourea derivatives **(4 a-j)**.

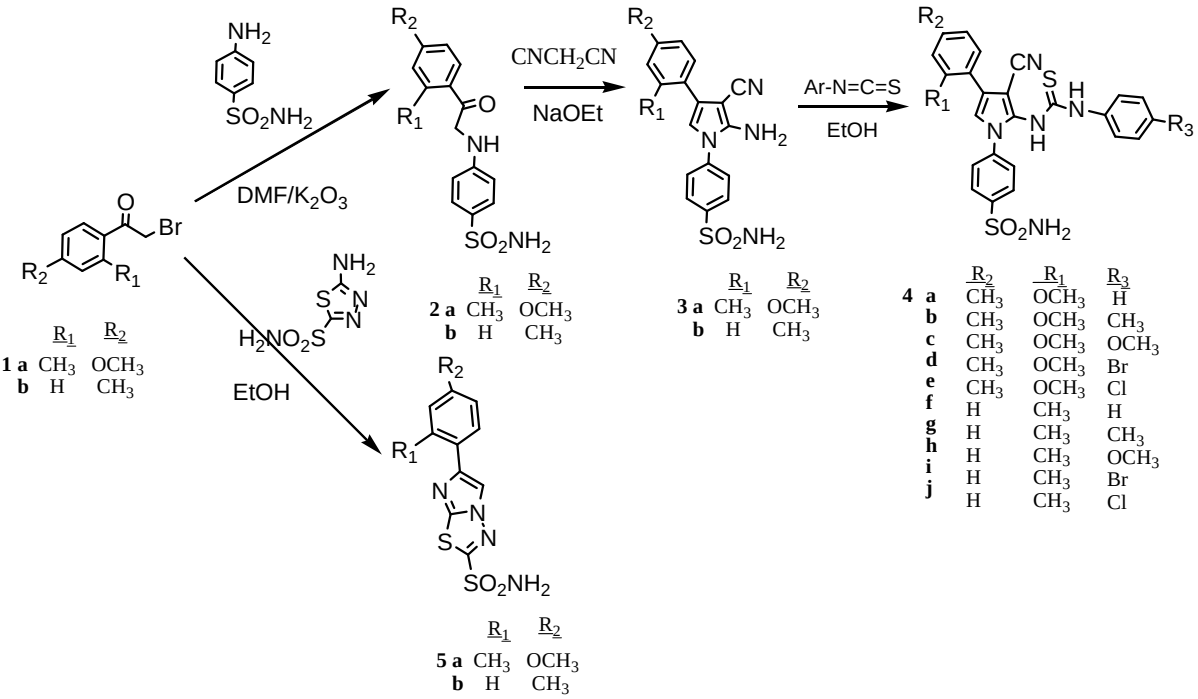
On the other hand, 2-bromo-1-(substitutedphenyl)ethanone **(1a, b)** allowed to react with 5-amino-1,3,4-thiadiazole-2-sulfonamide in boiling dry ethanol to generate 6-(4-methoxy-2-methylphenyl) imidazo[2,1-b][1,3,4]thiadiazole-2-sulfonamide **(5a, b).** The reaction proceeds via the formation of the

iminothiadiazole intermediate, followed by dehydrative cyclization to form the desired fused heterocycle.[23]

The structures of the synthesized compounds were elucidated by spectral data. The IR spectrum of compounds **(2a, b)** showed the presence of the characteristic bands for the NH, NH_2 and C=O groups. Also, the ^{1}H NMR spectrum indicated the presence of a singlet at 4.64 ppm, which could be assigned to the CH_2 group. The IR spectrum of compounds **(3a, b)** exhibited bands for the NH_2 and CN functions. In addition, the ^{1}H NMR spectra of compounds **(3a, b)** revealed two D_2O exchangeable signals, one at 6.06 ppm assigned to the NH_2 group and another at 7.96 ppm for the SO_2NH_2 group. IR spectra of compounds **(4 a-j)** showed the presence of a characteristic C=S band in the range of 1243-1261 cm^{-1}. While, the ^{1}H NMR spectra of compounds **(4 a-j)** showed disappearance of signal around 6.06 ppm assigned to the NH_2 group and appearance of two D_2O exchangeable signals, around 9.40 and 10.31 ppm for the two NH groups of substituted thiourea.

