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Novel thiourea, quinazoline, thiazolidine, thieno[2,3-d]-pyrimidine, 4-thiazolidinone, pyrrole, pyrrolo[2,3-d]pyrimidine derivatives containing sulfamoyl moiety

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ABSTRACT

4-Isothiocyanato-N-(2,6-dimethoxypyrimidin-4-yl)benzenesulf-onamide (2) was used as starting material for the synthesis of some novel carbamothioates (3a,b), 1,2,4-triazole (4), 2-thioxothiazolidin-4-one (5), quinazolinone (6), thieno[2,3-d]pyrimidine (11), benzi-midazole (17) derivatives, the non-isolated adduct (19) was used as key intermediate to synthesize some novel 4-aminothiazole (20) and 4-thiazolidinone (22) derivatives to evaluate their anti tumor activity.

Keywords: *carbamothioates, 1,2,4-triazole, 2-thioxothiazolidin-4-one, quin-azolinone, thienopyrimidine, benzimidazole and anticancer activity.*

INTRODUCTION

The chemistry of pyrimidine derivatives have been increasing interest since many of these compounds have found useful applications as moderate anthelmintic[1], antiviral, antibacterial and antifungal activities[2-4]. Pyrimidine ring is incorporated into many of the commercially available pharmaceuticals[5] which showed analgesic, antiinflammatory[6],antihypertensive[7]antipyretic activities[8]; e.g. phenyl butazone and oxyphenbutazone also azapropazone (prolixane) that is a fused pyrazolidindione. Furthermore it acts as intermediate for agricultural microbicides and herbicides[9]. In view of the above mentioned findings and in continuation of our interest in biologically active compounds[10-14], we report herein the synthesis of some heterocyclic compounds starting from isothiocyanate derivative (2).

MATERIALS AND METHODS

Chemistry:

Melting points were uncorrected and determined in an open capillary tube. IR spectra were recorded on FTIR Shimadzu spectrometer. 1H NMR spectra were recorded in DMSO-*d6* on avance 300 MHz spectrometer using TMS as an internal standard. The mass spectra were

recorded on EI-Shimadzu-GC-MS spectrometer. Elemental analyses were performed on a Carlo Erba 106 Perkin-Elmer model 240 analyzer

***N*-(2,6-Dimethoxypyrimidin-4-yl)-4-isothiocyanatobenzene sulfonamide (2).**

4-Amino-N-(2,6-dimethoxypyrimidin-4-yl)benzenesulfonamide **1** (0.01 mole) were dissolved in H_2O (200 mL) containing (50 ml) of concentrated HCl. To this (0.012 mole) of $CSCl_2$ was added in one portion. Stirring was begin immediately and continued until all of the red color of $CSCl_2$ had disappeared (1hr) and the product was precipitate as white crystals. The resulting solid was filtered off, dried and recrystallized from acetone to give **2**.

Yield: 97%; m.p. 170-172ºC; IR (KBr) *ν* (cm^{-1}): 3445 (NH), 3001 (CH-arom.), 2030 (NCS), 1586 (C=N), 1345, 1163 (SO_2) and 1090 (C=S). MS: m/z: 353 (M^+; 17.49%), 292 (7.26%), 256 (6.45%), 198 (9.52%), 158 (100%), 97 (21.66%), 77 (14.87%). Anal. calcd. for $C_{13}H_{12}N_4O_4S_2$ (352): C,44.31; H, 3.43; N, 15.90. Found: C, 44.10; H, 3.52; N, 15.62.

Formation of O-Methyl 4-(N-(2,6-dimethoxypyrimidin4yl)sulfamoyl)phenyl-carbamothioate (3).

A solution of **2** (0.01 mole) in methanol and/ or ethanol (30 mL) was heated under reflux for 13h. The solid obtained was collected by filtration and recrystallized from dioxane to gave **3**, respectively.

Yield: 90%; m.p. 120-122ºC; IR (KBr) *ν*(cm^{-1}): 3300, 3260 (2NH), 3066 (CH-arom.), 2946 (CH-aliph.), 1597 (C=N), 1348, 1158 (SO_2) and 1082 (C=S). MS: m/z 384 (M^+; 0.48%), 302 (7.26%), 288 (6.45%), 255 (100%), 214 (9.52%), 134 (21.66%), 107 (14.87%), 75 (16.27%). Anal. calcd. for $C_{14}H_{16}N_4O_5S_2$ (384): C, 43.74; H, 4.20; N, 14.57. Found: C, 43.43; H, 3.89; N, 14.39.

4-(3-Amino-5-thioxo-1H-1,2,4-triazol-4(5H)-yl)-N-(2,6-dimethoxypyrimidin-4-yl)benzenesulfona - mide (4).

A mixture of **2** (0.01mole) and thiosemicarbazide (0.01mole) in dioxane (30 mL) containing a few drops of triethylamine was refluxed for (48hrs). 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 **4**.

Yield: 69%; m.p. 210-212ºC; IR (KBr) *ν* (cm^{-1}): 3408, 3350 (NH_2/ NH), 2925 (CH-aliph.), 1597 (C=N), 1310, 1153 (SO_2) and 1081 (C=S). MS: m/z 409 (77.78%) 348 (88.89%), 221 (77.78%), 189 (83.33%), 131 (100%), and 69 (94.44%). Anal. calcd. for $C_{14}H_{15}N_7O_4S_2$ (409): C, 41.07; H, 3.69; N, 23.95. Found: C, 41.29; H, 3.31; N, 23.71.

N-(2,6-Dimethoxypyrimidin-4-yl)-4-(4-oxo-2-thioxothiazolidin-3-yl)benzenesulfonamide (5).

A mixture of **2** (0.01mole) and thioglycolic acid (0.01mole) in dioxane (30 mL) containing a few drops of triethylamine was heated under reflux for (3hr.). The reaction mixture then cooled and poured into cold water and acidified with dilute HCl. The solid product was recrystallized from ethanol to give **5**.

Yield: 79%; m.p. 170-172ºC; IR (KBr) *ν* (cm^{-1}): 3447 (NH), 2985(CH-aliph.), 1716 (C=O), 1599 (C=N), 1309, 1157 (SO_2) and 1081 (C=S). MS: m/z 428 (M^{+2}; 36.96%) 345 (45.65%), 312 (28.26%), 193 (58.70%), 107 (100%), 157 (50.00%), and 65 (63.04%). ^{1}HNMR: δ 3.66, 4.31 (2s, 6H, $2OCH_3$), 4.39 (s, 2H, CH_2-thiazolidinone), 6.75 (s, 1H, pyrimidine-H), 7.93-8.01 (d-d, 4H, Ar-H) and 10.4 (s, 1H, $NHSO_2$). Anal. calcd. for $C_{15}H_{14}N_4O_5S_2$ (426): C, 42.24; H, 3.31; N, 13.14. Found: C, 41.94; H, 3.01; N, 12.92.

