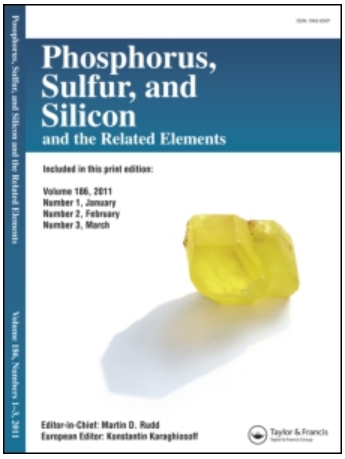

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Synthesis and Antitumor Activity of Some Novel Pyrazole and Thienopyrimidine Derivatives

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SYNTHESIS AND ANTITUMOR ACTIVITY OF SOME NOVEL PYRAZOLE AND THIENOPYRIMIDINE DERIVATIVES

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The novel thiosemicarbazide derivative was prepared by hydrazinolysis of isothiocyanatosulfonamide with hydrazine hydrate. It was used as a starting material for the synthesis of some novel pyrazolosulphaphenazole, phthalazine, thiourea, and 1,2,4-triazolbenzenesulfonamide derivatives. Isothiocyanato sulfonamide was cyclized with sulfanyl acetic acid to furnish the novel 2-thioxothiazolidine derivative. Treatment of p-substituted sulfamoylphenyl isothiocyanate derivatives with various O-aminoesters of thiophene derivatives yielded dimethyl thiophene-carboxylate, methylthiophene carboxylate, and thienopyrimidine derivatives. Some of synthesized compounds were evaluated for one cell line. Compounds 3, 9, 15a, 15b, and 18 exhibited remarkable antitumor activity against MCF7 (breast) human cells.

Supplemental materials are available for this article. Go to the publisher's online edition of* Phosphorus, Sulfur, and Silicon and the Related Elements *to view the free supplemental file.

Keywords Antitumor activity; dimethyl thiophenecarboxylate; methylthiophene carboxylate; thienopyrimidine; thiosemicarbazide; 2-thioxothiazolidine

INTRODUCTION

Pyrazole[1] and 1,2,5-thiadiazole[2,3] derivatives are biologically important compounds. Substituted 1,2,5-thiadiazoles were found to be efficient muscarine[4] receptor agonists as well as inhibitors of HIV-1 replication.[5] For example, 1-(1,1-di-methylethylamino)-3-(4-morpholino-1,2,5-thiadiazol-3-yloxy)-2-propanol (timolol) is one of the most important medicines for the treatment of glaucoma.[6,7] Furthermore, antibacterial,[8] antifungal,[9] insulin releasing,[10] carbonic anhydrase inhibitory,[11] anti-inflammatory,[12] and antitumor[13] properties of the sulfamoyl moiety have been described. With these facts, and in continuation of my efforts to synthesize biologically active heterocyclic compounds from readily available starting materials,[14–17] the synthesis and antitumor activity of some novel pyrazole and 1,2,5-thiadiazole derivatives containing sulfamoyl moiety are reported here.

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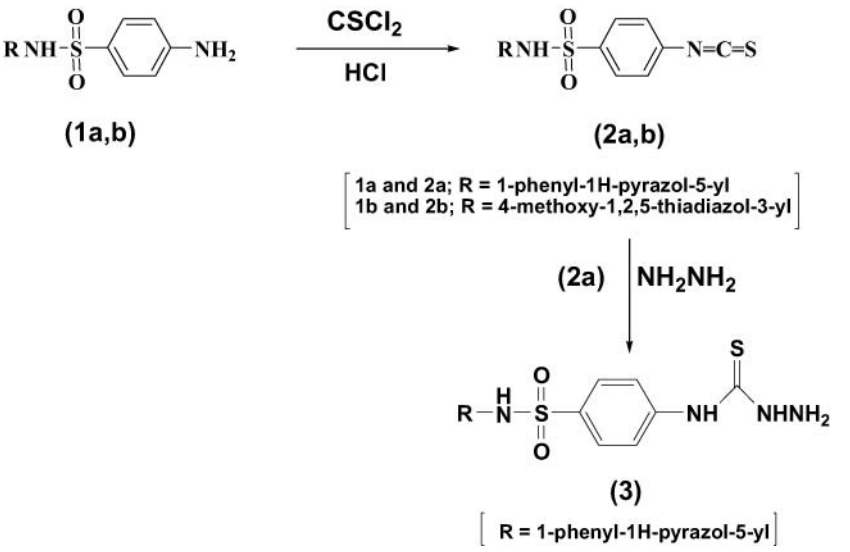


Scheme 1

RESULTS AND DISCUSSION

Isothiocyanate derivatives are useful and widely used building blocks in the synthesis of nitrogen, sulfur, and oxygen heterocyclic compounds and organometallic compounds of academic, pharmaceutical, and industrial interest.[18,19] Isothiocyanatosulfonamides (**2a**,**b**) were synthesized by the treatment of sulfonamide derivatives (**1a**,**b**) with thiophosgene in the presence of dilute hydrochloric acid at room temperature in quantitative yields (Scheme 1).