The disappearance of the NH_2 and carbonyl absorption bands in the IR spectra of compounds **(5a, b)** as well as the absence of the exchangeable singlets of this group in their 1H-NMR spectra, in addition to the presence of singlets at 6.67-6.68 ppm for imidazole protons confirmed the structures of **(5a, b)**.

Scheme 1



***In vitro* cytotoxic activity**

Cytotoxic activity results were summarized in table 1. The in vitro anticancer activity of the target compounds **(4 a-j)** and **(5 a, b)** was evaluated against the breast cancer cell line MCF-7 using Sulforhodamine B (SRB) colorimetric assay.[34] Most of the synthesized compounds showed moderate to good activity compared to the reference drug, doxorubicin. The 4-methoxy-2-methylphenyl-pyrrole derivatives **(4 a-e)** showed good cytotoxic activity with IC_{50} ranges 1.23-2.33 µM, while, the 2-phenylthioureido derivative (4 a) was the best active compound among this series with IC_{50} of 1.23 µM. on the other hand, replacement of the 4-methoxy-2-methylphenyl-pyrrole derivatives **(4 a-e)** with 4-(p-tolyl)-pyrrole derivatives **(4 f-j)** decreased the cytotoxic activity with IC_{50} ranges 1.92-3.26 µM. However, the activity decreased with the p-bromo **(4i)** and p-chloro **(4j)** phenylthioureido derivatives (IC_{50} values 2.98 and 3.26 µM respectively). This indicated that para electron withdrawing groups decreased the cytotoxic activity. Finally, the imidazo[2,1-b][1,3,4]thiadiazole-2-sulfonamide derivatives **(5a)** and **(5 b)** showed moderate activities with IC_{50} of 4.48 and 5.01 µM respectively.

Table 1: *In vitro* cytotoxic activity of the synthesized compounds against MCF7 cell line.

Compound No	[a]IC_{50} (µM)	Compound No	[a]IC_{50} (µM)
4 a	1.23	**4 g**	3.43
4 b	2.72	**4 h**	2.01
4 c	1.55	**4 i**	2.98
4 d	2.03	**4 j**	3.26
4 e	2.33	**5 a**	4.48
4 f	1.92	**5 b**	5.01
Doxorubicin	0.82	**Doxorubicin**	0.82

[a]**IC_{50}** is a concentration that cause 50% growth inhibition.

EXPERIMENTAL

Chemistry

Melting points are uncorrected and were determined on a Stuart melting point apparatus (Stuart Scientific, Redhill, UK). The FT-IR spectra (KBr) were recorded on Shimadzu FT-IR 110 spectrophotometer (Shimadzu, Koyoto, Japan) by using 1% potassium bromide discs. ^{1}H-NMR spectra were recorded on a Bruker proton 300 MHz (Bruker, Munuch, Germany) spectrometer using DMSO-d_6 as a solvent and tetramethylsilane (TMS) as internal standard. Chemical shift values are listed in δ scale. Mass spectra were determined using a GC/MS Mat 112 S at 70ev spectrometer. Completion of the reaction was monitored by thin layer chromatography (TLC) using precoated aluminium sheets silica gel (Merck, 60 F254). Visualization was accomplished with ultraviolet UV lamp (Merck, Damstadt, Germany). Synthesized compounds were purified by the re-crystallization process. The purity of the compounds was checked by a single spot in TLC and solvent system for TLC was determined on a trial and error basis. All the chemicals and solvents used were of commercial grade.

