Microwave-Assisted One-Pot Three Component Synthesis of Some Thiazolyl(Hydrazonoethyl)Thiazoles as Potential Anti-Breast Cancer Agents

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ABSTRACT

In the present work, 1-(4-methyl-2-(2-(1-(thiophen-2-yl)ethylidene)hydrazinyl)thiazol-5-yl)ethanone was used as building block for synthesis of novel four series of 5-(1-(2-(thiazol-2-yl)hydrazono)ethyl) thiazole derivatives in a one-pot three-component reaction using both thermal heating and microwave irradiation for comparison. All the structures of the synthesized compounds were elucidated based on their elemental analyses and spectral measurements. The bioactivities of the synthesized compounds were evaluated their antitumor activities against MCF-7 tumor cells in comparison with vinblastine sulfate and cisplatin reference drugs using MTT assay and the results revealed promising activities of five compounds (4d, 8b, 12e, 4a, and 12d).

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Introduction

Cancer is a generic term, which encompasses a wide group of diseases characterized essentially by an uncontrolled growth and propagation of cells with errors in the division mechanisms known as cell cycle. Cancer constitutes a major public health problem worldwide, since it is the second leading cause of death globally, with 9.6 million deaths estimated in 2018.1 Due to the limitations and side effects associated with available cancer treatments nowadays, it is an urgent challenge for medicinal researchers to develop more safe and selective anticancer drugs. Among the design strategies in drug discovery, special attention has been paid to molecules containing sulfur heterocycles in their structures. Several studies have been carried out with plenty of sulfur heterocycles, including thiophene and thiazole, toward different pathologies. Heterocyclic compounds possessing the thiophene core have attracted tremendous interest in the field of medicinal chemistry due to their diverse and wide range of biological properties, including antimicrobial, analgesic, antidepressant, anti-inflammatory, anti-rhinitis, anti-dermatitis, and anticonvulsant activities.2–6 On the other hand, the 1,3-thiazole core structure has been considered extensively in the identification of new lead compounds and drug discovery. Thiazole-containing drugs have demonstrated their involvement in a variety of commercially available anti-cancer medications, such as tiazofurin (inhibitor of IMP dehydrogenase),7 dasatinib (Bcr-Abl tyrosine kinase inhibitor),8 dabrafenib (inhibitor of enzyme B-RAF),9 ixabepilone (stabilization of microtubules),10 and epothilone (inhibition of microtubule function)11 (Figure 1). In particular,
the potential application of thiazole scaffold in the design of anticancer agents has been studied by numerous drug discovery teams.\textsuperscript{12–15}

Molecular hybridization is a beneficial approach to structural alteration involving the integration in a single species of two or more pharmacophores. Over the last several years, hybrid drug design has developed as a prime method for the development of novel anticancer therapies that can theoretically solve much of the pharmacokinetic disadvantages of traditional anticancer drugs. Thus a number of studies have indicated that thiazole-thiophene hybrids and their bis derivatives have important anticancer activity.\textsuperscript{4,16–19} Based on the above-mentioned promising aspects, the strategy of this work includes gathering the two bioactive entities thiophene-thiazole in one compact structure for the purpose of synergism and examined the prepared compounds as anticancer agents.

Multi-component reactions (MCR) are one-pot processes which always occupy a great importance in the repertoire of sustainable synthetic tools because of their high efficiency and atom-economy.\textsuperscript{20,21} Also, MCR under microwave irradiation in synthesis of heterocyclic compounds enhanced the reaction rates and improve the regioselectivity.\textsuperscript{22–26}

As a part of our ongoing studies on the synthesis of new heterocyclic compounds via one-pot, multicomponent reactions,\textsuperscript{27–36} herein this study describes a convenient and rapid method for the synthesis of thiazolyl-hydrazono-ethylthiazoles incorporating the thiophene moiety by one-pot three-component reactions using 1-(4-methyl-2-(2-(1-(thiophen-2-yl)ethylidene)hydrazinyl)thiazol-5-yl)ethanone 1, thiosemicarbazide 2 or thiocarbohydrazide 7 and the appropriate hydrazonoyl chlorides 3 or 9 under microwave irradiation in dioxane, in the presence of a catalytic amount of TEA. The \textit{In vitro} cytotoxic potential of the newly synthesized compounds was examined against the human breast cancer cell line (MCF-7) using the MTT assay and the results showed some compounds have promising activity.

**Results and discussion**

**Chemistry**

The chemical reactivity of acetylthiazole 1 toward thiosemicarbazide 2 or thiocarbohydrazide 7 and hydrazonoyl halides 3 or 9 was studied aiming to synthesize a series of novel bioactive
thiazole derivatives. The synthetic pathways used to obtain thiazoles 4a–f, 8a–e, 10a–d, and 12a–e are outlined in Schemes 1–4.

1-(4-Methyl-2-(2-(1-(thiophen-2-yl)ethylidene)hydrazinyl)thiazol-5-yl)ethanone (1),37 thiosemicarbazide (2) and the appropriate N-aryl-2-oxopropanehydrazonoyl chlorides 3a–f38 were allowed to react in a one-pot three-component reaction in dioxane under reflux or microwave irradiation and in presence of triethylamine as basic catalyst afforded in each case one product as evidenced by thin-layer chromatography (TLC) analysis of the crude products. These products were identified as arylazothiazoles 4a–f (Scheme 1) based on spectral data and elemental analysis; For instance, the 1H-NMR spectra of 4a–f showed that generally four singlets at δ ~ 2.08, 2.15, 2.20, and 2.35 ppm due to the four CH3 groups, a multiplet δ ~ 6.97–8.01 ppm assignable to the aromatic protons, beside two broad singlets (D2O exchangeable) at δ ~ 10.57 and 11.20 ppm due to the two NH protons. IR spectra showed two absorption bands due to the two NH groups at ν ~ 3434–3194 cm⁻¹. Moreover, the mass spectrum of 4a revealed a molecular ion peak at m/z = 494 which is consistent with its molecular weight. Elemental analyses for 4a–f are in good accordance with the proposed structures.
In addition, we compare efficiency of microwave irradiation (time, yield) with conventional heating. It is clear from Table 1 that microwave irradiation is simpler, more efficient and less time consuming for the synthesis of arylazothiazoles 4a–f. Microwave irradiation facilitates the polarization of the molecules under irradiation causing rapid reaction to occur. This is consistent with the reaction mechanism, which involves a polar transition state.

