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New Approaches for the Synthesis of Thiophene Derivatives with Antitumor Activities

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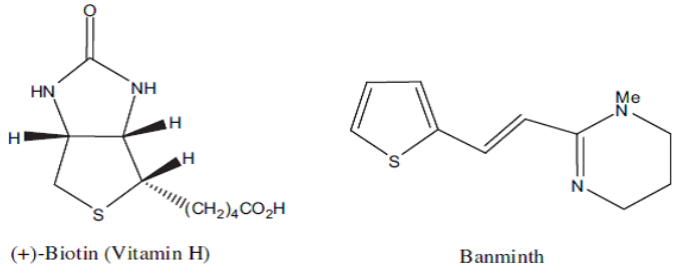
TETRAHYDROBENZO[B]THIOPHENE derivatives 3a‹b and 5a,b were synthesized followed by the alkylation of some derivatives. The antitumor evaluation of the newly synthesized products against three cancer cell lines, namely breast adenocarcinoma (MCF-7), non-small cell lung cancer (NCI-H460) and CNS cancer (SF-268) was recorded. Some of the synthesized compounds show high inhibitory effects.

Keywords: Thiophene, Pyridine, Pyrazole and Antitumor.

Aromatic thiophenes play a part in animal metabolism; for examples, in Fig. 1, Biotin, one of the vitamins (Vitamin H), is a tetrahydrothiophene, however aromatic thiophenes do occur in some plants, in association with polyacetylenes with which they are biogenetically linked and Banminth_ (pyrantel), available anthelmintic used in animal husbandry, is one of the thiophene compounds in chemotherapy . Thiophenes with a wide spectrum of biological activities are known, several of these derivatives possess potent analgesis[1,2], anticonvulsant, anti-inflammatory and antibacterial[3-6] , antipyretics[7], antitumor[8,9] , antiparasitics [10] , antimicrobial [11] , antihistaminic (H1)[12], antianexiety test in mice[13] , antiarrhythmic[14] and serotonin antagonist [15] . In a previous work we have found that certain substituted pyrimidines and their heterocyclic derivatives show antimicrobial and anti-inflammatory[16-19] and antitumor activities[20,22] . On the other hand, thioxopyrimidine and thiazolopyrimidine derivatives have promising biological and anticancer activities[23-25] .



(+)-Biotin (Vitamin H) Banminth

Fig.1. Chemical structures of (+)-Biotin and Banminth.

In the present work we would like to investigate some reactions of the 4,5,6,7-tetrahydrobenzothiophene derivatives in order to give new heterocyclic derivatives together with their evaluations as antitumor agents against cancer cell lines.

Results and Discussion

The reaction of cyclohexanone (1) with either cyanoacetanilide or 4-chloroacetanilide in presence of elemental sulfur gave the 4,5,6,7-tetrahydrobenzo [b] thiophene derivatives 3a and 3b, respectively. The structures of the latter products were established on the basis of analytical and spectral data .^{1}H NMR spectrum of 3b ،as an example showed 1.79-2.02 (m, 8H, 4CH_2), 4.44)s, 2H, NH_2 7.27-7.36) m, 4H, benzene-CH), 8.64) (s, 1H, NH, D_2O-exchangeable). The 2-amino present in compounds 3a,b showed interesting activity towards anilide formation. Thus, compounds 3a،b reacted with ethyl cyanoacetate (4) in the presence of DNF, under reflux to give the anilide derivatives 5a . The analytical and spectral data of the latter products are in agreement with their respective structures. Thus, the ^{1}H NMR spectrum of 5a owed 1.71-1.84 (m, 8H, 4CH_2) 3.88 (s, 2H, CH_2), 3.88 (s,2H, CH_2),7.27-7.36 (m, H, benzene-CH), 8.22,8.61 (2s, 2H, 2NH, D_2O- exchangeable). The 2-amino-3-cyano-4,5,6,7 tetrahydrobenzo [b] thiophene (6) reacted with ethyl acetoacetate in dry conditions, in an oil bath at 120^{o}C to afford the amide derivative 8 . The 1H NMR spectrum of the latter product showed 1.74-2.44 (m, 8H, 4CH_2; 3.31 (s, 3H, CH_3); 3.76 (s, 2H, CH_2); 11.57 (s, 1H, NH). Compound 8 reacted with bromine in acetic acid at 60 ^{o}C to afford the α-bromo derivative 9. The latter compound reacted with thiourea (10) to give the thiazole derivative 11 .