General procedure for Synthesis of 4-(2-(4-methoxy-2-methylphenyl)-2-oxoethylamino)benzenesulfonamides (2 a, b)

A mixture of 2-bromo-1-(substitutedphenyl)ethanone **(1a, b)** (10 mmol), sulfanilamide (10 mmol) and was dissolved in DMF (30 mL). To that solution potassium carbonate (1.38 g, 10 mmol) was added and the mixture was stirred overnight. The reaction mixture was then added to water (160 mL) and the precipitate was vacuum filtered and left to dry. The solid residue was recrystallized from ethyl acetate to produce **(2 a, b).**

4-(2-(4-Methoxy-2-methylphenyl)-2-oxoethylamino)benzenesulfonamide (2 a)

Yield 59%, mp 194-196° C. IR (KBr, cm^{-1}): 1688, 3095, 3223, 3354, 3426. ^{1}H NMR (300 MHz, DMSO-d_6): 2.37 (s, 3H, CH_3), 3.83 (s, 3H, OCH_3), 4.64 (s, 2H, CH_2), 6.91-8.15 (m, 9H, Ar-H + SO_2NH_2), 8.52 (s, 1H, NH, D_2O exchangeable). MS: (m/z) 334 (M^+) observed for $C_{16}H_{18}N_2O_4S$

4-((2-Oxo-2-(p-tolyl)ethyl)amino)benzenesulfonamide (2 b)

Yield 58%, mp 183-185° C. IR (KBr, cm^{-1}): 1690, 3090, 3229, 3356, 3428. ^{1}H NMR (300 MHz, DMSO-d_6): 2.37 (s, 3H, CH_3), 4.63 (s, 2H, CH_2), 6.93-8.31 (m, 10H, Ar-H + SO_2NH_2), 8.54 (s, 1H, NH, D_2O exchangeable). MS: (m/z) 304 (M^+) observed for $C_{15}H_{16}N_2O_3S$

General procedure for Synthesis of 4-(2-amino-3-cyano-4-(4-methoxy-2-methylphenyl)-1H-pyrrol-1-yl)benzenesulfonamides (3 a, b)

To compounds **(2a, b)** (0.01 mol), malononitrile (0.66 g, 0.01 mol) in absolute ethanol (20 ml) containing sodium ethoxide (0.5 g) were added and refluxed for 8 h. The reaction mixture was cooled and acidified with dil. HCl. The precipitate obtained was filtered off and recrystallized from dioxane to give **(3a, b).**

4-(2-Amino-3-cyano-4-(4-methoxy-2-methylphenyl)-1H-pyrrol-1-yl)benzenesulfonamide (3 a)

Yield 76%, mp 231-233 °C. IR (KBr, cm^{-1}): 2210, 3095, 3238, 3365, 3419. ^{1}H NMR (300 MHz, DMSO-d_6): 2.22 (s, 3H, CH_3), 3.87 (s, 3H, OCH_3), 6.06 (s, 2H, NH_2, D_2O exchangeable), 6.90 (s, 1H, CH pyrrole), 7.43-7.96 (m, 9H, Ar-H + SO_2NH_2). MS: (m/z) 389 (M^+) observed for $C_{19}H_{18}N_4O_3S$

4-(2-Amino-3-cyano-4-(p-tolyl)-1H-pyrrol-1-yl)benzenesulfonamide (3 b)

Yield 78%, mp 221-223 °C. IR (KBr, cm^{-1}): 2220, 3092, 3241, 3368, 3425. ^{1}H NMR (300 MHz, DMSO-d_6): 2.23 (s, 3H, CH_3), 6.08 (s, 2H, NH_2, D_2O exchangeable), 6.92 (s, 1H, CH pyrrole), 7.48-7.98 (m, 10H, Ar-H + SO_2NH_2). MS: (m/z) 352 (M^+) observed for $C_{18}H_{16}N_4O_2S$

General procedure for Synthesis of 4-(4-(substitutedphenyl)-3-cyano-2-(3-substitutedphenylthioureido)-1H-pyrrol-1-yl)benzene-sulfonamide (4 a-j)

A mixture of compound **(3 a) or (3 b)** (0.01 mol) and aryl isothiocyanates (0.01 mol) in absolute ethanol (30 ml) was refluxed for 6 h. The reaction mixture was cooled and the obtained solid was recrystallized from dioxan to give compounds **(4 a-j)**.