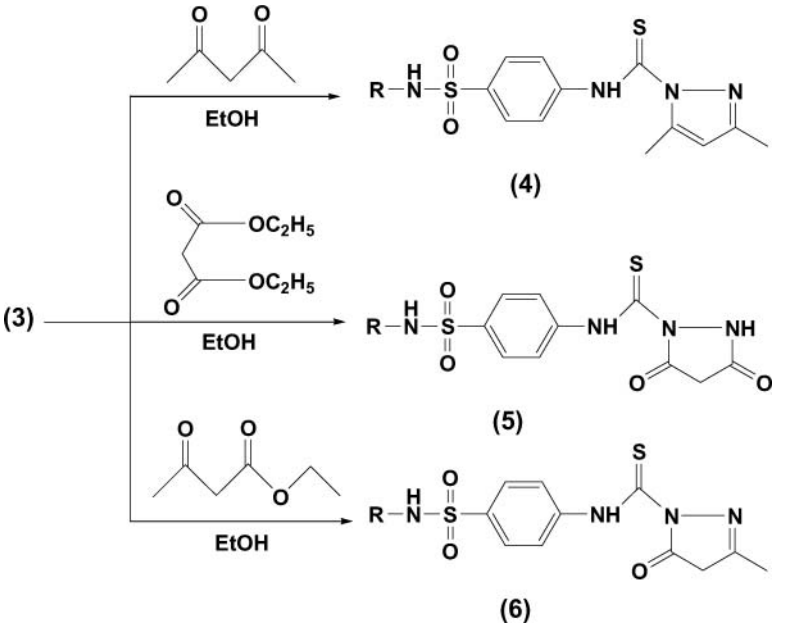
In the IR spectra of compound **(2a)**, the NH and N=C=S bands were observed in the 3460–3445 cm^{-1} and 2030 cm^{-1} regions, respectively. The ^1H NMR spectrum of compound (**2a**; DMSO-d_6) exhibited the following signals: 5.5, 6.6 (2s, 2H, pyrazole-H), 7.5–7.71 (m, 9H, Ar-H), and 10.5 ppm (s, H, $NHSO_2$). Also, its mass spectrum displayed a molecular ion peak at m/z 356 (M^+, 17.49%), and the base peak was found in the spectrum at m/z 158 (100%), where mass spectral fragmentation of **(2a)** was in agreement with its structure (Chart 1, available online in the Supplementary Materials). The IR spectrum of **(2b)** revealed the absorption bands at 3330–3226 (NH), 2100 (NCS), 1332, 1162 cm^{-1}(SO_2). The ^1H NMR spectrum of compound (**2b**; DMSO-d_6) exhibited the following signals: 3.98 (s, 3H, OCH_3), 7.4–7.7 (m, 4H, Ar-H), 10.2 (s, H, $NHSO_2$). Also, its mass spectrum revealed a molecular ion peak m/z at 328 (M^+, 17.40%), with a base peak at 134 (100%). The reaction of isothiocyanate derivative **(2a)** with some nitrogen, sulfur, and carbon nucleophiles was investigated. The strategic starting material N-(4-(N-(1-phenyl-1H-pyrazol-5yl) sulfamoyl) phenyl)hydrazinecarbothioamide **(3)** was obtained in good yield via hydrazinolysis of the corresponding isothiocyanate derivative **(2a)** with hydrazine hydrate in refluxing ethanol at room temperature (Scheme 1).

The structure of **(3)** was established by elemental analysis and spectral data (Table I). Its infrared spectrum showed the absence of N=C=S band and exhibited the following absorption bands: 3356, 3190 (NH_2), 1628 (C=N), and 1338, 1160 cm^{-1} (SO_2). The ^1H NMR spectrum of (**3**; in DMSO-d6) showed the following signals: 5.7, 6.5 (2s, 2H,

Table I Spectral data of the newly synthesized compounds (**2a–18**)

