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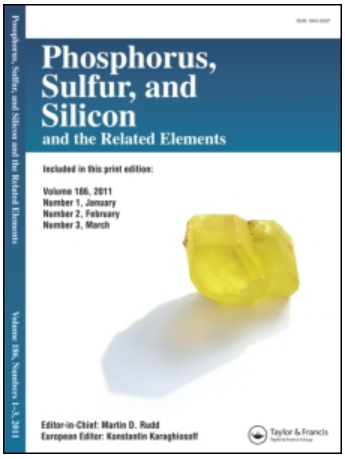

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Antitumor Activity of Some Novel 1,2,5-Thiadiazole Derivatives

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To cite this Article Ismail, Z. H. , Ghorab, M. M. , Mohamed, E. M. A. , Aly, H. M. and El-Gaby, M. S. A.(2008) 'Antitumor Activity of Some Novel 1,2,5-Thiadiazole Derivatives', Phosphorus, Sulfur, and Silicon and the Related Elements, 183: 10, 2541 — 2554
To link to this Article: DOI: 10.1080/10426500801967815
URL: http://dx.doi.org/10.1080/10426500801967815

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Phosphorus, Sulfur, and Silicon, 183:2541–2554, 2008
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ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426500801967815

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Antitumor Activity of Some Novel 1,2,5-Thiadiazole Derivatives

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Some novel thiourea,1,2,4-triazole, quinazoline, thieno[2,3-d]pyrimi-dine, and thiazolidine derivatives were synthesized to evaluate their antitumor activity. Compound (3f) is nearly as active as reference drug, (Doxorubicin) as positive control.

Keywords 1,2,5-Thiadiazole; antitumor activity; pyrazole; quinazoline derivatives; thiourea

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INTRODUCTION

Pyrazole[1] and 1,2,5-thiadiazole[2,3] derivatives are biological 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-dimethylethylamino)-3-(4-morpholino-1,2,5-thiadiazol-3-ylo-xy)-2-propanol (Timolol) is one of the most important medicines for 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 sulfamoyl moiety were described. Having the above facts in mind, and in continuation of our efforts to synthesize biologically active heterocyclic compounds from readily available starting materials,[14–17] we report here on the synthesis and antitumor activity of some novel pyrazole and 1,2,5-thiadiazole derivatives containing sulfamoyl moiety.

Received 11 December 2007; accepted 17 January 2008.
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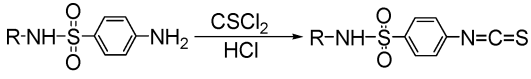
RESULTS AND DISCUSSION

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] Isothio-cyanatosulfonamides (**2a**,**b**) were synthesized by treatment of sulfonamide derivatives (**1a**,**b**) with thiophosgene in the presence of dilute hydrochloric acid at room temperature in quantitative yields, Scheme 1.

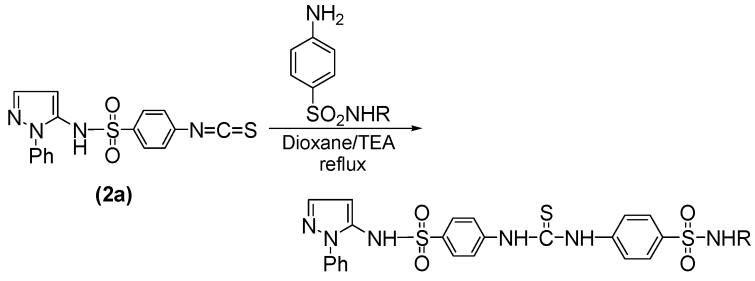


(1a,b) **(2a,b)**

1a and **2a**; R = 1-phenyl-1H-pyrazol-5-yl
1b and **2b**; R = 4-methoxy-1,2,5-thiadiazol-3-yl

SCHEME 1

The reactivity of isothiocyanates (**2a**,**b**) towards some nucleophilic reagents was studied. Condensation of isothiocyanate derivative (**2a**) with sulfonamide derivatives in refluxing dioxane in the presence of triethylamine furnished the 1,3-disubstituted thiourea derivatives (**3a–i**), Scheme 2. The structures of compounds (**3a–i**) were supported by analytical and spectral data. The infrared spectra of compounds (**3a–i**)



(2a) **(3a-i)**

3a; R = H, 3b; R = $COCH_3$

3c; R = C (NH)(NH_2), 3d; R = 2-Thiazolyl

3e; R = 5-(3-Methyl)isoxazolyl, 3f; R = 2-(4,6-Dimethylpyrimidinyl)