4-(4-(4-Methoxy-2-methylphenyl)-3-cyano-2-(3-phenylthioureido)-1H-pyrrol-1-yl)benzene-sulfonamide (4 a)

Yield 83%, mp 168-170° C. IR (KBr, cm^{-1}): 1260, 2220, 3060, 3218, 3391, 3412. ^{1}H NMR (300 MHz, DMSO-d_6): 2.10 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 6.23 (s, 1H,

CH pyrrole), 6.81-8.22 (m, 14H, Ar-H + SO_2NH_2), 9.43, 10.32 (2s, 2H, 2NH, D_2O-exchangeable). MS: (m/z) 517 (M^+) observed for $C_{26}H_{23}N_5O_3S_2$

4-(3-Cyano-4-(4-methoxy-2-methylphenyl)-2-(3-(p-tolyl)thioureido)-1H-pyrrol-1-yl)benzenesulfonamide (4 b).
Yield 85%, mp 187-189° C. IR (KBr, cm^{-1}): 1256, 2225, 3064, 3218, 3390, 3413. ^1H NMR (300 MHz, DMSO-d_6): 1.91, 2.12 (2s, 6H, $2CH_3$), 3.84 (s, 3H, OCH_3), 6.20 (s, 1H, CH pyrrole), 6.78-8.17 (m, 13H, Ar-H +SO_2NH_2), 9.40, 10.34 (2s, 2H, 2NH, D_2O-exchangeable). MS: (m/z) 531 (M^+) observed for $C_{27}H_{25}N_5O_3S_2$

4-(3-Cyano-4-(4-methoxy-2-methylphenyl)-2-(3-(p-tolyl)thioureido)-1H-pyrrol-1-yl)benzenesulfonamide (4 c).
Yield 80%, mp 190-192° C. IR (KBr, cm^{-1}): 1247, 2222, 3064, 3220, 3394, 3410. ^1H NMR (300 MHz, DMSO-d_6): 2.12 (1s, 3H, $1CH_3$), 3.87, 3.84 (2s, 6H, $2OCH_3$), 6.25 (s, 1H, CH pyrrole), 6.76-8.31 (m, 13H, Ar-H +SO_2NH_2), 9.44, 10.30 (2s, 2H, 2NH, D_2O-exchangeable). MS: (m/z) 547 (M^+) observed for $C_{28}H_{25}N_5O_4S_2$

4-(2-(3-(4-Bromophenyl)thioureido)-3-cyano-4-(4-methoxy-2-methylphenyl)-1H-pyrrol-1-yl)benzenesulfonamide (4 d).
Yield 85%, mp 210-212° C. IR (KBr, cm^{-1}): 1244, 2223, 3060, 3212, 3396, 3424. ^1H NMR (300 MHz, DMSO-d_6): 2.10 (s, 3H, CH_3), 3.87 (s, 3H, OCH_3), 6.44 (s, 1H, CH pyrrole), 6.90-8.32 (m, 13H, Ar-H +SO_2NH_2), 9.46, 10.35 (2s, 2H, 2NH, D_2O-exchangeable). MS: (m/z) 598/596 (M^++2) /(M^+) observed for $C_{26}H_{22}BrN_5O_3S_2$