4-(6,8-Dichloro-4-oxo-2-thioxo-1,2-dihydroquinazolin-3-(4H)-yl)-*N*-(2,6-dimethoxypyrimidin-4-yl)benzenesulfonamide (6).
A mixture of **2** (0.01mole) and 3,5-dichloroanthranilic acid (0.01 mole) in dioxane (20 mL) containing 3 drops of triethylamine was heated under reflux for 1hr, filtered while hot and the solid obtained was recrystallized from dioxane/dimethylformamide to give **6**.

Yield: 81%; m.p. 200-202ºC; IR (KBr) *ν* (cm^{-1}): 3367 (NH), 3078 (CH-arom.), 2925 (CH-aliph.), 1678 (C=O), 1311, 1152 (SO_2) and 1082 (C=S). ^{1}HNMR: δ 3.39, 4.02 (2s, 6H, $2OCH_3$), 6.77 (s, 1H, pyrimidine-H), and 7.62, 7.70 (d-d, 4H, CH-arom). Anal. calcd. for $C_{20}H_{15}N_5O_5S_2Cl_2$ (538): C, 44.45; H, 2.80; N, 12.96. Found: C, 44.21; H, 3.05; N, 12.78.

Formation of thiourea derivatives 7 and 8: General procedure: A mixture of **2** (0.01 mole) and ethyl-2-amino-4,5-dimethyl thio-phene-3-carboxylate (0.01 mole) or ethyl 2-amino-4-methyl-5-acetyl thio-phene-3-carboxylate (0.01 mole) in ethanol (50 mL) containing 3 drops of triethylamine was heated under reflux for 3hrs. The solid obtained was collected and recrystallized from dioxane to give **7,8.**

Ethyl 2-(3-(4-(N-(2,6-dimethoxypyrimidin-4-yl)sulfamoyl)phen-yl)thioureido)-4,5-dimethylthio -phene-3-carboxylate (7).
Yield: 85%; m.p. 140-142ºC; IR (KBr) *ν* (cm^{-1}): 3244, 3187, 3110 (3NH), 3054 (CH-arom.), 2950 (CH-aliph.), 1732 (C=O), 1596 (C=N), 1375, 1177 (SO_2) and 1081 (C=S). MS: m/z 550 (M-1; 6.04%) 330 (1.23%), 255 (100%), 213 (29.86%), 134 (25.52%) and 54 (13.58%). Anal. calcd. for $C_{22}H_{25}N_5O_6S_3$ (551): C, 47.90; H, 4.57; N, 12.70. Found: C, 47.58; H, 4.18; N, 12.48.

Ethyl 4-acetyl-2-(3-(4-(N-(2,6-dimethoxypyrimidin-4-yl)sulfamo-yl)phenyl)thioureido)-5-methylthio -phene-3-carboxylate (8).
Yield: 90%; m.p. 100-102ºC; IR (KBr) *ν* (cm^{-1}): 3294, 3241, 3183 (3NH), 3047 (CH-arom), 2986 (CH-aliph.), 1726 (C=O), 1586 (C=N), 1372, 1175(SO_2) and 1080 (C=S). MS: m/z 580 (M^{+1}; 0.13%), 500 (0.08%), 389 (0.12%), 330 (2.62%), 255 (100%), 213 (25.82%), 134 (29.31%), 90 (21.66%). ^{1}HNMR: δ 1.03 (s, 3H, CH_3), 1.36 (t, 3H, CH_3-ethyl), 2.73 (s, 3H, $COCH_3$), 4.18 (q, 2H, CH_2-ethyl), 4.49, 4.53 (2s, 6H, $2OCH_3$), 6.56 (s, 1H, pyrimidine-H) and 7.88-8.0 (m, 7H, Ar-H + NH). Anal. calcd. for $C_{23}H_{25}N_5O_7S_3$ (579): C, 47.66; H, 4.35; N, 12.08. Found: C, 47.39; H, 4.59; N, 12.42.

Formation of compounds (10) and (11): General procedure :
A mixture of **2** (0.01mole) and 2-amino-3-cyano-4,5-dimethylthio-phene (0.01mole), in ethanol (50 mL) containing 3 drops of triethyl-amine was refluxed for (3hrs). The reaction mixture was filtered while hot and recrystallized from dioxane to give **11**, the obtained solid after cooling was filtered off and recrystallized from dioxane to give **10**.

4-(3-(3-Cyano-4,5-dimethylthiophen-2-yl)thioureido)-N-(2,6-dimethoxypyrimidin-4-yl)benzenesulfon -amide (10).
Yield: 40%; m.p. 130-132ºC; IR (KBr) *ν* (cm^{-1}): 3432, 3338, 3228 (3NH), 2964 (CH-aliph.), 2194 (C≡N), 1626 (C=N) and 1304, 1160 (SO_2). MS: m/z 504 (M^+; 50.00%) 387 (60.00%), 337 (65.00%), 284 (70.00%), 195 (90.00%), 167 (100%), and 76 (75.00%). ^{1}HNMR: δ 1.12, 1.33 (2s, 6H, $2CH_3$), 3.4, 4.2 (2s, 6H, $2OCH_3$), 6.7 (s, 1H, pyrimidine-H) and 7.66-7.95 (d-d, 4H, CH-arom), 8.63, 10.0, 11.2 (3s, 3H, 3NH). Anal. calcd. for $C_{20}H_{20}N_6O_4S_3$ (504): C, 47.60; H, 3.99; N, 16.65. Found: C, 47.96; H, 4.37; N, 16.36

***N*-(2,6-Dimethoxypyrimidin-4-yl)-4-(4-imino-5,6-dimethyl-2-thioxo-1,2-dihydrothieno[2,3-d]pyrimi -din-3(4H)-yl)benzene-sulfonamide (11).**
Yield: 48%; m.p. 118-120ºC; IR (KBr) *ν* (cm^{-1}): 3448, 3189 (2NH), 2920 (CH-aliph.), 1599 (C=N), 1356, 1154 (SO_2) and 1084 (C=S). ^{1}HNMR: δ 1.12, 1.16 (2s, 6H, $2CH_3$), 3.41, 4.06 (2s, 6H, $2OCH_3$), 6.72 (s, 1H, pyrimidine-H), 7.78-8.03 (m, 5H, Ar-H + NH), 9.00 (s, 1H, NH) and 10.09 (hump, 1H, $NHSO_2$). Anal. calcd. for $C_{20}H_{20}N_6O_4S_3$ (504): C, 47.60; H, 3.99; N, 16.65. Found: C, 47.76; H, 3.81; N, 16.86.

Formation of thiourea derivatives (12-14): General procedure:
A mixture of isothiocyanate derivative **2** (0.01mole) and the requisite heteroamine compound (namely; 2,4-diamino-6-hydroxypyrimidine, 2-amino-6-hydroxypyrimidine, 2-amino-thiazole (0.01 mole) in dioxane (20 mL) containing triethylamine (0.5 mL) was heated under reflux for 2hrs. 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 **12-14**.