3g; R = 2-(4-Methylpyrimidinyl), 3h; R = 1-Phenyl-1H-pyrazol-5-yl

3i; R=2-Quinoxalinyl

SCHEME 2

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showed the absence of N=C=S functional group in addition to the presence of NH and SO_2 functional groups. Mass spectrum of compound (**3a**) revealed a molecular ion peak corresponding to the formula $C_{22}H_{20}N_6O_4S_3$ ($M^+ = 528$; 28.21%) with a base peak at m/z 80 (100%), Table I. Also, mass spectrum of compound (**3e**) showed a molecular ion peak at m/z 609(31.7%) and the base peak was observed in the spectrum at m/z 71(100%). Mass spectrum of compound (**3f**) revealed a molecular ion peak at m/z 634(0.73%) with a base peak at m/z 52(100%), Chart 1. The ^{1}H NMR spectrum of compound (**3b**; DMSO-d_6) exhibited the following signals: 1.87 (s, 3H, $COCH_3$), 5.8, 6.56 (2s, 2H, pyrazole-H), 7.3 –7.58 (m, 14H, Ar-H+NH) and 9.8, 10.4, 11.6 ppm (3s, 3H, 3NH; exchangeable). Also, the ^{1}H NMR spectrum of compound (**3g**; DMSO-d_6) showed the following signals: 2.3 (s, 3H, CH_3), 5.9, 6.8 (2s, 2H, pyrazole-H),7.3 –7.72 (m, 16H, Ar-H + NH) and 7.9,8.4,10.4 ppm (3s, 3H, 3NH; exchangeable).

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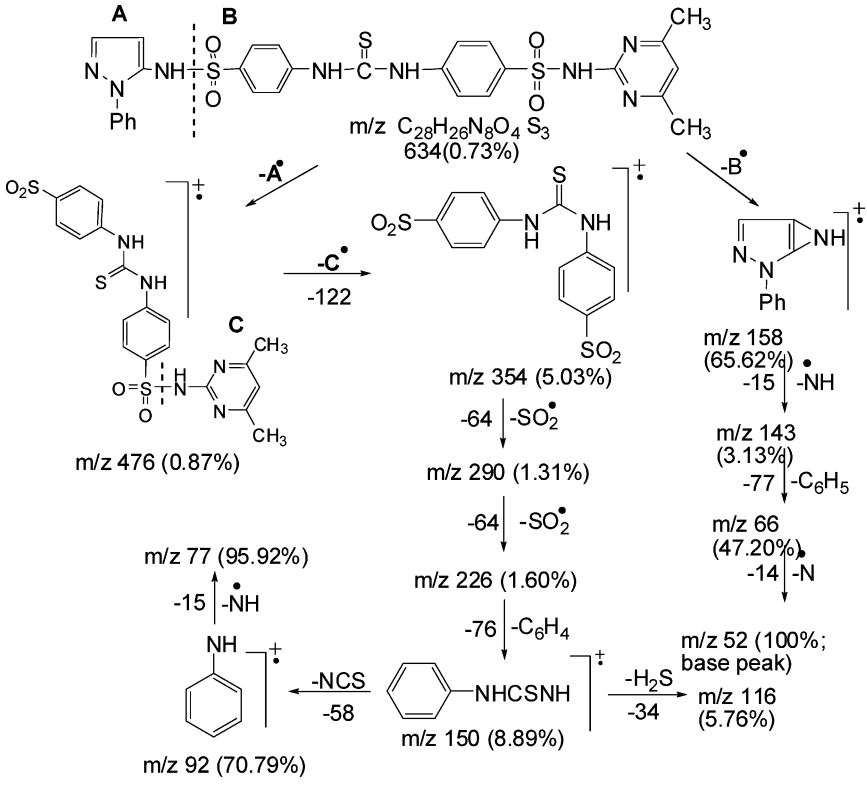

CHART 1 Mass fragmentation pattern of compound **(3f).**

TABLE I Spectral Data of the Newly Synthesized Compounds (2a–13)