4-(2-(3-(4-Chlorophenyl)thioureido)-3-cyano-4-(4-methoxy-2-methylphenyl)-1H-pyrrol-1-yl)benzenesulfonamide (4 e).
Yield 81%, mp 205-207° C. IR (KBr, cm^{-1}): 1250, 2220, 3060, 3213, 3394, 3424. ^1H NMR (300 MHz, DMSO-d_6): 2.12 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 6.41 (s, 1H, CH pyrrole), 6.80-8.30 (m, 13H, Ar-H +SO_2NH_2), 9.42, 10.30 (2s, 2H, 2NH, D_2O-exchangeable). MS: (m/z) 552 (M^+) observed for $C_{26}H_{22}ClN_5O_3S_2$

4-(3-Cyano-2-(3-phenylthioureido)-4-(p-tolyl)-1H-pyrrol-1-yl)benzenesulfonamide (4 f)
Yield 80%, mp 175-177° C. IR (KBr, cm^{-1}): 1260, 2221, 3066, 3218, 3390, 3412. ^1H NMR (300 MHz, DMSO-d_6): 2.11 (s, 3H, CH_3), 6.22 (s, 1H, CH pyrrole), 6.80-8.21 (m, 15H, Ar-H + SO_2NH_2), 9.43, 10.30 (2s, 2H, 2NH, D_2O-exchangeable). MS: (m/z) 487 (M^+) observed for $C_{25}H_{21}N_5O_2S_2$

4-(3-Cyano-4-(p-tolyl)-2-(3-(p-tolyl)thioureido)-1H-pyrrol-1-yl)benzenesulfonamide (4 g).
Yield 83%, mp 194-196° C. IR (KBr, cm^{-1}): 1253, 2224, 3065, 3215, 3396, 3416. ^1H NMR (300 MHz, DMSO-d_6): 1.93, 2.11 (2s, 6H, $2CH_3$), 6.22 (s, 1H, CH pyrrole), 6.76-8.16 (m, 14H, Ar-H +SO_2NH_2), 9.38, 10.32 (2s, 2H, 2NH, D_2O-exchangeable). MS: (m/z) 501 (M^+) observed for $C_{26}H_{23}N_5O_2S_2$

4-(3-Cyano-2-(3-(4-methoxyphenyl)thioureido)-4-(p-tolyl)-1H-pyrrol-1-yl)benzene-sulfonamide (4 h).
Yield 77%, mp 197-199 °C. IR (KBr, cm^{-1}): 1245, 2221, 3060, 3221, 3395, 3417. ^1H NMR (300 MHz, DMSO-d_6): 2.11 (1s, 3H, $1CH_3$), 6.26 (s, 1H, CH pyrrole), 6.78-8.30 (m, 14H, Ar-H + SO_2NH_2), 9.43, 10.31 (2s, 2H, 2NH, D_2O-exchangeable). MS: (m/z) 517 (M^+) observed for $C_{26}H_{23}N_5O_3S_2$

4-(2-(3-(4-Bromophenyl)thioureido)-3-cyano-4-(p-tolyl)-1H-pyrrol-1-yl)benzenesulfon-amide (4 i)
Yield 80%, mp 224-226° C. IR (KBr, cm^{-1}): 1246, 2220, 3067, 3218, 3390, 3425. ^1H NMR (300 MHz, DMSO-d_6): 2.13 (s, 3H, CH_3), 6.44 (s, 1H, CH pyrrole), 6.89-8.30 (m, 14H, Ar-H + SO_2NH_2), 9.44, 10.33 (2s, 2H, 2NH, D_2O-exchangeable). MS: (m/z) 567/565 (M^++2)/(M^+) observed for $C_{25}H_{20}BrN_5O_2S_2$

4-(2-(3-(4-Chlorophenyl)thioureido)-3-cyano-4-(p-tolyl)-1H-pyrrol-1-yl)benzene-sulfonamide (4 j)
Yield 78%, mp 214-216° C. IR (KBr, cm^{-1}): 1256, 2224, 3067, 3220, 3394, 3425. ^1H NMR (300 MHz, DMSO-d_6): 2.11 (s, 3H, CH_3), 6.42 (s, 1H, CH pyrrole), 6.82-8.34 (m, 14H, Ar-H + SO_2NH_2), 9.40, 10.32 (2s, 2H, 2NH, D_2O-exchangeable). MS: (m/z) 521 (M^+) observed for $C_{25}H_{20}ClN_5O_2S_2$

