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Research Article

Utility of Activated Nitriles in the Synthesis of Novel Heterocyclic Compounds with Antitumor Activity

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Reaction of cyanoacetic acid hydrazide (**1**) with 4-methoxyacetophenone and 4-chlorobenzaldehyde (**2a,b**) afforded the corresponding 2-cyanoacetohydrazide derivatives (**3a,b**) respectively. The latter compounds were utilized as a key intermediate for the synthesis of new heterocyclic compounds. Newly synthesized compounds were characterized by elemental analyses and spectral data. The antitumor evaluation of some newly synthesized compounds was screened *in vitro* against human breast cancer cell line (MCF-7).

1. Introduction

In many reports, hydrazide-hydrazones are considered to be good candidates for different pharmaceutical applications, where such compounds were considered to exert anticonvulsant [1], analgesic [2], anti-inflammatory [3], antiplatelet [4], antimalarial [5], antimicrobial [6], antitumoral [7, 8], vasodilator [9], and antiviral activity [10]. With the aim of obtaining new hydrazide-hydrazones with such wide spectrum of pharmaceutical applications, in this research, synthesis of a series of hydrazide-hydrazones and some of their heterocyclic transformations, followed by antitumor evaluations of newly synthesized products was done.

2. Experimental

All melting points were determined in open glass capillaries on a Gallenkamp apparatus and are uncorrected. IR spectra (cm^{-1}) were recorded on a Pye-Unicam spectrophotometer type 1200 using KBr discs. ^{1}H-NMR spectra were recorded on a Varian EM-390 (90 MHz) spectrometer using TMS as an internal standard and DMSO-d6 as a solvent. Chemical shifts were expressed in δ (ppm) values and mass spectra were determined on Finnigan Incos 500 (70 ev). Elemental analyses were determined using a Parkin-Elmer 240C Microanalyzer. The microanalyses were performed at the Microanalytical Unit, Faculty of Science, Cairo University.

*2.1. General Procedure for Synthesis of **3a,b**.* To a solution of 2-cyanoacetohydrazide (0. 99 g, 0.01 mol) in ethanol (20 mL), 4-methoxyacetophenone and/or *p*-chlorobenzaldehyde (0.01 mol) was added. The reaction mixture was heated under reflux for 2 h, then left to cool, and poured into ice/water. The obtained product was filtered, washed with water, and recrystallized from the appropriate solvent to give **3a**,**b**.

*2.1.1. Cyano-N′-[1-(4-methoxyphenyl)ethylidene]acetohydrazide (**3a**).* Yield, 75%; m.p. 186–188°C (ethanol); IR (KBr, cm^{-1}): 3204 (NH), 1675 (CO), 2256 (CN); ^{1}H NMR (DMSO: δ ppm): 2.23 (s, 3H, CH_3), 3.81 (s, 3H, OCH_3), 4.18 (s, 2H, CH_2), 10.90 (s, 1H, NH), 6.93–7.76 (m, 4H Ar–H); MS *m/z* (%): 231 (M^+, 98.11), 216 (27.99), 191 (40.26), 163 (48.64), 148 (80.06), 134 (87.96), 121 (39.49), 119 (56.71), 92 (100). Anal. for $C_{12}H_{13}N_3O_2$ (231.25); Calcd.: C, 62.33; H, 5.67; N, 18.17. Found: C, 62.00; H, 5.33; N, 18.02%.

*2.1.2. N′-[(4-Chlorophenyl)methylene]-2-cyanoacetohydrazide (**3b**).* Yield, 80%; m.p. 210–214°C (ethanol); IR (KBr, cm^{-1}): 3185 (NH), 1673 (CO), 2258 (CN); ^{1}H NMR (DMSO, δ ppm): 4.21 (s, 2H, CH_2), 11.82 (s, 1H, NH), 7.48–7.99 (m, 4H Ar–H), 8.16 (s, 1H, =CH); MS *m/z* (%): 221 (M^+, 2.35), 153 (5.54), 138 (100), 126 (15.89), 76 (15.35). Anal. for $C_{10}H_8ClN_3O$ (221.64); Calcd.: C, 54.19; H, 3.64; Cl, 16.00; N, 18.96. Found: C, 54.00; H, 3.42; Cl, 15.82; N, 18.65%.

*2.2. General Procedure for Synthesis of **4a,b**.* To a mixture of **3a**,**b** (0.01 mol), and salicylaldehyde (1.22 g, 0.01 mol) in ethanol (15 mL) were added few drops of TEA. The reaction was heated on water bath for 4 h and poured into ice water. The obtained product was filtered, washed with water, and recrystallized from the appropriate solvent to give **4a**,**b**.

*2.2.1. 2-Imino-N′-[1-(4-methoxyphenyl)ethylidene]-2H-chromene-3-carbohydrazide (**4a**).* Yield, 80%; m.p. 210–212°C (ethanol); IR (KBr, cm^{-1}): 3430, 3300 (2NH), 1671 (CO); ^{1}H NMR (DMSO, δ ppm): 3.80 (s, 3H, OCH_3), 2.48 (s, 3H, CH_3), 6.98–7.83 (m, 9H, Ar–H and C4-H coumarin), 9.27 (s, 1H, NH), 13.47 (s, 1H, NH); MS *m/z* (%): 335 (M^+, 100), 320 (18.43), 148 (3.90), 145 (95.72), 134 (12.36). Anal. for $C_{19}H_{17}N_3O_3$ (335.35); Calcd.: C, 68.05; H, 5.11; N, 12.53. Found: C, 68.00; H, 5.09; N, 12.23%.

*2.2.2. N′-[(4-Chlorophenyl)methylene]-2-imino-2H-chromene-3-carbohydrazide(**4b**).* Yield, 75%; m.p. 170–172°C (ethanol); IR (KBr, cm^{-1}): 3422, 3310 (2NH), 1618 (CO); ^{1}H NMR (DMSO, δ ppm): 6.94–7.70 (m, 10H, Ar–H, C4-H coumarin and =CH), 9.00 (s, 1H, NH), 11.10 (s, 1H, NH); MS *m/z* (%): 324 (M^+–1, 1.54), 310 (3.73), 239 (32.03), 165 (100). Anal. for $C_{17}H_{12}ClN_3O_2$ (325.74); Calcd.: C, 62.68; H, 3.71; Cl, 10.88; N, 12.90. Found: C, 62.38; H, 3.41; Cl, 10.52; N, 12.69%.

*2.3. General Procedure for Synthesis of Arylidene Derivatives (**5a**–**d**).* A solution of **3a**,**b** (0.01 mol) in ethanol (30 mL) was treated with 0.01 mol of aromatic aldehydes such as 4-methoxybenzaldehyde and/or 4-chlorobenzaldehyde and few drops of TEA. The reaction mixture was heated under reflux for 6 h. The reaction mixture was left to cool at room temperature and poured into ice/water containing few drops of hydrochloric acid, and the formed solid was collected by filtration and recrystallized from the appropriate solvent to give **5a**–**d**.