Compd. no.	IR/$_{max}$ (cm^{-1})	^{1}H NMR (DMSO-d_6) (δ/ppm)
2a	3445 (NH), 300 (CH- arom.), 2030 (NCS), 1586 (C=N), 1345, 1163 (SO_2).	5.5, 6.6 (2s, 2H, pyrazole-H), 7.5–7.71 (m, 9H, Ar-H), 10.5 (s, H, $NHSO_2$).
2b	3226 (NH), 3099 (CH arom.), 2100 (NCS), 1332, 1162 (SO_2).	3.98 (s, 3H, OCH_3), 7.4–7.7 (m, 4H, Ar-H), 10.2 (s, H, $NHSO_2$).
3	3356, 3190 (NH_2), 3068 (CH-arom.), 1628 (C=N) and 1338, 1160 (SO_2).	5.7, 6.5 (2s, 2H, pyrazole-H), 7.42–7.71 (m, 11H, Ar-H+2 NH), 10.6 (s, H, $NHSO_2$), 11.3 (s, H, NH_2).
4	3380, 3200 (2NH), 3055 (CH-arom.), 2927, 2898 (2CH-aliph.), 1654(C=N), 1384, 1153 (SO_2), 1088 (C=S).	1.2 (s, 3H, CH_3), 1.3 (s, 3H, CH_3), 5.4, 5.9, 6.5 (3s, 3H, 2pyrazole-H cyclic), 7.42–7.68 (m, 9H, Ar-H), 9.8 (s, H, NH), 10.3 (s, H, $NHSO_2$).
5	3367, 3254 (2NH), 3066 (CH-arom.), 1751,1740 (2C=O), 1681 (C=N), 1384, 1154 (SO_2), 1070 (C=S).	5.8 (s, 2H, CH_2CO pyrazoline), 5.5, 6.6 (2s, 2H, pyrazole-H), 7.35–7.95 (m, 10H, Ar-H), 9.4 (s, 1H, NH) and 10.5 (s, 1H, $NHSO_2$).
6	3310, 3230 (2NH), 3055 (CH-arom.), 2980 (CH-aliph.), 1670 (C=O), 1545 (C=N), 1380, 1150 (SO_2), 1093 (C=S).	1.23 (s, 3H, CH_3), 5.8 (s, 2H, CH_2CO pyrazoline), 5.54, 6.68 (2s, 2H, pyrazole-H), 7.22–7.55 (m, 9H, Ar-H), 8.9 (s, H, NH), 9.9 (s, 1H, $NHSO_2$).
7	3210 (NH), 1740, 1733 (2C=O), 1378, 1168 (SO_2), 1089 (C=S).	5.5, 6.7 (2s, 2H, pyrazole-H), 7.5–8.3 (m, 15H, Ar-H+NH), 10.3 (s, H, $NHSO_2$).
8	3300, 3330 (NH, NH_2), 1378, 1165 (SO_2), 1067, 1089 (2C=S).	5.3, 6.5 (2s, 2H, pyrazole-H), 7.42–8.0 (m, 10H, Ar-H+NH), 9.8, 9.9(2s, 2H, 2NH), 10.6 (s, H, $NHSO_2$), 11.0 (s, H, NH_2).
9	3200 (NH),1358, 1167 (SO_2), 1058 (C=S).	5.3, 6.4 (2s, 2H, pyrazole-H), 7.6–8.2 (m, 10H, Ar-H+NH), 10.5 (s, H, $NHSO_2$).
10	3222 (NH), 3120 (CH-arom.) and 1740 cm^{-1} (C=O; thiazolidinone), 1376, 1168 (SO_2), and 1093 (C=S).	4.2 (s, 2H, CH_2 thiazolidinone), 5.3, 6.6 (2s, 2H, pyrazole-H), 7.2–8.1 (m, 10H, Ar-H+SO_2NH).
12a	3330, 3243, 3236 (3NH), 3165 (CH-arom.), 2987 (CH-aliph.), 1775 (C=O), 1545 (C=N), 1350, 1165 (SO_2), 1063 (C=S).	0.87, 1.2 (2s, 6H, $2CH_3$), 1.3 (t, 3H, CH_3), 4.0 (q, 2H, CH_2), 5.6, 6.6 (2s, 2H, pyrazole-H), 7.5–7.9 (m, 10H, Ar-H+NH), 8.0(s, H, NH), 11.1 (s, H, $NHSO_2$).
12b	3494, 3242, 3105 (3NH), 2985 (CH-aliph.), 1759(C=O), 1534 (C=N), 1321, 1155 (SO_2), 1069 (C=S).	0.9, 1.1(2s, 6H, $2CH_3$), 1.30 (t, 3H, CH_3), 4.10 (s, 3H, OCH_3), 4.2 (q, 2H, CH_2), 7.1–7.5 (m, 5H, Ar-H+NH), 8.0 (s, H, NH), 9.9 (s, H, $NHSO_2$).
15a	3330, 3207, 3199 (3NH), 3168 (CH-arom.), 2996 (CH-aliph.), 1775, 1696 (2C=O), 1598 (C=N), 1376, 1166 (SO_2), 1059 (C=S).	0.89 (s, 3H, CH_3), 1.2 (t, 3H, CH_3), 3.3 (s, 3H, $COCH_3$), 4.1 (q, 2H, CH_2), 5.8, 6.4 (2s, 2H, pyrazole-H), 7.4–7.9 (m, 11H, Ar-H+2NH), 10.9 (s, H, $NHSO_2$).
15b	3384–3204 (br, 3NH), 3015 (CH arom.), 2976 (CH-aliph.), 1736, 1685 (2C=O), 1311, 1146 (SO_2), and 1067 (C=S).	1.0 (s, 3H, $2CH_3$), 1.2 (t, 3H, CH_3), 3.4 (s, 3H, $COCH_3$), 4.14 (s, 3H, OCH_3), 4.2 (q, 2H, CH_2), 7.4–7.9 (m, 7H, Ar-H+3NH).
18	3243 (NH), 3134 (CH-arom.), 2976 (CH-aliph.), 1715 (C=O), 1565 (C=N), 1366, 1145 (SO_2), 1057 (C=S).	0.89, 1.1 (2s, 6H, $2CH_3$), 3.4 (s, 3H, $COCH_3$), 5.54, 6.59 (2s, 2H, pyrazole-H), 7.5–7.9 (m, 10H, Ar-H+NH), 10.5 (s, H, $NHSO_2$).