Scheme 2. Synthesis of arylazothiazoles 8a–e.

Scheme 3. Synthesis of arylhydrazothiazoles 10a–d.

In addition, we compare efficiency of microwave irradiation (time, yield) with conventional heating. It is clear from Table 1 that microwave irradiation is simpler, more efficient and less time consuming for the synthesis of arylazothiazoles 4a–f. Microwave irradiation facilitates the polarization of the molecules under irradiation causing rapid reaction to occur. This is consistent with the reaction mechanism, which involves a polar transition state.
Compound 4a was alternatively synthesized by reacting thiosemicarbazone derivative 5 (prepared separately from heating of acetylthiazole 1 and thiosemicarbazide 2 in ethanol in the presence of HCl drops under microwave irradiation at 500 W and 150 °C for 3 min.) with 2-oxo-N'-(phenylpropanehydrazonoyl chloride (3a) in dioxane containing TEA in microwave oven at 500 W and 150 °C for 6 min. (Scheme 1). The obtained product was found to be identical with 4a in all respects (TLC, m.p. and IR spectrum) which affords further evidence to all structures 4a–f.

The reaction of thiosemicarbazone 5 with the hydrazonoyl chloride 3a was proceeded via the s-alkylation of the thiosemicarbazone 5 to form the nonisolable intermediate 6 followed by in situ cyclization with elimination of water molecule to afford the final products 4a (Scheme 1).

In a similar way, acetylthiazole 1 reacted with thiocarbohydrazide 7 and the appropriate hydrazoneyl chlorides 3a–d,g in a one-pot three-component reaction using conventional and microwave methods to afford the respective N-amino-arylazothiazoles 8a–e (Scheme 2). The structures of compounds 8a–e were confirmed by 1H-NMR, IR and MS. For example, the IR spectra of products 8a showed the exhibited presence of stretching bands for NH and NH2 groups at the normal wave number v. The 1H-NMR spectrum of 8a displayed four singlet signals at δ 2.32, 2.42, 2.46, 2.58 ppm for the four CH3 groups, δ 3.06, 11.20 ppm for NH2 and NH protons, respectively, in addition to multiplet signal at δ 7.07-8.03 ppm for the expected eight aromatic protons. The mass spectra of the products 8a–e revealed in each case a molecular ion peak m/z at the expected molecular weight calculated for each compound (see Experimental).

Table 1. Comparison of synthesis of arylazothiazoles 4a–f under microwave irradiation and conventional heating.

| Product No. | Conventional | Microwave |
|-------------|--------------|-----------|
|             | Time (h)     | Yield (%) | Time (min) | Yield (%) |
| 4a          | 4            | 74        | 5          | 91        |
| 4b          | 3            | 73        | 5          | 92        |
| 4c          | 3            | 70        | 4          | 93        |
| 4d          | 4            | 76        | 5          | 89        |
| 4e          | 4            | 74        | 5          | 90        |
| 4f          | 3            | 72        | 4          | 91        |

Scheme 4. Synthesis of arylhydrazothiazoles 12a–e.

Ar = a, C6H5; b, 4-CH3-C6H4; c, 4-Cl-C6H4; d, 4-NO2-C6H4; e, 4-Br-C6H4
The results obtained Table 2 indicate that, unlike conventional heating, microwave irradiation results in higher yields, shorter reaction times and cleaner reactions for all the carried reactions.

Also, the chemical reactivity of acetylthiazole 1 toward thiosemicarbazide 2 and ester type of hydrazonoyl halides 9a–d was also studied aiming to synthesize another series of novel thiazole derivatives. Thus, reaction of compound 1 with 2 and 9a–d in dioxane/TEA under reflux or microwave irradiation led to the formation of arylhydrazothiazoles 10a–d (Scheme 3). Analytical and spectral data of these reaction products are in complete agreement with their proposed structures. The IR spectra of the products showed three NH absorption bands in 10a at 3390–3208 cm\(^{-1}\) and one sharp absorption band at 1716 cm\(^{-1}\) for C=O group. The \(^1\)H-NMR spectra of compounds 10a–d revealed the characteristic three singlet signals for the 3CH\(_3\) at \(\delta\) 2.15, 2.31, 2.45 ppm, multiplet group at \(\delta\) 6.94–8.12 ppm, and also three broad singlet signals at \(\delta\) 10.48, 10.82 and 11.06 ppm due to 3NH groups.

To support this mechanism; compound 5 was irradiated with ethyl 2-chloro-2-(2-phenylhydrazono)acetate (9a) in dioxane/TEA to afford a product identically similar to 10a (Scheme 3).

In the same manner as expected, one-pot three-component reaction of acetylthiazole 1, thiocarbohydrazide 7 and C-1-(ethoxycarbonyl)-N-4-arylhydrazonoyl chlorides 9a–e in dioxane/TEA under reflux or microwave irradiation led to the formation of arylazothiazolones 12a–e (Scheme 4). The purity of the compounds was checked by the TLC and elemental analyses, and the structures of compounds were identified by spectral data (see Experimental part).