*2.3.12-Cyano-3-(4-methoxyphenyl)-N′-[1-(4-methoxyphenyl)-ethylidene]acrylohydrazide(**5a**).* Yield, 60%; m.p. 158–160°C (ethanol); IR (KBr, cm^{-1}): 3367 (NH), 2199 (CN), 1686 (CO); ^{1}H NMR (DMSO, δ ppm): 3.77 (s, 6H, $2OCH_3$), 2.49 (s, 3H, CH_3), 6.91–8.17 (m, 9H, Ar–H and =CH proton), 10.10 (s, 1H, NH); Anal. for $C_{20}H_{19}N_3O_3$ (349.38; Calcd.: C, 68.75; H, 5.48; N, 12.03. Found: C, 68.55; H, 5.28; N, 12.00%.

*2.3.2. N′-[(4-Chlorophenyl)methylene]-2-cyano-3-(4-methoxyphenyl)acrylohydrazide (**5b**).* Yield, 65%; m.p. 168–170°C (ethanol); IR (KBr, cm^{-1}): 3287 (NH), 2209 (CN), 1680 (CO); ^{1}H NMR (DMSO, δ ppm): 3.87 (s, 3H, OCH_3), 6.91–8.17 (m, 10H, Ar–H and =CH proton), 8.71 (s, 1H, NH); MS *m/z* (%): 339 (M^+, 3.15), 201 (100), 186 (93.94), 158 (38.79). Anal. for $C_{18}H_{14}ClN_3O_2$ (339.77); Calcd.: C, 63.63; H, 4.15; Cl, 10.43; N, 12.37. Found: C, 63.43; H, 4.00; Cl, 10.23; N, 12.00%.

*2.3.3. 3-(4-Chlorophenyl)-2-cyano-N′-[1-(4-methoxyphenyl)-ethylidene]acrylohydrazide (**5c**).* Yield, 50%; m.p. 148–150°C (ethanol); IR (KBr, cm^{-1}): 3313 (NH), 2211 (CN), 1636 (CO); ^{1}H NMR (DMSO; δ ppm): 3.78 (s, 3H, OCH_3), 2.50 (s, 3H, CH_3), 6.92–8.06 (m, 9H, Ar–H and =CH proton), 10.06 (br, 1H, NH); Anal. for $C_{19}H_{16}ClN_3O_2$ (353.80); Calcd.: C, 64.50; H, 4.56; Cl, 10.02; N, 11.88. Found: C, 64.33; H, 4.32; Cl, 10.00; N, 11.65%.

*2.3.4. 3-(4-Chlorophenyl)-N′-[(4-chlorophenyl)methylene]-2-cyanoacrylohydrazide (**5d**).* Yield, 60%; m.p. 228–230°C (ethanol); IR (KBr, cm^{-1}): 3282 (NH), 2212 (CN), 1682 (CO); ^{1}H NMR (DMSO, δ ppm): 7.52–8.02 (m, 9H, Ar–H and =CH proton), 8.27 (s, 1H, =CH), 8.71 (s, 1H, NH). Anal. for $C_{17}H_{11}Cl_2N_3O$ (344.19); Calcd.: C, 59.32; H, 3.22; Cl, 20.60; N, 12.21. Found: C, 59.11; H, 3.10; Cl, 20.50; N, 12.01%.

*2.4. General Procedure for Synthesis of Pyrazole-4-carbohydrazide (**6a,b**).* A mixture of **5a**,**b** (0.01) and hydrazine hydrate (0.50 g, 0.01 mol, 95%) was refluxed for 6 h. After cooling, the formed solid was filtered, washed with water, and recrystallized from the appropriate solvent to give **6a**,**b**.

*2.4.1. 5-Amino-3-(4-methoxyphenyl)-N′-[1-(4-methoxyphenyl) ethylidene]-1H-pyrazole-4-carbohydrazide(**6a**).* Yield, 50%; m.p. 120–124°C (ethanol); IR (KBr, cm^{-1}): 3340, 333, 3210 (NH, NH_2), 1663 (CO); ^{1}H NMR (DMSO, δ ppm): 3.82 (s, 6H, $2OCH_3$), 2.56 (s, 3H, CH_3), 6.99–7.84 (m, 8H, Ar–H), 8.13 (s, 1H, NH), 8.17 (br, 1H, NH), 6.86 (s, 2H, NH_2). Anal. for $C_{20}H_{21}N_5O_3$ (379.41); Calcd.: C, 63.31; H, 5.58; N, 18.46. Found: C, 63.00; H, 5.32; N, 18.31%.

*2.4.2. 5-Amino-N′-[(4-chlorophenyl)methylene]-3-(4-methoxyphenyl)-1H-pyrazole-4-carbohydrazide (**6b**).* Yield, 55%; m.p. 140–142°C (ethanol); IR (KBr, cm^{-1}): 3417, 3307, 3287, (NH, NH_2), 1660 (CO); ^{1}H NMR (DMSO, δ ppm): 3.74 (s, 3H, OCH_3), 7.03–7.91 (m, 9H, Ar–H and =CH proton), 8.62 (s, 1H, NH), 8.71 (s, 1H, NH), 6.86 (s, 2H, NH_2); MS *m/z* (%): 369 (M^+, 1.26), 280 (34.72), 267 (43.68), 134 (100). Anal. for $C_{18}H_{16}ClN_5O_2$ (369.80); Calcd.: C, 58.46; H, 4.36; Cl, 9.59; N, 18.94. Found: C, 58.22; H, 4.21; Cl, 9.32; N, 18.75%.

*2.5. 2-Amino-4-(4-chlorophenyl)-5-cyano-1-{[1-(4-methoxyphenyl)ethylidene]amino}-6-oxo-1,6-dihydropyridine-3-carboxamide (**8**).* To a solution of compound **3a** (2.31 g, 0.01 mol) in 1,4-dioxane (30 mL) containing few drops of TEA, 3-(4-chlorophenyl)-2-cyanoacrylamide (2.06 g, 0.01 mol) was added. The reaction mixture was heated under reflux for 4 h, then poured into ice/water, and the solid obtained was recrystallized from ethanol to give **8**. Yield, 85%; m.p. 258–260°C; IR (KBr, cm^{-1}): 3435, 3313, 3210, 3129 ($2NH_2$), 1671, 1660 (2CO), 2211 (CN); ^{1}H NMR (DMSO, δ ppm): 3.73 (s, 3H, OCH_3), 2.48 (s, 3H, CH_3), 7.45–7.82 (m, 8H, Ar–H), 6.92 (br, 2H, NH_2), 6.95 (br, 2H, NH_2); MS *m/z* (%): 435 (M^+, 8.76), 383 (77.70), 282 (14.04). Anal. for $C_{22}H_{18}ClN_5O_3$ (435.86); Calcd.: C, 60.62; H, 4.16; Cl, 8.13; N, 16.07%. Found: C, 60.42; H, 4.00; Cl, 8.00; N, 16.00%.

