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Synthesis of novel 1,2,4-triazoles and triazolo-thiadiazines as anticancer agents

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Abstract: A new series of 7-arylazo-5*H*-3-(trifluoromethyl)-6-methyl-1,2,4-triazolo-[3,4-*b*]-1,3,4-thiadiazines was prepared by reaction of 4-amino-3-trifluoromethyl-5-mercapto-1,2,4-triazoles with *N*-aryl-2-oxo-propane hydrazonoyl chloride in dioxane under reflux in the presence of triethylamine. Furthermore, Schiff bases of 4-amino-5-mercapto-1,2,4-triazole derivatives were reacted with a variety of hydrazonoyl chlorides and gave the respective hydrazonothioates. In addition, the novel *bis*-(1,2,4-triazole-3-thione) was reacted with the appropriate hydrazonoyl chloride in dioxane under reflux in the presence of triethylamine to give the corresponding *bis*-(1,2,4-triazolethiohydrazonoate). The structures of the new compounds were established based on elemental and spectral data. The mechanism of the studied reaction was also discussed. Moreover, some of the new products were screened for their anticancer activity and the results obtained are promising and indicate that compounds **4a** and **4i** are the most active inhibitors against HEPG-2 and compounds **4a** and **13b** are active against HCT cell lines.

Key words: 4-Amino-3-trifluoromethyl-5-mercapto-1,2,4-triazole, hydrazonoyl halides, anticancer activity, triazolo[3,4-*b*][1,3,4]thiadiazines

1. Introduction

4-Amino-5-mercapto-1,2,4-triazole derivative is a readymade building block for construction of various organic heterocycles since they contain two nucleophilic groups, amino and thiol groups. On the other hand, Schiff bases of 1,2,4-triazoles find diverse applications and extensive biological activity. For example, Schiff bases derived from 3-substituted-4-amino-5-mercapto-1,2,4-triazoles show analgesic, antimicrobial, anti-inflammatory, antiproliferative, and antidepressant activities.[1,2]

On the other hand, 4-amino-5-mercapto-1,2,4-triazoles react with different types of hydrazonoyl halides to give a wide variety of fused 1,2,4-triazoles.[3–5] Moreover, the fluorine substituent in the heterocyclic compounds improves their biological activities.[6,7] From all the above findings and in continuation of our previous work on hydrazonoyl halides,[8–15] we were interested in studying the reaction of hydrazonoyl halides with 4-amino-3-trifluoromethyl-5-mercapto-1,2,4-triazoles and the respective Schiff bases. Our objective after such a study was to shed some light on the site-selectivity of such reactions and also to test the biological activity of the products against HPG-2 and HCT cancer cell lines.

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2. Results and discussion

2.1. Chemistry

The required starting material, namely 4-amino-3-trifluoromethyl-5-mercapto-1,2,4-triazole **1**, was prepared as previously reported.[6] Thus, the reaction of trifluoroacetic acid hydrazide with carbon disulfide in alcoholic solution of potassium hydroxide gave potassium trifluoroacetyldithiocarbazate, which upon refluxing with hydrazine hydrate produced 4-amino-5-trifluoromethyl-4*H*-1,2,4-triazole-3-thiol **1**.[6] Reaction of **1** with *N*-aryl-2-oxopropanehydrazonoyl chloride **2** in dioxane under reflux in the presence of triethylamine afforded in each case one isolable product as evidenced by TLC analysis (Figure 1). The products were assigned structure **4** or **7** rather than structure **6** since they were free of sulfur. Moreover, elemental analysis and spectral data are in agreement with structure **4** rather than structure **7**. For example, IR spectra of the products revealed in each case the absence of the NH_2 group, the acetyl carbonyl group, and the C=S group and at the same time showed only absorption bands at 3439–3317 cm^{-1}, which were assigned to the hydrazone NH group. The ^{1}H NMR spectra revealed a singlet signal at δ 11.02–10.29 ppm assigned to the hydrazone NH proton, in addition to the expected signals for the methyl and aromatic protons. The mass spectra revealed in each case a molecular ion peak corresponding to elimination of water molecule from intermediate **3**, and in agreement with the molecular formula of the products **4**. In addition, the electronic absorption spectra of compounds **4a**–**j** in dioxane revealed in each case two characteristic absorption bands in the regions λ_{max} 386–357 and 277–244 nm (Table 1). Such an absorption pattern is similar to that of typical hydrazone chromophore **4A**.[9]

Table 1. UV spectral data of compounds **4a**–**j** in dioxane.

Compd. no.	λ_{max} (log ε)
4a	385 (4.56), 275 (5.09)
4b	357 (6.45), 244 (6.17)
4c	377(5.34), 251 (5.75)
4d*	374 (6.35), 246 (6.36)
4e	370 (5.57), 256 (5.83)
4f	370 (6.07), 246 (6.06)
4g	363 (5.45), 253 (5.91)
4h	386 (5.30), 244 (5.40)
4i	378 (5.39), 277 (5.33)
4j	375 (5.70), 277 (5.60)

* Solvent λ_{max} (log ε): chloroform: 376 (6.09), 244 (6.23); ethanol: 383 (5.55), 225 (5.52); DMF 359 (4.17), 304 (4.60).

Our study was extended to examine the chemical reactivity of Schiff bases of 4-amino-5-mercapto-1,2,4-triazole derivative **1** towards a variety of hydrazonoyl halides **2**. The Schiff bases **8** were prepared as previously reported by reaction of triazole derivative **1** with the appropriate aromatic aldehyde[16,17] under reflux for 5 h in glacial acetic acid. Products **8** in turn reacted with hydrazonoyl halides **2** in dioxane under reflux to give the intermediate thiohydrazonoate ester **9** (Figure 2). The other isomeric structures *N*-triazolyltriazoles **10** and **11** were discarded based on IR and ^{1}H NMR spectral data. For example, the IR spectra of products **9** revealed the absence of the absorption band of the SH group at 2500–2600 cm^{-1} and revealed the presence of an absorption band near 3430 cm^{-1} assigned to the NH group.[18] The ^{1}H NMR spectra of the products **9** exhibited in each case a singlet signal at δ 8.07–9.48 ppm characteristic for the azomethine–N=CH– protons, which is similar to compound **I**[2,19,20] and differ from the CH triazoles types **II** and **III**[21–24] (Figure 3). More