The microwave irradiation method was more convenient for synthesis of the targeted thiazole derivatives the reaction between acetylthiazole 1, hydrazonoyl halides 9 and thiosemicarbazide 2 or thiocarbohydrazide 7 due to its higher yield, shorter reaction time, and safe handling compared with the conventional method, as presented in Table 3.

**Anticancer activity**

As a continuation of our studies on 1,3-thiazole and thiophene derivatives as anticancer agents\(^{39–43}\) and in a search for novel potent anticancer compounds, we herein report the synthesis

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**Table 2.** Comparison of synthesis of arylazothiazoles 8a–e under microwave irradiation and conventional heating.

| Product No. | Conventional | Microwave |
|-------------|--------------|------------|
|             | Time (h)    | Yield (%)  | Time (min) | Yield (%) |
| 8a          | 4           | 70         | 4          | 90        |
| 8b          | 3           | 69         | 5          | 88        |
| 8c          | 3           | 70         | 5          | 87        |
| 8d          | 4           | 71         | 4          | 89        |
| 8e          | 4           | 72         | 5          | 88        |

**Table 3.** Comparison of synthesis of arylazothiazoles 10a–e and 12a–e under microwave irradiation and conventional heating.

| Product No. | Conventional | Microwave |
|-------------|--------------|------------|
|             | Time (h)    | Yield (%)  | Time (min) | Yield (%) |
| 10a         | 4           | 72         | 7          | 90        |
| 10b         | 4           | 68         | 6          | 91        |
| 10c         | 3           | 68         | 7          | 89        |
| 10d         | 4           | 72         | 5          | 88        |
| 10e         | 3           | 69         | 6          | 90        |
| 12a         | 4           | 68         | 4          | 92        |
| 12b         | 3           | 69         | 8          | 91        |
| 12c         | 4           | 70         | 4          | 88        |
| 12d         | 3           | 68         | 6          | 89        |
| 12e         | 4           | 69         | 8          | 92        |
of a series of novel thiazolyl-hydrazono-ethylthiazoles incorporating thiophene moiety and evaluation for their anticancer activities. Thus, the pharmacological activities of the synthesized thiazoles 4a,c,d, 5, 8b–e, 10a–d, and 12b–e were investigated for their human breast cancer (MCF-7) cell line in comparison with cisplatin and vinblastine sulfate as reference drugs using colorimetric MTT assay. The relation between drug concentration and surviving cells is plotted to get the survival curve. The 50% inhibitory concentration (IC50) was obtained and the anti-proliferative activity was expressed as the mean IC50 of 3 independent experiments (µg/mL) ± standard deviation from three replicates.

From the data of Table 4 and Figure 2, we concluded the following structure–activity relationships (SARs):

- The results revealed that all the tested compounds exhibited inhibitory activity against the tumor cell lines in a concentration-dependent manner.
- Compounds 4d, 8b, 12e, 4a, and 12e are proved to have the highest cytotoxic activity, while the rest compounds exhibited medium activity.
- Among the arylazothiazole derivatives, thiazole 4d (IC50 = 3.2 ± 0.1 µg/mL) showed much better cytotoxic activity than vinblastine sulfate (IC50 = 3.96 ± 0.62 µg/mL) and cisplatin (IC50 = 5.18 ± 0.94 µg/mL) toward the MCF-7 cell line may due to the presence of nitro group (electron withdrawing group) at position 4 of the phenyl ring which increases activity.
- 1,3-Thiazole derivatives 4 have more cytotoxic activity than N-amino-1,3-thiazole derivatives 8 due to the presence of N-amino group (electron donating group) which decreases activity. So cytotoxicity of thiazole derivative 4c (IC50 = 10.3 ± 0.4 µM) > N-aminothiazole derivative 8c (IC50 = 30.0 ± 1.3 µM) and thiazole derivative 4d (IC50 = 3.2 ± 0.1 µM) > N-aminothiazole derivative 8d (IC50 = 21.1 ± 0.8 µM).
- 1,3-Thiazolone derivatives 10 have less cytotoxic activity than N-amino-1,3-thiazole derivatives 12 may be due to increasing cytotoxicity of thiazolone derivatives with +1 effect of N-

### Table 4. In vitro cytotoxic activity of the newly synthesized compounds 4a,c,d, 5, 8b–e, 10a–d, and 12b–e against the human breast cancer cell line (MCF-7).

| Tested compounds | X  | IC50 (µg/mL) | Tested compounds | X  | IC50 (µg/mL) |
|------------------|----|-------------|------------------|----|-------------|
| 4a               | H  | 7.66 ± 0.36 | 10b              | Me | 17.6 ± 0.8  |
| 4c               | Cl | 10.3 ± 0.4  | 10c              | Cl | 19.8 ± 0.6  |
| 4d               | NO2| 3.2 ± 0.1   | 10d              | NO2| 57.4 ± 1.7  |
| 5                | -- | 27.6 ± 1.2  | 12b              | Me | 15.3 ± 0.5  |
| 8b               | Me | 6.87 ± 0.45 | 12c              | Cl | 23.4 ± 0.9  |
| 8c               | Cl | 30.0 ± 1.3  | 12d              | NO2| 7.74 ± 0.3  |
| 8d               | NO2| 21.1 ± 0.8  | 12e              | Br | 7.2 ± 0.2   |
| 8e               | OMe| 9.58 ± 0.61 | Cisplatin        | -- | 5.18 ± 0.94 |
| 10a              | H  | 24 ± 0.9    | Vinblastine sulfate | -- | 3.96 ± 0.62 |

Figure 2. The descending order of the activity toward the MCF-7 cell line.
amino group. So cytotoxicity of thiazole derivative 10b < N-aminothiazole derivative 12b and thiazole derivative 10d < N-aminothiazole derivative 12d.