Compound 8 reacted with p-nitrobenzenediazonium chloride to give the arylhydrazone derivative 12 . Compound 12 reacted with either malononitrile (13) or ethyl cyanoacetate (4) in the presence of ammonium acetate in an oil bath at 120^{o}C to give the Knowevenagel condensation products 14a & b, respectively. Analytical and spectral data are the tools of their structural elucidation. Compounds 14a & b underwent ready cyclization in the presence of sodium ethoxide solution to give the pyridine derivatives 15a & b, respectively. Formation of the latter products is explained in terms of two different mechanisms. Formation of 15a is assumed to occur via Michael addition of the NH- of NHCO group to the CN group. However, cyclization of 15b is explained in terms of ethanol elimination.

The compounds described in this work were evaluated towards three cancer cell lines namely breast adenocarcinoma (MCF-7), non-small cell lung cancer (NCI-H460) and CNS cancer (SF-268).

Biological Evaluation

Reagent and method of antitumor evaluation

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).

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 μg/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.

Tumor cell growth assay

The effects of 3a,b– 15a,b on the in vitro growth of human tumor cell lines were evaluated according to the procedure adopted by the National Cancer Institute (NCI, USA) in the '*In vitro* Anticancer Drug Discovery Screen' that uses the protein-binding dye sulforhodamine B to assess cell growth. Briefly, exponentially, cells growing in 96-well plates were then exposed for 48 hr to five serial concentrations of each compound, starting from a maximum concentration of 150 μM. Following this exposure period adherent cells were fixed, washed, and stained. The bound stain was solubilized and the absorbance was measured at 492 nm in a plate reader (Bio-Tek Instruments Inc., Powerwave XS, Wincoski, USA). For each test compound and cell line, a dose–response curve was obtained and the growth inhibition of 50% (GI_{50}), corresponding to the concentration of the compounds that inhibited 50% of the net cell growth, was calculated as described elsewhere. Doxorubicin was used as a positive control and tested in the same manner.

Effect on the growth of human tumor cell lines

The effect of compounds 3-12b 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 for 48hr. The results are summarized in Table 1. All of the tested compounds were able to inhibit the growth of the tested human tumor cell lines in a dose-dependant manner (data not shown). The results indicated through Table 1 revealed that "compound 9, 12, 14b and 15b showed the highest inhibitory effect against all the three tumor cell lines breast adenocarcinoma (MCF-7), non-small cell lung cancer (NCI-H460) and CNS cancer (SF-268). However, compounds 5a, 8, 11, 15a showed the lowest activity towards the three cancer cell lines while compounds 3a, 3b, 5b and 14a showed the intermediate activity.

TABLE 1. Effect of the newly synthesized products on the growth of three human tumor cell lines.

Compound	GI_{50} (µM)		
	MCF-7	**NCI-H460**	**SF-268**
3a	10.1± 0.6	9.3 ± 1.4	6.3 ±0.8
3b	20.1 ± 0.4	24.3 ± 0.8	20 ± 0.8
5a	33.6 ± 16.9	32.9 ± 1.8	34.8 ± 8.6
5b	22.6 ± 12.6	32.6 ± 8.6	60.4 ± 14.8
8	38.4 ± 10.2	24.1 ± 0.8	18.9 ± 6.8
9	0.01 ± 0.004	0.01 ± 0.008	0.02 ± 0.006
11	30.7 ± 17.5	42.2 ± 12.8	33.0 ± 6.01
12	0.03 ± 0.007	0.02 ± 0.005	0.04 ± 0.008
14a	26.0 ± 0.2	22.6 ± 1.4	28.4 ± 0.6
14b	0.01 ± 0.006	0.03 ± 0.008	0.06 ± 0.004
15a	36.0 ± 1.8	40.0 ± 0.8	18.5 ± 1.1
15b	4.0 ± 0.2	2.6 ± 0.8	4.4 ± 0.6
Doxorubicin	0.0428 ± 0.008	0.0940 ± 0.008	0.0940 ± 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 were determined in open capillaries and are uncorrected. Elemental analyses were performed on a Yanaco CHNS Corder elemental analyzer (Japan). IR spectra were measured using KBr discs on a Pye Unicam SP-1000 spectrophotometer. ^{1}H NMR spectra were measured on a Varian EM 390-200 M*Hz* instrument in CD_3SOCD_3 as solvent using TMS as internal standard and chemical shifts are expressed as δ ppm. Elemental analyses were carried out by the Micro-analytical Data Center at Cairo University and were performed on Vario EL III Elemental CHNS analyzer.