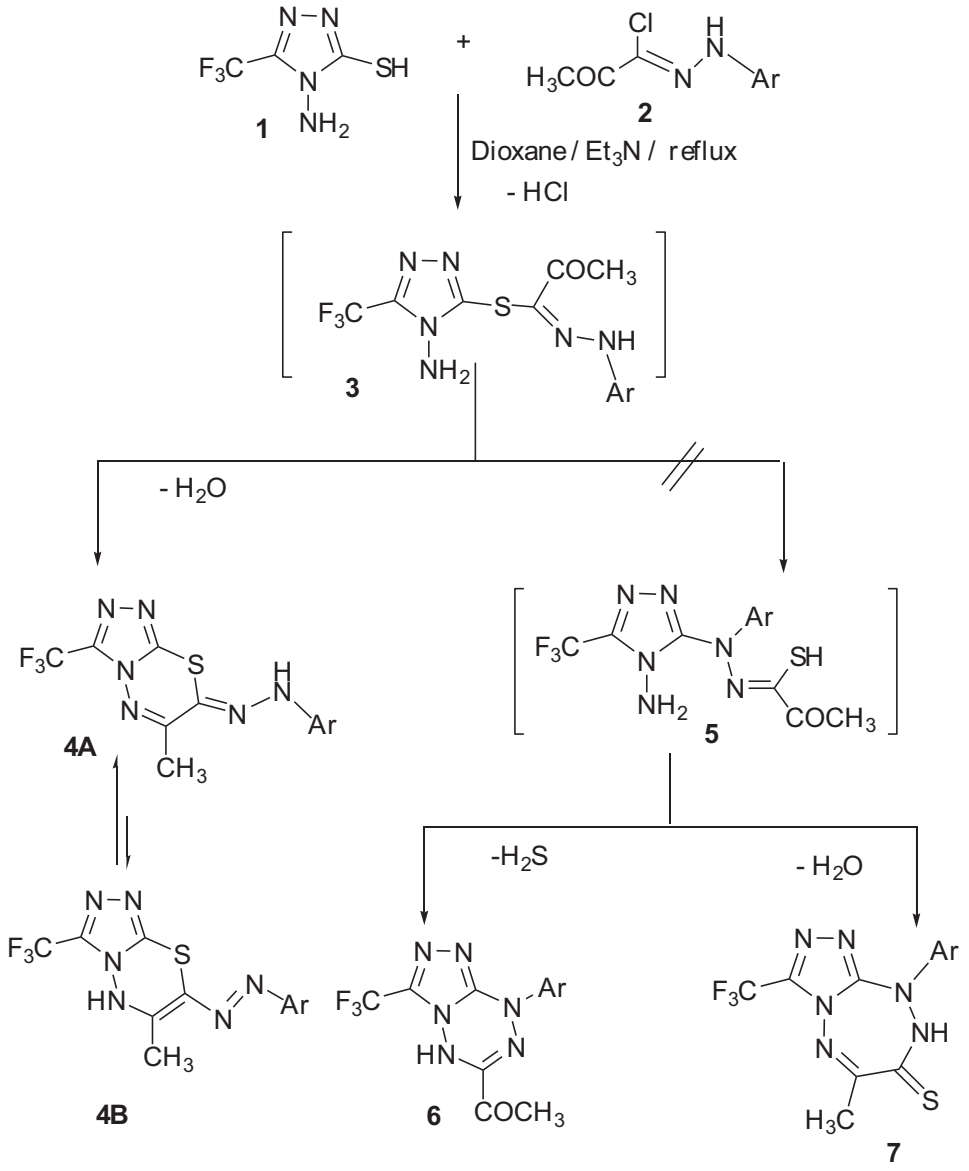
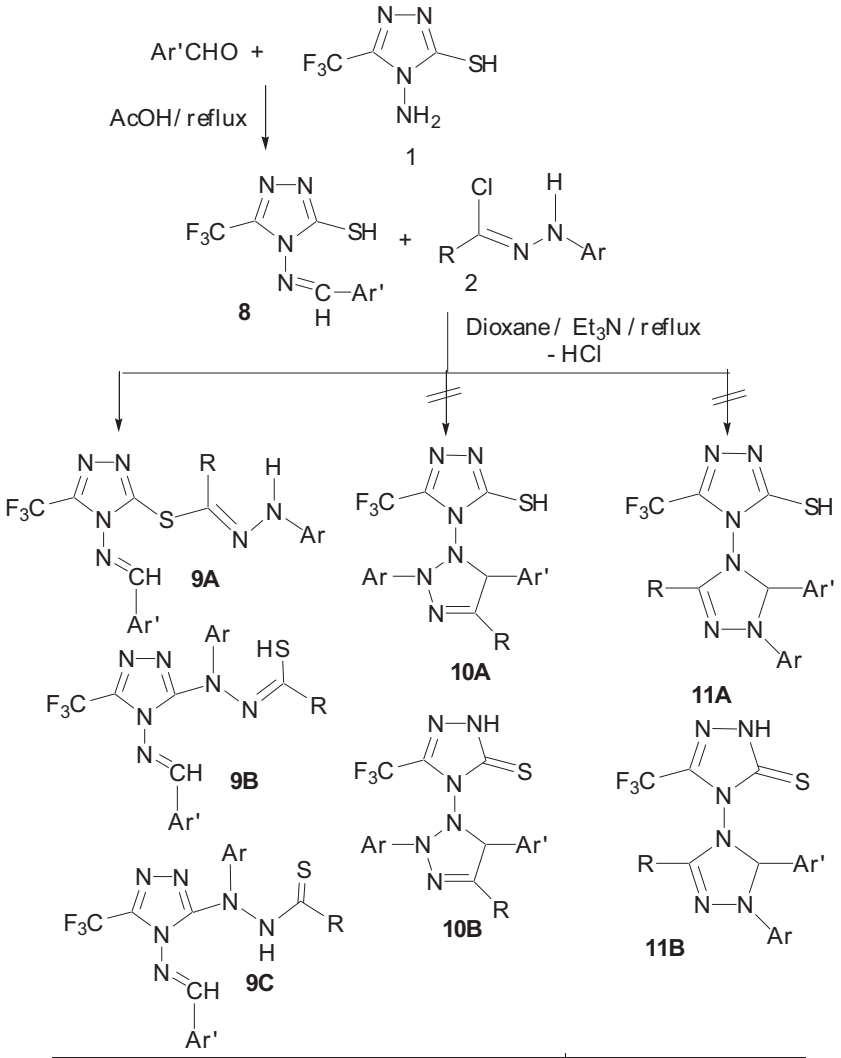


Figure 1. Synthesis of compounds **4a**–**j**.

evidence for the elucidation of the structure **9** rather than **10** or **11** is the ^{13}C NMR of the isolated products. As shown in Figure 3, the ^{13}C NMR of compounds **9a** and **9k** revealed the absence of the signals of the C-3 or C-4 for the triazoles **II** or **III**,[23–25] which are similar to compounds **10** and **11** in Scheme 2. Instead the ^{13}C NMR of compounds **9a** and **9k** showed signals at 150.4 ppm and 150.1 ppm, respectively. Furthermore, the ^{13}C NMR spectra of the products **9a** and **9k** supported the assigned structure **9A** for the isolated products, which revealed the absence of a thiohydrazide carbon (N–C=S) signal near δ 170–180 ppm and the presence

of a signal near δ 141–142 ppm due to the carbon atom of the –S–C=N–NH– group.[26–28] All the above data proved that the isolated products have structure **9A**.



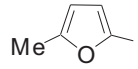
Comp. No.	R	Ar	Ar'
9a	MeCO	Ph	Ph
9b	MeCO	4-MeC_6H_4	Ph
9c	MeCO	4-ClC_6H_4	Ph
9d	MeCO	4-$NO_2C_6H_4$	Ph
9e	EtOCO	Ph	Ph
9f	EtOCO	4-MeC_6H_4	Ph
9g	EtOCO	4-ClC_6H_4	Ph
9h	EtOCO	4-$NO_2C_6H_4$	Ph
9i	MeCO	Ph	3,4-$(MeO)_2C_6H_3$
9j	EtOCO	Ph	3,4-$(MeO)_2C_6H_3$
9k	Ph	Ph	3,4-$(MeO)_2C_6H_3$
9l	EtOCO	Ph	

Figure 2. Synthesis of compounds **9a**–**l**.