4-(3-(4-Amino-6-hydroxypyrimidin-2-yl)thioureido)-N-(2,6-dime-thoxypyrimidin-4-yl)benzene -sulfonamide (12).
Yield: 45%; m.p. 220-222ºC; IR (KBr) *ν* (cm^{-1}): 3339, 3171 (OH,NH), 1597 (C=N), 1312, 1140 (SO_2) and 1081 (C=S). MS: m/z 480 (M+2; 37.14%), 307 (54.29%), 217 (51.43%), 170 (51.43%), 129 (60%), and 55 (100%). Anal. calcd. for $C_{17}H_{18}N_8O_5S_2$ (478): C,42.67; H, 3.79; N, 23.42. Found: C, 42.41; H, 3.41; N, 23.66.

N-(2,6-Dimethoxy-pyrimidin-4-yl)-4-(3-(4-hydroxypyrimidin-2-yl)thioureido)benzenesulfonamide (13).
Yield: 81%; m.p. >360ºC; IR (KBr) *ν* (cm^{-1}): 3446, 3375 (OH, NH), 1615 (C=N), 1321, 1148 (SO_2) and 1079 (C=S). ^{1}HNMR: δ 3.27, 3.49 (2s, 6H, $2OCH_3$), 6.54, 6.59, 6.72 (3s, 3H, pyrimidine-H), 7.62-8.6 (m, 4H, Ar-H), 9.83, 10.19 (2s, 2H, 2NH), 10.95 (s, 1H, $NHSO_2$) and 11.2 (s, 1H, OH). Anal. calcd. for $C_{17}H_{17}N_7O_5S_2$ (463): C, 44.05; H, 3.70; N, 21.15. Found: C, 43.79; H, H, 3.32; N, 21.39.

N-(2,6-Dimethoxypyrimidin-4-yl)-4-(3-thiazol-2-ylthioureido)-benzene sulfonamide (14).
Yield: 43%; m.p. 200-202ºC; IR (KBr) *ν* (cm^{-1}): 3337 (NH), 3060 (CH-arom), 1595 (C=N) and 1352, 1155 (SO_2). MS: m/z 454 (M+2; 34.38%), 396 (37.5%), 263 (40.63%), 244 (59.38%), 154 (56.25%), 143 (62.50%) and 87 (100%). Anal. calcd. for $C_{16}H_{16}N_6O_4S_3$ (452): C,42.47; H, 3.56; N,18.57. Found: C, 42.73; H, 3.18; N, 18.81.

1,4-Bisthiourea derivative (15).
A mixture of **2** (0.02 mole) and p-phenylenediamine (0.012 mole) in dimethylformamide (20 mL), containing 3 drops of triethylamine was refluxed for 12h. The solid obtained was recrystallized from dioxane to give **15**.

Yield: 80%; m.p. 90-92ºC; IR (KBr) *ν* (cm^{-1}): 3341-3221 (6NH), 1595 (C=N), 1346, 1150 (SO_2) and 1079 (2C=S). MS: m/z 814 (M+2; 6.04%), 724 (7.15%), 576 (7.69%), 411 (37.91%), 337 (32.42%), 265 (32.42%) and 166 (100%). Anal. calcd. for $C_{32}H_{32}N_{10}O_8S_4$ (812): C,47.28; H, 3.97; N, 17.32. Found: C, 46.99; H, 3.64; N, 17.67.

4-(1H-Benzo[d]imidazol-2-ylamino)-N-(2,6-dimethoxypyrimidin-4-yl) benzenesulfonamide (16).
A mixture of **2** (0.01 mole) and 1,2-phenylenediamine (0.01 mole) in dimethylformamide (20 mL), containing 3 drops of triethylamine was refluxed until evaluation of hydrogen sulfide had stopped (lead acetate paper) for 5h. After cooling, the reaction mixture was poured into crushed ice water, and the solid product obtained was recrystallized from DMF/ethanol to give **16**.

Yield: 40%; m.p. 100-102ºC; IR (KBr) *ν* (cm^{-1}): 3399, 3289, 3220 (NH), 3060 (CH-arom.), 2974 (CH-aliph.), 1593 (C=N) and 1344, 1149 (SO_2). MS: m/z at 426 (M^+; 5.03%), 368 (1.20%), 199 (100%), 153 (7.00%), 125 (1.00%) and 91 (40.02%). Anal. calcd. for $C_{19}H_{18}N_6O_4S$ (426): C, 53.51; H, 4.25; N, 19.71. Found: C, 53.33; H, 4.54; N, 19.39.

N-(2,6-Dimethoxypyrimidin-4-yl)-4-(3-(2-hydroxyphenyl)thio-ureido) benzenesulfonamide(17).
A mixture of **2** (0.01 mole) and 2-aminophenol (0.01mole) in dimethylformamide (20 mL), containing 3 drops of triethylamine was refluxed for 5h. After cooling, the reaction mixture was poured into crushed ice water and acidified with dil. HCl and the solid product obtained was recrystallized from dioxane to give 17.

Yield: 75%; m.p. 109-110ºC; IR (KBr) ν (cm−1): 3383 (OH), 3340, 3235, 3137 (3NH), 3066 (CH-arom.), 2926 (CH-aliph.), 1598 (C=N), 1340, 1166 (SO2) and 1092 (C=S). MS: m/z at 462 (M+1; 0.66%), 381 (65.38%), 311 (57.69%), 265 (69.23%), 232 (65.38%), 158 (100%), 135 (80.77%) and 51 (88.46 %). Anal. calcd. for C19H19N5 O5S2 (461): C, 49.45; H, 4.15; N, 15.17. Found: C, 49.19; H, 3.95; N, 15.43.

Formation of compounds 20 & 22: Genaral procedure:
To a suspension of finely powdered potassium hydroxide (0.01 mole) in dry DMF (15 mL), malononitrile (0.01 mole) and then isothiocyanate derivative 2 (0.01 mole) were added in portions. The reaction mixture was stirred at room temperature for 3hrs., then with chloroacetonitrile and/ or ethyl chloroacetate (0.01 mole) and left at room temperature for 24hrs. The reaction mixture then poured into ice/water and acidified with 0.1N HCl. The resulting precipitate was filtered off, dried and recrystallized from dioxane to give 20 and 22.

4-(4-Amino-2-(dicyanomethylene)thiazol-3(2H)-yl)-N-(2,6-dime-thoxy pyrimidin-4-yl)benzenesulfo -namide (20).
Yield: 70%; m.p. 88-90ºC; IR (KBr) ν (cm−1): 3481, 3232 (NH2), 3098 (CH-arom.), 2927 (CH-aliph.), 2215 (C≡N) and 1598 (C=C). MS: m/z at 459 (M+2; 50.00%), 401 (81.82%), 350 (50%), 259 (77.27%), 254 (54.55%), 198 (100%), 151 (50%) and 92 (81.82 %). Anal. calcd. for C18H15N7O4S2 (457): C,47.26; H, 3.30; N, 21.43. Found: C, 47.60; H, 2.94; N, 21.11.