- The cytotoxic activity of 1,3-thiazole derivatives 4 > 1,3-thiazolone derivatives 10. So cytotoxicity of thiazole derivatives 4a > 10a, 4c > 10c and 4d > 10d.

**Materials and methods**

**Chemistry**

Melting points were measured on an Electrothermal 1A 9000 series digital melting point apparatus (Bibby Sci. Lim. Stone, Staffordshire, UK). IR spectra were recorded in potassium bromide disks on PyeUnicam SP 3300 and Shimadzu FTIR 8101PC infrared spectrophotometers (Shimadzu, Tokyo, Japan). NMR spectra were measured on a Varian Mercury VX-300 NMR spectrometer (Varian, Inc., Karlsruhe, Germany). 1HNMR spectra were recorded at 300 MHz in deuterated dimethyl sulfoxide (DMSO-d6). Mass spectra were run on a Shimadzu GCMS-QP1000 EX mass spectrometer (Tokyo, Japan) at 70 eV. Elemental analyses were measured using a German made Elementalvario LIII CHNS analyzer. Antitumor activity of the products was measured at the Regional Center for Mycology and Biotechnology at Al-Azhar University, Cairo, Egypt.

**General procedure for synthesis of thiazole derivatives 4a–f, 8a–e, 10a–d, and 12a–e method A**

A mixture of 1-(4-methyl-2-(2-(1-(thiophen-2-yl)ethylidene)hydrazinyl)thiazol-5-yl) ethanone (1) (0.279 g, 1 mmol), thiosemicarbazide 2 (0.091 g, 1 mmol) or thiocarbohydrazide 7 (0.106 g, 1 mmol) and the appropriate hydrazonoyl chlorides 3a–g or 9a–e (1 mmol) in dioxane (20 mL) containing catalytic amounts of TEA, was refluxed for 2–4 h (monitored by TLC). The formed precipitate was isolated by filtration, washed with methanol, dried and recrystallized from appropriate solvent to give products 4a–f, 8a–e, 10a–d, and 12a–e, respectively.

**Method B**

Repetition of the same reactions of method A with heating in microwave oven at 500 W and 150°C for 4–8 min, gave products identical in all respects with those separated from method A. The spectral data and physical properties of the obtained products 4a–f, 8a–e, 10a–d, and 12a–e are listed below.

4-Methyl-2-(2-(1-(4-methyl-2-(2-(1-(thiophen-2-yl)ethylidene)hydrazinyl)thiazol-5-yl)ethylidene)-hydrazinyl)-5-(phenyldiazenyl)thiazole (4a)

Dark brown solid, m.p. 170-172°C (EtOH); IR (KBr): ν 3434-3213 (2NH), 1592 (C¼N) cm⁻¹; ¹H-NMR (DMSO-d6): δ 2.08 (s, 3H, CH₃), 2.15 (s, 3H, CH₃), 2.20 (s, 3H, CH₃), 2.35 (s, 3H, CH₃), 6.97-8.01 (m, 8H, Ar-H), 10.57 (brs, 1H, NH), 11.20 (brs, 1H, NH); MS m/z (%): 495 (M⁺+1, 1), 494 (M⁺, 2), 396 (51), 382 (19), 341 (32), 313 (69), 289 (5), 256 (33), 202 (18), 187 (15), 153 (8), 139 (11), 118 (30), 77 (100), 71 (67). Anal. Calcd for C₂₂H₂₂N₈S₃ (494.66): C, 53.42; H, 4.48; N, 22.65. Found: C, 53.33; H, 4.56; N, 22.49%.

4-Methyl-2-(2-(1-(4-methyl-2-(2-(1-(thiophen-2-yl)ethylidene)hydrazinyl)thiazol-5-yl)ethylidene)-hydrazinyl)-5-(p-tolyldiazenyl)thiazole (4b)

Red solid, m.p. 188-190°C (DMF); IR (KBr): ν 3424-3206 (2NH), 1600 (C¼N) cm⁻¹; ¹H-NMR (DMSO-d₆): δ 2.10 (s, 3H, CH₃), 2.27 (s, 3H, CH₃), 2.27 (s, 3H, CH₃), 2.34 (s, 3H, CH₃), 2.56 (s,
3H, CH₃), 6.80-7.99 (m, 7H, Ar-H), 9.28 (br s, 1H, NH), 10.82 (br s, 1H, NH); MS m/z (%): 509 (M⁺+1, 1), 508 (M⁺, 1), 487 (31), 385 (63), 376 (56), 327 (64), 289 (48), 216 (27), 139 (50), 91 (100), 71 (49). Anal. Calcd for C₂₂H₂₄N₈S₃ (508.69): C, 54.31; H, 4.76; N, 22.03. Found: C, 54.42; H, 4.66; N, 22.21%.

