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New Approaches for the Uses of 2-Cyanomethyl Thiazole in the Synthesis of Fused Heterocyclic Derivatives with Anti-Tumor Activities

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2-(4,5-DIHYDRO-4-oxothiazol-2-yl)acetonitrile (1) reacted with 2-acetylcoumarin (2) to give the 2-(4,5-dihydro-4-oxothiazol-2-yl)-3-(2-oxo-2H-chromen-3-yl)but-2-enenitrile (3). The reactivity of the latter product towards aromatic aldehydes 4a-d, cyanomethylene reagents 6a,b, aryl diazonium salts 10a-d, was studied to give products that were evaluated against the three cancer cells namely breast adenocarcinoma (MCF-7), non-small cell lung cancer (NCI-H460) and CNS cancer (SF-268). Some of them have high inhibitory effect towards three cell lines and compounds 14 and 16 were found to be more active than the standard on NCI-H460 and SF-268.

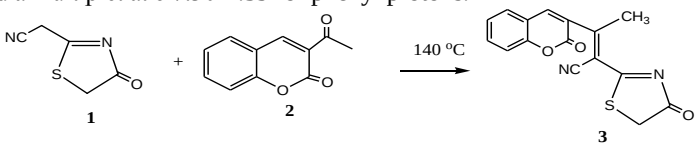
Keywords: Thiazole, Coumarin, Pyrazole, Pyridazine and Anti-tumor.

Thiazoles play a prominent role in nature. For example, the thiazolium ring present in vitamin B1 serves as an electron sink and its coenzyme form is important for the decarboxylation of α-keto acids[(1)]. Various pesticides possessing a thiazole nucleus are well known in agriculture. Large numbers of thiazole derivatives have emerged as active pharmaceutical ingredients in several drugs for their potential anti-inflammatory[(2)], anti-tumor[(3)] anti-hyperlipidemic[(4)], anti-hypertensive[(5)] and several other biological properties[(6)]. Besides, thiazoles are also synthetic intermediates and common substructures in numerous biologically active compounds[(7-13)].

Results and Discussion

Chemistry

In this work we describe the uses of 2-(4,5-dihydro-4-oxothiazol-2-yl)acetonitrile(1), which was obtained earlier[(14,15)], through the reaction of malononitrile with thioglycollic acid in acetic acid . Compound 1 reacts with acetophenone(2) in the presence of ammonium acetate at 140^{o}C to give the Knoevenagel condensation product 3. The structure of compound 3 was based on analytical and spectral data. Thus, the ^{1}HNMR spectrum showed a singlet at δ 2.89 ppm corresponding for the CH_3 group, a singlet at δ 5.65 ppm corresponding to the CH_2, and a multiplet at δ 7.30-7.39 for phenyl protons.



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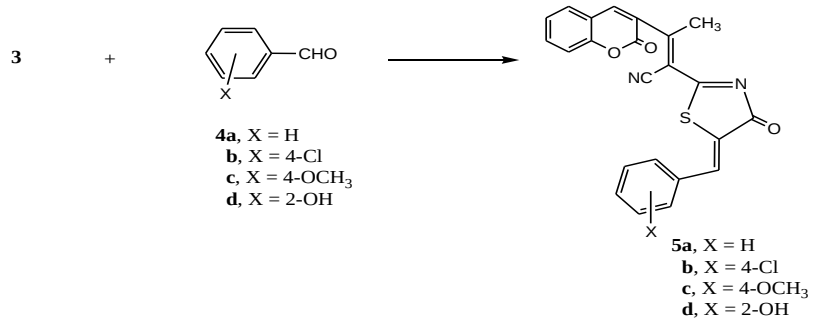
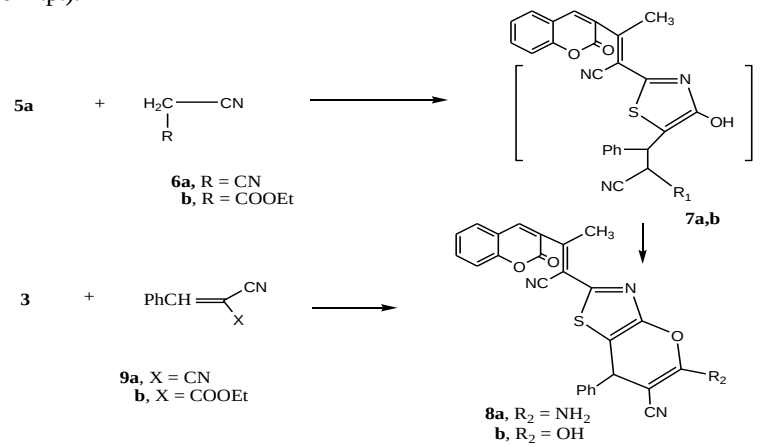
The reaction of compound 3 with aromatic aldehydes was studied to give arylidine derivatives with potential biological activities. Thus, compound 3 reacts with either benzaldehyde (4a), 4-chlorobenzaldehyde (4b), 4-methoxy-benzaldehyde (4c) or salicylaldehyde (4d), to give in each case a single product for them either structures 5a-d were assigned. Structures of the latter products were based on analytical and spectral data (see experimental section).