4-(2-(Dicyanomethylene)-4-oxothiazolidin-3-yl)-N-(2,6-dimetho-xypyrimidin-4-yl)benzenesulfon -amide (22).
Yield: 63%; m.p. 118-120ºC; IR (KBr) ν (cm−1): 3193, 3101 (2NH), 2924 (CH-aliph.), 2212 (C≡N) and 1719 (C=O). MS: m/z at 458 (m+;10.50%), 384 (0.34%), 250 (0.25%), 206 (100%), 170 (03.53%) and 91 (17.00%). 1HNMR: δ 4.03, 4.07(2s, 6H, 2OCH3), 4.33 (s, 2H, CH2), 6.75 (s, 1H, pyrimidine-H) and 7.31, 8.13 (m, 5H, Ar-H + NH). Anal. calcd. for C18H14N6O5S2 (458): C, 47.16; H, 3.08; N, 18.33. Found: C, 46.88; H, 2.96; N, 18.61.

2-Chloro-N-(4-(N-(2,6-dimethoxypyrimidin-4-yl)sulfamoyl)phen-yl)acetamide (24).
A mixture of 1 (0.01 mole), and chloroacetyl chloride (0.01 mole) in dimethylformamide (20 mL) was stirred at room temperature for 1hr. The reaction mixture was poured onto cold water and the solid that obtained was collected and recrystallized from dioxane to give 24.

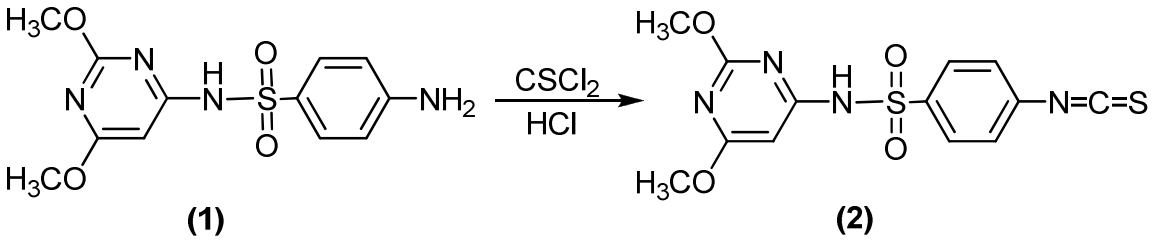
Yield: 90%; m.p. 145-147ºC; IR (KBr) ν (cm−1): 3190 (NH), 2993 (CH-arom.), 2935 (CH-aliph.), 1685 (C=O), 1593 (C=N) and 1384, 1126 (SO2). MS: m/z at 387 (M+; 28.57%), 341 (50.00%), 308 (30.36%), 230 (25.00%), 213 (62.50%), 139(53%), 120(64.29 %) and 65 (100%). Anal. calcd. for C14H15N4O5SCl (386): C, 43.47; H, 3.91; N, 14.48. Found: C, 43.71; H, 3.54; N, 14.65.

N-(4-(N-(2,6-Dimethoxypyrimidin-4-yl)sulfamoyl)phenyl)-2-thio-cyanatoacetamide (25).
A mixture of 24 (0.01 mole) and potassium thiocyanate (0.01 mole) in acetonitrile (30 mL) was heated under refluxed for 3h. The reaction mixture then cooled and poured into cold water. The solid product was collected and recrystallized from ethanol to give 25.

Yield: 83%; m.p. 136-138ºC; IR (KBr) ν (cm−1): 3217 (NH), 2923 (CH-aliph.) and 1674 (C=O). MS: m/z 409 (M+; 57.50%), 351 (55%), 281 (55%), 204 (37.50%), 159 (85%), 121 (70%) and 55 (100%). Anal. calcd. for C15H15N5O5S2 (409): C,44.00; H, 3.69; N, 17.10. Found: C, 44.21; H, 3.33; N, 17.26.

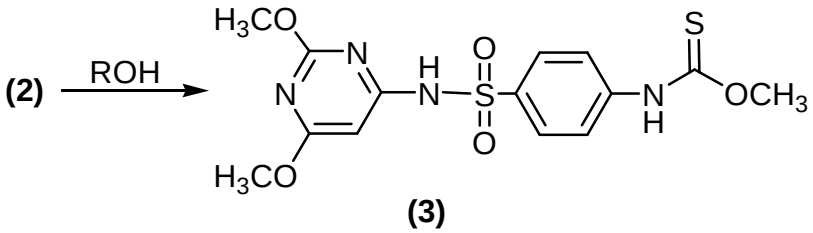
RESULTS AND DISCUSSION

Isothiocyanate derivatives are useful and widely used building blocks in the synthesis of nitrogen, sulfur and oxygen heterocyclic compounds and organometallic compounds of academic, pharma-ceutical and industrial interest.[15,16] Isothiocyanatosulfonamides (2) were synthesized by treatment of sulfonamide derivatives (1) with thiophosgene in the presence of dilute hydrochloric acid at room temperature, Scheme (1).