*2.6. 5-(4-Chlorophenyl)-8-{[1-(4-methoxyphenyl)ethylidene]-amino}-4,7-dioxo-2-(4-nitrophenyl)-3,4,7,8-tetrahydropyrido [2,3-d]pyrimidine-6-carbonitrile (**9**).* A mixture of compound **8** (4.35 g, 0.01 mol) and 4-nitrobenzaldehyde (0.01 mol) in ethanol (20 mL) with few drops of TEA was refluxed in oil bath with stirring for 10–12 h. The reaction mixture was

cooled, and poured into ice/water and the solid obtained was recrystallized from ethanol to give **9**. Yield, 50%; m.p. 190–192°C; IR (KBr, cm^{-1}): 3332 (NH), 1660, 1675 (2CO), 2212 (CN); ^{1}H NMR (DMSO, δ ppm): 3.83 (s, 3H, OCH_3), 2.50 (s, 3H, CH_3), 7.46–7.94 (m, 12H, Ar–H), 8.22 (br, 1H, NH). Anal. for $C_{29}H_{19}ClN_6O_5$ (566.95); Calcd.: C, 61.44; H, 3.38; Cl, 6.25; N, 14.82. Found: C, 61.21; H, 3.08; Cl, 6.00; N, 14.52%.

*2.7. 5-(4-Chlorophenyl)-8-{[1-(4-methoxyphenyl)ethylidene] amino}-4,7-dioxo-2-thioxo-1,2,3,4,7,8-hexahydropyrido[2,3-d]pyrimidine-6-carbonitrile (**10**).* To a stirred solution of **8** (4.35 g, 0.01 mol) in DMF (10 mL), carbon disulfide (0.76 mL, 0.01 mol) and NaOH (0.2 g, 0.005 mol) were added. The reaction mixture was stirred at room temperature for 6 h, then diluted with an equal volume of water, and treated with dilute HCl (pH 4). The separated solid product was filtered, washed with water, and recrystallized from DMF to give **10**. Yield, 50%; m.p. 130–132°C; IR (KBr, cm^{-1}): 3332, 3188 (NH), 1660, 1668 (2CO), 2206 (CN), 1243 (C=S); ^{1}H NMR (DMSO, δ ppm): 3.83 (s, 3H, OCH_3), 2.51 (s, 3H, CH_3), 6.93–7.60 (m, 8H, Ar–H), 8.62 (br, 1H, NH), 8.50 (br, 1H, NH); MS *m/z* (%): 478 (M^+ +1, 1.58), 270 (12.99), 229 (17.15), 143 (100). Anal. for $C_{23}H_{16}$ ClN_5O_3S (477.92); Calcd.: C, 57.80; H, 3.37; Cl, 7.42; N, 14.65; S, 6.71. Found: C, 57.50; H, 3.30; Cl, 7.25; N, 14.38; S, 6.52%.

*2.8. General Procedure for Synthesis of 4,5,6,7-Tetrahydrobenzo[b]thiophene-2-carbohydrazide Derivatives (**11a,b**).* To a solution of **3a**,**b** (0.01 mol) in ethanol (20 mL) containing TEA (1 mL) and elemental sulfur (0.01 mol), cyclohexanone (0.01 mol) was added. The reaction mixture was heated under reflux for 3 h, then poured into ice/water. The formed solid product was collected by filtration and recrystallized from the appropriate solvent to give **11a**,**b**.

*2.8.1. 3-Amino-N′-[1-(4-methoxyphenyl)ethylidene]-4,5,6,7-tetrahydrobenzo[b]thiophene-2-carbohydrazide (**11a**).* Yield; 70%; m.p. 118–120°C (pot.ether 60–80); IR (KBr, cm^{-1}): 3391, 3298, 3267 (NH, NH_2), 1698 (CO); ^{1}H NMR (DMSO, δ ppm): 3.80 (s, 3H, OCH_3), 2.51 (s, 3H, CH_3), 6.94–7.84 (m, 4H, Ar–H), 6.40 (br, 2H, NH_2), 10.40 (br, 1H, NH), 1.71–1.73 (m, 4H, $2CH_2$), 2.19–2.44 (m, 4H, $2CH_2$). Anal. for $C_{18}H_{21}$ N_3O_2S (343.44); Calcd.: C, 62.95; H, 6.16; N, 12.23; S, 9.34. Found: C, 62.65; H, 6.00; N, 12.00; S, 9.11%.

*2.8.2. 3-Amino-N′-[(4-chlorophenyl)methylene]-4,5,6,7-tetrahydrobenzo[b]thiophene-2-carbohydrazide (**11b**).* Yield, 85%; m.p. 110–112°C (ethanol); IR (KBr, cm^{-1}), 3425, 3298, 3267 (NH, NH_2), 1624 (CO); ^{1}H NMR (DMSO, δ ppm): 7.30–7.41 (m, 5H, Ar–H and =CH), 4.30 (br, 2H, NH_2), 8.42 (br, 1H, NH), 2.48–2.50 (m, 8H, $4CH_2$). Anal. for $C_{16}H_{16}$ Cl N_3OS (333.83); Calcd.: C, 57.56; H, 4.83; Cl, 10.62; N, 12.59; S, 9.61. Found: C, 57.32; H, 4.52; Cl, 10.42; N, 12.41; S, 9.32%.

*2.9. 2-Cyano-N′-[1-(4-methoxyphenyl)ethylidene]-2-(4-oxo-3-phenyl-1,3-thiazolidin-2-ylidene)ethanehydrazide (**14**).* To a stirred suspension of finely powdered potassium hydroxide (0.01 mole) in dry DMF (10 mL), cyanoacetohydrazide (**3a**) (2.31 g, 0.01 mole) was added and continuous stirring was done for 30 min. Then phenylisothiocyanate (1.35 mL, 0.01 mol) was added slowly over the course of 10 min. After complete addition, stirring of the reaction mixture was done at room temperature for 12 h. Then ethyl chloroacetate (1.22 mL, 0.01 mole) was added to the reaction mixture and stirred for 6 h. The reaction mixture was poured into crushed ice. The resulting precipitate was filtrated off, dried, and recrystallized from ethanol/DMF to give **14**. Yield, 85%; m.p. 264–266°C; IR (KBr, cm^{-1}), 3370 (NH), 1742, 1667 (2CO), 2184 (CN); ^{1}H NMR (DMSO, δ ppm): 3.79 (s, 3H, OCH_3), 2.43 (s, 3H, CH_3), 4.02 (s, 2H, C 4-2H-thiazolidinone), 6.94–7.76 (m, 9H, Ar–H), 9.83 (br, 1H, NH); MS *m/z* (%): 406 (M^+, 41.28), 391 (13.87), 360 (11.96), 314 (10.32), 281 (33.41), 134 (100). Anal. for $C_{21}H_{18}N_4O_3S$ (406.45); Calcd.: C, 62.05; H, 4.46; N, 13.78; S, 7.89. Found: C, 61.88; H, 4.22; N, 13.62; S, 7.55%.