Compd. no.	IR / ν_{max} (cm^{-1})	m/z (%)
2a	3445 (NH), 3000 (CH-arom.), 2030 (NCS), 1586 (C═N), 1345, 1163 (SO_2).	356 (M^+; 17.49%), 292 (11.10%), 256 (3.36%), 198 (9.31%), 158 (100%; base peak), 131 (33.46%), 97 (18.30%), 77 (38.60%), 55 (17.49%) .
2b	3226 (NH), 3099 (CH arom.), 2100 (NCS), 1555 (C═N), 1332, 1162 (SO_2).	328 (M^+; 17.40%), 264 (43.98%), 231 (4.88%), 198 (61.96%), 167(7.97%), 134 (100%; base peak), 111 (24.14%), 97 (37.02%), 71 (40.15%), 57 (41.79%).
3a	3342, 3250 (NH_2), 1592 (C═N), 1326, 1156 (SO_2).	528 (M^+; 28.21%), 397 (46%), 321 (28%), 281 (56%), 199 (43%), 131 (41%), 80 (100%; base peak).
3b	3476, 3430 (2NH), 1708 (C═O), 1592 (C═N),1330, 1160 (SO_2).	—
3c	3414, 3360 (NH_2), 1630, 1590 (C═N), 1328, 1162 (SO_2).	—
3d	3476, 3350, 3102 (3NH), 1620 (C═N), 1398, 1148 (SO_2).	—
3e	3422, 3100 (2NH), 1592 (C═N), 1392, 1160 (SO_2).	609 (M^+; 31.7%),213 (34%),130(31%), 86 (53%), 71 (100%; base peak), 64 (58%), 57 (58%).
3f	3450, 3394 (2NH), 3094 (CH-arom.), 1626 (C═N), 1384, 1162 (SO_2).	632 (M-2; 0.7%), 476 (0.8%), 356 (5.03%), 314 (4.1%), 255 (51%), 156 (40%), 134 (5.6%), 65 (88%), 52 (100%; base peak).
3g	3482, 3300 (2NH), 1564 (C═N), 1328, 1158 (SO_2).	—
3h	3460, 3230 (2NH), 3076 (CH-arom.), 1592 (C═N), 1390, 1158 (SO_2).	670 (M^+;0.51%), 551(4.51%),437 (1.54%), 367 (4.47%), 356 (8%), 250 (5.93%), 159 (100%; base peak).
3i	3464, 3380 (2NH), 1598 (C═N), 1326, 1154 (SO_2).	656 (M^+; 0.7%), 592 (1.43%), 523 (6.4%), 495 (5.3%), 356 (27%), 277 (100%; base peak), 236 (2%), 158 (98%), 77 (56%)

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TABLE I Spectral Data of the Newly Synthesized Compounds (2a–13) (continued)

Compd. no.	IR / ν_{max} (cm^{-1})	m/z (%)
5	3398, 3350 (NH_2), 2923 (CH-aliph.), 1627 (C═N), 1334, 1141 (SO_2).	290 [M-($NHSO_2$+ NH_2); 30%], 261 (15%), 217 (19.6%), 213 (100%; base peak), 185 (29%), 73 (0.5%).
7	3267 (NH), 3082 (CH- arom.), 2923 (CH- aliph.), 1651 (C═N), 1323, 1157 (SO_2).	—
9	3406, 3271, 3116 (3NH), 3062 (CH-arom.), 2931 (CH-aliph.), 1647 (C═O), 1610 (C═N), 1330, 1161 (SO_2).	—
11	3429, 3332, 3224 (3NH), 2943 (CH-aliph.), 2198 (C≡N), 1620 (C═N), 1330, 1134 (SO_2).	506 (M^+; 0.54%), 467 (0.7%), 411(2.5%), 395 (1.05%), 313 (2.8%), 266 (4.3%), 170 (0.3%), 150 (100%; base peak), 69(8%)
12	3436, 3186 (2NH), 2935 (CH-aliph.),1596 (C═N),1342, 1161 (SO_2).	506 (M^+; 10.54%), 465 (19%), 402 (23%), 348 (18%), 321 (100%; base peak), 276 (58%), 174 (69%), 113 (93%), 69 (64%), 231 (56%).
13	3222 (NH), 2983 (CH- aliph.), 1740 (C═O), 1591 (C═N), 1324, 1157 (SO_2).	—