Scheme 1

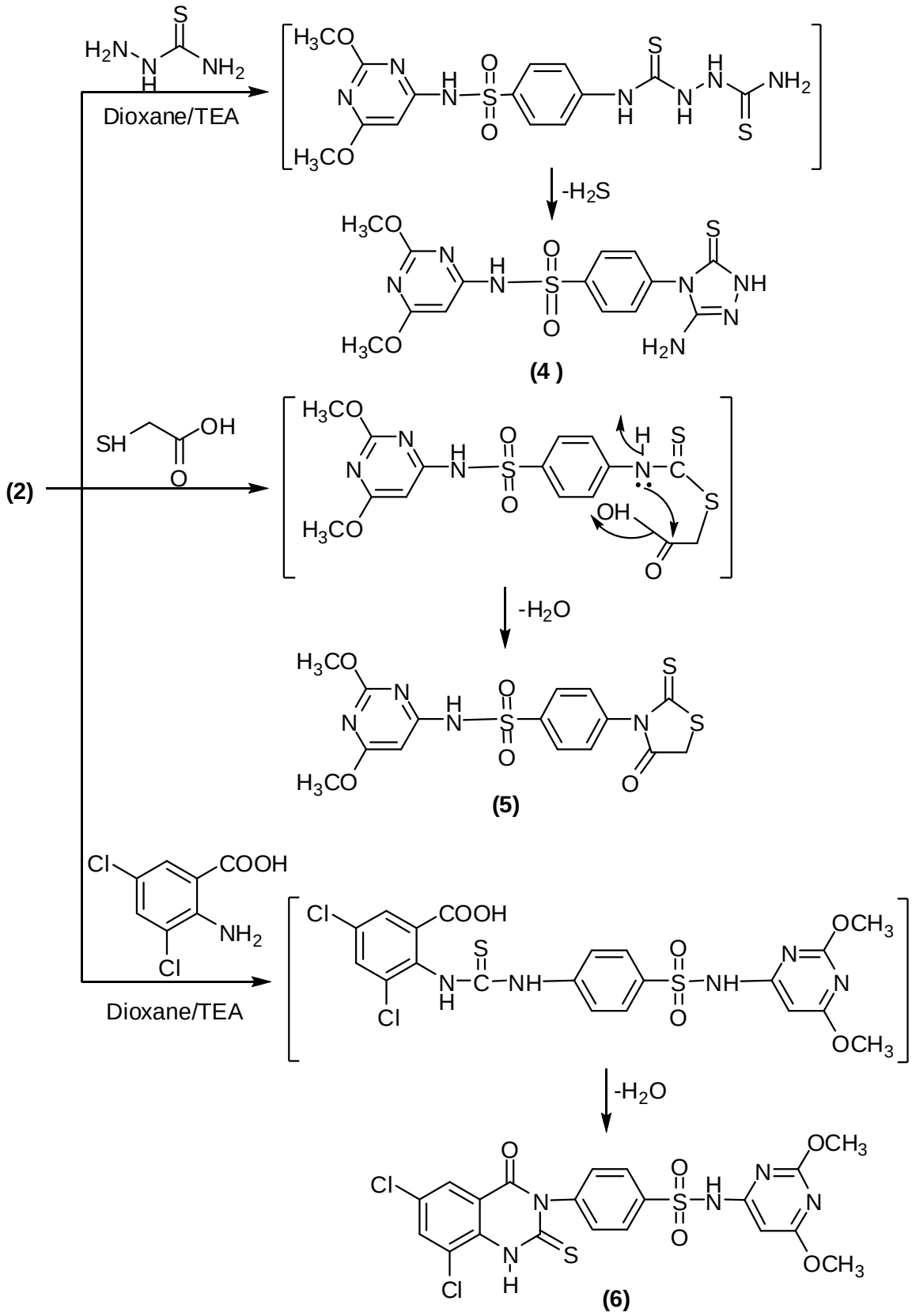
Phenylcarbamothioate derivative (3) were achieved by reaction of isothiocyanate derivative (2) with methanol and/or ethanol, respectively. The structures of carbamothioate derivatives (3) were confirmed by analytical and spectral data.



Scheme 2

Refluxing of isothiocyanate derivative (2) with thiosemicarba-zide in dioxane in the presence of triethylamine afforded 3-amino-5-thioxo-1H-1,2,4-triazole derivative (4) on the basis of analytical and spectral data, Scheme (3). The formation of triazole derivative (4) is assumed to proceed via initial formation of the intermediate and followed by elimination of hydrogen sulfide[17].

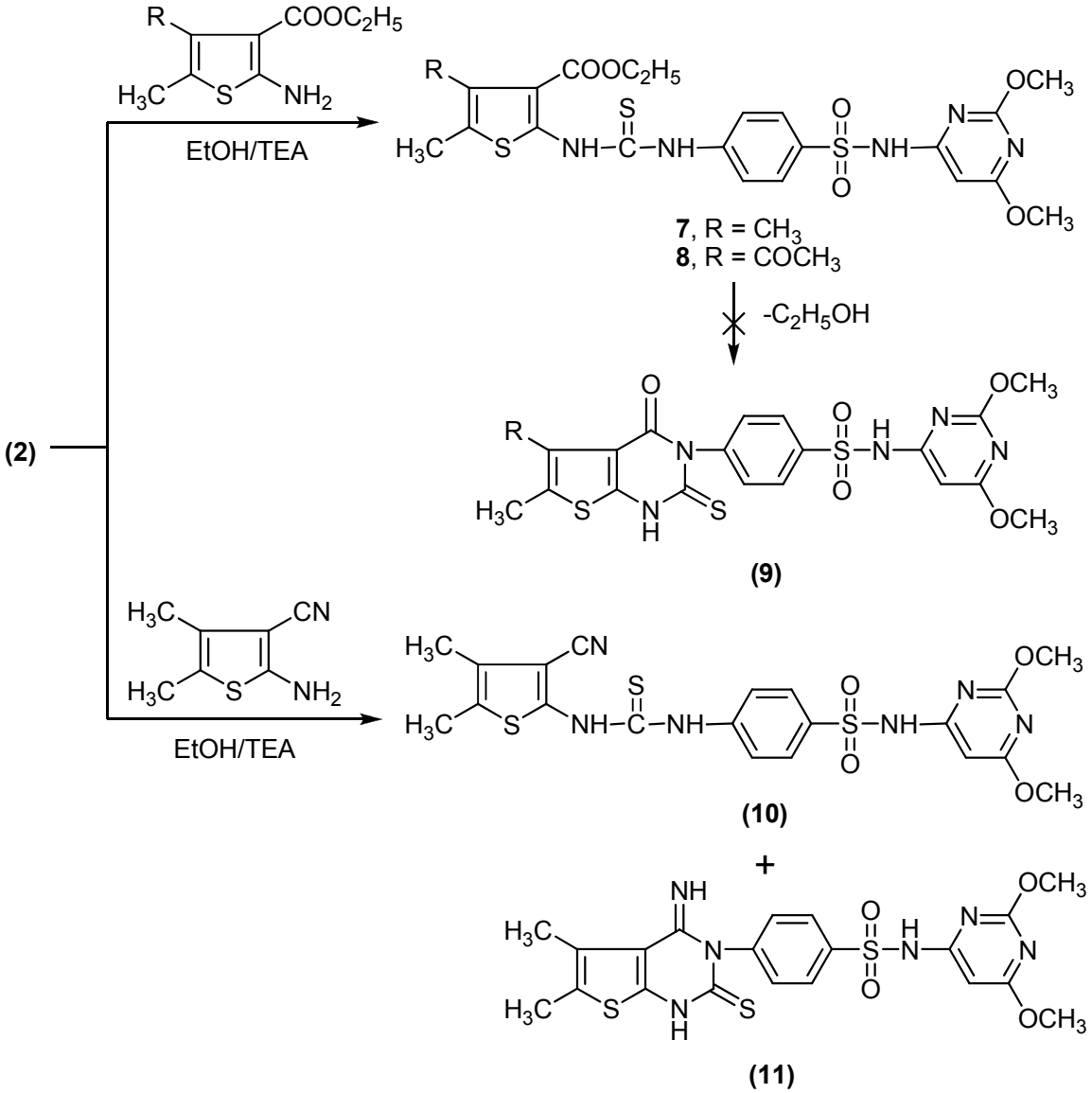
Isothiocyanate derivative (2) cyclized with sulfanylacetic acid in refluxing dioxane containing a catalytic amount of triethylamine to furnish 2-thioxothiazolidin-4-one derivative (5), Scheme (3). The formation of compound (5) is assumed to proceed through initial nucleophilic attack of mercapto group to thiocarbanyl moiety of isothiocyanate followed by intramolecular cyclization via dehydration. The structure of (5) was established via analytical and spectral data.