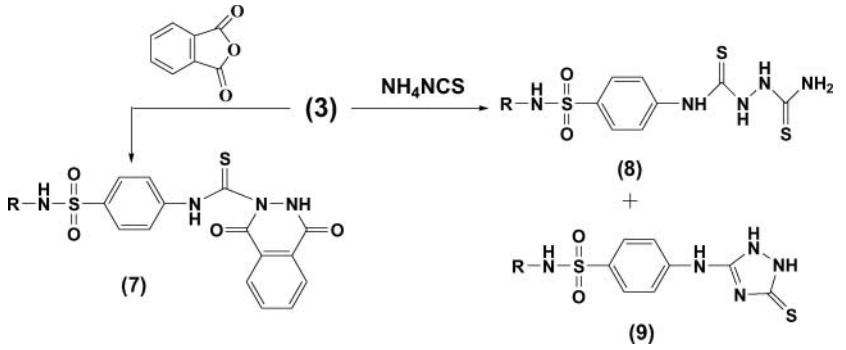
pyrazole-H), 7.42–7.71 (m, 11H, Ar-H+2 NH), 10.6 (s, H, $NHSO_2$), and 11.3 ppm (s, H, NH_2). Its mass spectrum revealed a molecular ion peak corresponding to the formula $C_{16}H_{16}N_6O_2S_2$ (387, M-1), and the base peak was found in the spectrum at m/z 77 (100%), which is characteristic for phenyl group (see Chart 1, Supplemental Materials).



Scheme 2

Thiosemicarbazide derivative **(3)** was exploited as starting material for further functionalization and heterocyclization. It was planned to investigate the reactivity of thiosemicarbazide derivative **(3)** toward an active methylene compound, where the pyrazole ring system has important and versatile biological activities.[20,21] Thus, when thiosemicarbazide derivative **(3)** reacted with acetylacetone, diethylmalonate, and/or ethylacetoacetate, the dimethylpyrazoline **(4)**, pyrazolindione **(5)**, pyrazolinone **(6)** derivatives were obtained (Scheme 2). The structures of pyrazolosulphaphenazole (**4–6**) were elucidated by elemental analysis and spectral data. The infrared spectrum of all compounds **(4–6)** exhibited the disappearance of characteristic bands for NH_2 group of the hydrazide **(3)**. The ^{1}H NMR spectrum of (**4**; DMSO-d_6) showed new resonances assigned to the $2CH_3$; proton at δ 1.2 and δ 1.3 provided evidence for 3,5-dimethylpyrazole formation. The infrared spectrum of **(5)** showed the following bands: 1751, 1740 (2C=O), 1681 (C=N), 1384, 1154 (SO_2), and 1070 cm^{-1}(C=S). Also, its ^{1}H NMR spectrum (in DMSO-d_6) revealed the following signals: 5.8 (s, 2H, CH_2CO pyrazoline), 9.4 (s, 1H, NH), and 10.5 ppm (s, 1H, $NHSO_2$).

The infrared spectrum of compound **(6)** exhibited the following absorption bands: 3310, 3230 (2NH), 1670 (C=O), 1380, 1150 (SO_2), and 1093 cm^{-1} (C=S). The ^{1}H NMR spectrum of (**6**; DMSO-d_6) showed a singlet at δ 1.23 assigned to the CH_3 group and singlet at δ 5.8 assigned to the CH_2CO pyrazoline and 5.54, 6.68 (2s, 2H, pyrazole-H), 7.22–7.55 (m, 9H, Ar-H), 8.9 (s, H, NH), 9.9 ppm (s, 1H, $NHSO_2$). The phthalazine derivative (**7**) was obtained in a good yield via reaction of thiosemicarbazide derivative (**3**) with phthalic anhydride (Scheme 3). The structure of **(7)** was established via analytical and spectral data (Table I). Its spectrum showed the following absorption bands: 3210 (NH), 1740, 1733 cm^{-1}(2C=O). ^{1}H NMR spectrum of **(7)** (in DMSO-d_6) showed the following signals: 5.5, 6.7 (2s, 2H, pyrazole-H), 7.5–8.3 (m, 15H, Ar-H+NH), and 10.3 ppm (s, H, $NHSO_2$). The mass spectrum of **(7)** revealed a molecular ion peak m/z at 518 (M^+, 2.77%) with a