*2.10. 3-Anilino-2-cyano-N′-[1-(4-methoxyphenyl)ethylidene]-3-methylthio-acrylohydrazide (**15**).* Compound **15** was synthesized as mentioned for the synthesis of **14** but using dimethylsulfate instead of ethylchloroacetate; the resulting product was crystallized from ethanol to give **15**.

Yield, 70%, m.p. 156–158°C; IR (KBr, cm^{-1}), 3374, 3318 (2NH), 1642 (CO), 2182 (CN); ^{1}H NMR (DMSO, δ ppm): 3.81 (s, 3H, OCH_3), 2.33 (s, 3H, CH_3), 2.51 (s, 3H, SCH_3), 6.94–7.82 (m, 9H, Ar–H), 10.11 (br, 1H, NH Ph), 11.00 (br, 1H, NH); MS *m/z* (%): 380 (M^+, 25.28), 333 (53.86), 365 (1.83), 318 (7.81), 231 (2.55), 217 (40.63), 163 (55.56). Anal. for C $_{20}H_{20}$ N_4O_2 S (380.46); Calcd.: C, 63.14; H, 5.30; N, 14.73; S, 8.43. Found: C, 63.00; H, 5.00; N, 14.52; S, 8.30%.

*2.11. 5-Amino-3-anilino-N′-[1-(4-methoxyphenyl)ethylidene]-1H-pyrazole-4-carbohydrazide (**16**).* A mixture of **15** (3.80 g, 0.01 mol) and hydrazine hydrate (0.012 mol) in ethanol (30 mL) was heated under reflux for 3 h. and allowed to cool. The solid product obtained was filtered and recrystallized from ethanol to give **16**. Yield, 55%; m.p. 122–125°C; IR (KBr, cm^{-1}): 3391, 3298, 3242 (NH, NH_2), 1641 (CO); ^{1}H NMR (DMSO, δ ppm): 3.77 (s, 3H, OCH_3), 2.27 (s, 3H, CH_3), 6.85–7.57 (m, 9H, Ar–H), 6.13 (s, 2H, NH_2), 8.00 (br, 1H, NH Ph), 8.20 (br, 1H, NHCO), 10.10 (br, 1H, NH); MS *m/z* (%): 364 (M^+, 0.41), 348 (0.47), 318 (2.92), 281 (28.52), 267 (22.88), 256 (0.71), 201 (1.60), 148 (47.34), 134 (100). Anal. for $C_{19}H_{20}$ N_6O_2 (364.40); Calcd: C, 62.62; H, 5.53; N, 23.06. Found: C, 62.32; H, 5.23; N, 23.00%.

*2.12. General Procedure for Synthesis of 3,3-Dimercaptoacrylohydrazide Derivatives (**18a,b**).* To suspension of finely powdered potassium hydroxide (0.04 mol) in dry DMF (20 mL) at 0°C the cyanoacetohydrazide **3a**,**b** (0.04 mol) was added for 30 min, carbon disulfide (3.04 mL, 0.04 mol) was added to the resulting mixture, stirring was continued for 12 h, and then hydrochloric acid (2 M, 20 mL was added dropwise, and stirring continued for additional 1 h. Then, the reaction mixture was poured into ice water. The solid product that formed was filtered off, dried, and recrystallized from the appropriate solvent to give **18a**,**b**.

*2.12.1. 2-Cyano-3,3-dimercapto-N′-[1-(4-methoxyphenyl)ethylidene]acrylohydrazide (**18a**).* Yield, 70%; m.p. 248–250°C (ethanol); IR (KBr, cm^{-1}): 3225 (NH), 1663 (CO); ^{1}H NMR (DMSO, δ ppm): 3.7 (s, 3H, OCH_3), 2.49 (s, 3H, CH_3), 6.97–7.95 (m, 4H, Ar–H), 10.26 (br, 1H, NHCO), 2.73 (s, 2H, 2SH); MS *m/z* (%): 306 (M^+ –1, 3.66), 281 (1.93), 274 (8.92), 241 (5.42), 215 (6.25), 163 (22.05), 134 (100). Anal. for $C_{13}H_{13}N_3O_2S_2$ (307.39); Calcd.: C, 50.79; H, 4.26; N, 13.67; S, 20.86%. Found: C, 50.45; H, 4.00; N, 13.32; S, 20.52%.

*2.12.2. N′-[(4-Chlorophenyl)methylene]-2-cyano-3,3-dimercaptoacrylohydrazide (**18b**).* Yield: 75%; m.p. 190–192°C (ethanol); IR (KBr, cm^{-1}): 3333 (NH), 1673 (CO); ^{1}H NMR (DMSO, δ ppm): 8.16 (s, 1H, CH=N), 7.48–7.99 (m, 4H, Ar–H), 11.82 (br, 1H, NH CO), 2.48 (s, 2H, 2SH). MS *m/z* (%): 297 (M^+, 4.75), 271 (3.86), 264 (4.55), 231 (3.45), 205 (4.63), 161 (26.97), 158 (4.02), 153 (16.19), 143 (11.75), 138 (100), 115 (8.28), 78 (51.02). Anal. for $C_{11}H_8ClN_3OS_2$ (297.78); Calcd.: C, 44.37; H, 2.71; Cl, 11.91; N, 14.11; S, 21.54%. Found: C, 44.00; H, 2.32; Cl, 11.66; N, 14.00; S, 21.22%.

*2.13. General Procedure for Synthesis of Ethyl [2-Cyano-1-mercapto-3-oxoprop-1-enyl)thio]acetate Derivatives (**19a,b**).* To a stirred suspension of finely powdered potassium hydroxide (0.02 mole) in dry DMF (10 mL), cyanoacetohydrazides, **3a**,**b**, (0.01 mole) were added. The resulted mixture was cooled at 10°C in an ice bath; then (0.01 mol) carbon disulfide was added slowly over the course of 10 min. After complete addition, stirring of the reaction mixture was continued for 6 h Then ethyl chloroacetate (1.22, 0.01 mol) was added to the mixture and stirring continued for 3 h, then the mixture was poured into crushed ice and HCl; the resulting precipitate was filtrated off, dried, and recrystallized from the appropriate solvent to give **19a**,**b**.

*2.13.1. Ethyl [2-Cyano-1-mercapto-3-{2-[1-(4-methoxyphenyl) ethylidene]hydrazino}-3-oxoprop-1-enyl)thio]acetate (**19a**).* Yield, 70%; m.p. 236–240°C (ethanol); IR (KBr, cm^{-1}): 3331 (NH); 2216 (CN); ^{1}H NMR (DMSO δ ppm): 3.84 (s, 3H, OCH_3), 2.51 (s, 3H, CH_3), 7.02–7.94 (m, 4H, Ar–H), 11.28 (br, 1H, NH), 11.54 (br, 1H, SH), 1.03 (t, 3H, CH_3), 4.33 (s, 2H, CH_2), 4.12 (q, 2H, CH_2). Anal. for $C_{17}H_{19}N_3O_4S_2$ (393.48); Calcd.: C, 51.86; H, 4.87; N, 10.68; S, 16.30. Found: C, 51.53; H, 4.52; N, 10.51; S, 16.00%.