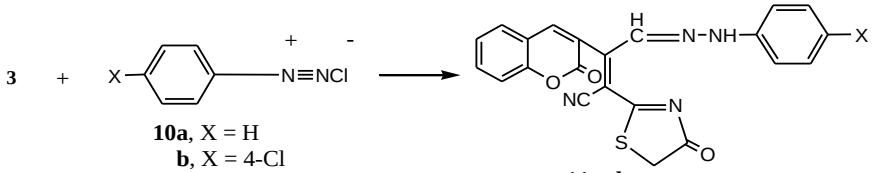


The reaction of compound 5a with either malononitrile (6a) or ethyl cyanoacetate (6b) gave the polyfunctionally substituted pyrano[2,3-d]thiazole derivatives 8a,b. The reaction took place via the intermediate formation of 7a,b (Scheme 1). Structures of compounds 8a and 8b were established on the basis of analytical and spectral data (see experimental section). Further confirmation for structures 8a,b was obtained through the synthesis of these compounds using another reaction routes. Thus, the reaction of compound 3 with either α-cyano cinmamonitrile (9a) or ethyl α-cyanocinmamate (9b) (Scheme 1) in the presence of 1,4-dioxan and a catalytic amount of triethylamine gave the same polyfunctionally substituted pyrano[2,3-d]thiazole derivatives 8a and 8b, respectively (finger print IR spectrum, m.p. and mixed m.p.).



The reaction of compound 3 with either benzenediazonium chloride (10a), 4-chlorobenzenediazonium chloride (10b), 4-methybenzenediazonium chloride

(10c) or 4-methoxybenzenediazonium chloride (10d) gave aryl-hydrazone derivatives 11a-d respectively. The analytical and spectral data of the latter products are consistent with the proposed structures (see experimental section).



10a, X = H
b, X = 4-Cl
c, X = 4-CH_3
d, X = 4-OCH_3

11a-d

Antitumor activity

Material , methods & reagents

Fetal bovine serum (FBS) and L-glutamine, were from Gibco Invitrogen Co. (Scotland, UK). RPMI-1640 medium was from Cambrex (New Jersey, USA). Dimethyl sulfoxide (DMSO), doxorubicin, penicillin, streptomycin and sulforhodamine B (SRB) were from Sigma Chemical Co. (Saint Louis, USA). Samples: Stock solutions of selected compounds from 3-11a-d were prepared in DMSO and kept at -20 ^{o}C. Appropriate dilutions of the compounds were freshly prepared just prior the assays. Final concentrations of DMSO did not interfere with the cell growth.

Cell cultures

Three human tumor cell lines, MCF-7 (breast adenocarcinoma), NCI-H460 (non-small cell lung cancer) and SF-268 (CNS cancer) were used. MCF-7 was obtained from the European Collection of Cell Cultures (ECACC, Salisbury, UK) and NCI-H460 and SF-268 were kindly provided by the National Cancer Institute (NCI, Cairo, Egypt). They grow as monolayer and routinely maintained in RPMI-1640 medium supplemented with 5% heat inactivated FBS, 2 mM glutamine and antibiotics (penicillin 100 µ/ml, streptomycin 100 µ g/ml), at 37^{o}C in a humidified atmosphere containing 5% CO_2. Exponentially growing cells were obtained by plating 1.5 X 10^5 cells/ml for MCF-7 and SF-268 and 0.75 X 10^4 cells/ml for NCI-H460, followed by 24 hr of incubation. The effect of the vehicle solvent (DMSO) on the growth of these cell lines was evaluated in all the experiments by exposing untreated control cells to the maximum concentration (0.5%) of DMSO used in each assay.