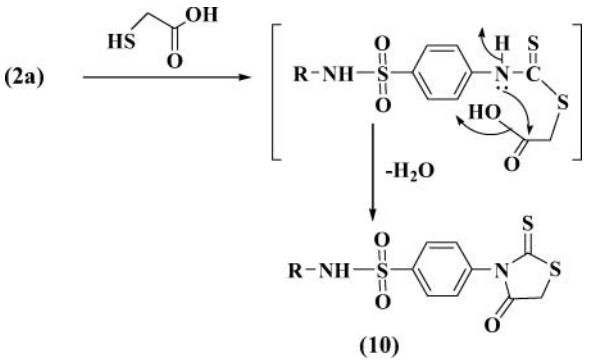


Scheme 3

base peak at 104 (100%). Treatment of thiosemicarbazide derivative (**3**) with ammonium thiocyanate in ethanol in the presence of concentrated hydrochloric acid afforded the thiourea derivative **(8)** after cooling of the filtrated product, while 1,2,4-triazol benzenesulfonamide derivative **(9)** was separated while hot. The structure of compounds **(8)** and **(9)** are supported by their elemental analysis and spectral data. Infrared spectrum of compound **(8)** showed the presence of an absorption band at 3300, 3330 cm^{-1}, which is characteristic for the NH_2 functional group in addition to absorption bands due to NH group, 1378, 1165 (SO_2), and 1067, 1089 cm^{-1} (2C=S). ^1H NMR spectrum of **(8)** (in DMSO-d_6) showed the following signals: 5.3, 6.5 (2s, 2H, pyrazole-H), 7.42–8.0 (m, 10H, Ar-H+NH), 9.8, 9.9(2s, 2H, 2NH), 10.6 (s, H, $NHSO_2$), and 11.0 ppm (s, H, NH_2). Also, its mass spectrum afforded a molecular ion peak m/z at 449 (M+2, 24.98%) in addition to the base peak at m/z 56 (100%). ^1H NMR spectrum of **(9)** (in DMSO-d_6) showed the following signals: 5.3, 6.4 (2s, 2H, pyrazole-H), 7.6–8.2 (m, 10H, Ar-H+NH), and 10.5 ppm (s, H, $NHSO_2$). Its mass spectrum furnished a molecular ion peak corresponding to the formula $C_{17}H_{15}N_7O_2S_2$ at 414 (M+1, 31.7%) and the base peak was found in the spectrum m/z at 104 (100%). The formation of 1,2,4-triazol benzenesulfonamide derivative **(9)** is assumed to proceed via the formation of thiourea derivative **(8)**, followed by intramolecular cyclization through initial nucleophilic attack of amino group to C=S followed by intramolecular cyclization via elimination of hydrogen sulfide.

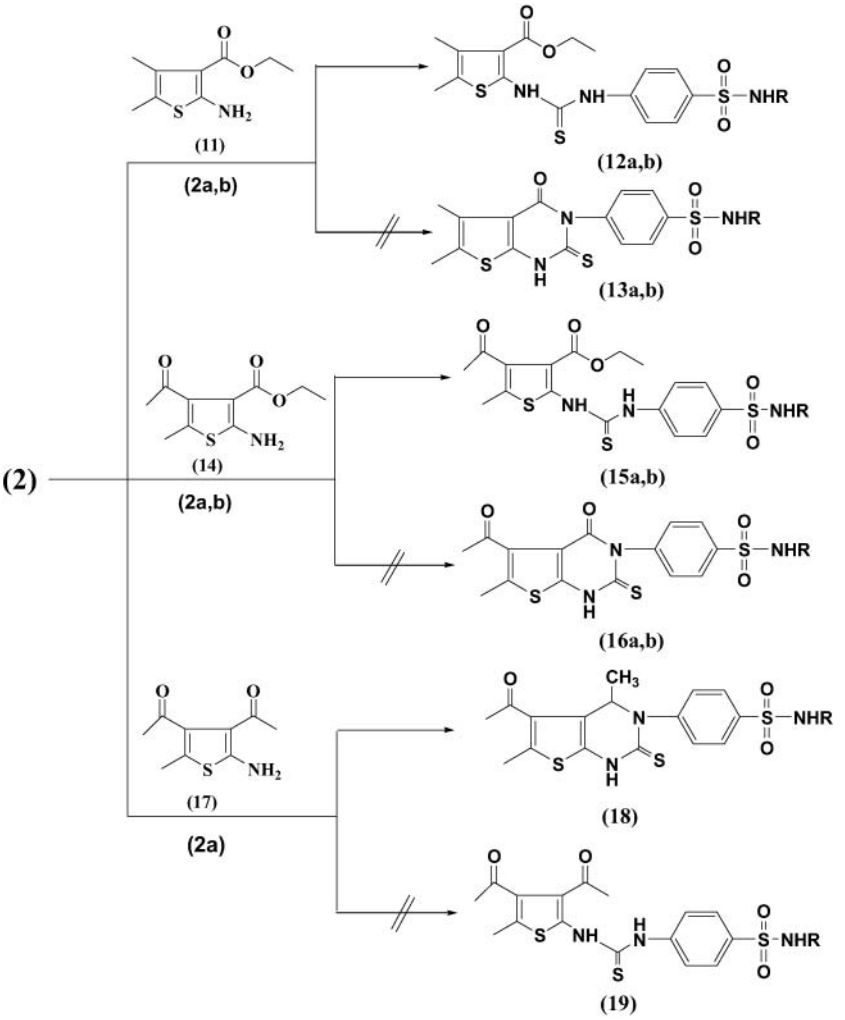
Cyclocondensation of isothiocyanate derivative **(2a)** with 2-mercaptoacetic acid in refluxing acetic acid to furnish 2-thioxothiazolidine derivative **(10)** (Scheme 4). The structure of **(10)** was established via analytical and spectral data. Its spectrum showed the following absorption bands: 3222 (NH), 1740 cm^{-1} characteristic for the C=O functional group of thiazolidinone moiety and 1093 cm^{-1} (C=S). Also, its ^{1}HNMR spectrum revealed a signal at δ 4.2 assigned to the -CH_2 of thiazolidinone moiety and multiplet at δ 7.2–8.1 ppm assigned to aromatic protons and SO_2NH. Also, mass spectrum furnished a molecular ion peak m/z at 430 (M^+, 28%), and the base peak was found in the spectrum m/z at 52 (100%).