(4-Chlorophenyl)diazenyl)-4-methyl-2-(2-(1-(4-methyl-2-(2-(1-(thiophen-2-yl)ethylidene)hydrazinyl)thiazol-5-yl)ethylidene)hydrazinyl)thiazole (4c)
Red solid, m.p. 215-217°C (DMF); IR (KBr): v 3423-3251 (2NH), 1600 (C¼N) cm⁻¹; ¹H-NMR (DMSO-d₆): δ 2.12 (s, 3H, CH₃), 2.18 (s, 3H, CH₃), 2.27 (s, 3H, CH₃), 2.42 (s, 3H, CH₃), 7.09-8.13 (m, 7H, Ar-H), 10.62 (brs, 1H, NH), 11.154 (brs, 1H, NH); MS m/z (%): 531 (M⁺+2, 1), 529 (M⁺, 2), 528 (M⁺-1, 4), 468 (31), 405 (18), 377 (52), 359 (52), 289 (65), 252 (58), 221 (20), 152 (39), 127 (99), 111 (100), 97 (43), 71 (60). Anal. Calcd for C₂₂H₂₁ClN₈S₃ (529.10): C, 49.94; H, 4.00; N, 21.18. Found: C, 49.84; H, 4.21; N, 21.05%.

4-Methyl-2-(2-(1-(4-methyl-2-(2-(1-(thiophen-2-yl)ethylidene)hydrazinyl)thiazol-5-yl)ethylidene)-hydrazinyl)-5-((4-nitrophenyl)diazenyl)thiazole (4d)
Red solid, m.p. 166-168°C (EtOH); IR (KBr): v 3426-3194 (2NH), 1589 (C¼N) cm⁻¹; ¹H-NMR (DMSO-d₆): δ 2.28 (s, 3H, CH₃), 2.33 (s, 3H, CH₃), 2.40 (s, 3H, CH₃), 2.47 (s, 3H, CH₃), 7.06-8.21 (m, 7H, Ar-H), 10.31 (brs, 1H, NH), 11.28 (brs, 1H, NH); MS m/z (%): 540 (M⁺+1, 0.21), 539 (M⁺, 0.32), 470 (3), 432 (2), 400 (11), 388 (53), 345 (43), 328 (26), 303 (44), 277 (12), 249 (47), 205 (33), 180 (96), 136 (43), 110 (100), 90 (63), 71 (49). Anal. Calcd for C₂₂H₂₁N₉O₂S₃ (539.66): C, 48.96; H, 3.92; N, 23.36. Found: C, 48.85; H, 3.74; N, 23.50%.

5-((2,4-Dichlorophenyl)diazenyl)-4-methyl-2-(2-(1-(4-methyl-2-(2-(1-(thiophen-2-yl)ethylidene)hydrazinyl)thiazol-5-yl)ethylidene)hydrazinyl)thiazole (4e)
Dark brown solid, m.p. 210-212°C (DMF); IR (KBr): v 3417-3202 (2NH), 1601 (C¼N) cm⁻¹; ¹H-NMR (DMSO-d₆): δ 2.10 (s, 3H, CH₃), 2.23 (s, 3H, CH₃), 2.27 (s, 3H, CH₃), 2.58 (s, 3H, CH₃), 7.10-8.23 (m, 6H, Ar-H), 10.32 (brs, 1H, NH), 11.62 (brs, 1H, NH); MS m/z (%): 564 (M⁺+1, 1), 563 (M⁺, 5), 442 (21), 431 (61), 393 (24), 367 (52), 360 (24), 313 (55), 299 (63), 278 (62), 239 (48), 186 (63), 161 (69), 124 (83), 110 (87), 71 (78), 57 (100). Anal. Calcd for C₂₂H₂₀Cl₂N₈S₃ (563.55): C, 48.69; H, 3.92; N, 23.36. Found: C, 48.85; H, 3.74; N, 23.50%.

4-Methyl-2-((1-(4-methyl-2-(2-(1-(thiophen-2-yl)ethylidene)hydrazinyl)thiazol-5-yl)ethylidene)-hydrazono)-5-(phenyldiazenyl)thiazol-3(2H)-amine (8a)
Dark brown solid, m.p. 210-212°C (DMF); IR (KBr): v 3387, 3163 (NH₂ and NH), 1597 (C¼N) cm⁻¹; ¹H-NMR (DMSO-d₆): δ 2.32 (s, 3H, CH₃), 2.42 (s, 3H, CH₃), 2.46 (s, 3H, CH₃), 3.06 (brs, 2H, NH₂), 7.07-8.03 (m, 8H, Ar-H), 11.20 (brs, 1H, NH); MS m/z (%): 509
4-Methyl-2-((1-(4-methyl-2-(2-(1-(thiophen-2-yl)ethylidene)hydrazinyl)thiazol-5-yl)ethylidene)hydrazono)-5-(p-tolyldiazenyl)thiazol-3(2H)-amine (8b)
Brown solid, m.p. 120-122 °C (DMF); IR (KBr): ν 3371-3163 (NH₂ and NH), 1597 (C=N) cm⁻¹; ¹H-NMR (DMSO-d₆): δ 2.09 (s, 3H, CH₃), 2.28 (s, 3H, CH₃), 2.34 (s, 3H, CH₃), 2.42 (s, 3H, CH₃), 2.54 (s, 3H, CH₃), 3.05 (brs, 2H, NH₂), 7.03-7.48 (m, 7H, Ar-H), 11.21 (brs, 1H, NH); MS m/z (%): 523 (M⁺, 38). Anal. Calcd for C₂₃H₂₅N₉S₃ (523.70): C, 52.75; H, 4.81; N, 24.07. Found: C, 52.62; H, 4.69; N, 24.03%.