Effect on the growth of human tumor cell lines

The effect of selected compounds from the newly synthesized products 3-11a-d was evaluated on the *in vitro* growth of three human tumor cell lines representing different tumor types, namely, breast adenocarcinoma (MCF-7), non-small cell lung cancer (NCI-H460) and CNS cancer (SF-268), after a continuous exposure of 48 hr. The results are summarized in Table 1.

All the compounds were able to inhibit the growth of the human tumor cell lines in a dose-dependent manner (data not shown). The 2-pyridylthiazole derivative 14 and the 2-thiophenylthiazole derivatives 16 showed the best results, exhibiting an equivalent potency in all the three tumor cell lines which is still much lower than the gram positive control doxorubicin, On the other hand, compounds 5a, 8a, 11b, 11d and 12a showed moderated growth inhibitory effect. Comparing the activities of 12a & b it is observed that the N-phenyl group in 12a presents a stronger growth inhibitory effect than the N-p-chloroaryl substituent in 12b although the results in NCI-H460 cell line, are comparable. It is clear from Table 1 that some compounds like 5d, 11a, 11c and 12d showed very low activity towards certain cell line, MCF-7 and moderate activity towards other cell lines.

TABLE 1. Effect of compounds selected on the growth of three human tumor cell lines.

Compound	GI50 (μ□mol L^{-1})		
	MCF-7	**NCI-H460**	**SF-268**
3	30 □± 2.9	16.0 ± 4.8	28.0 ± 2.8
5a	33 □ ± 11.6	29.3 ± 4.2	38 ± 3.9
5b	0.4 ± 0.02	2.0 ± 0.8	0.9 ± 0.6
5c	60 □± 12.2	48.0 ± 6.4	58 ± 12.6
5d	30.4 ± 0.02	22.4 ± 6.2	11.2 ± 2.8
8a	18.6 ± 4.6	10.5 ± 1.8	22.4 ± 2.8
8b	12.8 ± 6.6	18.2 ± 4.2	20.2 ± 4.5
11a	0.1 ± 0.08	0.7 ± 0.06	0.4 ± 0.06
11b	20.1 ± 2.4	36.2 ± 2.4	38.0 ± 2.7
11c	30.0 ± 2.6	40.2 ± 4.5	20.2 ± 4.8
11d	66.2 ± 12.8	48.1 ± 4.6	55.8 ± 8.3
Doxorubicin	0.04 ± 0.008	0.09 ± 0.008	0.09 ± 0.007
Doxorubicin	□□□□□□□0.04 ± 0.008		0.09 ± 0.008
0.09 ± 0.007			

Results are given in concentrations that were able to cause 50 % of cell growth inhibition (GI_{50}) after a continuous exposure of 48 hr and show means ± SEM of three-independent experiments performed in duplicate.

Experimental

All melting points are uncorrected. IR spectra were recorded for (KBr) discs on Pye Unicam SP-1000 Spectrophotometer ^{1}HNMR Spectra were measured on a Varian EM-390-200 MHz and Bruker AVANCE DRX-500-300 MHz in CD_3SOCD_3 as solvent using TMS as internal standard and chemical shifts are expressed as δ. ^{13}CNMR spectra were measured on Bruker AVANCE DRX-500.

Analytical data were obtained from Micro Analytical Data Unit at Cairo University, Giza, Egypt.

2-(4,5-Dihydro-4-oxothiazol-2-yl)-3-(2-oxo-2H-chomen-3-yl)but-2-enenitrile (3)

To a dry mixture of compound 1 (0.01 mol, 1.87 g), 3-acetylcoumarin (1.88g, 0.01 mol) was added in the presence of ammonium acetate (2.0 g). The reaction mixture was heated in an oil bath (at 140 ^{o}C) for 1 hr, then left to cool. The solid product formed after boiling in ethanol, was collected by filtration. Yellow crystals from ethanol, yield g (80 %); mp 188-190 ^{o}C. IR: υ 3387-3232 (OH), 2986 (CH_3), 2223 (CN), 1708, 1688 (2CO), 1636 (C=C) cm^{-1}. MS: *m/z* (%) = 310 (100, M^+). ^{1}HNMR: δ 2.72 (s, 3H, CH_3), 5.68 (s, 2H, CH_2), 6.02 (s, 1H, coumarin H-4), 7.28-7.37 (m, 9H, C_6H_5, C_6H_4). *Calculated for* $C_{16}H_{10}N_2O_3S$ (310.33): C, 61.93; H, 3.25; N, 9.03; S, 10.33. Found: C, 62.02; H, 3.36; N, 9.21; S, 10.60.