The formation of thiazolidinone **(10)** is assumed to proceed through the initial nucleophilic attack of the mercapto group to the thiocarbanyl moiety of the isothiocyanate followed by intramolecular cyclization via dehydration. The reactivity of isothiocyanates **(2a**,**b)** towards some nitrogen nucleophiles was investigated. Thus, interaction of isothiocyanatosulfonamides **(2a**,**b)** with 2-amino-4,5-dimethyl-3-thio-phenecarboxylic acid ethyl ester **(11)** and 4-acetyl-2-amino-5-methyl-3-thio-phenecarboxylic acid methyl ester **(14)** furnished dimethyl thiophenecarboxylate derivative **(12a**,**b)** and methylthiophene



Scheme 4

carboxylate derivative **(15a**,**b)** rather than the expected products **(13a**,**b)** and **(16a**,**b)**, which were ruled out on the basis of analytical and spectral data (Scheme 5). The structures of **(12a**,**b)** and **(15a**,**b)** were supported via analytical and spectral data (Table I). The infrared spectrum of compound **(12a)** displayed the absence of NCS functional group and showed the following absorption bands: 3330, 3243, 3236 (3NH), 3165 (CH-arom.), 2987 (CH-aliph.), 1775 (C=O), 1545 (C=N), 1350, 1165 (SO_2), 1063 cm^{-1} (C=S). Also, its ^1H NMR spectrum (in DMSO-d_6) revealed the following signals: 0.87, 1.2 (2s, 6H, $2CH_3$), 1.3 (t, 3H, CH_3), 4.0 (q, 2H, CH_2), 5.6, 6.6 (2s, 2H, pyrazole-H), 7.5–7.9 (m, 10H, Ar-H+NH), 8.0 (s, H, NH), and 11.1 ppm (s, H, $NHSO_2$). The infrared spectrum of compound **(12b)** exhibited the following absorption bands: 3494, 3242, 3105 (3NH), 2985 (CH-aliph.), 1759(C=O), 1534 (C=N), 1321, 1155 (SO_2), 1069 cm^{-1} (C=S). Its ^1H NMR spectrum (in DMSO-d_6) revealed the following signals: 0.9, 1.1(2s, 6H, $2CH_3$), 1.30 (t, 3H, CH_3), 4.10 (s, 3H, OCH_3), 4.2 (q, 2H, CH_2), 7.1–7.5 (m, 5H, Ar-H+NH), 8.0 (s, H, NH), 9.9 ppm (s, H, $NHSO_2$). The IR spectrum of **(15a)** revealed the absorption bands at 3330, 3207, 3199 (3NH), 3168 (CH-arom.), 2996 (CH-aliph.), 1775, 1696 (2C=O), 1598 (C=N), 1376, 1166 (SO_2), 1059 cm^{-1} (C=S). Its ^1H NMR spectrum (in DMSO-d_6) revealed the following signals: 0.89 (s, 3H, CH_3), 1.2 (t, 3H, CH_3), 3.3 (s, 3H, $COCH_3$), 4.1 (q, 2H, CH_2), 5.8, 6.4 (2s, 2H, pyrazole-H), 7.4–7.9 (m, 11H, Ar-H+2NH), 10.9 (s, H, $NHSO_2$). The IR spectrum of **(15b)** exhibited absorption bands at 3384–3204 (br, 3NH), 3015 (CH arom.), 2976 (CH-aliph.), 1736, 1685 (2C=O), 1311, 1146 (SO_2), and 1067 cm^{-1} (C=S). Also, its ^1H NMR spectrum (in DMSO-d_6) revealed the following signals: 1.0 (s, 3H, $2CH_3$), 1.2 (t, 3H, CH_3), 3.4 (s, 3H, $COCH_3$), 4.14 (s, 3H, OCH_3), 4.2 (q, 2H, CH_2), 7.4–7.9 ppm (m, 7H, Ar-H+3NH). Alternatively, treatment of 4-isothiocyanato-N-(1-phenyl-1H-pyrazol-5-yl)benzene- sulfonamide **(2a)** with 1,1'-(2-amino-5-methyl-thiophene-3,4-diyl) diethanone **(17)** yielded thienopyrimidine derivative **(18)** and eliminated the other possible structure **(19)** on the basis of analytical and spectral data (Scheme 5). Its infrared spectrum exhibited the following absorption bands: 3243 (NH), 3134 (CH-arom.), 2976 (CH-aliph.), 1715 (C=O), 1565 (C=N), 1366, 1145 (SO_2), 1057 cm^{-1} (C=S) (Table I). Its ^1H NMR spectrum (in DMSO-d_6) revealed the following signals: 0.89, 1.1 (2s, 6H, $2CH_3$), 3.4 (s, 3H, $COCH_3$), 5.54, 6.59 (2s, 2H, pyrazole-H), 7.5–7.9 (m, 10H, Ar-H+NH), 10.5 ppm (s, H, $NHSO_2$). The mass spectrum of compound **(18)** showed the molecular ion peak m/z at 537 (M^+, 18.60%), and the base peak was found in the spectrum m/z at 130 (100%).