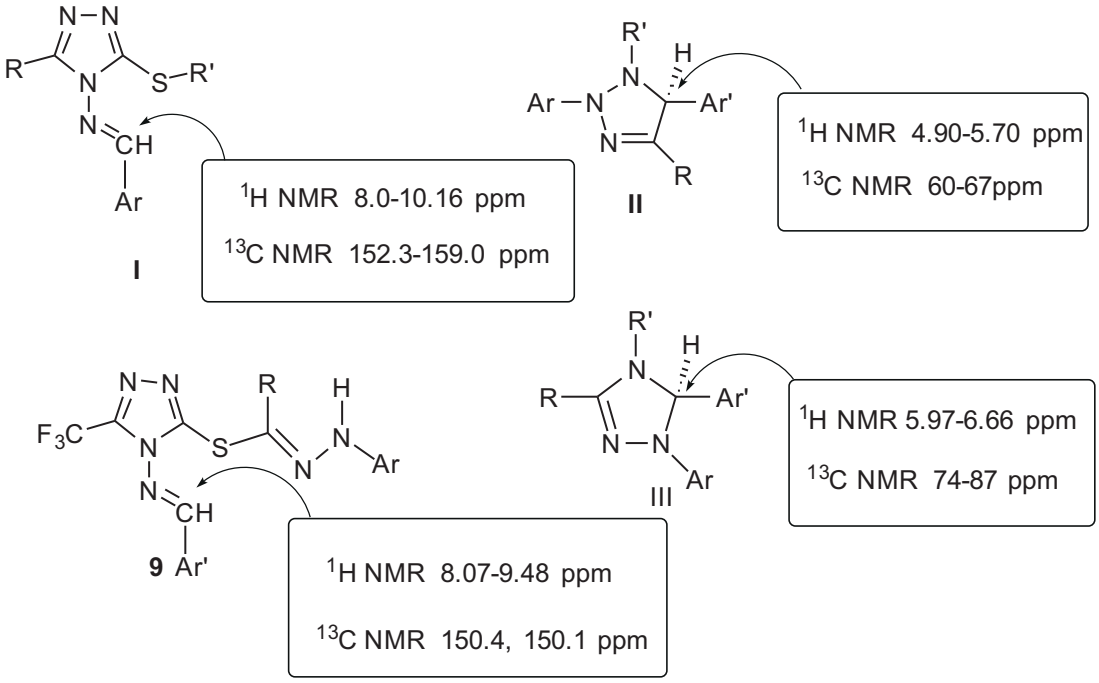


Figure 3. ^{1}H and ^{13}C NMR of compounds **I**–**III** and **9**.

In order to increase the biological activity of triazole derivatives, we also synthesized a new symmetric dimeric derivative, namely 1,4-*bis*(iminomethyl-3-trifluoromethyl-5-mercapto-1,2,4-triazole-4-benzene **12**. Thus, reaction of 2 moles of 4-amino-5-mercapto-3-trifluoromethyl-1,2,4-triazole **1** with terephthaldehyde in acetic acid under reflux for 5 h furnished the corresponding *bis*-Schiff base **12**, which was obtained in good yield (90%) (Figure 4). Reaction of the latter with 2 mole equivalents of the appropriate hydrazonoyl chloride **2** in dioxane under reflux in the presence of triethylamine afforded in each case the corresponding *bis*-thiohydrazonoate esters **13** rather than the *bis*(*N*-triazolyltriazole) **14** or its regioisomer **15**. Elemental analyses and spectral data are in support of structure **13** for the products. For example, the IR spectrum of compound **13a** showed a characteristic absorption band at 3431 and 1629 cm^{-1} for the hydrazone –NH and the azomethine groups, respectively. Moreover, the ^{1}H NMR spectrum displayed three singlet signals at δ 10.69, 8.27, and 2.49 ppm for two –NH, two –CH=N–, and two methyl protons, in addition to the other expected signals assigned for the aromatic protons in the structural formula.

2.2. Antitumor activity

The compounds **4a**, **4i**, **4j**, **9a**, **9b**, **9e**, **9i**, **9j**, **13a**, and **13b** were assayed for their cytotoxicity against HEPG 2 cell line and HCT cell line. The results depicted in Table 2 indicated that the most active ones were compounds **9b** and **9i** since their inhibitory effect was 82.3%. The other compounds, **4** and **13**, are also active but relatively less than compounds **9b** and **9i** (HEPG-2 cell line). On the other hand, compounds **4a** and **9i** are the most active HCT cell line as depicted in Table 3. Compounds **4**, **9**, and **13a** have moderate activity in comparison with compounds **4a** and **9i**.

From the above data, we recorded the IC_{50} of the most reactive compounds against the two cancer cell lines, HepG2 (hepatic cancer) and HCT (colon carcinoma).

Table 2. Single dose experiment on HPG2 cell line (100 μg/mL).

Sample no.	Surviving %	Inhibition %
4a	22	78
4i	25	75
4j	27	73
9a	30	70
9b	17.7	82.3
9e	42	58
9i	17.7	82.3
9j	26	74
13a	30	70
13b	29	71

Table 3. Single dose experiment on HCT cell line (100 μg/mL).

Sample no.	Surviving %	Inhibition %
4a	25	75
4i	36.4	63.6
4j	32.7	67.3
9a	45.5	54.5
9b	36.4	63.6
9e	51.4	48.6
9i	19.3	80.7
9j	37.5	62.5
13a	31	69
13b	28	72

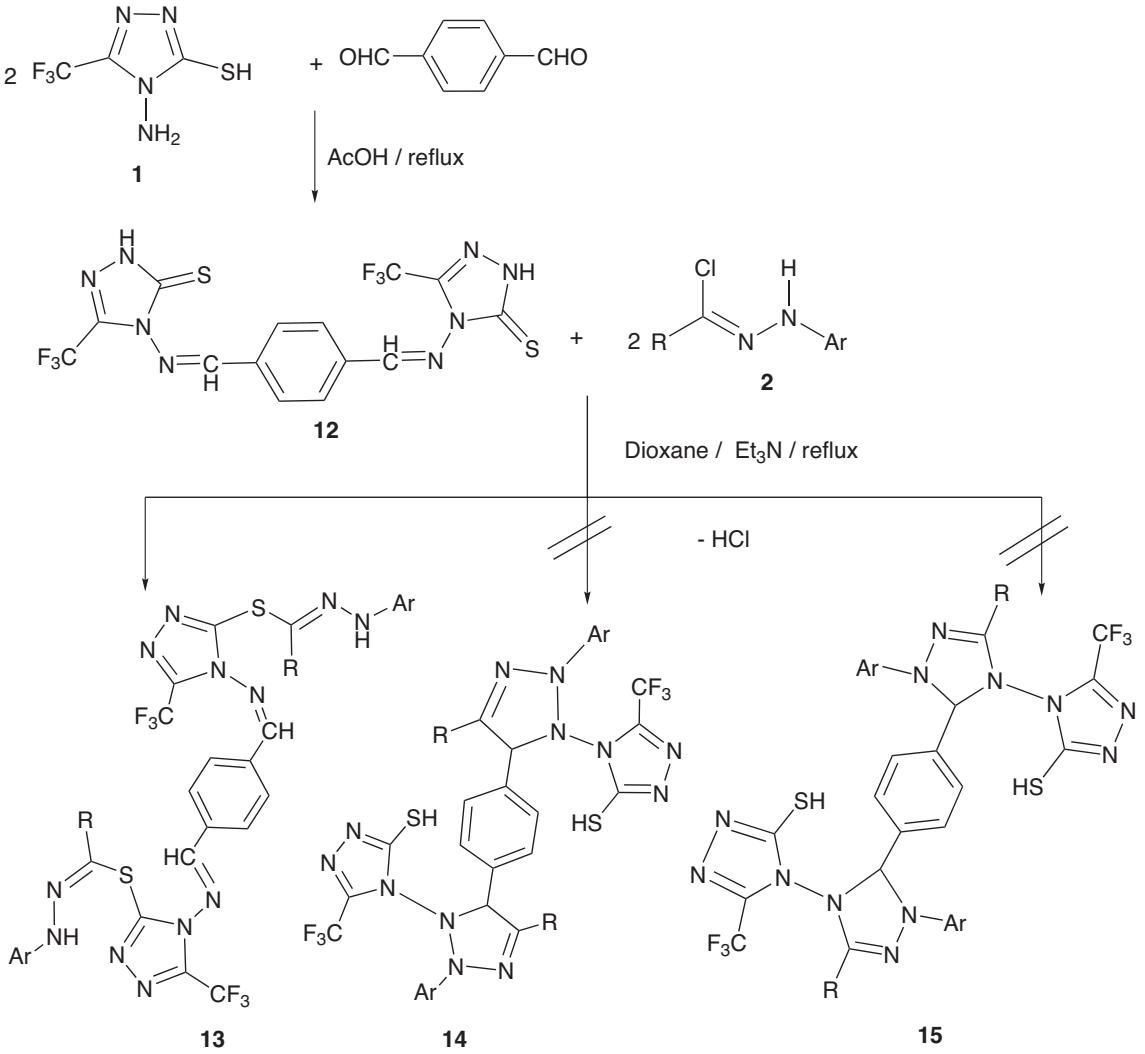


Figure 4. Synthesis of compounds **13**.