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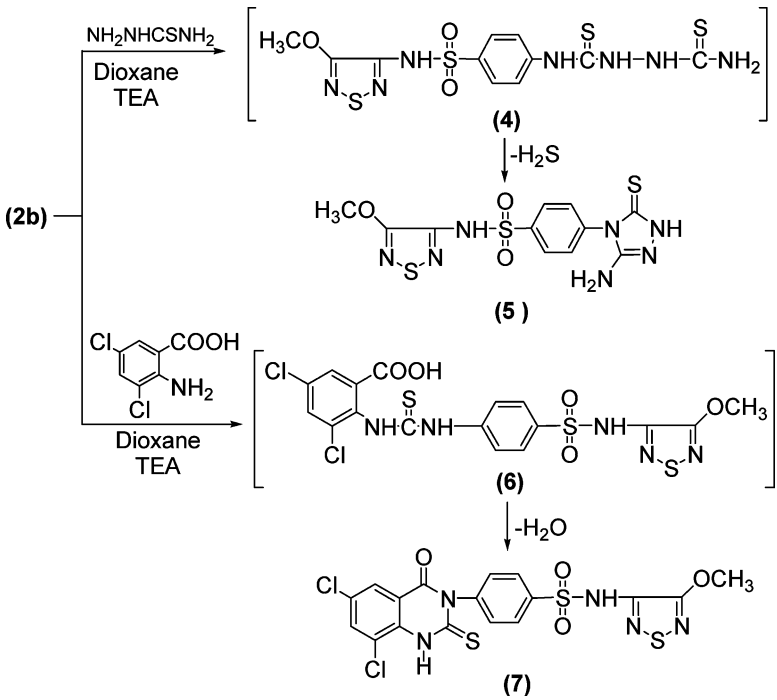
Refluxing of isothiocyanate derivative (**2b**) with thiosemicarb-azide in ethanol in the presence of triethylamine afforded 3-amino-5-thioxo-1H-1,2,4-triazole derivative (**5**) on the basis of analytical and spectral data, Scheme 3. Its infrared spectrum showed the following absorption bands: 3398, 3350 (NH, NH_2), 2923 (CH-aliph.), and 1627cm^{-1}(C = N). Also, its mass spectrum revealed a molecular ion peak at m/z 290 [30%; M^+-($NHSO_2$+ NH_2)] and the base peak was found in the spectrum at m/z 213 (100%). The formation of triazole derivative (**5**) is assumed to proceed via initial formation of the intermediate (**4**) followed by elimination of hydrogen sulfide. Cyclocondensation of 3,5-dichloroanthranilic acid with isothiocyanate derivative (**2b**) under reflux in dioxane in the presence of triethylamine yielded the corresponding 6,8-dichloro-4-oxo-2-thioxo-1,2-dihydroquinazoline derivative (**7**). The molecular structure of (**7**) was identified by analytical and spectral data. Its ^{1}H NMR spectrum (DMSO-d_6) showed the following signals: 4.01 (s, 3H, OCH_3), 7.6 –8.2 (m, 7H, Ar-H + NH), and 11.1 ppm (s, 1H, NH; exchangeable). The formation of quinazoline derivative (**7**)



SCHEME 3

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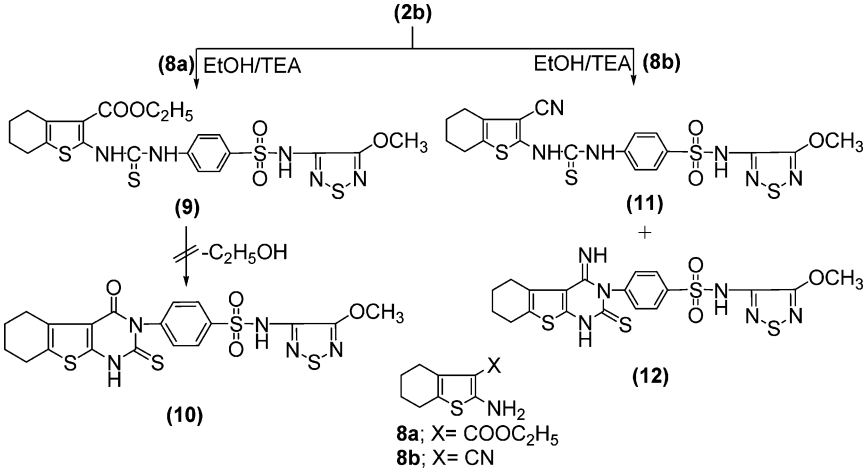
is assumed to proceed via the formation of thiourea inter-mediate (**6**) followed by intramolecular cyclization through elimination of water,[20] Scheme 3.