*2.13.2.Ethyl ({3-[2-(4-Chlorobenzylidene)hydrazino]-2-cyano-1-mercapto-3-oxoprop-1-enyl}thio)acetate (**19b**).* Yield, 65%; m.p. 148–150°C (ethanol); IR (KBr, cm^{-1}): 3359 (NH), 2360 (CN); ^{1}H NMR (DMSO; δ ppm): 7.38–7.65 (m, 4H, Ar–H), 8.27 (s, 1H, CH=C), 1.05 (t, 3H, CH_3), 4.22 (q, 2H, CH_2), 4.02 (s, 2H, CH_2), 9.07 (br, 1H, NH), 10.02 (br, 1H, SH). Anal. for $C_{15}H_{14}ClN_3O_3S_2$ (383.87); Calcd.: C, 46.93; H, 3.68; Cl, 9.24; N, 10.95; S, 16.71. Found: C, 46.73; H, 3.34; Cl, 9.00; N, 10.65; S, 16.45%.

*2.14. General Procedure for Synthesis of 3,3-Bis(methylthio) acrylohydrazide Derivatives (**20a,b**).* Compounds **20a**,**b** were synthesized as mentioned for synthesis of **19**, but using dimethyl sulfate instead of ethyl chloroacetate, the resulting product was recrystallized from the appropriate solvent to give **20a**,**b**.

*2.14.1. 2-Cyano-N′-[(1-(4-methoxyphenyl)ethylidene]-3,3-bis-(methylthio)-acrylohydrazide (**20a**).* Yield, 70%; m.p. 168–170°C (pot.ether 60–80/benzene): IR (KBr, cm^{-1}), 3203 (NH), 1681 (CO); ^{1}H NMR (DMSO, δ ppm): 3.78 (s, 3H, OCH_3), 2.49 (s, 3H, CH_3), 2.50 (s, 6H, $2SCH_3$), 6.93–7.76 (m, 4H, Ar–H), 10.90 (br, 1H, NH CO). Anal. for $C_{15}H_{17}N_3O_2S_2$ (335.44); Calcd.: C, 53.71; H, 5.11; N, 12.53; S, 19.12. Found: C, 53.52; H, 5.00; N, 12.23; S, 19.00%.

*2.14.2. N′-[(4-Chlorophenyl)methylene]-2-cyano-3,3-bis(methylthio)acrylohydrazide (**20b**).* Yield, 75%; m.p. 188–190°C (ethanol); IR (KBr, cm^{-1}), 3185 (NH), 1674 (CO); ^{1}H NMR (DMSO, δ ppm): 8.16 (s, 1H, CH=N), 7.48–7.99 (m, 4H, Ar–H), 11.82 (br, 1H, NH CO), 2.50 (s, 6H, $2SCH_3$); MS *m/z* (%): 325 (M^+, 10.74), 295 (17.07), 153 (5.49), 138 (100). Anal. for $C_{13}H_{12}ClN_3OS_2$ (325.83); Calcd.: C, 47.92; H, 3.71; Cl, 10.88; N, 12.90; S, 19.68. Found: C, 47.64; H, 3.42; Cl, 10.55; N, 12.65; S, 19.48%.

*2.15. General Procedure for Synthesis of 5-Amino-3-methylthio-pyrazole-4-carbohydrazide (**21** and **22**).* A mixture of **20a** (3.35 g, 0.01 mol), hydrazine hydrate, and/or 2-hydrazino-1,3-benzothiazole (1.89 g, 0.012 mol) in ethanol (30 mL) was heated under reflux for 3 hrs and allowed to cool. The solid product obtained was filtrate off and recrystallized from the appropriate solvent to give **21** and **22**.

*2.15.1. 5-Amino-N′-[1-(4-methoxyphenyl)ethylidene]-3-methylthio-pyrazole-4-carbohydrazide (**21**).* Yield, 65%; m.p. 120–122°C (ethanol); IR (KBr, cm^{-1}): 3392, 3300, 3243 (NH, NH_2); ^{1}H NMR (DMSO, δ ppm): 3.74 (s, 3H, OCH_3), 2.27 (s, 3H, CH_3), 2.50 (s, 3H, SCH_3), 6.85–7.56 (m, 4H, Ar–H), 6.13 (br, 2H, NH_2), 8.00 (br, 1H, NH), 10.10 (br, 1H, NH); MS *m/z* (%): 319 (M^+, 0.81), 275 (1.24), 259 (1.44), 246 (4.66), 228 (4.80), 210 (3.20), 176 (16.37), 162 (44.23), 128 (24.43), 134 (100). Anal. for $C_{14}H_{17}N_5O_2S$ (319.38); Calcd.: C, 52.65; H, 5.37; N, 21.93; S, 10.04. Found: C, 52.42; H, 5.21; N, 21.73; S, 10.00%.

*2.15.2. 5-Amino-1-(1,3-benzothiazol-2-yl)-N′-[1-(4-methoxyphenyl)ethylidene]-3-methylthio-pyrazole-4-carbohydrazide (**22**).* Yield, 70%; m.p. 150–152°C (acetone); IR (KBr, cm^{-1}): 3392, 3300, 3243 (NH, NH_2); ^{1}H-NMR (DMSO, δ ppm): 3.76 (s, 3H, OCH_3), 2.23 (s, 3H, CH_3), 2.50 (s, 3H, SCH_3), 6.85–7.56 (m, 8H, Ar–H), 6.13 (s, 2H, NH_2), 10.44 (br, 1H, NH), 453 (M^+ +1, 16.51), 420 (12.55), 342 (5.93), 267 (2.54), 253 (4.46), 235 (100), 237 (8.19). Anal. for $C_{21}H_{20}N_6O_2S_2$ (452.55); Calcd.: C, 55.73; H, 4.45; N, 18.57; S, 14.17. Found: C, 55.52; H, 4.12; N, 18.23; S, 14.00%.

2.16. Antitumor Activity. Antitumor activity was performed in Regional Center for Mycology and Biotechnology, Al-Azhar University, Cairo, Egypt. Compounds **3a**, **3b**, **4a**, **4b**,

Table 1: *In vitro* anticancer screening of the synthesized compounds against human breast cancer cell line (MCF-7) at different concentration.