Synthesis of compounds 5a-d

General procedure

An equimolar amount of either compound 3 (0.01 mol, 3.10 g) in ethanol (30 ml) containing pipridine (0.5 ml) either benzaldehyde (0.01 mol, 1.06 ml), p-chlorobenzaldehyde (1.40 g, 0.01 mol), p-methoxy-benzaldhyde (1.36 g, 0.01 mol), or salicylaldehyde (1.22 g, 0.01 mol) was added. The reaction mixture was heated under reflux for 3hr then poured into ice/water mixture containing few drops of hydrochloric acid. The solid product formed, in each case, was collected by filtration.

2-(5-Benzylidene-4,5-dihydro-4-oxothiazol-2-yl)-3- (2-oxo-2H- chomen-3-yl) but- 2- enenitrile (5a)

Yellow crystals from ethanol, yield 2.78 g (70 %), mp 231-234^{o}C. IR: υ 3066 (CH aromatic), 2986, 2869 (CH3), 1690, 1685 (2 CO), 1633 (C=C) cm^{-1}. ^{1}H NMR: δ 2.89 (s, 3H, CH_3), 6.23 (s, 1H, coumarin H-4), 7.28-7.33 (m, 15H, $2C_6H_4$, C_6H_5, CH). *Calculated for* $C_{23}H_{14}N_2O_3S$ (398.43): C, 69.33; H, 3.54; N, 7.03; S, 8.05. Found: C, 69.77; H, 3.79; N, 7.38; S, 8.11.

2-(5-4-Chlorobenzylidene-4,5- dihydro-4- oxothiazol-2-yl)-3- (2-oxo-2H-chomen -3- yl) but-2- enenitrile (5b)

Yellow crystals from ethanol, yield 2.59 g (60 %); mp 190-192 ^{o}C. IR: υ 3060 (CH aromatic), 2937 (CH_3), 1692, 1685 (2 CO), 1620 (C=C) cm^{-1}. ^{1}HNMR δ = 2.77 (s, 3H, CH_3),6.20 (s, 1H, coumarib H-4), 7.30-7.40 (m, 14H, $2C_6H_4$, C_6H_5, CH). *Calculated for* $C_{23}H_{13}ClN_2O_3S$ (432.03) C, 63.82; H, 3.03; N, 6.47; S, 7.41. Found: C, 63.82; H, 3.24; N, 6.73; S, 7.82.

2-(5-4-methyoxybenzylidene -4,5-dihydro -4-oxothiazol-2-yl) -3-(2-oxo-2H-chomen -3-yl) but -2-enenitrile (5c)

Yellow crystals from ethanol; yield 3.29 g (80 %); mp 180-183 ^{o}C. IR: υ 3054 (CH aromatic), 2970 (CH_3), 1688, 1684 (2 C=O), 1631 (C=C) cm^{-1}. ^{1}HNMR: δ 2.88, 3.32 (2s, 6H, $2CH_3$), 6.20 (s, 1H, coumarin H-4), 7.26-7.40 (m,

14H, $2C_6H_4$, Ph, CH). *Calculated for* $C_{24}H_{16}N_2O_3S$ (412.46): C, 69.89; H, 3.91; N, 6.79; S, 7.77. Found: C, 69.87; H, 4.03; N, 6.82; S, 8.02.

2-(5-4-methoxybenzylidene -4,5-dihydro -4-oxothiazol-2-yl) -3-(2-oxo-2H-chomen -3-yl) but-2-enenitrile (5d)

Yellow crystals from ethanol, yield 2.99 g (70 %); mp 170-173 ^oC. IR: υ 3566-3233 (OH), 3060 (CH aromatic), 2960 (CH_3), 1690, 1686 (2 CO), 1631 (C=C) cm^{-1}. ^{1}HNMR: δ 2.86, 3.11 (2s, 6H, $2CH_3$), 6.21 (s, 1H, cumarin H-4), 7.28-7.34 (m, 14H, C_6H_5, $2C_6H_4$, CH). *Calculated for* $C_{24}H_{16}N_2O_4S$ (428.46): C, 67.28, H, 3.76: N, 6.54; S, 7.48. Found: C, 67.53; H, 3.61; N, 7.59; S, 7.362.