The novel thiourea derivative (**9**) was obtained when isothiocyanate derivative (**2b**) was allowed to react with ethyl-2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbo-xylate (**8a**) in refluxing ethanol in the presence of triethylamine. Trials to cyclize thiourea derivative (**9**) into the corresponding thieno[2,3-d]pyrimidine derivative (**10**) under different conditions failed. The molecular structure of thiourea derivative (**9**) was readily established based on analytical and spectral data, Scheme 4. ^{1}HNMR spectrum of (9; in DMSO-d_6) showed the following signals: 1.3 (t, 3H, CH_3), 1.6 (m, 8H, cyclohexyl), 4.0 (s, 3H, OCH_3), 4.1 (q, 2H, CH_2), 7.8 –8.0 (m, 4H, Ar-H), and 11.3, 11.8, 11.9 ppm (3s, 3H, 3NH; exchangeable). On the other hand, when isothiocyanate derivative (**2b**) was allowed to react with 2-amino-3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophene (**8b**) in ethanol in the presence of triethylamine under reflux, the thiourea derivative (**11**) was obtained after cooling



SCHEME 4

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of the filtrate, while thieno[2,3-d]pyrimidine derivative (**12**) was separated while hot. The structures of compounds (**11**) and (**12**) are supported by their elemental analysis and spectral data. Infrared spectrum of compound(**11**) showed the presence of absorption band at 2198 cm^{-1} that is characteristic for C≡N functional group in addition to absorption bands due to NH group. Also, its mass spectrum afforded a molecular ion peak at m/z 506 (M^+; 0.54%) in addition to the base peak at m/z 150(100%), Chart 2. The infrared spectrum of compound(**12**) displayed the absence of C≡N functional group. Its mass spectrum furnished a molecular ion peak at m/z 506 (10.64%) and the base peak was found in the spectrum at m/z 321(100%), Chart 3. The formation of thieno[2,3-d]pyrimidine derivative (**12**) is assumed to proceed via the formation of thiourea derivative (**11**) followed by intramolecular cyclization through nucleophilic addition of amino group to the cyano group.

Isothiocyanate derivative (**2b**) was cyclized with sulfanyl-acetic acid in refluxing acetic acid to furnish 2-thioxothiazolidine derivative (**13**), Scheme 5. The structure of (**13**) was established via analytical and spectral data. Its spectrum showed the following absorption bands: 3222 (NH), 2983, 2937(CH-aliph.), and 1740 cm^{-1}(C=O; thiazolidinone). Also, its ^1H NMR spectrum (DMSO-d_6) revealed the following signals: 3.7(s, 3H, OCH_3), 4.2 (s, 2H, CH_2), and 7.2–8.1 ppm (m, 5H, Ar-H + NH). The formation of thiazolidinone (**13**) is assumed to proceed through initial nucleophilic attack of mercapto group to thiocarbanyl

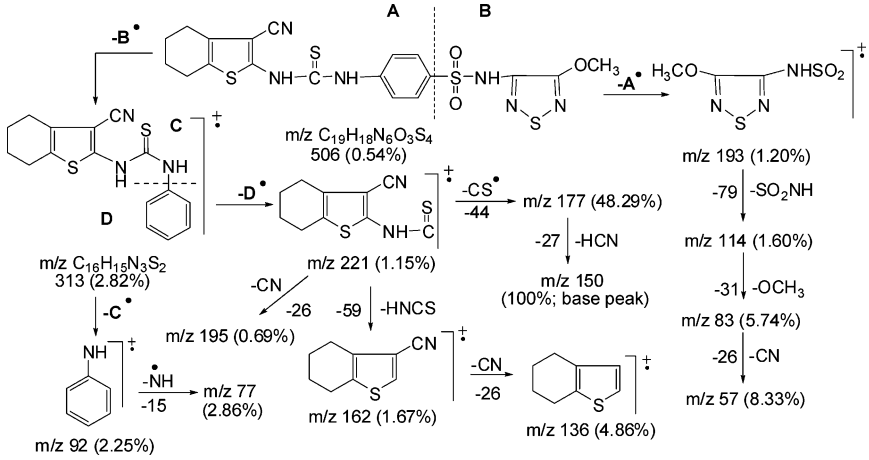

CHART 2 Mass fragmentation pattern of compound (**11**).