Scheme 3

Cyclocondensation of 3,5-dichloroanthranilic acid with isothio-cyanate derivative (2) under reflux in dioxane in the presence of triethylamine yielded the corresponding 6,8-dichloro-4-oxo-

2-thio-xo-1,2-dihydroquinazoline derivative (6). The molecular structure of (6) was identified by analytical and spectral data.



Scheme 4

The formation of quinazoline derivative (6) is assumed to proceed via the formation of thiourea intermediate and followed by intramolecular cyclization through elimination of water[18,19], Scheme (3).

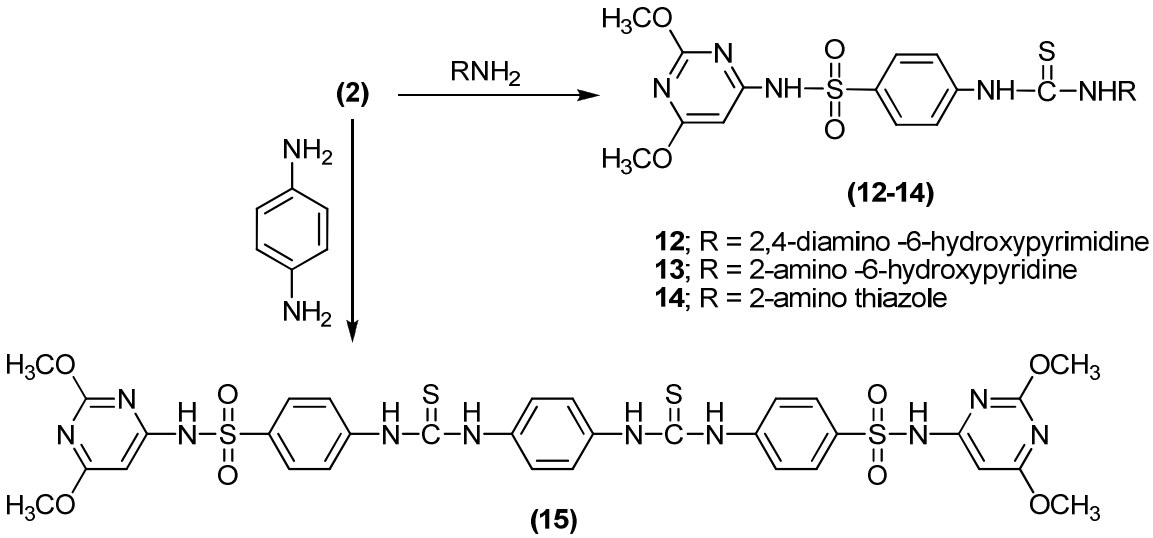
The novel thiourea derivatives (7,8) were obtained when iso-thiocyanate derivative (2) was allowed to react with ethyl-2-amino-4,5-dimethyl thiophene-3-carboxylate in refluxing ethanol in the presence of triethylamine. Trials to cyclize thiourea derivatives (7,8) into the corresponding thieno[2,3-d]pyrimidine derivatives under different conditions failed. The molecular weight of thiourea derivatives (7,8) was readily established on the basis of analytical and spectral data, Scheme (4).

On the other hand, when isothiocyanate derivative (2) was allowed to react with 2-amino-3-cyano-4,5-dimethyl thiophene in ethanol in the presence of triethylamine under reflux, the thiourea derivative (10) was obtained after cooling of the filtrate, while thieno-[2,3-d]pyrimidine

derivative (11) was separated while hot. The for-mation of thieno[2,3-d]pyrimidine derivative (11) is assumed to proceed via the formation of thiourea derivative (10) followed by intramolecular cyclization through nucleophilic addition of amino group to the cyano group. The structures of compounds (10) and (11) were supported by their elemental analyses and spectral data.

The reactivity of isothiocyanates (2) towards some nucleophilic reagents was studied. Condensation of isothiocyanate derivative (2) with hetero amine derivatives in refluxing dioxane in the presence of triethylamine furnished the 1,3-disubstituted thiourea derivatives (12-14), Scheme (5). The structures of compounds (12-14) were supported by analytical and spectral data.

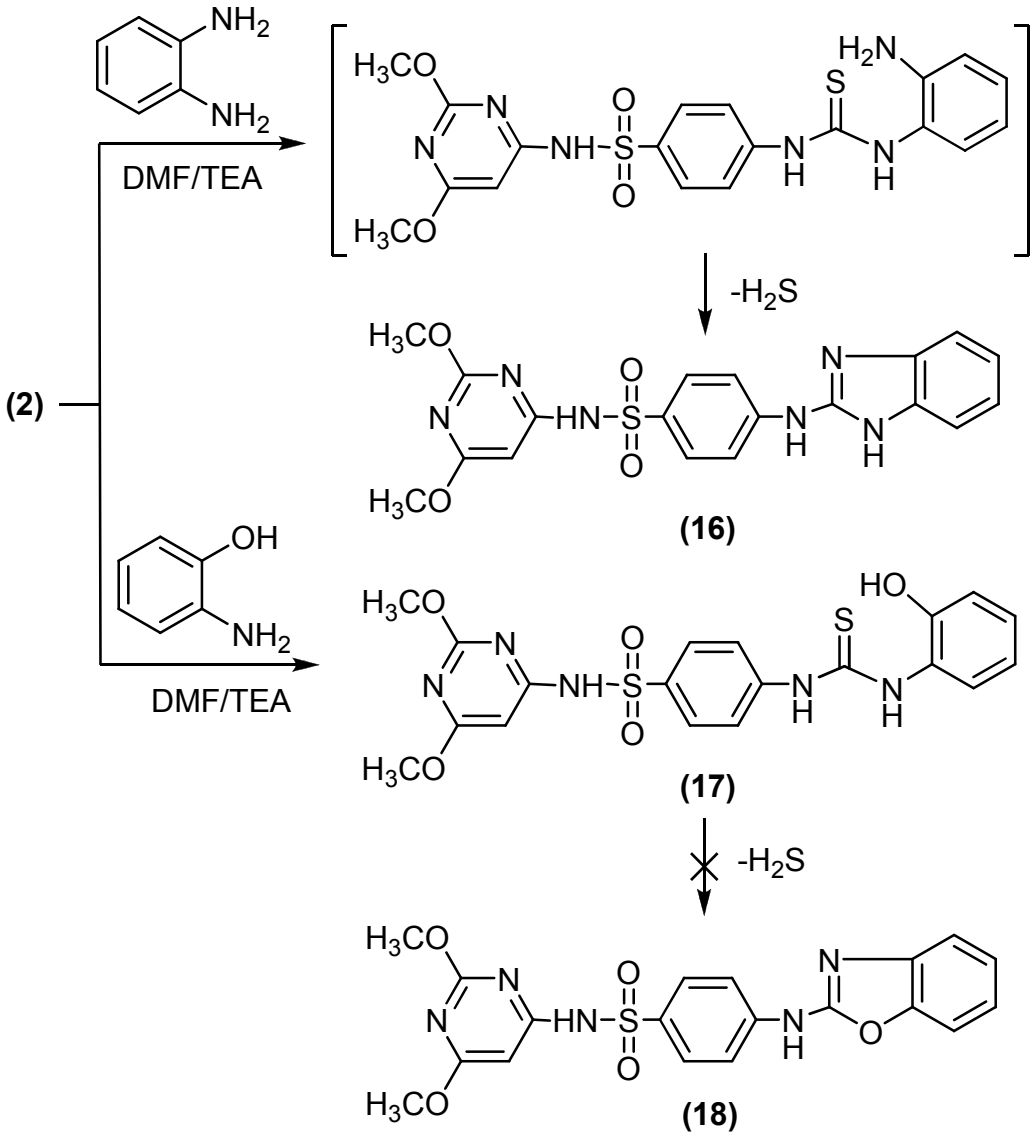
The reactivity of isothiocyanate derivative (2) towards binucleo-philes was discussed. Thus, Bisthiourea derivative (15) was achieved by condensation of isothiocyanate derivative (2) with 1,4-phenylenediamine (2 : 1 molar ratio), Scheme (5).