2-Amino-N-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (3a) and 2-amino-N-(4-chlorophenyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (3b)

To a solution of compound 1 (0.93 g, 0.01 mol) in 1,4-dioxane (30 ml) containing triethylamine, either cyanoacetanilide (1.60 g, 0.01 mol) or cyano-4-chloroacetanilide (1.95 g, 0.01 mol) was added followed by the addition of elemental sulfur (0.32 g, 0.01 mol). The reaction mixture was heated under reflux for 2 hr, then was left until the reaction mixture be cooled. The formed solid product was collected by filtration.

Compound 3a: Yellow crystals from 1,4-dioxane, 70 % (1.90 g) yield; mp. 160°C, MS: m/z = 274 (M^+), IR (KBr): υ/cm^{-1} = 3435-3320 (NH_2, NH), 3060 (CH_{Ar}), 1680 (CO), 1550 (C=N), ^{1}H NMR (DMSO-d_6): δ = 1.73-1.82 (m, 8H, 4CH_2), 4.42 (s, 2H, NH_2), 7.32-7.40 (m, 5H, benzene-CH), 8.62 (s, 1H, NH, D_2O-exchangeable). Analysis Calcd for $C_{15}H_{16}N_2OS$ (272.37): C, 66,15; H, 5.92; N, 10.29; S, 11.77 %. Found: C, 66.09; H, 6.15; N, 10.47; S, 11.60 %.

Compound 3b: Orange crystals from 1,4-dioxane, 78 % (2.30 g) yield; mp. 187°C, MS: m/z = 306 (M^+), IR (KBr): υ/cm^{-1} = 3438-3320 (NH_2, NH), 3055 (CH_{Ar}), 1682 (CO), 1558 (C=N), ^{1}H NMR (DMSO-d_6): δ = 1.79-2.02 (m, 8H, 4CH_2), 4.44 (s, 2H, NH_2), 7.27-7.36 (m, 4H, benzene-CH), 8.64 (s, 1H, NH, D_2O-exchangeable). Analysis Calcd for $C_{15}H_{15}ClN_2OS$ (306.81): C, 58.72; H, 4.93; N, 9.13; S, 10.45 %. Found: C, 58.64; H, 5.19; N, 9.41; S, 10.62 %.

2-(2-Cyanoacetamido)-N-phenyl-4,5,6,7- tetrahydrobenzo[b]thiophene-3-carboxamide (5a) and 2-(2-cyanoacetamido)- N-(4-chlorophenyl- 4,5, 6,7-tetrahydrobenzo [b] thiophene - 3-carboxamide (5b), General procedure

To a solution of either 3a (2.72 g, 0.01 mol) or 3b (3.06 g, 0.01 mol) in dimethylformamide, ethyl cyamoacetate (1.13 g, 0.01 mol) was added. The reaction mixture was heated under reflux for 2 hr then poured onto ice/water. The formed solid product, in each case, was collected by filtration.

Compound 5a: Yellow crystals from 1,4-dioxane, 82 % (2.77 g) yield; mp. 220°C, MS: m/z = 339 (M^+), IR (KBr): υ/cm^{-1} = 3455-3342 (NH), 3052 (CH_{Ar}), 2220 (CN), 1687, 1683 (2CO), 1566 (C=N), ^{1}H NMR (DMSO-d_6): δ = 1.71-1.84 (m, 8H, 4CH_2), 3.88 (s, 2H, CH_2), Analysis Calcd for $C_{18}H_{17}N_3O_2S$ (340.10): C, 63.70; H, 5.05; N, 12.38; S, 9.45 %. Found: C, 63.89; H, 5.39; N, 12.61; S, 9.69 %.