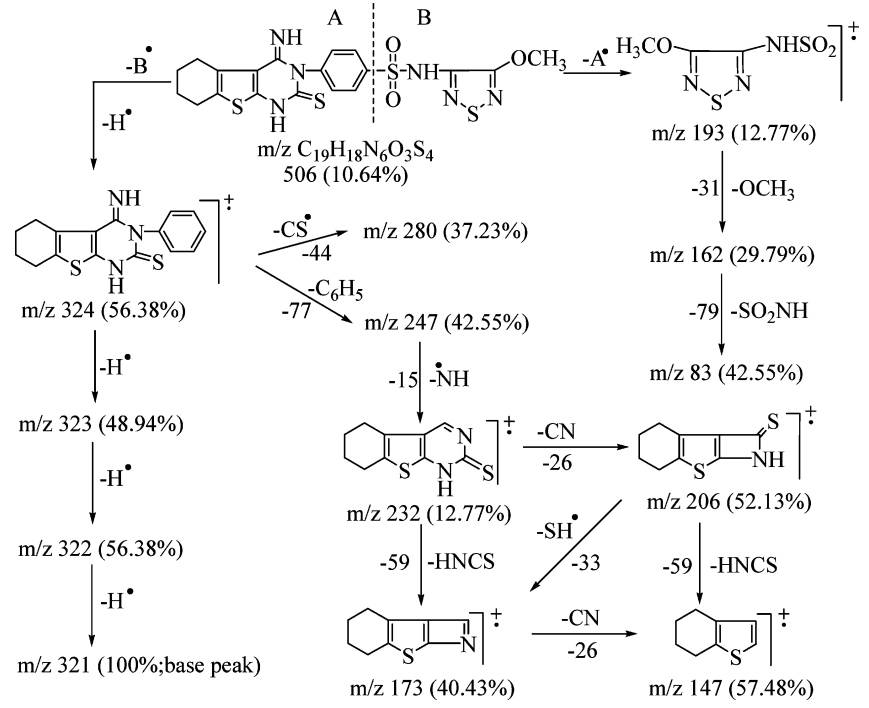

CHART 3 Mass fragmentation pattern of compound (**12**).

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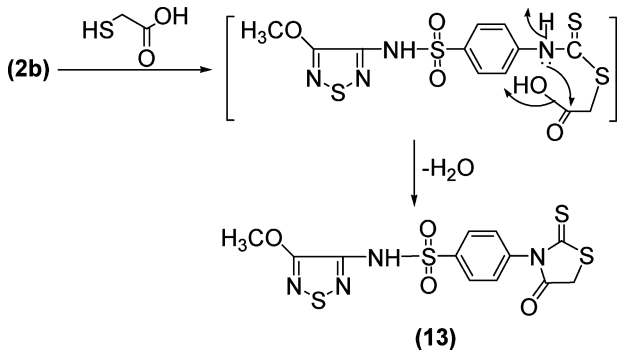

SCHEME 5

moiety of isothiocyanate followed by intramolecular cyclization via dehydration.[21]

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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 technique (Shimadzu, Japan). ^{1}H NMR spectra were measured on a BRUKER proton NMR-Avance 300 (300 MHz, 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)benzenesulfonam-ide (2a) and 4-isothiocyanato-N-(4-methoxy-1,2,5-thiadiazol-3-yl)benzenesulfonamide (2b) General Procedure

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

TABLE II Characterization Data for Newly Synthesized Compounds (2a–13)