5-((4-Chlorophenyl)diazenyl)-4-methyl-2-((1-(4-methyl-2-(2-(1-(thiophen-2-yl)ethylidene)hydrazinyl)thiazol-5-yl)ethylidene)hydrazono)thiazol-3(2H)-amine (8c)
Red solid, m.p. 118-120 °C (DMF); IR (KBr): ν 3340, 3155 (NH₂ and NH), 1597 (C=N) cm⁻¹; ¹H-NMR (DMSO-d₆): δ 2.10 (s, 3H, CH₃), 2.29 (s, 3H, CH₃), 2.42 (s, 3H, CH₃), 2.59 (s, 3H, CH₃), 3.05 (brs, 2H, NH₂), 7.07-8.01 (m, 7H, Ar-H), 11.10 (brs, 1H, NH); MS m/z (%): 546 (M⁺+2, 7), 544 (M⁺, 22). Anal. Calcd for C₂₂H₂₂ClN₉S₃ (544.12): C, 48.56; H, 4.08; N, 23.17. Found: C, 48.42; H, 4.01; N, 23.04%.

4-Methyl-2-((1-(4-methyl-2-(2-(1-(thiophen-2-yl)ethylidene)hydrazinyl)thiazol-5-yl)ethylidene)hydrazono)-5-((4-nitrophenyl)diazenyl)thiazol-3(2H)-amine (8d)
Brown solid, m.p. 166-168 °C (DMF); IR (KBr): ν 3332, 3186 (NH₂ and NH), 1597 (C=O) cm⁻¹; ¹H-NMR (DMSO-d₆): δ 2.31 (s, 3H, CH₃), 2.34 (s, 3H, CH₃), 2.39 (s, 3H, CH₃), 2.63 (s, 3H, CH₃), 3.08 (brs, 2H, NH₂), 7.06-8.45 (m, 7H, Ar-H), 11.27 (brs, 1H, NH); MS m/z (%): 554 (M⁺, 7). Anal. Calcd for C₂₂H₂₂N₁₀O₂S₃ (554.67): C, 47.64; H, 4.00; N, 25.25. Found: C, 47.49; H, 3.86; N, 25.15%.

5-((4-Methoxyphenyl)diazenyl)-4-methyl-2-((1-(4-methyl-2-(2-(1-(thiophen-2-yl)ethylidene)hydrazinyl)thiazol-5-yl)ethylidene)hydrazono)thiazol-3(2H)-amine (8e)
Dark brown solid, m.p. 160-162 °C (DMF); IR (KBr): ν 3464, 3179, 3163 (NH₂ and NH), 1597 (C=O) cm⁻¹; ¹H-NMR (DMSO-d₆): δ 2.25 (s, 3H, CH₃), 2.31 (s, 3H, CH₃), 2.44 (s, 3H, CH₃), 2.54 (s, 3H, CH₃), 3.57 (brs, 2H, NH₂), 3.78 (s, 3H, OCH₃), 6.99-7.83 (m, 7H, Ar-H), 11.33 (brs, 1H, NH); MS m/z (%): 539 (M⁺+, 55). Anal. Calcd for C₂₃H₂₅N₉OS₃ (539.70): C, 51.19; H, 4.67; N, 23.36. Found: C, 51.28; H, 4.63; N, 23.19%.

2-(2-(1-(4-Methyl-2-(2-(1-(thiophen-2-yl)ethylidene)hydrazinyl)thiazol-5-yl)ethylidene)hydrazinyl)-5-(2-phenylhydrazono)thiazol-4(5H)-one (10a)
Dark yellow crystal, m.p. 155-157 °C (DMF); IR (KBr): ν 3390-3208 (3NH), 1716 (C=O), 1593 (C=O) cm⁻¹; ¹H-NMR (DMSO-d₆): δ 2.15 (s, 3H, CH₃), 2.31 (s, 3H, CH₃), 2.45 (s, 3H, CH₃), 6.94-8.12 (m, 8H, Ar-H), 10.48 (brs, 1H, NH), 10.82 (brs, 1H, NH), 11.06 (brs, 1H, NH); MS m/z (%): 497 (M⁺+1, 1), 496 (M⁺, 2), 451 (17), 367 (31), 343 (44), 299 (74), 232 (31), 187 (61), 135 (19), 110 (73), 77 (100). Anal. Calcd for C₂₁H₂₀N₈O₃S (496.63): C, 50.79; H, 4.06; N, 22.56. Found: C, 50.68; H, 4.18; N, 22.65%. 
2-(2-(1-(4-Methyl-2-(2-(1-(thiophen-2-yl)ethylidene)hydrazinyl)thiazol-5-yl)ethylidene)hydrazinyl)-5-(2-(p-tolyl)hydrazono)thiazol-4(5H)-one (10b)

Dark yellow solid, m.p. 135-137°C (DMF); IR (KBr): υ 3428-3218 (3NH), 1710 (C=O), 1606 (C=NH) cm⁻¹; ¹H-NMR (DMSO-d₆): δ 2.09 (s, 3H, CH₃), 2.27 (s, 3H, CH₃), 2.30 (s, 3H, CH₃), 2.36 (s, 3H, CH₃), 6.94-8.18 (m, 7H, Ar-H), 10.38 (br s, 1H, NH), 10.77 (br s, 1H, NH), 11.28 (br s, 1H, NH); MS m/z (%): 511 (M⁺+1, 1), 510 (M⁺+1, 2), 431 (41), 387 (32), 369 (34), 357 (46), 303 (34), 285 (57), 263 (46), 215 (67), 182 (21), 166 (52), 140 (23), 124 (65), 110 (100), 69 (58). Anal. Calcd for C₁₄H₂₂N₈O₃S₃ (510.66): C, 51.74; H, 4.34; N, 21.94%. Found: C, 51.68; H, 4.52; N, 21.85%.