Synthesis of compounds 8a,b

General procedure

Method A : To a solution of compound 5a (0.01 mol, 3.98 g) in ethanol (30 mL) containing triethylamine (0.5 ml), either malononitrile (0.66 g, 0.01 mol) or ethyl cyanoacetate (1.13 g, 0.01 mol) was added, the reaction mixture was heated under reflux for 4hr. The solid product formed upon pouring onto ice/water mixture was collected by filtration.

Method B : To a solution of compound 3 (0.01 mol, 3.10 g) in ethanol (30 mL) containing triethylamine (0.5 ml), either α-cyanocinnamonitrile (1.70 g, 0.01mol) or ethyl α -cyanocinnamate (1.97 g, 0.01 mol) was added. The reaction mixture was heated under reflux for 5hr then the reaction mixture was poured onto ice/water mixture containing few drops of hydrochloric acid and the formed solid product was collected by filtration.

5-Ami o1-cyano-2- (2-oxo-2H- chomen-3-yl) prop-1-enyl) -7-phenyl -7H-pyrano [2,3-d] thiazole-6-carbonitrile (8a)

Orange crystals from ethanol, yield 2.78 g (60 %); mp 220-222^oC. IR: υ 3455-3320 (NH_2), 3050 (CH aromatic), 2946 (CH_3), 2222 (CN), 1688 (CO), 1564 (C=C). ^{1}HNMR: δ 2.87(s, 3H, CH_3), 5.58(s, 2H, NH_2), 6.03 (Coumarin H-4), 7.24-7.37 (m, 10H, C_6H_5, C_6H_4, pyran H-4). *Calculated for* $C_{26}H_{16}N_4O_3S$ (464.50): C, 67.23; H, 3.47; N, 12.06; S, 6.90. Found: C, 67.24; H, 3.37; N, 12.085; S, 7.16.

1-Cyano-2-(2-oxo-2H- chomen-3-yl) prop-1-enyl)-5-hydroxy-7-phenyl-7H-pyrano [2,3-d] thiazole -6-carbonitrile (8b)

Yellow crystals from ethanol, yield 3.58 g (77 %); mp 147-149^oC. IR: υ 3566-3132 (OH), 3053 (CH aromatic), 2966 (CH_3), 2220 (CN), 1678 (CO), 1632 (C=C) cm^{-1}. ^{1}HNMR: δ 2.83 (s, 3H, CH_3), 6.24 (coumarin H-4), 7.29- 7.41 (m, 10H, C_6H_5, C_6H_4, pyrane H-4), 9.22 (s, 1H, OH). Calculated *for* $C_{26}H_{15}N_3O_4S$ (465.48): C, 67.09; H, 3.25; N, 9.03; N, 9.03; S, 6.89. Found: C, 67.32; H, 3.51; N, 8.79; N, 8.94; S, 7.03.

Synthesis of compounds 11a-d

General Procedure

To a cold solution (0-5^{o}C) of compound 3 (2.89 g, 0.01 mol g) in acetic acid/ethanol (1:4) (50 ml) containing sodium hydroxide (5 ml, 10 %) either benzenediazonium chloride (0.01mol), 4-chlorobenzene- diazonium chloride (0.01 mol), 4-methylbenzenediazonium chloride (0.01 mol) or 4-methoxy-benzenediazonium chloride (0.01 mol) [prepared by adding sodium nitrite (0.02 mol, 1.38 g) solution to a cold solution (0-5 ^{o}C) of aniline (0.93 g, 0.01 mol), 4-chloroaniline (1.27g, 0.01 mol,), 4-methylaniline (1.07g, 0.01 mol) or 4-methoxyaniline (1.23g, 0.01 mol) containing the appropriate amount of hydrochloric acid with continuous stirring] was added with stirring. The reaction mixture was left at 0-5^{o}C for 4hr and the formed solid product, in each case, was collected by filtration.