Compd. no.	M.p. (°C)	Yield (%)	Mol. formula (mol.wt.)	Elemental analyses Calcd. (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)
3a	152–154	85	$C_{22}H_{20}N_6O_4S_3$ (528)	49.99 (49.80)	3.81 (3.60)	15.90 (15.60)
3b	132–134	81	$C_{24}H_{22}N_6O_5S_3$ (570)	50.51 (50.31)	3.89 (3.70)	14.73 (14.50)
3c	180–182	83	$C_{23}H_{22}N_8O_4S_3$ (570)	48.41 (48.30)	3.89 (3.60)	19.64 (19.50)
3d	230–232	85	$C_{25}H_{21}N_7O_4S_4$ (611)	49.08 (49.30)	3.46 (3.20)	16.03 (16.30)
3e	110–112	80	$C_{26}H_{23}N_7O_5S_3$ (609)	51.22 (51.40)	3.80 (3.50)	16.08 (16.30)
3f	142–144	84	$C_{28}H_{26}N_8O_4S_3$ (634)	52.98 (52.70)	4.13 (4.40)	17.65 (17.90)
3g	125–126	85	$C_{27}H_{24}N_8O_4S_3$ (620)	52.24 (52.60)	3.90 (3.60)	18.05 (18.30)
3h	134–136	83	$C_{31}H_{26}N_8O_4S_3$ (670)	55.51 (55.80)	3.91 (3.60)	16.70 (16.40)
3i	128–130	85	$C_{30}H_{24}N_8O_4S_3$ (656)	54.86 (54.60)	3.68 (3.30)	17.06 (17.30)
5	230–232	69	$C_{11}H_{11}N_7O_3S_3$ (385)	34.28 (34.50)	2.88 (2.50)	25.44 (25.20)
7	220–222	81	$C_{17}H_{11}Cl_2N_5O_4S_3$ (516)	39.54 (39.30)	2.15 (2.40)	13.56 (13.20)
9	148–150	76	$C_{21}H_{23}N_5O_5S_4$ (553)	45.55 (45.20)	4.19 (4.50)	12.65 (12.40)
11	224–226	40	$C_{19}H_{18}N_6O_3S_4$ (506)	45.04 (45.40)	3.58 (3.20)	16.59 (16.30)
12	118–120	48	$C_{19}H_{18}N_6O_3S_4$ (506)	45.04 (45.20)	3.58 (3.40)	16.59 (16.80)
13	213–215	79	$C_{12}H_{10}N_4O_4S_4$ (402)	35.81 (35.51)	2.50 (2.80)	13.92 (13.70)

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N-(1-phenyl-1H-pyrazol-5-yl)-4-(3-(4-sulfamoylphenyl)thioureido)-benzenesulfonamide (3a), N-(diaminomethylene)-4-(3-(4-(N-(1-phenyl-1H-pyrazol-5-yl)-sulfamoyl)-phenyl)thioureido)benzene-sulfonamide(3b), N-(4,6-dimethylpyrimidin-2-yl)-4-(3-(4-(N-(1-phe-nyl 1H-pyrazol-5-yl)sulfamoyl)phenyl)thioureido)benzenesulfon-amide (3c), N-(5-methylisoxazol-3-yl)-4-(3-(4-(N-(1-phenyl-1H-pyr-azol-5-yl)sulfamoyl)phenyl)thioureido)benzenesulfonamide (3d), N-(1-phenyl-1H-pyrazol-5-yl)-4-(3-(4-(N-thiazol-2-yl-sulfamoyl)phe-nyl)-thioureido)benzenesulfonamide (3e), N-(4-(3-(4-(N-(1-phenyl-1H-pyrazol-5-yl)sulfamoyl)phenyl)thioureido)phenylsulfonyl)-acetamide (3f), N-(4-methyl-pyrimidin-2-yl)-4-(3-(4-(N-(1-phenyl-1H-pyrazol-5-yl)sulfamoyl)-phenyl)-thioureido)-benzenesulfon-amide (3g), 4,4′-thiocarbonyl-bis(azanediyl)-bis(N-(1-phenyl-1H-pyrazol-5-yl)benzenesulfonamide) (3h) and N-(1-phenyl-1H-pyra-zol-5-yl)-4-(3-(4-(N-quinoxalin-2-yl-sulfamoyl)-phenyl)thioureido)-benzenesulfonamide (3i)

A mixture of isothiocyanate derivative **2a** (0.01 mol) and sulfonamide derivatives in dioxane (20 mL) containing triethyl-amine (0.5 mL) was heated under reflux for 2 h. The reaction mixture then cooled and poured into cold water and acidified with HCl. The solid product was collected and recrystallized from dioxane to give **3a–i**, (Table II).

4-(3-Amino-5-thioxo-1H-1,2,4-triazol-4(5H)-yl)-N-(4-methoxy-1,2,5-thiadiazol-3-yl) benzenesulfonamide (5)

A mixture of **2b** (0.01 mol) and thiosemicarbazide (0.01 mol) in dioxane (30 mL) containing a few drops of triethylamine was refluxed for 48 h. The reaction mixture then cooled and poured into cold water and acidified with dilute HCl. The solid product was collected and recrystallized from ethanol to give 5, (Table II).

4-(6,8-Dichloro-4-oxo-2-thioxo-1,2-dihydroquinazolin-3(4H)-yl)-N-(4-methoxy-1,2,5-thiadiazol-3-yl)benzenesulfonamide (7)

A mixture of **2b** (0.01 mol) and 3,5-dichloroanthranilic acid (0.01 mol) in dioxane (20 mL) containing 3 drops of triethylamine was heated under reflux for 1 h, filtered while hot and the solid obtained was recrystallized from dioxane to gave 7, (Table II).