Compound 5b: Orange crystals from 1,4-dioxane, 64 % (2.38 g) yield; mp. 210°C, MS: m/z = 373 (M^+), IR (KBr): υ/cm^{-1} = 3463-3351 (NH), 3053 (CH_{Ar}), 2222 (CN), 1687, 1684 (2CO), 1562 (C=N), ^{1}H NMR (DMSO-d_6): δ = 1.74-1.99 (m, 8H, 4CH_2), 3.93 (s, 2H, CH_2), 7.29-7.38 (m, 4H, benzene-CH), 8.26, 8.62 (2s, 2H, 2NH, D_2O-exchangeable). Analysis Calcd for $C_{18}H_{16}ClN_3O_2S$ (373.86): C, 57.83; H, 4.31; N, 11.24; S, 8.58 %. Found: C, 57.69; H, 4.59; N, 11.08; S, 8.78 %.

N-(3-Cyano-4,5,6,7-tetrahydrobenzo[b]thiophe-2-yl)-3-oxobutanamide (8)

Ethyl acetoacetate (13.0 g, 0.1 mol) was heated till 140 °C then compound 6 (17.8 g, 0.1 mol)) was added with continuous heating till the temperature reached 125 °C and the whole reaction mixture was heated under reflux for 20 min then left to cool. The formed solid product was triturated with ethanol and the formed solid product, in each case, was collected by filtration.

Yellow crystals, yield 2.04 g (78%), mp 217-219°C (EtOH). MS: m/z = 262 (M^+), IR spectrum, ν, cm^{-1}: 3445-3224 (NH); 2936, 2850 (CH_3, CH_2); 2217 (CN); 1699-1690 (2CO). ^{1}H NMR spectrum ^{1}H NMR (DMSO-d_6): 1.74-2.44 (m, 8H, 4CH_2); 3.31 (s, 3H, CH_3); 3.76 (s, 2H, CH_2); 11.57 (s, 1H, NH). Found, %: C 59.6; H 5.6; N 10.59; S, 11.89. $C_{13}H_{14}N_2O_2S$. Calculated, %: C 59.52; H 5.38; N 10.68; S 12.22.

4-Bromo-N-(3-cyano-4,5,5,7-tetrahydrobenzo[b]thiophen-2-yl)-3-oxobutanamide (9)

To a solution of compound 8 (2.62 g, 0.01 mol) in acetic acid (40 ml) was heated till 60 ^{o}C then bromine (1.60 g, 0.01 mol) in acetic acid (10 ml) was added dropwise. The whole reaction mixture was stirred at room temperature for 30 min then poured onto ice/water. The formed solid product was collected by filtration.

Compound 9: Orange crystals from acetic acid, 77 % (2.62 g) yield; mp. -160-163 ^{o}C, MS: m/z = 341 (M^{+}), IR (KBr): υ/cm^{-1} = 3477-3340 (NH), 2227 (CN), 1692, 1686 (2CO), 1560 (C=N), ^{1}H NMR (DMSO-d_6): δ = 1.71-1.82 (m, 8H, 4CH_2), 4.41, 5.22 (2s, 3H, 2CH_2), 8.28 (s, 1H, NH, D_2O-exchangeable). Analysis Calcd for $C_{13}H_{13}BrN_2O_2S$ (341.22): C, 45.76; H, 3.84; N, 8.21; S, 9.40%. Found: C, 45.76; H, 4.22; N, 8.51; S, 9.27 %.

2-(2-Aminothiazol-4-yl)-N- (3-cyano-4,5,6,7- tetrahydrobenzo[b]- thiophene-2-yl) acetamide (11)

To a solution of compound 9 (3.41 g, 0.01 mol) in ethanol (96 %, 40 ml), thiourea (10) was added. The reaction mixture was heated under reflux for 3 hr then left to cool. The solid product, so formed, upon pouring onto ice/water containing few drops of sodium hydroxide solution (10 %) was collected by filtration.

Compound 11: Orange crystals from ethanol, 80 % (2.54 g) yield; mp. -222-224^{o}C, MS: m/z = 318 (M^{+}), IR (KBr): υ/cm^{-1} = 3482-3352 (NH_2, NH), 2221 (CN), 1688 (CO), 1558 (C=N), ^{1}H NMR (DMSO-d_6): δ = 1.73-1.87 (m, 8H, 4CH_2), 4.33 (s, 2H, CH_2), 4.49 (s, 2H, NH_2), 6.20 (s, 1H, thiazole H-5), 8.25 (s, 1H, NH, D_2O-exchangeable). Analysis Calcd for $C_{14}H_{14}N_4OS_2$ (319.42): C, 52.81; H, 4.43; N, 17.60; S, 20.14 %. Found: C, 52.67; H, 4.62; N, 17.42; S, 20.33 %.