Compd. no.	Compound concentrations (μg/mL)						
	1.56 (μg/mL)	3.125 (μg/mL)	6.25 (μg/mL)	12.5 (μg/mL)	25 (μg/mL)	50 (μg/mL)	IC50 (μg/mL)
doxorubicin	30.86	21.18	17.22	11.74	6.55	3.24	0.426
3a	94.28	85.92	73.36	98.63	47.25	14.94	23.4
3b	94.76	89.14	80.92	67.48	54.3	22.38	28.4
4a	95.08	88.93	79.34	67.68	47.92	16.58	23.7
4b	98.48	93.07	87.12	72.35	51.94	27.19	27
6a	97.32	86.46	77.95	48.52	27.04	10.71	12.2
6b	100	97.68	89.73	73.48	51.42	19.17	26.1
11b	84.58	69.75	56.84	23.08	19.32	10.58	7.5
14	100	98.17	91.98	86.3	63.62	29.56	35
15	100	96.54	88.72	73.91	60.58	28.92	33.4
16	91.96	82.55	71.67	50.11	41.36	29.18	12.6
18b	96.98	93.14	76.92	68.45	59.73	31.08	33.5
19a	100	98.42	93.16	90.34	78.19	61.92	50
19b	89.34	81.9	69.79	53.41	38.18	26.87	15.3
21	93.81	88.94	79.22	63.75	16.28	9.64	16.1
22	80.36	69.42	61.87	56.39	41.81	18.26	18

IC50 value: corresponds to the concentration required for 50% inhibition of cell viability.

6a, **6b**, **11b**, **14**, **15**, **16**, **18b**, **19a**, **19b**, **21**, and **22** were tested for their cytotoxicity *in vitro*, in comparison with doxorubicin (DXR) as a reference drug against human breast cancer cell line (MCF-7). MCF-7 cells (1×10^4) were incubated with synthesized compounds at various concentrations of 0.39, 0.78, 1.56, 3.125, 6.25, 12.5, 25, and 50 μg/mL (incorporated with 10 μL DMSO) at 37°C for 48 h, and viable cells yield was determined by colorimetric method [11]. Experiments were carried out in triplicate, and results are reported in Table 1.

3. Results and Discussion

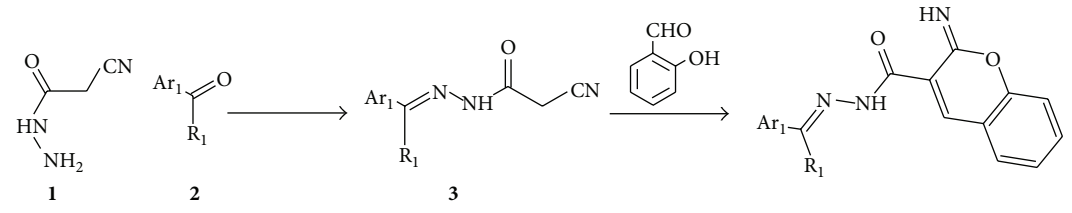
3.1. Synthesis. The Schemes 1–4 describe the synthesis of the target molecules. Condensation of cyanoacetic acid hydrazide (1) with 4-methoxyacetophenone and 4-chlorobenzaldehyde(**2a**,**b**) in hot 1,4-dioxane afforded hydrazone derivatives (**3a**,**b**). The structures of compounds (**3a**,**b**) were established on the basis of analytical and spectral data. IR spectrum of **3a** showed bands at 3204 cm^{-1} (NH), 2256 (CN), and 1675 (C=O). ^{1}H NMR spectrum of **3a** showed the presence of a singlet at δ 2.23 ppm corresponding to CH_3 group, a singlet at δ 3.81 ppm for methoxy group, a singlet at 4.18 ppm for CH_2 group, and a singlet at δ 10.90 ppm for an NH group. Further evidence for the structures of **3a**,**b** was obtained through studying their chemical reactivity through some chemical reagents. Thus, cyclocondensation of compounds **3a**,**b** with salicylaldehyde in boiling ethanol and in the presence of a few drops of triethylamine (TEA) [12] afforded the corresponding 2H-chromene-3-carbohydrazide derivatives, **4a**,**b**.

Condensed **3a**,**b** with aryl aldehydes such as 4-methoxybenzaldehyde and/or 4-chlorobenzaldehyde [13] afforded the corresponding arylidene derivatives **5a**–**d**. The structures of compounds **5a**–**d** were based on analytical and spectral data (see Section 2). When compounds **5a**,**b** reacted with hydrazine hydrate [14], they afforded the corresponding 1H-pyrazole-4-carbohydrazide derivatives, **6a**,**b**. The structure of **6** was inferred from its ^{1}H NMR spectrum which appeared as new signals for NH_2 group (Scheme 1).

Reactivity of hydrazide-hydrazone derivative **3a** toward cinnamonitrile derivative was studied [15]. Thus, the reaction of **3a** with 3-(4-chlorophenyl)-2-cyanoacrylamide afforded the corresponding pyridinone derivative **8**; the reaction took place through the intermediate **7**. Treatment of pyridinone derivative **8** with 4-nitrobenzaldehyde in the presence of ethanol and catalytic amount of triethylamine (TEA) afforded the corresponding pyrido[2,3-d]pyrimidine-6-carbonitrile derivative **9**. On the other hand, 2-thioxo-pyrido[2,3-d]pyrimidine-6-carbonitrile **10** was obtained by cyclizing **8** with carbon disulfide in the presence of sodium hydroxide at room temperature [16] followed by acidification with diluted hydrochloric acid. Structures of new compounds were based on analytical and spectral data. Thus, the ^{1}H NMR spectrum of **8** showed the presence of a singlet at δ 6.92 and 6.95 corresponding to the two NH_2 groups. The IR spectrum of **10** displayed absorption bands at 3332, 3188 cm^{-1} due to the 2NH function and 1243 cm^{-1} due to C=S group.

Reaction of compounds **3a**,**b** with cyclohexanone and elemental sulfur in the presence of TEA afforded the corresponding 4,5,6,7-tetrahydrobenzo[b]thiophene derivatives, **11a**,**b**. Formation of **11** took place according to the similar reported reactions of cyclohexanone with methylene reagents and elemental sulfur [17]. Structure of compound **11** was based on analytical and spectral data (Scheme 2).

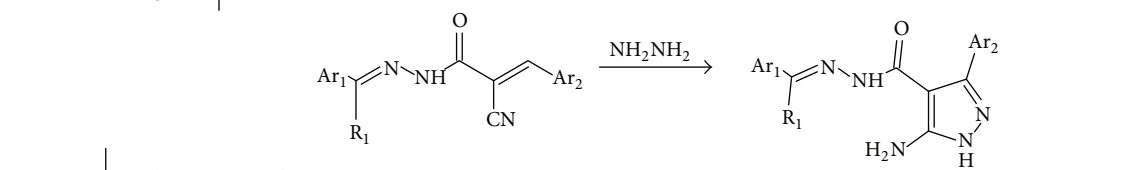
The active methylene moiety of 2-cyano-N′-[1-(4-methoxyphenyl)ethylidene]acetohydrazide (**3a**) allowed reacting with phenylisothiocyanate in dry *N, N*-dimethylformamide DMF containing catalytic amount of potassium hydroxide