5-(2-(4-Chlorophenyl)hydrazono)-2-(2-(1-(4-methyl-2-(2-(1-(thiophen-2-yl)ethylidene)hydrazinyl)thiazol-5-yl)ethylidene)hydrazinyl)thiazol-4(5H)-one (10c)

Brown solid, m.p. 160-162°C (DMF); IR (KBr): υ 3418-3206 (3NH), 1709 (C=O), 1599 (C=NH) cm⁻¹; ¹H-NMR (DMSO-d₆): δ 2.12 (s, 3H, CH₃), 2.28 (s, 3H, CH₃), 2.47 (s, 3H, CH₃), 7.05-8.22 (m, 7H, Ar-H), 10.33 (br s, 1H, NH), 10.65 (br s, 1H, NH), 11.16 (br s, 1H, NH); MS m/z (%): 533 (M⁺+2, 1), 532 (M⁺+1, 1), 531 (M⁺, 3), 494 (31), 386 (42), 333 (53), 305 (58), 278 (35), 233 (28), 194 (78), 139 (58), 127 (100), 97 (37), 71 (40). Anal. Calcd for C₂₁H₁₉ClN₈O₃S₃ (531.08): C, 47.49; H, 3.61; N, 21.10. Found: C, 47.55; H, 3.80; N, 21.22%.

2-(2-(1-(4-Methyl-2-(2-(1-(thiophen-2-yl)ethylidene)hydrazinyl)thiazol-5-yl)ethylidene)hydrazinyl)-5-(2-(4-nitrophenyl)hydrazono)thiazol-4(5H)-one (10d)

Dark brown solid, m.p. 220-222°C (DMF); IR (KBr): υ 3427-3202 (3NH), 1717 (C=O), 1594 (C=NH) cm⁻¹; ¹H-NMR (DMSO-d₆): δ 2.08 (s, 3H, CH₃), 2.26 (s, 3H, CH₃), 2.39 (s, 3H, CH₃), 7.07-8.35 (m, 7H, Ar-H), 10.33 (br s, 1H, NH), 10.65 (br s, 1H, NH), 11.16 (br s, 1H, NH); MS m/z (%): 542 (M⁺+1, 3), 541 (M⁺, 5), 470 (28), 398 (33), 358 (52), 276 (37), 215 (38), 205 (51), 165 (100), 136 (78), 115 (49), 97 (23), 71 (63). Anal. Calcd for C₂₁H₁₉N₉O₃S₃ (541.63): C, 46.57; H, 3.54; N, 23.27. Found: C, 46.36; H, 3.65; N, 23.46%.

3-Amino-2-((1-(4-methyl-2-(2-(1-(thiophen-2-yl)ethylidene)hydrazinyl)thiazol-5-yl)ethylidene)hydrazono)-5-(2-phenylhydrazono)thiazolidin-4-one (12a)

Dark brown solid, m.p. 126-128°C (DMF); IR (KBr): υ 3379-3178 (NH₂ and 2NH), 1712 (C=O), 1604 (C=NH) cm⁻¹; ¹H-NMR (DMSO-d₆): δ 2.19 (s, 3H, CH₃), 2.35 (s, 3H, CH₃), 2.63 (s, 3H, CH₃), 3.56 (br s, 2H, NH₂), 6.96-8.00 (m, 8H, Ar-H), 8.73 (br s, 1H, NH), 10.86 (br s, 1H, NH); MS m/z (%): 511 (M⁺, 8). Anal. Calcd for C₂₁H₂₁N₉O₃S₃ (511.65): C, 49.30; H, 4.14; N, 24.64. Found: C, 49.14; H, 4.05; N, 24.41%.

3-Amino-2-((1-(4-methyl-2-(2-(1-(thiophen-2-yl)ethylidene)hydrazinyl)thiazol-5-yl)ethylidene)hydrazono)-5-(2-phenylhydrazono)thiazolidin-4-one (12b)

Dark brown solid, m.p. 182-184°C (DMF); IR (KBr): υ 3410-3171 (NH₂ and 2NH), 1705 (C=O), 1597 (C=NH) cm⁻¹; ¹H-NMR (DMSO-d₆): δ 2.27 (s, 3H, CH₃), 2.33 (s, 3H, CH₃), 2.36 (s, 3H, CH₃), 2.39 (s, 3H, CH₃), 2.54 (br s, 2H, NH₂), 7.08-7.93 (m, 7H, Ar-H), 8.93 (br s, 1H, NH), 10.89 (br s, 1H, NH); MS m/z (%): 525 (M⁺, 27). Anal. Calcd for C₂₂H₂₃N₉O₃S₃ (525.67): C, 50.27; H, 4.41; N, 23.98. Found: C, 50.14; H, 4.47; N, 23.76%.
3-Amino-5-(2-(4-chlorophenyl)hydrazono)-2-((1-(4-methyl-2-(1-(thiophen-2-yl)ethylidene)hydrazinyl)thiazol-5-yl)ethylidene)hydrazono)thiazolidin-4-one (12c)

Brown solid, m.p. 140-142°C (DMF); IR (KBr): ν 3464-3170 (NH₂ and 2NH), 1720 (C=O), 1597 (C=O) cm⁻¹; ¹H-NMR (DMSO-d₆): δ 2.15 (s, 3H, CH₃), 2.34 (s, 3H, CH₃), 2.42 (s, 3H, CH₃), 3.62 (br.s, 2H, NH₂), 7.06-7.90 (m, 7H, Ar-H), 9.17 (br.s, 1H, NH), 10.92 (br.s, 1H, NH); MS m/z (%): 548 (M⁺+2, 4), 546 (M⁺, 13). Anal. Calcd for C₂₁H₂₀ClN₉OS₃ (546.09): C, 46.19; H, 3.69; N, 23.08. Found: C, 46.04; H, 3.50; N, 23.01%.