N-(3- cyano-4,5,6,7- tetrahydrobenzo[b] thiophen-2-yl)- 2-(2-(4-nitrophenyl) hydrazono)-3-oxobutanamide (12)

To a cold solution of compound 8 (2.52 g, 0.01 mol) in ethanol (40 ml) containing sodium hydroxide (5 ml, 10 %), 4-nitrobenzenediazonium chloride (0.01 mol) [prepared by adding sodium nitrite solution (0.70 g, 0.01 mol, in water 10 ml) to a cold solution (0-5 ^{o}C) of 4-nitroaniline (1.38 g, 0.01 mol) in the appropriate amount of concentrated hydrochloric acid, dropwise with continuous stirring] was added with continuous stirring. The whole reaction mixture was stirred at room temperature for an additional 1 hr. The formed solid product was collected by filtration.

Compound 12: Orange crystals from acetic acid, yield 60 % (2.46 g); mp. 222-225 ^{o}C, MS: m/z = 411 (M^{+}), IR (KBr): υ/cm^{-1} = 3480-3341(NH), 3054 (CH_{Ar}), 2224 (CN), 1684, 1682 (2CO), 1573 (C=N), ^{1}H NMR (DMSO-d_6): δ = 1.71-1.83 (m, 8H, 4CH_2), 2.48 (s. 3H, CH_3), 7.27-7.37 (m, 4H, benzene-CH), 8.22, 8.58 (2s, 2H, 2NH, D_2O-exchangeable). Analysis Calcd for $C_{19}H_{17}N_5O_4S$ (411.43): C, 55.47; H, 4.16; N, 17.02; S, 7.79 %. Found: C, 55.72; H, 4.38; N, 16.82; S, 7.88 %.

4.4-Dicyano-N-(3-cyano-4,5,6,7- tetrahydrobenzo[b]thiophene-2-yl)-3-methyl-2-(2-4-nitrophenyl)hydrazono)but-3-enamide (14a) and ethyl 2-cyano-4,5,6,7-tetrahydrobenzo [b]thiophene-2-yl)- 3-methyl-2-(2-4-nitro-phenyl)hydrazono)-5-oxopent-2-enoate (14b)

General procedure

To a solution of compound 11 (3.19 g, 0.01 mol) in 1,4-dioxane (30 ml) containing triethylamine (0.50 ml), either malononitrile (0.66 g, 0.01 mol) or ethyl cyanoacetate (1.07 g, 0.01 mol) was added. The reaction mixture was heated under reflux for 3 hr then poured onto ice/water followed by the addition of few drops of hydrochloric acid and the formed solid product was collected by filtration.

Compound 14a: Yellow crystals from 1,4-dioxane, 68 % (3.12 g) yield; mp. 190-193 ^{o}C, MS: m/z = 459 (M^{+}), IR (KBr): υ/cm^{-1} = 3466-3331(NH), 3056 (CH_{Ar}), 2227-2220 (3 CN), 1688 (CO), 1569 (C=N), ^{1}H NMR (DMSO-d_6): δ = 1.73-1.81 (m, 8H, 4CH_2), 2.44 (s. 3H, CH_3), 7.25-7.39 (m, 4H, benzene-CH), 8.20, 8.55 (2s, 2H, 2NH, D_2O-exchangeable). Analysis Calcd for $C_{22}H_{17}N_7O_3S$ (485.48): C, 57.51; H, 3.73; N, 21.34; S, 6.98 %. Found: C, 57.91; H, 5.72; N, 21.17; S, 7.04 %.

Compound 14b: Reddish brown crystals from ethanol, 72 % (3.64 g) yield; mp. 166 ^{o}C, MS: m/z = 509 (M^{+}), IR (KBr): υ/cm^{-1} = 3452-3327 (NH), 3058 (CH_{Ar}), 2225, 2220 (2CN), 1687, 1684 (2CO), 1568 (C=N), ^{1}H NMR (DMSO-d_6): δ = 1.12 (t, 3H, CH_3), 1.72-1.93 (m, 8H, 4CH_2), 4.22 (q, 2H, CH_2), 7.27-7.39 (m, 4H, benzene-CH), 8.29, 8.68 (2s, 2H, 2NH, D_2O-exchangeable). *Analysis Calcd for* $C_{24}H_{22}N_6O_5S$ (506.14): C, 56.91; H, 4.38; N, 16.59; S, 6.33 %. Found: C, 57.32; H, 4.39; N, 16.83; S, 6.56 %.