2 and 3	Ar_1	R_1
a	*p*-CH_3OPh	CH_3
b	*p*-ClPh	H

4a; Ar_1 = *p*-CH_3OPh $R_1 = CH_3$

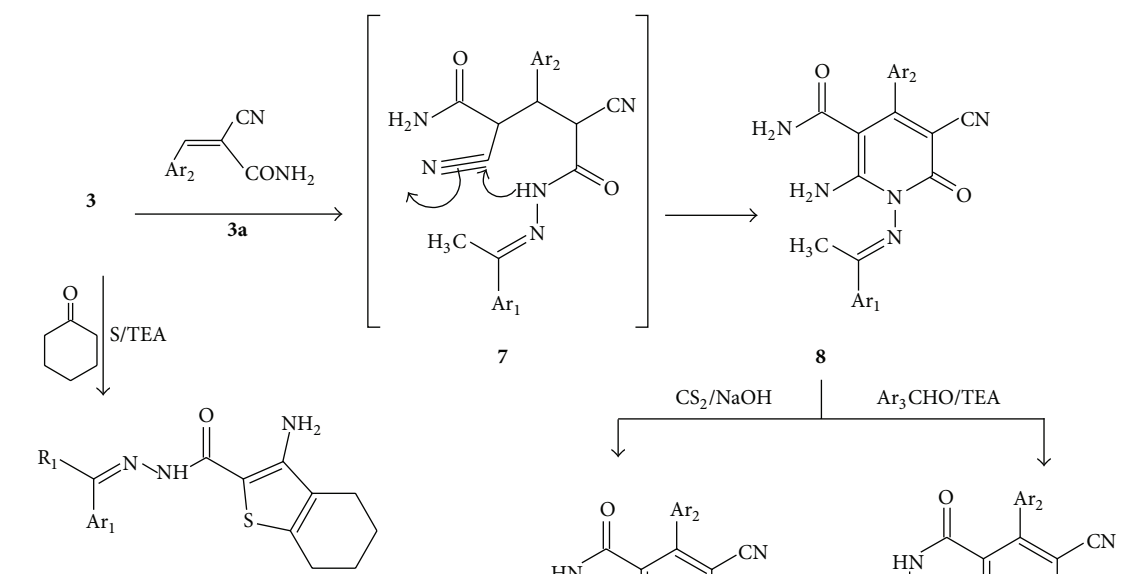
b; Ar_1 = *p*-ClPh R_1 = H



5	Ar_1	Ar_2	R_1
a	*p*-CH_3OPh	*p*-CH_3OPh	CH_3
b	*p*-ClPh	*p*-CH_3OPh	H
c	*p*-CH_3OPh	*p*-ClPh	CH_3
d	*p*-ClPh	*p*-ClPh	H