Doxorobucin was used as the reference drug for screening, exerting IC_{50} 3.6 and 4.28 μg/L against HepG2 and HCT, respectively.

HepG-2 was the cell line that showed highest sensitivity towards four tested compounds, 4a, 4i, 9b, and 9i. Compounds 4i and 4a displayed the highest activity against HepG2 exerting the following IC_{50} 5.63 and 8.63 μg/mL. On the other hand, 9i and 9b showed mild anti-HepG2 activity representing IC_{50} of 18.7 and 22.7 μg/mL respectively, compared to the reference drug (Table 4). For colon carcinoma cancer cell line HCT, compounds 4a and 13b were the most prominent anti-HCT among the test compounds. They exhibited IC_{50} of 8.33 and 8.45 μg/mL compared to doxorubicin. In addition, the activity of 9i cannot be ignored: IC_{50} 14.9 μg/mL compared to the reference drug (Table 5). The dose response profile was illustrated for the most sensitive cell lines HepG2 and HCT of the tested compounds compared to the reference drug doxorubicin (Figures 5 and 6).

Table 4. IC_{50} of compounds **4a**, **4i**, **9b**, and **9i** against HEPG-2.

Comp. no.	$IC_{50}\mu$g/mL
4a	8.63
4i	5.63
9b	22.7
9i	19.7
DOX	3.6

Table 5. IC_{50} of compounds **4a**, **9i**, and **13b** against HCT.

Comp. no.	$IC_{50}\mu$g/mL
4a	8.33
9i	14.9
13b	8.45
DOX	4.28

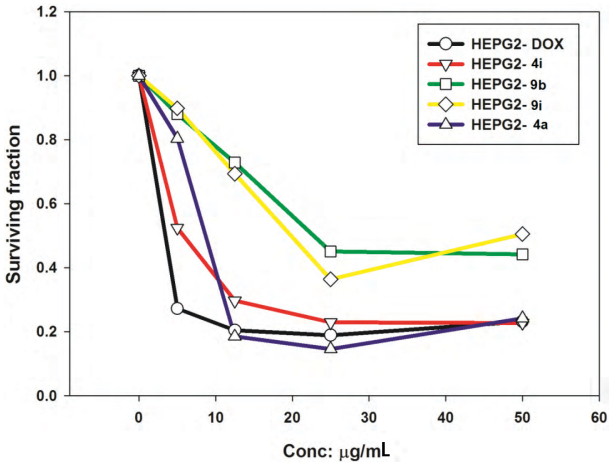


Figure 5. Dose-response profiles of compounds **4a**, **4i**, **9b**, and **9i** against HEPG2 cell line.

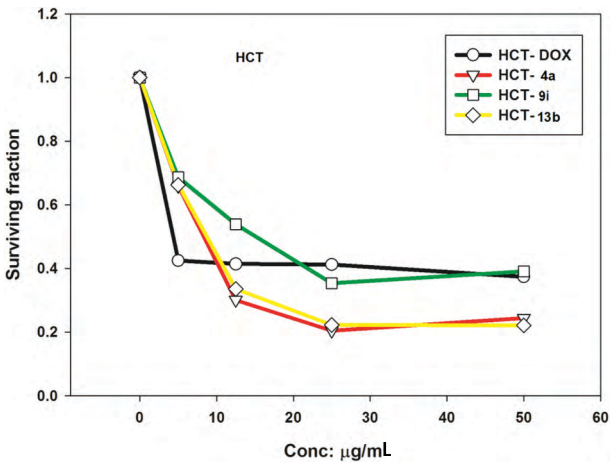


Figure 6. Dose-response profiles of compounds **4a**, **9i**, and **13b** against HCT cell line.

3. Conclusion

In summary, we described a facile one-pot synthesis of a novel series of 3,6,7-trisubstituted-1,2,4-triazolo-[3,4-*b*][1,3,4]thiadiazines (**4a**–**j**) using 3-trifluoromethyl-4-amino-5-mercapto-1,2,4-triazole (**1**) as the key synthon for their preparation. Moreover, 3-substituted-4-arylideneamino-1,2,4-triazol-5-yl)thiohydrazonate esters (**9a**–**l**) were also synthesized by reaction of Schiff bases (**8**) each with a variety of hydrazonoyl halides (**2**). A new symmetric dimeric Schiff base (**12**) was also synthesized and reacted with hydrazonoyl halides (**2**) to give the

respective *bis*-(1,2,4-triazol-5-yl-thiohydrazonoate) (**13**). The structure of the newly synthesized compounds was elucidated on the basis of elemental analysis and spectral data (IR, ^{1}H NMR, and MS spectra). Moreover, some substituted 1,2,4-triazole derivatives were assayed for anticancer activity. The results showed that compounds **4a**, **4i**, and **13b** are the most active inhibitors against HEGP-2 cell line and/or HCT cell line, which provides a good lead for the design and discovery of new high potent drugs by structure-based molecular modification.

4. Experimental

4.1. General

Melting points were determined on a Gallenkamp apparatus. IR spectra were recorded in potassium bromide using PerkinElmer FTIR 1650 and Pye-Unicam SP300 infrared spectrophotometers. ^{1}H NMR spectra were recorded in deuterated dimethyl sulfoxide using a Varian Gemini 300 NMR spectrometer. Mass spectra were recorded on a GCMS-QP 1000 EX Shimadzu and a GCMS 5988-A HP spectrometer. Electronic absorption spectra were recorded on a PerkinElmer Lambda 40 spectrophotometer. Elemental analyses were carried out using a German made Elementar vario LIII CHNS analyzer at the Microanalytical Laboratory of Cairo University, Giza, Egypt. Antitumor activities were recorded at J-Natl-Cancer Inst., Cairo, Egypt. Hydrazonoyl chlorides **2**[29] were prepared as previously described.

4.2. Reaction of compound 1 with hydrazonoyl chloride 2

To a mixture of **1** (0.46 g, 2.5 mmol) and the hydrazonoyl chloride **2** (2.5 mmol) in dioxane (30 mL) was added triethylamine (0.35 mL), and the mixture was heated under reflux for 5 h. The reaction mixture was then poured on ice water and acidified with HCl. The solid produced was collected by filtration and crystallized from the appropriate solvent to give the corresponding compounds **4a**–**j**. The products **4a**–**j** together with their physical constants are listed below.

4.2.1. 6-Methyl-3-trifluoromethyl-7-(4-methoxyphenylhydrazono)[1,2,4]triazolo [3,4-*b*][1,3,4]thiadiazine (4a)

Yellow solid, yield (0.53 g, 60%), mp 226–228 °C, dioxane/ethanol (1:1), IR (KBr, cm^{-1}): 3434 (NH), 3050, 2951, 1597, 1536, 1505, 1459, 142, 1393, 1356, 1299, 1234, 1164, 1033 cm^{-1}. ^{1}H NMR (DMSO-d$_6$) 2.46 (s, 3H, CH_3), 3.73 (s, 3H, OCH_3), 6.92 (d, J = 9.0 Hz, 2H, Ar-H), 7.29 (d, J = 9.0 Hz, 2H, Ar-H), 10.29 (s, 1H, NH). MS m/z (%) 357 (M^++1, 4), 356 (M^+, 24), 122 (100), 107 (11), 95 (17), 77 (7). Anal. Calcd. for $C_{13}H_{11}N_6SF_3O$ (356.32) Calcd: C, 43.81; H, 3.11; N, 23.58. Found: C, 43.57; H, 3.29; N, 23.29%.