3-Amino-2-((1-(4-methyl-2-(2-(1-(thiophen-2-yl)ethylidene)hydrazinyl)thiazol-5-yl)ethylidene)hydrazono)-5-(2-(4-nitrophenyl)hydrazono)thiazolidin-4-one (12d)

Brown solid, m.p. 200-202°C (DMF); IR (KBr): ν 3379-3163 (NH₂ and 2NH), 1705 (C=O), 1597 (C=N) cm⁻¹; ¹H-NMR (DMSO-d₆): δ 2.30 (s, 3H, CH₃), 2.36 (s, 3H, CH₃), 2.43 (s, 3H, CH₃), 3.50 (br.s, 2H, NH₂), 7.10-8.43 (m, 7H, Ar-H), 9.83 (br.s, 1H, NH), 11.06 (br.s, 1H, NH); MS m/z (%): 556 (M⁺, 45). Anal. Calcd for C₂₁H₂₀N₁₀O₃S₃ (556.64): C, 45.31; H, 3.62; N, 25.16. Found: C, 45.46; H, 3.47; N, 25.00%.

3-Amino-5-(2-(4-bromophenyl)hydrazono)-2-((1-(4-methyl-2-(2-(1-(thiophen-2-yl)ethylidene)hydrazinyl)thiazol-5-yl)ethylidene)hydrazono)thiazolidin-4-one (12e)

Dark brown solid, m.p. 162-164°C (DMF); IR (KBr): ν 3340-3209 (NH₂ and 2NH), 1720 (C=O), 1597 (C=N) cm⁻¹; ¹H-NMR (DMSO-d₆): δ 2.08 (s, 3H, CH₃), 2.34 (s, 3H, CH₃), 2.46 (s, 3H, CH₃), 3.57 (br.s, 2H, NH₂), 7.07-7.80 (m, 7H, Ar-H), 8.93 (br.s, 1H, NH), 11.06 (br.s, 1H, NH); MS m/z (%): 592 (M⁺+2, 19), 590 (M⁺, 21). Anal. Calcd for C₂₁H₂₀BrN₉OS₃ (590.54): C, 42.71; H, 3.41; N, 21.35. Found: C, 42.80; H, 3.22; N, 21.16%.

Alternate synthesis for 4a and 10a

Synthesis of 2-(1-(4-methyl-2-(2-(1-(thiophen-2-yl)ethylidene)hydrazinyl)thiazol-5-yl)ethylidene)hydrazincarbothioamide (5).

A mixture of 1-(4-methyl-2-(2-(1-(thiophen-2-yl)ethylidene)hydrazinyl)ethanone (1) (2.79 g, 10 mmol) and thiosemicarbazide (2) (0.91 g, 10 mmol) in EtOH (20 mL) containing catalytic amounts of HCl, was heated in microwave oven at 500 W and 150°C for 3 min. The formed precipitate was isolated by filtration, washed with methanol, dried and recrystallized from dioxane to give thiosemicarbazone derivative 5 as yellow solid, 80% yield, m.p. 162-164°C (DMF); IR (KBr): ν 3340-3209 (NH₂ and 2NH), 1705 (C=O), 1597 (C=N) cm⁻¹; ¹H-NMR (DMSO-d₆): δ 2.33 (s, 3H, CH₃), 2.37 (s, 3H, CH₃), 2.39 (s, 3H, CH₃), 7.07-7.80 (m, 7H, Ar-H), 8.93 (br.s, 1H, NH), 10.89 (br.s, 1H, NH); MS m/z (%): 354 (M⁺+1, 2), 353 (M⁺, 1), 281 (47), 239 (67), 199 (58), 155 (66), 140 (70), 124 (22), 101 (32), 83 (45), 57 (100). Anal. Calcd for C₁₃H₁₆N₆S₃ (352.50): C, 44.29; H, 4.58; N, 23.84. Found: C, 44.33; H, 4.45; N, 23.65%.

Reaction of 5 with hydrazonoyl chlorides 3a and 9a.

A mixture of thiosemicarbazone derivative (5) (2.79 g, 10 mmol) and the appropriate 2-oxo-N'-phenylpropanehydrazonoyl chloride (3a) or ethyl 2-chloro-2-(2-phenylhydrazono)acetate (9a) (1 mmol) in dioxane (20 mL) containing catalytic amount of HCl was heated in microwave oven at 500 W and 150°C for 6 min. (monitored by TLC). The formed precipitate was isolated by filtration, washed with methanol, dried and recrystallized from dioxane to give product proved to be identical in all respects (m.p., mixed mp and IR spectra) with the products 4a or 10a which obtained from reaction of 1 + 2 + 3a or 1 + 2 + 9a, respectively.
Anticancer activity

The cytotoxic potential of the newly synthesized compounds was examined against MCF-7 cells using the MTT assay after 24 h of incubation. For more details, see the supporting information file.44

Conclusion

We have reported the synthesis, spectral studies and preliminary in vitro anti-tumor activity of a novel series of 5-(1-(2-(thiazol-2-yl)hydrazono)ethyl)thiazole derivatives in a one-pot three-component reaction under conventional and microwave irradiation utilizing 1-(4-methyl-2-(2-(1-(thiophen-2-yl)ethylidene)hydrazinyl)thiazol-5-yl)ethanone as building block. It was found that the products were obtained in higher yield in case of using microwave irradiation compared with conventional heating. Also, the reaction time was reduced when using microwave irradiation, making this methodology much more convenient than the conventional methodology. The structures of the newly synthesized compounds were established on the basis of spectroscopic evidences and their synthesis by alternative methods. The in vitro growth inhibitory activity of the synthesized compounds against MCF-7 tumor cells were investigated in comparison with vincristine sulfate and cisplatin reference drugs using MTT assay and the results revealed promising activities of five compounds.

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