6	Ar_1	Ar_2	R_1
a	*p*-CH_3OPh	*p*-CH_3OPh	CH_3
b	*p*-ClPh	*p*-CH_3OPh	H

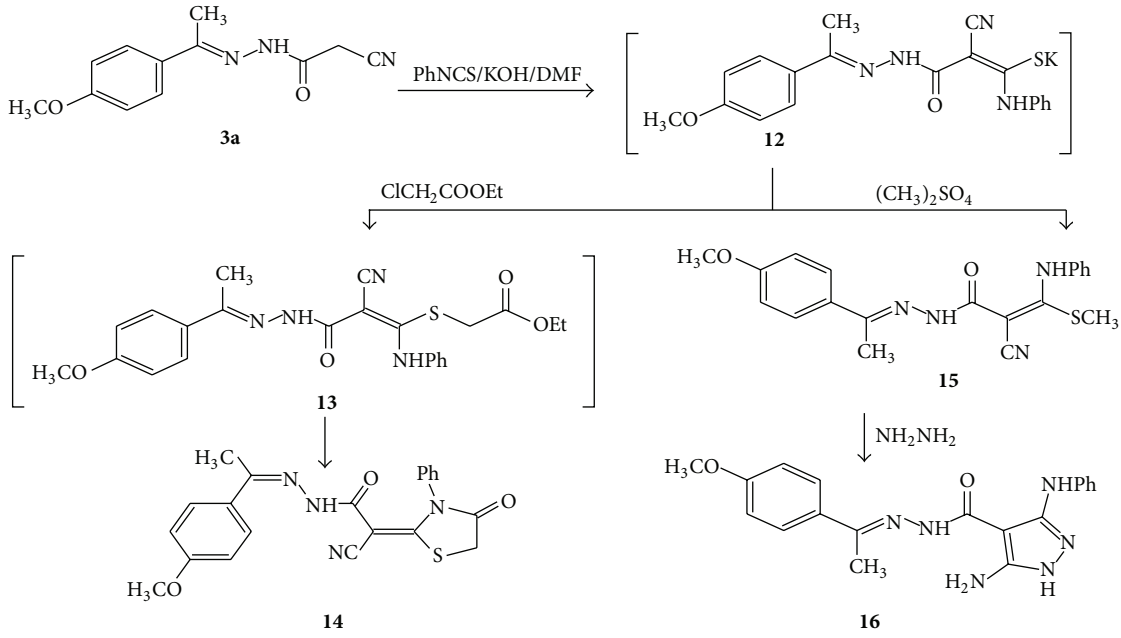
Scheme 1



11	Ar_1	R_1
a	*p*-CH_3OPh	CH_3
b	*p*-ClPh	H

Ar_1	Ar_2	Ar_3
p-CH_3OPh	*p*-ClPh	*p*-NO_2Ph

Scheme 2



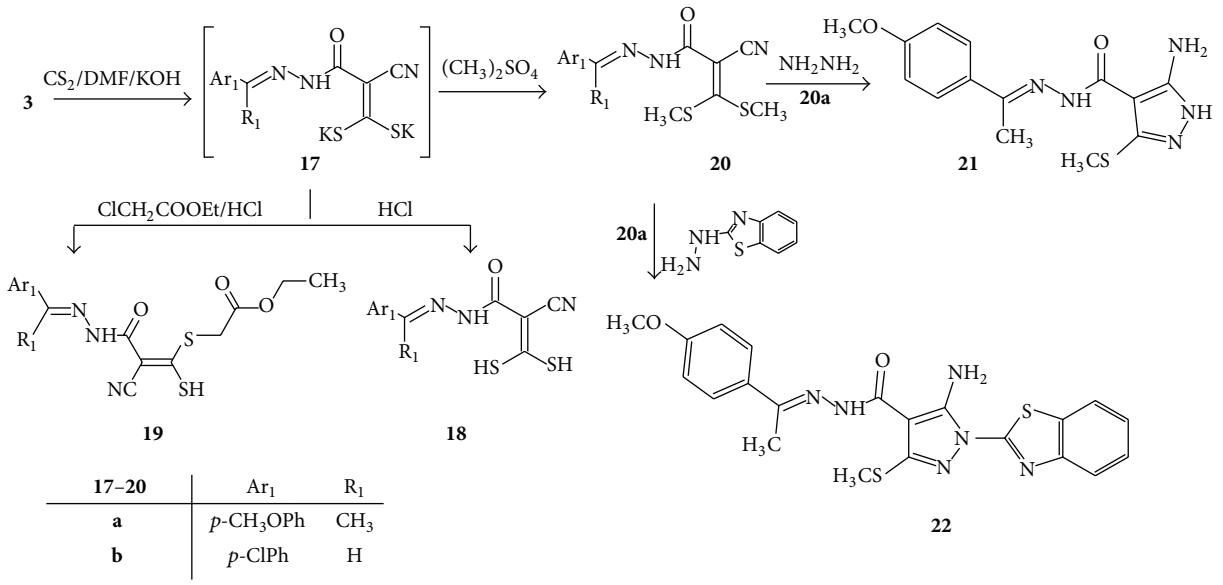
Scheme 3

[18] yielding the nonisolable intermediate potassium sulfide salt **12**, and then ethylchloroacetate was added affording 1,3-thiazolidinone derivative **14**. Probably, the reaction mechanism is assumed to proceed *via* S-alkylation to give the intermediate **13** which was cyclized to the corresponding thiazolidinone derivatives **14**. Elemental analyses and spectral data were in favor of these proposed 1,3-thiazolidinone structures. The IR spectrum of **14** showed absorption bands at 1742 cm^{-1} due to thiazolidinone CO. The ^{1}H NMR spectrum showed signals in the region at δ 4.02 ppm corresponding to C4 protons of the thiazolidinone ring. On the other hand, treatment of the nonisolable potassium sulfide salt **12** with dimethylsulfate afforded 3-anilino-2-cyano-3-methylthio-acrylohydrazide **15**. Cyclocondensation of the acrylohydrazide **15** with hydrazine hydrate in boiling ethanol afforded aminopyrazole derivative **16**. The structure of **15** and **16** was identified as the reaction product on the basis of their elemental analysis and spectroscopic data. ^{1}H NMR spectrum of **15** displayed the following signals at δ 2.50 corresponding to the SCH_3 group, δ 10.10 corresponding to the NHPh group, and δ 11.60 corresponding to the NHCO group. IR spectrum of **16** showed the lacks of absorption band assignable to the CN group and the presence of a new absorption band at 3298, 3242 cm^{-1} assignable to NH_2 group. Its ^{1}H NMR spectrum showed signals at δ 6.13 ppm corresponding to the NH_2 protons, another three singlet signals at δ 8.00, 8.20, and 10.10 ppm assignable to three NH protons (Scheme 3).

Reaction of compounds **3a**,**b** with carbon disulfide in boiling DMF containing catalytic amount of potassium hydroxide afforded nonisolable intermediate potassium sulfide salts **17a**,**b**. Treatment of the nonisolable potassium salts **17a**,**b** with dilute hydrochloric acid [19] afforded the corresponding dithiol derivatives **18a**,**b**. The structures of compounds **18a**,**b** were based on both elemental analyses and spectral data. The ^{1}H NMR spectrum of **18a** revealed signal at δ 2.73 and 2.88 ppm for two SH protons and at δ 10.50 ppm for NHCO proton. Moreover, Alkylation of dithiol derivatives **17a**,**b** with ethylchloroacetate yielded the corresponding ethyl [2-cyano-1-mercapto-3-oxoprop-1-enyl) thio]acetate derivatives **19a**,**b** [20]. The structures of **19a**,**b** were supported on the basis of elemental analyses and spectral data. Ketene *S*,*S*-dithio-acetals derivatives **20a**,**b** can be prepared by alkylation of dithiol derivatives **17a**,**b** with dimethylsulfate. The structure of **20** was elucidated on the basis of the elemental analyses and spectral data. The IR spectrums of **20a** showed the appearance of absorption band at 3203 for NH and 2256 cm^{-1} for CN groups. ^{1}H NMR spectrum of **20b** showed singlet signal at δ 2.50 ppm for 6 protons of two similar methyl protons, while a singlet signal for the methylene protons disappeared.

Cyclocondensation of bis-(methylthio)acrylohydrazide derivative **20a** with hydrazine derivatives such as hydrazine hydrate and 2-hydrazino-1,3-benzothiazole affords the corresponding 5-(methylthio) 1H-pyrazole-4-carbohydrazide **21** and **22**, respectively. The structures of compounds **21** and **22** were as established and confirmed as the reaction product on the basis of their elemental analyses and spectral data. The IR spectrum of **21** showed absorption band at 3300, 3243 cm^{-1} assignable for NH_2, in addition to disappearance of nitrile function signal. Its ^{1}H NMR spectrum revealed the presence of singlet signals at δ 6.13 ppm assignable to the NH_2 protons (Scheme 4).

3.2. Antitumor Activity. Some newly synthesized compounds **3a**, **3b**, **4a**, **4b**, **6a**, **6b**, **11b**, **14**, **15**, **16**, **18b**, **19a**, **19b**, **21**, and **22**, screened *in vitro* against human breast cancer cell line (MCF-7), using doxorubicin (Doxo) as a reference drug. The results



Scheme 4

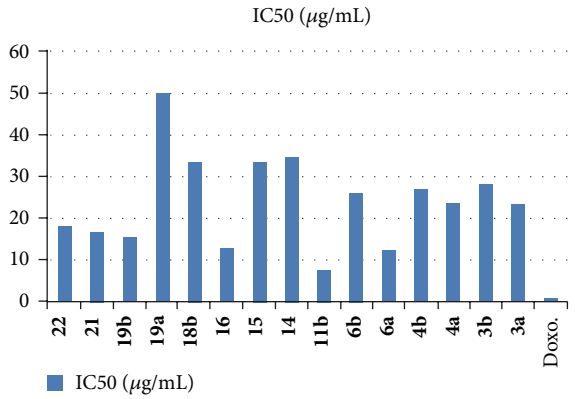


Figure 1: *In vitro* anticancer screening of the synthesized compounds against human breast cancer cell line (MCF-7).

were compared to the antiproliferative effects of the reference control doxorubicin (Table 1, plotted in Figure 1). The results indicated that most compounds demonstrated substantial growth inhibitory effects against the human tumor cells at the tested concentrations. The antiproliferative activity of the test compounds against tumor cell lines may be arranged in a descending order due to measured concentration required to inhibit tumor cell proliferation by IC50 μg/mL which corresponds to the concentration required for 50% inhibition of cell viability. In general, compounds **11b**, **6a**, **16**, **19b**, **21**, and **22** with IC50 values 7.5, 12.2, 12.6, 15.3, 16.1, and 18 μg/mL, respectively, showed significant activity on the tumor cell lines tested.

4. Conclusions

In this work, cyanoacetylhydrazine (**1**) reacted with 4-methoxy-acetophenone and 4-chlorobenzaldehyde (**2a**,**b**) to afford the hydrazide-hydrazone derivatives, **3a**,**b**. The latter was reacted with different reagents to give coumarin, pyridine, thiophene, and pyrazole derivatives. The antitumor evaluations of the newly synthesized products were carried out, showing that compound exhibited moderate activity.

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