General procedure for Synthesis of 6-(4-methoxy-2-methylphenyl)imidazo[2,1-b][1,3,4]thiadiazole-2-sulfonamide (5 a, b)
A mixture of equimolar quantities of 5-amino-1,3,4-thiadiazole-2-sulfonamide (0.01 mol) and 2-bromo-1-(substitutedphenyl)ethanone **(1a, b)** (0.01 mol) was refluxed in dry ethanol (50 mL) for 24 hours. The excess of solvent was distilled off and the solid hydrobromide salt that separated out was collected by filtration, suspended in water and neutralized by sodium carbonate to get free bases **(5a, b).** The product was filtered, washed with water, dried and crystallized from carbon tetrachloride.

6-(4-Methoxy-2-methylphenyl)imidazo[2,1-b][1,3,4]thiadiazole-2-sulfonamide (5a)
Yield 70%, mp 222-224° C. IR (KBr, cm^{-1}): 1595, 1630, 3060, 3230, 3394, 3425. ^1H NMR (300 MHz, DMSO-d_6): 2.12 (s, 3H, CH_3), 3.90 (s, 3H, OCH_3), 6.68 (s, 1H, CH imidazole), 6.84-8.21 (m, 6H, Ar-H +SO_2NH_2). MS: (m/z) 324 (M^+) observed for $C_{12}H_{12}N_4O_3S_2$

6-(p-Tolyl)imidazo[2,1-b][1,3,4]thiadiazole-2-sulfonamide (5b)
Yield 69%, mp 242-244° C. IR (KBr, cm^{-1}): 1596, 1636, 3067, 3232, 3396, 3424. ^1H NMR (300 MHz, DMSO-d_6): 2.13 (s, 3H, CH_3), 6.67 (s, 1H, CH imidazole), 6.86-8.24 (m, 7H, Ar-H + SO_2NH_2). MS: (m/z) 294 (M^+) observed for $C_{11}H_{10}N_4O_2S_2$

***In vitro* cytotoxic activity**

The final compounds have been tested for cytotoxic activity against human mammary carcinoma cell line (MCF7) in the National Cancer Institute, Cairo University. The screening involves a calculation of the percentage growth or the surviving fraction of the drug treated cell lines compared with untreated control using Sulforhodamine B (SRB) colorimetric assay.[34] Cells were plated in 96-multiwell plate (104 cells/well) for 24 h before treatment with the compounds to allow attachment of cells to the wall of the plate. Different concentrations of the compound under test (0.0, 1.0, 2.5, 5.0 and 10.0 µg/ml) were added to the cell monolayer. Triplicate wells were prepared for each individual dose. Monolayer cells were incubated with the compounds for 48 h at 37 ºC and in an atmosphere of 5% CO_2. After 48 h, cells were fixed, washed and stained with Sulforhodamine B stain. Excess stain was washed with acetic acid and attached stain was recovered with tri EDTA buffer. Color intensity was measured in an ELISA reader. The relation between surviving fraction and drug concentration is plotted to get the survival curve of the tumor cell line after the specified compound. The results were described in the **table 1**.

CONCLUSION

A series of sulfonamides containing pyrrole **(4 a-j)** and imidazo[2,1-b][1,3,4]thiadiazole **(5 a, b)** were synthesized as anticancer agents. The syntheized compounds were characterized using spectroscopic methods. The cytotoxic activity of these compounds were assessed against breast cancer cell line MCF7. The results of *in vitro* anticancer activity indicated that the tested compounds exhibited moderate to good activities. compound **(4 a)** showed the best activity among of series (IC_{50}= 1.23 µM).

CONFLICTS OF INTERESTS

Authors declare no conflicts of interest.

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