Scheme 5

Cyclocondensation of 1,2-phenylenediamine with isothiocyan-ate derivative (2) in dimethylformamide in the presence of triethyl-amine gave the 2-aminobenzimidazole derivative (16), Scheme (6). The formation of (16) is assumed to proceed via the initial formation of thiourea intermediate followed by intramolecular cyclization[20,21] through loss of hydrogen sulfide (tested by lead acetate paper). The structure of (16) was supported by analytical and spectral data.

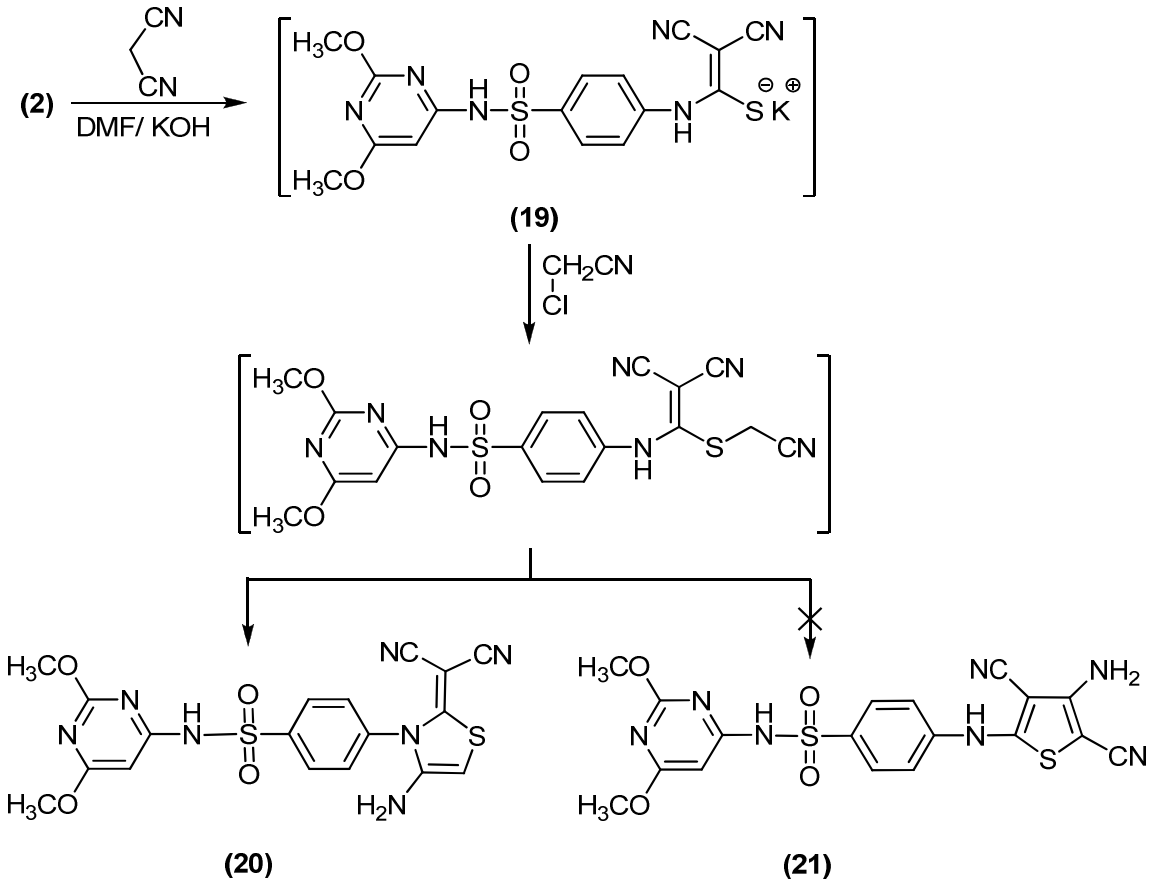
On the other hand, when isothiocyanate derivative (2) was reacted with 2-aminophenol in refluxing dimethylformamide and triethylamine, yielded the thiourea derivative (17). The structure of benzoxazole derivative (18) was ruled out on the basis of analytical and spectral data.