Scheme 5

Antitumor Evaluation and Discussion

Doxorubicin, the reference drug used in this study, is one of the most effective antitumor agents that is used to produce regression in acute leukemia, Hodgkin's disease, and other lymphomas. The novel synthesized compounds (**3**,**9**,**15a**,**15b**, and **18**) were evaluated in the MCF7 (Breast) cell line (see the Supplemental Materials online, Table III).

EXPERIMENTAL

All melting points are uncorrected and were determined on a Stuart melting point apparatus. IR spectra were recorded on a Shimadzu-440 IR spectrophotometer using the KBr

Table II Characterization data for newly synthesized compounds (**2a–18**)

Compd. No.	Mp (°C)	Yield (%)	Mol. Formula (Mol. Wt)	Elemental Analyses Calculated/(Found). C%	H%	N%
2a	118–120	85	$C_{16}H_{12}N_4O_2S_2$ (356)	53.92(53.60)	3.39(3.00)	15.72(15.90)
2b	148–150	90	$C_{10}H_8N_4O_3S_3$ (328)	36.57(36.30)	2.46(2.70)	17.06(17.40)
3	135–137	79	$C_{16}H_{16}N_6O_2S_2$ (388)	49.47(49.20)	4.15(4.50)	21.63(21.30)
4	158–160	77	$C_{21}H_{20}N_6O_2S_2$ (452)	55.73(55.53)	4.45(4.15)	18.57(18.67)
5	205–207	83	$C_{19}H_{16}N_6O_4S_2$ (456)	49.99(50.29)	3.53(3.63)	18.41(18.21)
6	230–232	75	$C_{20}H_{18}N_6O_3S_2$ (454)	52.85(52.55)	3.99(4.09)	18.49(18.69)
7	194–196	80	$C_{24}H_{18}N_6O_4S_2$ (518)	55.59(55.99)	3.50(3.80)	16.21(16.01)
8	142–144	82	$C_{17}H_{17}N_7O_2S_3$ (447)	45.62(45.32)	3.83(3.93)	21.91(21.61)
9	289–290	75	$C_{17}H_{15}N_7O_2S_2$ (413)	49.38(49.58)	3.66(3.86)	23.71(23.31)
10	158–160	83	$C_{18}H_{14}N_4O_3S_3$ (430)	50.22(50.52)	3.28(3.08)	13.01(13.31)
12a	228–230	85	$C_{25}H_{25}N_5O_4S_3$ (555)	54.03(53.73)	4.53(4.33)	12.60(12.40)
12b	180–182	69	$C_{19}H_{21}N_5O_5S_4$ (527)	43.25(43.15)	4.01(3.01)	13.27(12.87)
15a	210–211	81	$C_{27}H_{25}N_5O_5S_3$ (583)	53.50(53.70)	4.32(4.42)	13.71(14.01)
15b	148–150	76	$C_{20}H_{21}N_5O_6S_4$ (555)	43.23(43.53)	3.81(4.01)	12.60(12.70)
18	244–246	39	$C_{25}H_{23}N_5O_3S_3$ (537)	55.85(55.55)	4.31(4.11)	13.03(13.33)

technique (Shimadzu, Japan). ^{1}H NMR spectra were measured on a Bruker proton NMR-Avance 300 (300MHz, spectrometer), in DMSO-d_6 as a solvent, using tetramethylsilane (TMS) as an internal standard. The mass spectra were performed by Hewlett Packard Model MS-5988 spectrometer. Elemental analyses were carried out at the Microanalytical Unit, Faculty of Science, Cairo University.

4-Isothiocyanato-N-(1-phenyl-1H-pyrazol-5-yl)benzenesulfonamide (2a) and 4-Isothiocyanato-N-(4-methoxy-1,2,5-thiadiazol-3-yl) benzenesulfonamide (2b)

Sulfonamide derivative **1a**,**b** (0.01 mol) were dissolved in H_2O (200 mL) containing concentrated HCl (50 mL). To this, $CSCl_2$ (0.012 mol) was added in one portion. Stirring was begun immediately and continued until all of the red color of $CSCl_2$ had disappeared (1 h), and the product was precipitated as white crystals. The resulting solid was filtered off, dried, and recrystallized from acetone to give **2a**,**b**, respectively (Table II).

N-(4-(N-(1-Phenyl-1H-pyrazol-5yl)sulfamoyl)phenyl) hydrazinecarbothioamide (3)

Hydrazine hydrate and/or phenyl hydrazine (0.01 mol) was added to a solution of **2a** (0.01 mol) in ethanol (50 mL). The reaction mixture was stirred for 3 h, during which time a white precipitate formed. The product was recrystallized from ethanol to give **3** (Table II).