4.2.2. 6-Methyl-3-trifluoromethyl-7-(4-methylphenylhydrazono)-[1,2,4]triazolo [3,4-*b*][1,3,4]thiadiazine (4b)

Yellow solid, yield (0.62 g, 73%), mp 214–216 °C, dioxane/ethanol (2:1), IR (KBr, cm^{-1}): 3317 (NH), 3208, 3031, 1652, 1612, 1525, 1491, 1360, 1277, 1230, 1179, 1156, 1004 cm^{-1}. ^{1}H NMR (DMSO-d$_6$) 1.76 (s, 3H, CH_3), 2.23 (s, 3H, CH_3), 7.06–7.39 (m, 4H, Ar H), 10.87 (s, 1H, NH). MS m/z (%) 341 (M^++1, 10), 340 (M^+, 52), 185 (5), 174 (9), 119 (6), 106 (100), 91 (71), 79 (51), 77 (56), 65 (15). Anal. Calcd. For $C_{13}H_{11}N_6SF_3$ (340.33). Calcd: C, 45.87; H, 3.25; N, 24.69. Found: C, 45.57; H, 3.47; N, 24.89%.

4.2.3. 6-Methyl-3-trifluoromethyl-7-(3-methylphenylhydrazono)-[1,2,4]triazolo [3,4-b][1,3,4]thiadiazine (4c)

Yellow solid, yield (0.65 g, 76%), mp 286–288 °C, dioxane/ethanol (1:1), IR (KBr, cm^{-1}): 3436 (NH), 3208, 3052, 1609, 1540, 1507, 1459, 1390, 1318, 1261, 1190, 1159, 1040 cm^{-1}. ^{1}H NMR (DMSO-d_6) 2.31 (s, 3H, CH_3), 2.48 (s, 3H, CH_3), 6.8–7.18 (m, 4H, Ar H), 10.32 (s, 1H, NH). MS m/z (%) 341 (M^++1, 11), 340 (M^+, 59), 180 (7), 106 (68), 91 (100), 79 (60), 77 (60), 65 (17). Anal. Calcd. for$C_{13}H_{11}N_6SF_3$ (340.33) Calcd: C, 45.87; H, 3.25; N, 24.69. Found: C, 45.59; H, 3.46; N, 24.82%.

4.2.4. 6-Methyl-3-trifluoromethyl-7-phenylhydrazono-[1,2,4]triazolo[3,4-*b*][1,3,4]- thiadiazine (4d)

Yellow solid, yield (0.75 g, 70%), mp 276–278 °C, dioxane/ethanol (1:1), IR (KBr, cm^{-1}): 3432 (NH), 3050, 3010, 1598, 1536, 1498, 1459, 1393, 1360, 1242, 1162, 1077, 1041 cm^{-1}. ^{1}H NMR (DMSO-d_6) 2.47 (s, 3H, CH_3), 6.99 (d, J = 8.1 Hz, 2H, Ar-H), 7.34 (d, J = 8.1 Hz, 2H, Ar-H), 10.31 (s, 1H, NH). MS m/z (%) 327 (M^++1, 10), 326 (M^+, 60), 105 (13), 92 (91), 91 (46), 77 (100), 70 (11), 65 (77). Anal. Calcd. for $C_{12}H_9N_6SF_3$ (326.31) Calcd: C, 44.17; H, 2.78; N, 25.75. Found: C, 44.38; H, 3.01; N, 25.99%.

4.2.5. 7-(3-Chlorophenylhydrazono)-3-trifluoromethyl-6-methyl-[1,2,4]triazolo-[3,4-b][1,3,4] thiadiazine (4e)

Yellow solid, yield (0.63 g, 70%), mp 270–272 °C, dioxane/ethanol (2:1), IR (KBr, cm^{-1}): 3430 (NH), 1595, 1535, 1467, 1430, 1396, 1357, 1264, 1241, 1193, 1157, 1073, 1042, 1003 cm^{-1}. ^{1}H NMR (DMSO-d_6) 2.41 (s, 3H, CH_3), 7.0–7.36 (m, 4H, Ar-H), 10.56 (s, 1H, NH). MS m/z (%) 362 (M^++2, 20), 361 (M^++1, 10), 360 (M^+, 56), 180 (27), 139 (12), 128 (19), 126 (56), 111 (100), 101 (26), 99 (80), 90 (31), 75 (23), 70 (26), 63 (28). Anal. Calcd. for $C_{12}H_8N_6SF_3Cl$ (360.75) Calcd: C, 39.95; H, 2.23; N, 23.29. Found: C, 40.25; H, 2.48; N, 23.40%.

4.2.6. 7-(4-Chlorophenylhydrazono)-3-trifluoromethyl-6-methyl-[1,2,4]triazolo-[3,4-*b*][1,3,4]thiadiazine (4f)

Yellow solid, yield (0.68 g, 75%), mp 260–262 °C, dioxane/ethanol (2:1), IR (KBr, cm^{-1}): 3437 (NH), 1653, 1599, 1533, 1489, 1398, 1360, 1239, 1161, 1095, 1005 cm^{-1}. ^{1}H NMR (DMSO-d_6) 1.77 (s, 3H, CH_3), 7.16–7.49 (m, 4H, Ar-H), 10.42 (s, 1H, NH). MS m/z (%) 363 (M^++2, 4), 362 (M^++1, 19), 361 (M^+, 10), 360 (M^+–1, 48), 180 (17), 139 (13), 126 (100), 111 (72), 101 (25), 99 (74), 90 (27), 80 (89), 70 (26), 63 (98), 63 (28). Anal. Calcd. for $C_{12}H_8N_6SF_3Cl$ (360.75) Calcd: C, 39.95; H, 2.23; N, 23.29. Found: C, 40.11; H, 2.0; N, 23.57%.

4.2.7. 6-Methyl-3-trifluoromethyl-7-(3-nitrophenylhydrazono)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (4g)

Buff solid, yield (0.74 g, 80%), mp 256–258 °C, dioxane/ethanol (2:1), IR (KBr, cm^{-1}): 3428 (NH), 3085, 3043, 3018, 1617, 1543, 1531, 1478, 1457, 1397, 1347, 1271, 1242, 1185, 1154, 1079, 1039, 1003 cm^{-1}. ^{1}H NMR (DMSO-d_6) 2.49 (s, 3H, CH_3), 7.58–8.13 (m, 4H, Ar-H), 10.76 (s, 1H, NH). MS m/z (%) 372 (M^++1, 16), 371(M^+, 84), 180 (41), 137 (16), 122 (64), 91 (59), 80 (67), 79 (20), 70 (34), 64 (100), 63 (50). Anal. Calcd. for $C_{12}H_8N_7SF_3O_2$ (371.30) Calcd: C, 38.81; H, 2.17; N, 26.40. Found: C, 39.09; H, 2.45; N, 26.17%.

4.2.8. 6-Methyl-3-trifluoromethyl-7-(4-nitrophenylhydrazono)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (4h)

Buff solid, yield (0.65 g, 70%), mp 282–284 °C, dioxane, IR (KBr, cm^{-1}): 3390 (NH), 1596, 1505, 1405, 1330, 1249, 1154, 1112, 1033 cm^{-1}. ^{1}H NMR (DMSO-d_6) 2.49 (s, 3H, CH_3), 7.49 (d, J = 9.1 Hz, 2H, Ar-H), 8.21 (d, J = 9.2 Hz, 2H, Ar-H), 11.02 (s, 1H, NH). MS m/z (%) 372 (M^++1, 17), 371 (M^+, 100), 180 (42), 169 (7), 153 (13), 35 (17), 122 (83), 111 (12), 107 (31), 98 (10), 92 (20), 91 (37), 80 (52), 76 (22), 70 (38), 65 (75), 64 (16), 63 (49). Anal. Calcd. for $C_{12}H_8N_7SF_3O_2$ (371.30) Calcd: C, 38.81; H, 2.17; N, 26.40. Found: C, 38.56; H, 2.47; N, 26.64%.