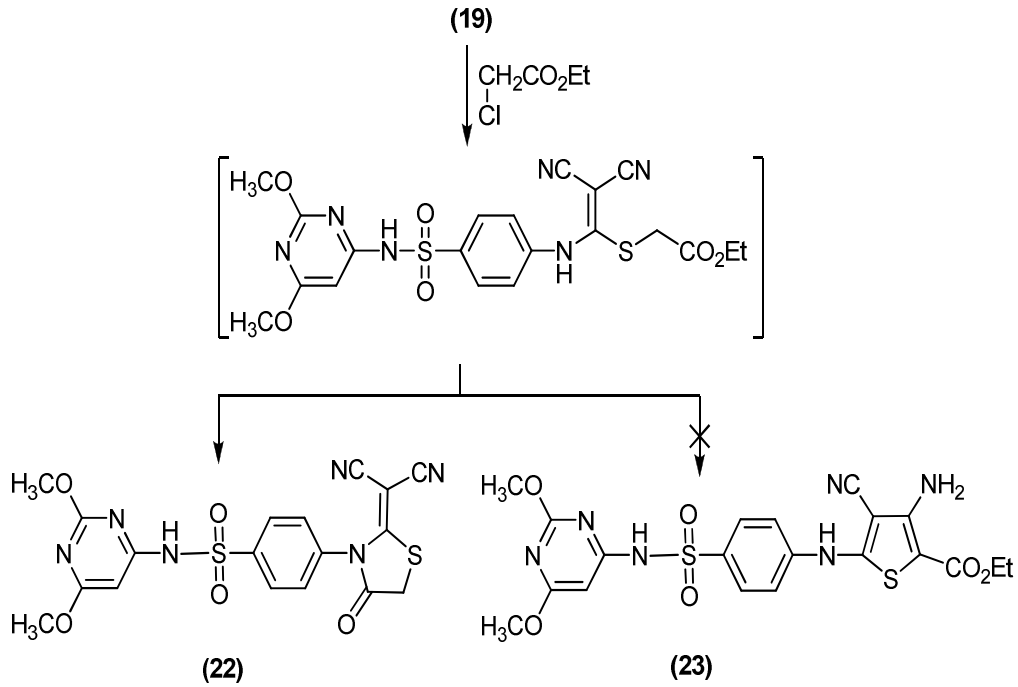
Scheme 6

The reactivity of isothiocyanate derivative (2) toward active methylene compounds in the presence of potassium hydroxide followed by in situ cyclization with α-halo compounds was discussed. Thus, the non-isolated adducts (19) was prepared by treatment of isothiocyanate derivative (2) with malononitrile. Treatment of the nonisolated[22]adduct (19) with chloroacetonitrile at room temperature furnished 4-amino-thiazole derivative (20). The other possible structure (21) was discarded on the basis of spectral data. The formation of compound (20) is assumed to proceed through the initial alkylation followed by heterocyclization[23] via nucleophilic addition of the secondary amino group to the cyano group and tautomerization, Scheme (7).

The reaction of the non-isolated adduct (19) with ethyl chloro-acetate at room temperature produced the novel 4-thiazolidinone derivative (22) and the other possible structure (23) was ruled out on the basis of analytical and spectral data, Scheme (8). The formation of (22) was assumed to proceed through initial alkylation followed by elimination of ethanol.



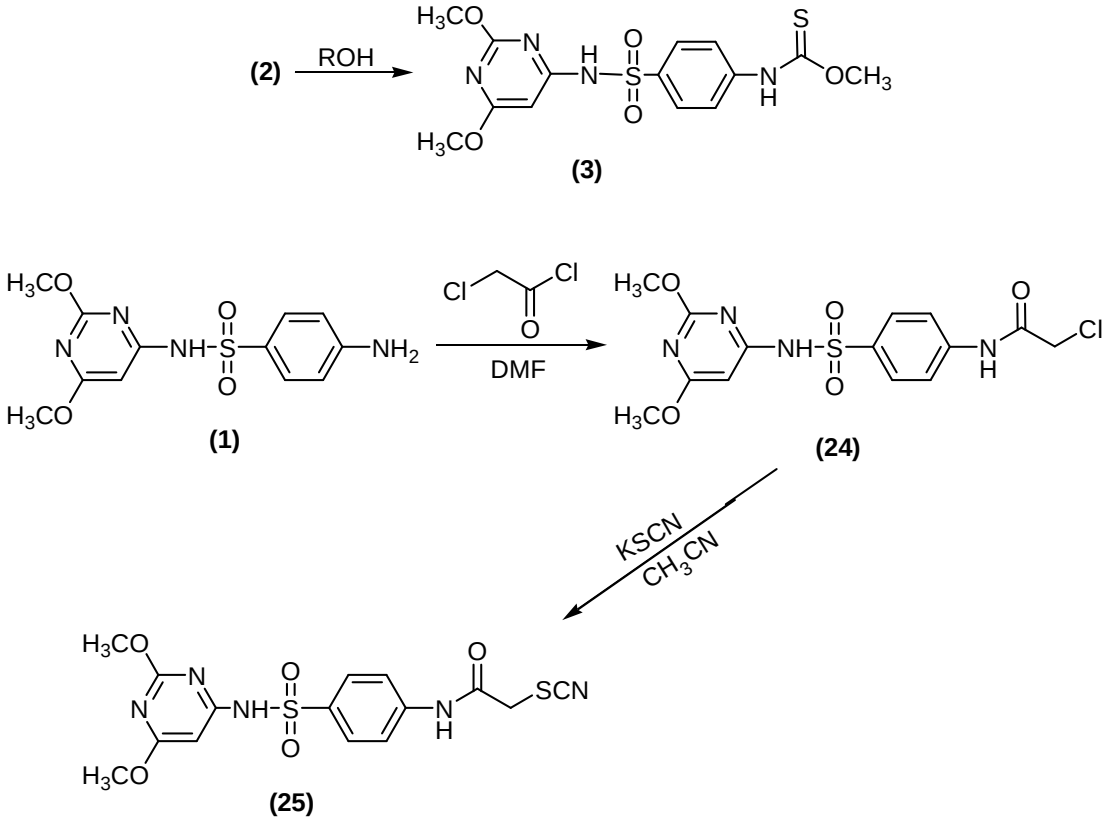
Scheme 7



Scheme 8

Treatment of (1) with chloroacetyl chloride in dimethylforma-mide at room temperature furnished chloroacetamide derivative (24) in good yield, Scheme 9. The structure of compound (24) was elucidated on the basis of elemental analysis and spectral data... Thiocyanate derivative (25) was achieved by treatment of chloroacetamide derivative (24) with potassium thiocyanate

under reflux in acetonitrile, Scheme 9. The structure of compound (25) was established on the basis of analytical and spectral data.



Scheme 9

Antitumor activity of the (E.A.C)
The method used is that of trypan blue exclusion.

Reagents :
1- RPMI 1640 medium (sigma).
2- Ehrlich Ascites Carcinoma cells (EAC) suspension (2.5x106/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 data of tested compounds are summarized in (Table 1).

Procedure
1 ml of tumor cells which is drawn from mice bearing (E.A.C).
1. EAC cells were obtained by needle aspiration of the ascetic fluid from preinoculated mice under aseptic conditions.[24]
2. In sterile test tubes, where 2.5 x 105 tumor cell/mL were suspended in phosphate buffer saline.
3. Three different concentration for each compound (25, 50, 100 µg/mL).
4. Added 2.5x105 tumor cells for each tube.
5. Incubate at 370c for 2 hours.
6. From sample cells + trypan blue volume by volume on slide.
7. Examine under microscope.
8. Dead cells stained blue and live cell not stained.

9. Trypan blue exclusion test[25] was carried out to carried out to calculate the percentage of non viable cells.
10. Doxorubicin [26](Adriablastina) is taken as a reference.

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

Screening test

Table (1): In-Vitro anti-tumor activity of some newly synthesized compounds using (E.A.C)

Compd. No.	Non-viable cells (%) Concentration (µg/mL)		
	100	50	25
4	10	0	0
5	10	0	0
6	10	0	0
9	10	0	0
11	20	10	0
13	20	10	0
20	95	50	15
25	90	45	10
Doxrubicin	100	55	20

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