3,5-Dimethyl-N-(4-(N-(1-phenyl-1H-pyrazol-5-yl)sulfamoyl)phenyl)-1H-pyrazole-1-carbothioamide (4)

A mixture of **3** (0.01 mol) and acetylacetone (0.01 mol) in absolute ethanol (50 mL) was heated under reflux for 7 h. The reaction mixture was cooled, and the precipitate formed was filtered off then recrystallized from ethanol to give **4** (Table II).

3,5-Dioxo-N-(4-(N-(1-phenyl-1H-pyrazol-5-yl)sulfamoyl)phenyl)pyrazolidine-1-carbothioamide (5)

A mixture of **3** (0.01 mol) and diethylmalonate (0.01 mol) in absolute ethanol (50 mL) was heated under reflux for 7 h. The reaction mixture was cooled, and the precipitate formed was filtered off then recrystallized from ethanol to give **5** (Table II).

3-Methyl-5-oxo-N-(4-(N-(1-phenyl-1H-pyrazol-5-yl)sulfamoyl)phenyl)-4,5-dihydro-pyrazole-1-carbothioamide (6)

A mixture of **3** (0.01 mol) and ethyl acetoacetate (0.01 mol) in absolute ethanol (50 mL) was heated under reflux for 7 h. The reaction mixture was cooled, and the precipitate formed was filtered off then recrystallized from ethanol to give **6** (Table II).

1,4-Dioxo-N-(4-(N-(1-phenyl-1H-pyrazol-5-yl)sulfamoyl)phenyl)-3,4-dihydro-phthalazine-2(1H)-carbothioamide (7)

A mixture of **3** (0.01 mol) in acetic acid and phthalic anhydride (0.01 mol) was added. The reaction mixture was then heated under reflux for 7 h, and the precipitate formed was filtered off then recrystallized from acetic acid to give **7** (Table II).

N^1-(4-(N-(1-Phenyl-1H-pyrazol-5-yl)sulfamoyl)phenyl)hydrazine-1,2-bis(carbothio-amide) (8) and N-(1-Phenyl-1H-pyrazol-5-yl)-4-(5-thioxo-2,5-dihydro-1H-1,2,4-triazol-3-ylamino)benzenesulfonamide (9)

A mixture of **3** (0.01mol) and ammonium thiocyanate (0.01mol) in ethanol (50 mL) containing concentrated hydrochloric acid (4 mL) was refluxed for 13 h. The reaction mixture was filtered while hot to give compound **9**. Compound **8** was obtained after cooling the filtered reaction mixture and recrystallized from dioxane (Table II).

4-(4-Oxo-2-thioxothiazolidin-3-yl)-N-(1-phenyl-1H-pyrazol-5-yl)benzenesulfonamide (10)

A mixture of **2a** (0.01 mol) and thioglycolic acid (0.01 mol) in dioxane (30 mL) containing a few drops of triethylamine was heated under reflux for 3 h. The reaction mixture was then cooled and poured into cold water and acidified with dilute HCl. The solid product was recrystallized from ethanol to give **10** (Table II).

Ethyl-4,5-dimethyl-2-(3-(4-(N-(1-phenyl-1H-pyrazol-5-yl)sulfamoyl)phenyl)thio-ureido)thiophene-3-carboxylate (12a) and Ethyl-2-(3-(4-(N-(4-methoxy-1,2,5-thia-diazol-3-yl)sulfamoyl)phenyl)thioureido)-4,5-dimethylthiophene-3-carboxylate (12b)

A mixture of isothiocyanatosulfonamides **2a**, **b** (0.01 mol) and ethyl 2-amino-4,5-dimethylthiophene-3-carboxylate **11** (0.01mol) in dioxane (30 mL) containing a few drops of triethylamine was heated under reflux for 13 h. The reaction mixture was cooled, and the solid product was recrystallized from ethanol to give **12a**,**b**, respectively (Table II).

Ethyl-4-acetyl-5-methyl-2-(3-(4-(N-(1-phenyl-1H-pyrazol-5-yl)sulfamoyl) phenyl) thioureido)thiophene-3-carboxylate (15a) and Ethyl-4-acetyl-2-(3-(4-(N-(4-methoxy-1,2,5-thiadiazol-3-yl)sulfamoyl) phenyl) thioureido) -5-methylthiophene-3-carboxylate (15b)

A mixture of isothiocyanatosulfonamides **2a**,**b** (0.01 mol) and methyl 4-acetyl-2-amino-5-methylthiophene-3-carboxylate **14** (0.01 mol) in dioxane (50 mL) containing a few drops of triethylamine was heated under reflux for 15 h. The reaction mixture was then cooled, and the solid product was recrystallized from ethanol to give **15a**, **b**, respectively (Table II).

4-(5-Acetyl-4,6-dimethyl-2-thioxo-1,2-dihydrothieno[2,3-d]pyrimidin-3 (4H)-yl)-N-(1-phenyl-1H-pyrazol-5-yl)benzenesulfonamide (18)

A mixture of isothiocyanatosulfonamide **2a** (0.01 mol) and 1,1'-(2-amino-5-methylthiophene-3,4-diyl)diethanone **17** (0.01 mol) in dioxane (50 mL) containing a few drops of triethylamine was heated under reflux for 13 h. The reaction mixture was cooled, and the solid product was recrystallized from ethanol to give **18** (Table II).

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