4.2.9. 7-(4-Acetylphenylhydrazono)-3-trifluoromethyl-6-methyl-[1,2,4]triazolo-[3,4-*b*][1,3,4]thiadiazine (4i)

Yellow solid, yield (0.65 g, 71%), mp 278–280 °C, dioxane/ethanol (1:1), IR (KBr, cm^{-1}): 3435 (NH), 1669 (CO), 1596, 1534, 1459, 1422, 1358, 1249, 1157, 1039 cm^{-1}. ^{1}H NMR (DMSO-d_6) 2.49 (s, 3H, CH_3), 2.51 (s, 3H, CH_3) 7.42 (d, J = 9.0 Hz, 2H, Ar-H), 7.93 (d, J = 9.0 Hz, 2H, Ar-H), 10.73 (s, 1H, NH). MS m/z (%) 369 (M^++1, 2), 368 (M^+, 9), 106 (4), 91 (7), 80 (100), 64 (47). Anal. Calcd. for $C_{14}H_{11}N_6SF_3O$ (368.34) Calcd: C, 45.65; H, 3.01; N, 22.81. Found: C, 45.92; H, 3.29; N, 23.06%.

4.2.10. 7-(4-Ethoxycarbonylphenylhydrazono)-3-trifluoromethyl-6-methyl-[1,2,4]-triazolo[3,4-*b*][1,3,4]thiadiazine (4j)

Yellow solid, yield (0.65 g, 65%), mp 268–270 °C, dioxane/ethanol (2:1), IR (KBr, cm^{-1}): 3439 (NH), 1703 (CO), 1603, 1532, 1458, 1392, 1243, 1157, 1013 cm^{-1}. ^{1}H NMR (DMSO-d6) 1.3 (t, J = 7.1 Hz, 3H, CH_3), 2.4 (s, 3H, CH_3), 4.25 (q, J = 7.1 Hz, 2H, CH_2), 7.37 (d, J = 8.9 Hz, 2H, Ar-H), 7.87 (d, J = 8.9 Hz, 2H, Ar-H), 10.79 (s, 1H, NH). MS m/z (%) 399 (M^++1, 20), 398 (M^+, 100), 370 (16), 179 (18), 149 (64), 135 (24), 121 (46), 119 (42), 108 (88), 103 (42), 91 (54), 81 (23), 76 (14), 65 (60). Anal. Calcd. for $C_{15}H_{13}N_6SF_3O_2$ (398.37) Calcd: C, 45.22; H, 3.28; N, 21.09. Found C, 45.49; H, 3.40; N, 21.32%.

4.3. Synthesis of compounds 8

A mixture of compound **1** (2.5 mmol) and the appropriate aromatic aldehyde (2.5 mmol) was refluxed in glacial acetic acid (20 mL) for 5 h. The solution was then cooled and the solid produced was filtered and recrystallized from the appropriate solvent.

Compounds **8a** and **b** were prepared by the same method described in the literature.[16,17]

4.3.1. 4-[(5-Methyl-furan-2-ylmethylene)-amino]-5-trifluoromethyl-4H-[1,2,4]-triazole-3-thiol (8c)

White solid, yield (0.54 g, 80%), mp 208–210 °C, dioxane/ethanol (1:1), IR (KBr, cm^{-1}): 3431 (NH), 2912, 2742, 1612, 1590, 1569, 1552, 1522, 1497, 1451, 1369, 1348, 1293, 1268, 1195, 1165, 1142, 1104, 1027 cm^{-1}. ^{1}H NMR (DMSO-d_6) 2.44 (s, 3H, CH_3), 6.46 (d, J = 4.3, 1H, CH), 7.33 (d, J = 4.3, 1H, CH), 9.48 (s, 1H, N=CH), 14.78 (s, 1H, NH). MS m/z (%) 276 (M^+, 2), 274 (13), 169 (43), 118 (13), 111 (20), 106 (100), 70 (12), 80 (67), 69 (56), 64 (83). Anal. Calcd. for $C_9H_7N_4SF_3O$ (276.24) Calcd: C, 39.13; H, 2.55; N, 20.28. Found: C, 39.31; H, 2.83; N, 20.01%.

4.4. Reaction of compounds 8 with hydrazonoyl chlorides 2

To a mixture of **8** (2.5 mmol of each) and the hydrazonoyl chloride **2** (2.5 mmol) in dioxane (30 mL) was added triethylamine (0.35 mL), and the mixture was heated to reflux for 5 h, and then the reaction mixture was poured on ice water and acidified with HCl. The solid produced was collected by filtration and crystallized from the appropriate solvent to give the corresponding compounds **9a**–**l**. The products **9a**–**l** together with their physical constants are listed below.

4.4.1. 4-[((E)-Benzylidene)amino]-5-(trifluoromethyl)-4H-1,2,4-triazol-3-yl (E)-2-oxo-N-phenylpropanehydrazonothioate (9a)

Orange solid, yield (0.76 g, 70%), mp 200–202 °C, dioxane/ethanol (1:1), IR (KBr, cm^{-1}): 3436 (NH), 1682 (CO), 1631, 1578, 1507, 1442, 1407, 1362, 1293, 1193, 1141, 1062, 1016 cm^{-1}. ^{1}H NMR (DMSO-d_6): 2.61 (s, 3H, $COCH_3$), 7.40–8.13 (m, 10H, Ar-H), 8.26 (s, 1H, =CH), 10.61 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): 24.9, 116.8, 122.0, 126.4, 127.0, 128.6, 129.0, 129.4, 133.9, 138.3, 141.4, 144.2, 150.3, 164.3, 189.2. MS m/z (%) 433 (M^++1, 3), 432 (M^+, 11), 273 (7), 228 (10), 135 (26), 118 (92), 104 (60), 91 (53), 77 (100). Anal. Calcd. for $C_{19}H_{15}N_6SF_3O$ (432.43) Calcd: C, 52.77; H, 3.49; N, 19.43. Found: C, 52.56; H, 3.76; N, 19.70%.

4.4.2. 4-[((E)-Benzylidene)amino]-5-(trifluoromethyl)-4H-1,2,4-triazol-3-yl (E)-2-oxo-N-(4-methylphenyl)propanehydrazonothioate (9b)

Orange solid, yield (0.76 g, 68%), mp 208–210 °C, dioxane/ethanol (1:1), IR (KBr, cm^{-1}): 3434 (NH), 1678 (CO), 1631, 1574, 1510, 1441, 1403, 1292, 1161, 1063, 1005 cm^{-1}. ^{1}H NMR (DMSO-d_6) 2.40 (s, 3H, CH_3), 2.60 (s, 3H, $COCH_3$), 7.37–7.46 (m, 5H, Ar-H), 7.61 (d, J = 8.2 Hz, 2H, Ar-H), 7.95 (d, J = 8.2 Hz, 2H, Ar-H), 8.26 (s, 1H, =CH), 10.56 (s, 1H, NH). MS m/z (%) 447 (M^++1, 3), 446 (M^+, 9), 149 (13), 132 (100), 118 (26), 105 (67), 91 (69), 77 (45). Anal. Calcd. for $C_{20}H_{17}N_6SF_3O$ (446.46) Calcd: C, 53.80; H, 3.83; N, 18.82. Found: C, 54.0; H, 3.54; N, 19.06%.

4.4.3. 4-[((E)-Benzylidene)amino]-5-(trifluoromethyl)-4H-1,2,4-triazol-3-yl (E)-N-(4-chlorophenyl)-2-oxopropanehydrazonothioate (9c)

Orange solid, yield (0.93 g, 85%), mp 230–232 °C dioxane, IR (KBr, cm^{-1}): 3428 (NH), 1687 (CO), 1632, 1574, 1531, 1487, 1440, 1402, 1366, 1286, 1193, 1152, 1059, 1011 cm^{-1}. ^{1}H NMR (DMSO-d_6) 2.49 (s, 3H, $COCH_3$), 7.40–7.46 (m, 5H, Ar-H), 7.61 (d, J = 12.2 Hz, 2H, Ar-H), 8.18 (d, J = 12.2 Hz, 2H, Ar-H), 8.28 (s, 1H, =CH), 10.63 (s, 1H, NH). MS m/z (%) 467 (M^++1, 20), 466 (M^+, 32), 295 (20), 262 (22), 214 (23), 169 (30), 152 (60), 125 (38), 104 (37), 103 (25), 96 (64), 77 (100). Anal. Calcd. for $C_{19}H_{14}N_6SF_3OCl$ (466.88) Calcd: C, 48.88; H, 3.02; N, 18.00. Found: C, 48.59; H, 3.28; N, 18.24%.