4-(2-(4-Phenyl)- hydrazono) -2-(4,5-dihydro -4-oxothiazol -2-yl)-3-(2-oxo-2H-chomen -3-yl) but -2-enenitrile (11a)

Red crystals from ethanol, yield 3.47 g (84 %); mp 220-223 ^{o}C. IR: υ 3473-3331 (NH), 3055 (CH aromatic), 1691, 1688 (2 CO), 1632 (C=C) cm^{-1}. ^{1}HNMR: δ 5.41 (s, 2H, thiazole CH_2), 6.04 (s, 1H, CH=N), 6.27 (s, 1H, coumarin H-4), 7.29- 7.37 (m, 9H, C_6H_5, C_6H_4), 8.40 (s, 1H, NH). *Calculated for* $C_{22}H_{14}N_4O_3S$ (414.44): C, 63.76; H, 3.40; N, 13.52; S, 7.74. Found: C, 63.84; H, 3.16; N, 13.62; S, 7.84.

4-(2-(4-chlorophenyl)-hydrazono)-2-(4,5-dihydro-4-oxothiazol-2-yl)-(2-oxo-2H-chomen-3-yl)but-2-enenitrile (11b)

Orange powder from ethanol, yield 3.58 g (80 %), mp 196-199^{o}C. IR: υ 3448-3338 (NH), 3052 (CH aromatic), 1688, 1668 (2 CO), 1638 (C=C) cm^{-1}. ^{1}HNMR: δ 5.70 (s, 2H, thiazole CH_2), 6.22 (s, 1H, CH=N), 6.23 (s, 1H, coumarin H-4), 7.29-7.35 (m, 8H, $2C_6H_4$), 9.40 (s, 1H, NH). *Calculated for* $C_{22}H_{13}ClN_4O_3S$ (228.88): C, 58.87; H, 2.92; N, 12.48; S, 7.14. Found: C, 58.67; H, 3.08; N, 12.68; S, 7.09.

4-(2-(4-mehylyphenyl)- hydrazono)-2-(4,5- dihydro-4-oxothiazol-2-yl) -3-(2-oxo-2H-chomen-3-yl)but-2-enenitrile (11c)

Brown crystals form ethanol, yield 2.57 g (60 %); mp 188-192^{o}C. IR: υ 3439-3325 (NH), 3062 (CH aromatic), 2955 (CH_3), 1688, 1680 (2 CO), 1631 (C=C) cm^{-1}. ^{1}HNMR: δ 3.24 (s, 3H, CH_3), 5.45 (s, 2H, thiazole CH_2), 6.01 (s, 1H, CH=N), 6.25 (s, 1H, coumarin H-4), 7.29-7.37 (m, 8H, $2C_6H_4$), 8.44 (s, 1H, NH). *Calculated for* $C_{23}H_{16}N_4O_3S$ (428.46): C, 64.47; H, 3.76; N, 13.08; S, 7.48. Found: C, 64.31; H, 3.79; N, 13.15; S, 7.58.

4-(2-(4- mehoxyphenyl) -hydrazono)-2-(4,5- dihydro-4- oxothiazol -2-yl)-3-phenylbut -2- enenitrile (11d)

Red crystals from ethanol, yield 3.06 g (69 %); mp 148°C. IR: υ 3446-3322 (NH), 3058 (CH aromatic), 2989 (CH aromatic), 2988 (CH_3), 1685, 1683 (2 CO), 1622 (C=C) cm^{-1}. ^{1}HNMR: δ 3.02 (s, 3H, CH_3), 5.62 (s, 2H, CH_2), 6.20 (s, 1H, CH=N), 6.26 (s, 1H, coumarin H-4), 7.30-7.48 (m, 8H, $2C_6H_5$), 8.96 (s, 1H, NH). *Calculated for* $C_{23}H_{16}N_4O_4S$ (444.46): C, 62.15; H, 3.63; N, 12.61; S, 7.21. Found: C, 62.28; H, 3.58; N, 12.79; S; 7.42.

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اتجاهات حديثة لاستخدامات مركب ٢- سيانو ثيازول لتحضير مركبات عضوية غير متجانسة الحلقة كمضادات للأورام

وجنات وهبة وردخان
هيئة الرقابة والبحوث الدوائية ص . ب . ٢٩ القاهرة – مصر.

مشتق الثيازول ١ تفاعل مع مركب ٢- أستيل كيومارين ليعطى المركب ٣ز المركب الأخير تم دراسة درجة نشاط المركب الأخير تجاه العديد من الكواشف الكيميائية ليعطى مركبات عضوية غير متجانسة الحلقة . وقد تم فى هذا البحث دراسة درجة نشاط المركبات الناتجة تجاه بعض الخلايا السرطانية وقد أثبتت الدراسة درجة نشاط عالية لبعض المركبات المحضرة .