Ethyl-2-(3-(4-(N-(4-methoxy-1,2,5-thiadiazol-3-yl)sulfamoyl)phen-yl)thioureido)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxy-late (9)

A mixture of **2b** (0.01 mole) and ethyl-2-amino-4,5,6,7-tetra-hydrobenzo [b]thiophene-3-carboxylate **8a** (0.01 mol) in ethanol (50 mL) containing 3 drops of triethylamine was heated under reflux for 3 h. The solid obtained was recrystallized from dioxane to give **9**, (Table II).

4-(3-(3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)thiourei-do)-N-(4-methoxy-1,2,5-thiadiazol-3-yl)benzenesulfonamide (11) and 4-(2-Thioxo-1,2,5,6,7-hexahydrobenzo[4,5]thieno[2,3-d]pyr-imidin-4-yl)-1-benzenesulfon amides (12)

A mixture of **2b** (0.01 mol) and 2-amino-3-cyano-4,5,6,7-tetrahydro-benzo[b]thiophene **8b** (0.01 mol), in ethanol (50 mL) containing 3 drops of triethyl-amine was refluxed for 3 h. The reaction mixture was filtered while hot to give compound **12**. The reaction mixture was diluted with water. The solid product so formed was collected by filtration and recrystallized to give **11**, Table II.

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N-(4-methoxy-1,2,5-thiadiazol-3-yl)-4-(4-oxo-2-thioxo-thiazolid-in-3-yl)benzenesulfonamide (13)

A mixture of **2b** (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 then cooled and poured into cold water and acidified with dilute HCl. The solid product was recrystallized from ethanol to give 13, (Table II).

Antitumor Activity (In-Vitro Study)

Reagents

1. RPMI 1640 medium (sigma).
2. Ehrlich Ascites Carcinoma cells (EAC) suspension (2.5×10^6/ml).
3. Trypan blue dye; A stock solution was prepared by dissolving one gram of the dye in distilled water (100 ml). The working solution was then prepared by diluting (1 ml) of the stock solution with (9 ml) of distilled water. The stain was used then for staining the dead EAC cells.
4. The compounds tested were (**3e**,**f**), (**9**), (**11**), and (**13**).

TABLE III In-Vitro Cytotoxic Activity of Some New Synthesized Compounds

Compd. no.	Non-viable cells (%) Concentration (μg/ml) 100	50	25	IC_{50} (μg/ml)
3e	0	0	0	$>100^a$
3f	100	50	20	50
9	20	10	5	$>100^a$
11	30	10	5	$>100^a$
13	0	0	0	$>100^a$
Doxorubicin (reference)	100	55	20	43

*$IC_{50} > 100$ (□ g/ml) is considered to be inactive

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Procedure

1. EAC cells were obtained by needle aspiration of the ascetic fluid from pre-inoculated mice under aseptic conditions.[22]
2. The cells were tested for viability and contamination by staining certain cell volume of this fluid by an equal volume of the working solution of trypan blue dye.[23–25]
3. The ascetic fluid was diluted with saline (1:10) to contain 2.5×10^6 cells on a hemocytometer.
4. In a set of sterile test tubes 0.1 ml of tumor cells suspension, 0.8 ml RPMI 1640 media, and 0.1 ml of each tested compound (corresponding to 100, 50, and 25 μg/ml) were mixed. The test tubes were incubated at 37°C for 2 h. Trypan blue exclusion test[22–23] was carried out to calculate the percentage of non-viable cells. Compounds producing more than 70% non viable cells are considered active.[24]
5. Doxorubicin (Adriablastina)is taken as a reference.

$$\%\,\text{of non-viable cells} = \frac{\text{No. of non viable}}{\text{Total No. of cells}} \times 100$$

The relationship between surviving fraction and drug concentration was plotted to obtain the survival curve of EAC cell. The response parameter calculated was IC_{50} value which corresponds to the compound concentration causing 50% mortality in net cells (Table III). The results obtained from this study showed that pyrazole having thiourea, pyrimidine, and sulfonamide moieties (**3f**) is nearly as active as the positive control Doxorubicin with IC_{50} of 50 μg/ml.Au: Insert asterisk into table. Is Box in parentheses supposed to be there.

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