4.4.4. 4-[((E)-benzylidene)amino]-5-(trifluoromethyl)-4H-1,2,4-triazol-3-yl (E)-N-(4-nitrophenyl)-2-oxopropanehydrazonothioate (9d)

Reddish brown solid, yield (0.72 g, 60%), mp 206–208 °C, dioxane, IR (KBr, cm^{-1}): 3428(NH), 1689 (CO), 1631, 1589, 1511, 1442, 1405, 1336, 1282, 1187, 1152, 1111, 1011 cm^{-1}. ^{1}H NMR (DMSO-d6) 2.65 (s, 3H, $COCH_3$), 7.44–7.69 (m, 5H, Ar-H), 8.23 (d, J = 7.1 Hz, 2H, Ar H), 8.40 (d, J = 7.1 Hz, 2H, Ar-H), 9.14 (s,

1H, =CH), 10.76 (s, 1H, NH). MS m/z (%) 478 (M^++1, 15), 477 (M^+, 21), 313 (16), 243 (23), 192 (14), 163 (19), 104 (59), 90 (53), 77 (100). Anal. Calcd. for $C_{19}H_{14}N_7SF_3O_3$ (477.43) Calcd: C, 47.79; H, 2.95; N, 20.52. Found: C, 47.99; H, 2.73; N, 20.27%.

4.4.5. Ethyl (E)-2-[(4-(((E)-benzylidene)amino]-5-(trifluoromethyl)-4H-1,2,4-triazol-3-yl)thio)-2-(2-phenylhydrazono)acetate (9e)

Orange solid, yield (0.98 g, 85%), mp 218–220 °C, dioxane/ethanol (1:1), IR (KBr, cm^{-1}): 3431 (NH), 1711 (CO), 1622, 1580, 1528, 1495, 1443, 1405, 1314, 1193, 1145, 1105, 1009 cm^{-1}. ^{1}H NMR (DMSO-d_6) 1.33 (t, J = 7.3 Hz, 3H, CH_3), 4.38 (q, J = 7.3 Hz, 2H, CH_2), 7.37–8.06 (m, 10H, Ar-H), 8.26 (s, 1H, =CH), 10.61 (s, 1H, NH). MS m/z (%) 463 (M^++1, 4), 462 (M^+, 16), 135 (23), 118 (18), 104 (43), 96 (37), 91 (77), 77 (100), 69 (18). Anal. Calcd. for $C_{20}H_{17}N_6SF_3O_2$ (462.46) Calcd: C, 51.94; H, 3.70; N, 18.17. C, 52.20; H, 3.99; N, 18.38%.

4.4.6. Ethyl (E)-2-[(4-(((E)-benzylidene)amino]-5-(trifluoromethyl)-4H-1,2,4-triazol-3-yl)thio)-2-(2-(p-tolyl)hydrazono)acetate (9f)

Yellow solid, yield (0.89 g, 75%), mp 196–198 °C, dioxane/ethanol (2:1), IR (KBr, cm^{-1}):, 3451 (NH), 1740 (CO), 1626, 1583, 1533, 1441, 1404, 1328, 1284, 1186, 1143, 1105, 1014 cm^{-1}. ^{1}H NMR (DMSO-d_6) 1.30 (t, J = 7 Hz, 3H, CH_3), 4.38 (q, J = 7 Hz, 2H, CH_2), 7.35–7.44 (m, 5H, Ar-H), 7.61 (d, J = 8.0 Hz, 2H, Ar-H), 7.88 (d, J = 8.0 Hz, 2H, Ar-H), 8.26 (s, 1H, =CH), 10.55 (s, 1H, NH). MS m/z (%) Anal. Calcd: for $C_{21}H_{19}N_6SF_3O_2$ (476.48) Calcd: C, 52.93; H, 4.01; N, 17.63. Found: C, 52.64; H, 4.31; N, 17.42%.

4.4.7. Ethyl (E)-2-[(4-(((E)-benzylidene)amino]-5-(trifluoromethyl)-4H-1,2,4-triazol-3-yl)thio)-2-(2-(4-chlorophenyl)hydrazono)acetate (9g)

Yellow solid, yield (0.74 g, 60%), mp 164–266 °C, dioxane/ethanol (3:1), IR (KBr, cm^{-1}):, 3437 (NH), 1732 (C=O), 1630, 1584, 1536, 1486, 1442, 1402, 1283, 1190, 1145, 1095, 1010 cm^{-1}. ^{1}H NMR (DMSO-d_6) 1.31 (t, J = 7.2 Hz, 3H, CH_3), 4.38 (q, J = 7.2 Hz, 2H, CH_2), 7.40 (d, J = 8.0 Hz, 2H, Ar-H), 7.56–7.64 (m, 5H, Ar-H), 8.08 (d, J = 8.0 Hz, 2H, Ar-H), 8.28 (s, 1H, =CH), 10.60 (s, 1H, NH). MS m/z (%) 498 (M^++2, 7), 497 (M^++1, 4), 496 (M^+, 18), 241 (5), 172 (11), 169 (29), 152 (19), 138 (19), 125 (100), 111 (34), 104 (47), 96 (93), 90 (61), 77 (99). Anal. Calcd. for $C_{20}H_{16}N_6SF_3O_2Cl$ (496.90) Calcd: C, 48.34; H, 3.24; N, 16.91. Found: C, 48.60; H, 3.44; N, 16.70%.

4.4.8. Ethyl (E)-2-[(4-(((E)-benzylidene)amino]-5-(trifluoromethyl)-4H-1,2,4-triazol-3-yl)thio)-2-(2-(4-nitrophenyl)hydrazono)acetate (9h)

Reddish brown solid, yield (1.08 g, 86%), mp 150–152 °C, dioxane/ethanol (2:1), IR (KBr, cm^{-1}): 3412 (NH), 1698 (CO), 1602, 1511, 1476, 1341, 1269, 1205, 1159, 1084, 1015 cm^{-1}. ^{1}H NMR (DMSO-d_6) 1.35 (t, J = 6.9 Hz, 3H, CH_3), 4.16 (q, J = 6.9 Hz, 2H, CH_2), 7.41 (d, J = 9.0 Hz, 2H, Ar-H), 7.60 (d, J = 9.0 Hz, 2H, Ar-H), 7.65–8.20 (m, 5H, Ar-H), 9.13 (s, 1H, =CH), 11.42 (s, 1H, NH). MS m/z (%) 508 (M^++1, 2), 507 (M^+, 7), 250 (10), 136 (12), 103 (42), 96 (14), 90 (31), 77 (100), 69 (22). Anal. Calcd. for $C_{20}H_{16}N_7SF_3O_4$ (507.45) Calcd: C, 47.33; H, 3.17; N, 19.32. Found: C, 47.60; H, 3.29; N, 19.58%.

4.4.9. 4-[((E)-3,4-Dimethoxybenzylidene)amino]-5-(trifluoromethyl)-4H-1,2,4-triazol-3-yl (E)-2-oxo-N-phenylpropanehydrazonothioate (9i)

Orange solid, yield (0.98 g, 80%), mp 174–176 °C, dioxane/ethanol (1:1), IR (KBr, cm^{-1}): 3435 (NH), 1691 (CO), 1631, 1579, 1513, 1438, 1409, 1368, 1268, 1191, 1145, 1017 cm^{-1}. ^{1}H NMR (DMSO-d_6) 2.49 (s, 3H, $COCH_3$), 3.76 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 6.99–8.12 (m, 8H, Ar-H), 8.16 (s, 1H, =CH), 10.47 (s, 1H, NH). MS m/z (%) 493 (M^++1, 0.3), 492 (M^+, 1), 273 (6), 163 (100), 148 (32), 137(10), 120 (21), 118 (11), 102 (11), 79 (26), 77 (44), 65 (18). Anal. Calcd. for $C_{21}H_{19}N_6SF_3O_3$ (492.48) Calcd: C, 51.21; H, 3.88; N, 17.06. Found: C, 51.39; H, 4.02; N, 17.33%.

4.4.10. Ethyl (E)-2-[(4-(((E)-3,4-dimethoxybenzylidene)amino)-5-(trifluoromethyl)-4H-1,2,4-triazol-3-yl)thio]-2-(2-phenylhydrazono)acetate (9j)

Yellow solid, yield (1.1 g, 85%), mp 170–172 °C, dioxane/ethanol (3:1), IR (KBr, cm^{-1}): 3432 (NH), 1733 (CO), 1636, 1581, 1518, 1439, 1406, 1273, 1190, 1136, 1018 cm^{-1}. ^{1}H NMR (DMSO-d_6) 1.30 (t, J = 7.2 Hz, 3H, CH_3), 3.76 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 4.35 (q, J = 7.2 Hz, 2H, CH_2), 6.99–8.05 (m, 10H, Ar-H), 8.16 (s, 1H, =CH), 10.48 (s, 1H, NH). MS m/z (%) Anal. Calcd. for $C_{22}H_{21}N_6SF_3O_4$ (522.51) Calcd: C, 50.57; H, 4.05; N, 16.08. Found: C, 50.34; H, 4.33; N, 16.30%.

4.4.11. 4-[((E)-3,4-dimethoxybenzylidene)amino]-5-(trifluoromethyl)-4H-1,2,4-triazol-3-yl (E)-N-phenylbenzohydrazonothioate (9k)

Orange solid, yield (1.0 g, 78%), mp 192–194 °C, dioxane/ethanol (2:1), IR (KBr, cm^{-1}): 3436 (NH), 1622, 1591, 1511, 1440, 1411, 1329, 1264, 1197, 1134, 1020 cm^{-1}. ^{1}H NMR (DMSO-d_6): 3.77 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 6.99–8.20 (m, 13H, Ar-H), 8.22 (s, 1H, =CH), 10.44 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): 55.2, 55.5, 108.4, 111.5, 112.0, 120.5, 121.3, 125.8, 126.0, 126.8, 128.8, 129.1, 129.2, 130.9, 139.0, 140.8, 143.8, 148.7, 150.0, 150.1, 163.4. MS m/z (%) 527 (M^++1, 2), 526 (M^+, 70, 362 (8), 194 (53), 91 (100), 77 (33), 64 (15). Anal. Calcd. for $C_{25}H_{21}N_6SF_3O_2$ (526.54) Calcd: C, 57.02; H, 4.02; N, 15.96. Found: C, 57.32; H, 4.22; N, 15.67%.

4.4.12. Ethyl (E)-2-[(4-(((E)-(5-methylfuran-2-yl)methylene)amino)-5-(trifluoro-methyl)-4H-1,2,4-triazol-3-yl)thio]-2-(2-phenylhydrazono)acetate (9l)

Orange solid, yield (0.94 g, 81%), mp 150–152 °C, dioxane/ethanol (2:1), IR (KBr, cm^{-1}): 3409 (NH), 1711 (CO), 1620, 1530, 1491, 1437, 1407, 1313, 1186, 1099, 1013 cm^{-1}. ^{1}H NMR (DMSO-d_6) 1.30 (t, J = 7.0 Hz, 3H, CH_3), 2.31 (s, 3H, CH_3), 4.37 (q, J = 7.0 Hz, 2H, CH_2), 6.21 (d, J = 2.3 Hz, 1H, CH), 6.69 (d, J = 2.3 Hz, 1H, CH), 7.40–8.04 (m, 5H, Ar-H), 8.07 (s, 1H, =CH), 10.40 (s, 1H, NH). MS m/z (%) 467 (M^++1, 4), 466 (M^+, 18), 217 (22), 135 (16), 108 (23), 96 (15), 91 (100), 79 (19), 77 (31). Anal. Calcd. for $C_{19}H_{17}N_6SF_3O_3$ (466.44) Calcd: C, 48.92; H, 3.67; N, 18.02. Found: C, 48.64; H, 3.95; N, 18.31%.

4.5. Synthesis of compound 12

A mixture of compound **1** (0.92 g, 5 mmol) and terephthaldehyde (2.5 mmol) was refluxed in glacial acetic acid (30 mL) for 5 h. The solution was then cooled and the solid produced was filtered and recrystallized from

dioxane to give compound **12** as yellowish white solid, yield (1.29 g, 90%), mp 250 °C, dioxane, IR (KBr, cm^{-1}): cm^{-1} 1658 (2C=N), ^{1}H NMR (DMSO-d6): 7.97 (d, J = 8.0 Hz, 2H, Ar H), 8.06 (d, J = 8.0 Hz, 2H, Ar H), 8.1 (s, 2H, 2=CH), 10.69 (s, 2H, 2SH). MS m/z (%) 467 (M^++1, 4), 466 (M^+, 4), 300 (11), 170 (82), 132 (49), 130 (100), 104 (31), 102 (44), 89 (33), 77 (69), 69 (45). Anal. Calcd. for $C_{14}H_8N_8S_2F_6$ (466.39) Calcd: C, 36.05; H, 1.72; N, 24.02. Found: C, 36.25; H, 1.45; N, 24.32%.

4.6. Reaction of compound 12 with hydrazonoyl chlorides 2

To a mixture of **12** (1.17 g, 2.5 mmol) and the hydrazonoyl chloride **2** (5 mmol) in dioxane (40 mL) was added triethylamine (0.7 mL), and the mixture was heated to reflux for 5 h, and then the reaction mixture was poured on ice water and acidified with HCl. The solid produced was collected by filtration and crystallized from the appropriate solvent to give the corresponding compounds **13a** and **b**.

4.6.1. (13a)

Yellow solid, yield (2.3 g, 85%), mp 240–242 °C, dioxane, IR (KBr, cm^{-1}): 3431 (2NH), 1688 (2C=O) 1629 (2C=N), ^{1}H NMR (DMSO-d_6): 2.49 (s, 6H, 2$COCH_3$), 7.44–7.56 (m, 10H, Ar H), 7.59 (d, J= 7.8 Hz, 2H, Ar H), 8.1 (d, J = 7.8 Hz, 2H, Ar H), 8.27 (s, 2H, 2=CH), 10.69 (s, 2H, 2NH). Anal. Calcd. for $C_{32}H_{24}N_{12}S_2F_6O_2$ (786.75) Calcd: C, 48.85; H, 3.07; N, 21.36. Found: C, 48.65; H, 3.29; N, 21.25%.

4.6.2. (13b)

Orange solid, yield (2.4 g, 87%), mp 262–264 °C, dioxane/ethanol (1:1), IR (KBr, cm^{-1}): 3428 (NH), 1711 (C=O), 1623 (C=N), ^{1}H NMR (DMSO-d_6) 1.32 (t, J = 7.0 Hz, 6H, 2CH_3), 4.38 (q, J = 7.0 Hz, 2H, CH_2), 7.42–8.05 (m, 14H, Ar H), 8.27 (s, 2H, 2=CH), 10.68 (s, 2H, 2NH). Anal. Calcd. for $C_{34}H_{28}N_{12}S_2F_6O_4$ (846.80) Calcd: C, 48.22; H, 3.33; N, 19.85. Found: C, 48.40; H, 3.07; N, 20.01%.

4.7. Biological activity

4.7.1. Measurement of cytotoxicity by SRB assay

Potential cytotoxicity of the compounds was tested using the method of Skehan et al.[30] Cells were plated in a 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. A single concentration of the compound under test (100 μg/mL) was added to the cell monolayer triplicate wells prepared for each individual dose. Monolayer cells were incubated with the compounds for 48 h at 37 °C and in atmosphere of 5% CO_2.

After 48 h, cells were fixed, washed, and stained with sulfo-Rhodamine-B stain. Excess stain was washed with acetic acid and attached stain was recovered with Tris EDTA buffer. Color intensity was measured in an ELISA reader. The relation between inhibition % and drug concentration was calculated.[30]

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