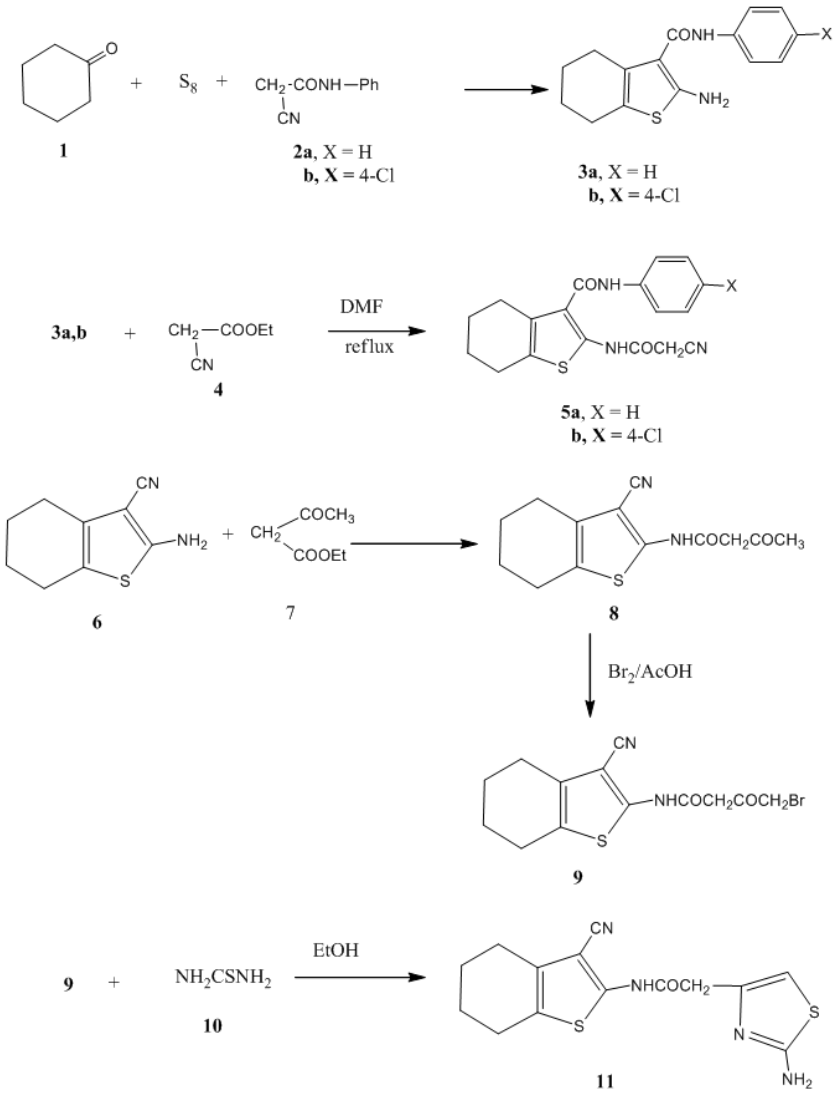
2-Amino-1-(3-cyano-4,5,6,7- tetrahydrobenzo[b] thiophen-2-yl)- 4-methyl-5-((4-nitrophenyl)diazenyl)-6-oxo-1,6-dihydropyridine-3-carbonitrile (15a) and 1-(3-cyano- 4,5,6,7- tetrahydrobenzo [b] thiophen-2-yl)- 2-hydroxy-4-methyl-5-((4-nitrophenyl)diazenyl)-6-oxo-1,6-dihydropyridine-3-carbonitrile (15b)

A solution of either 14a (4.85 g, 0.01 mol) or 14b (5.06g, 0.01 mol) in ethanol (40 ml) containing sodium hydroxide (0.50 g) was heated under reflux for 2 hr. The solid product, so formed, upon pouring onto ice/water containing few drops of hydrochloric acid was collected by filtration.

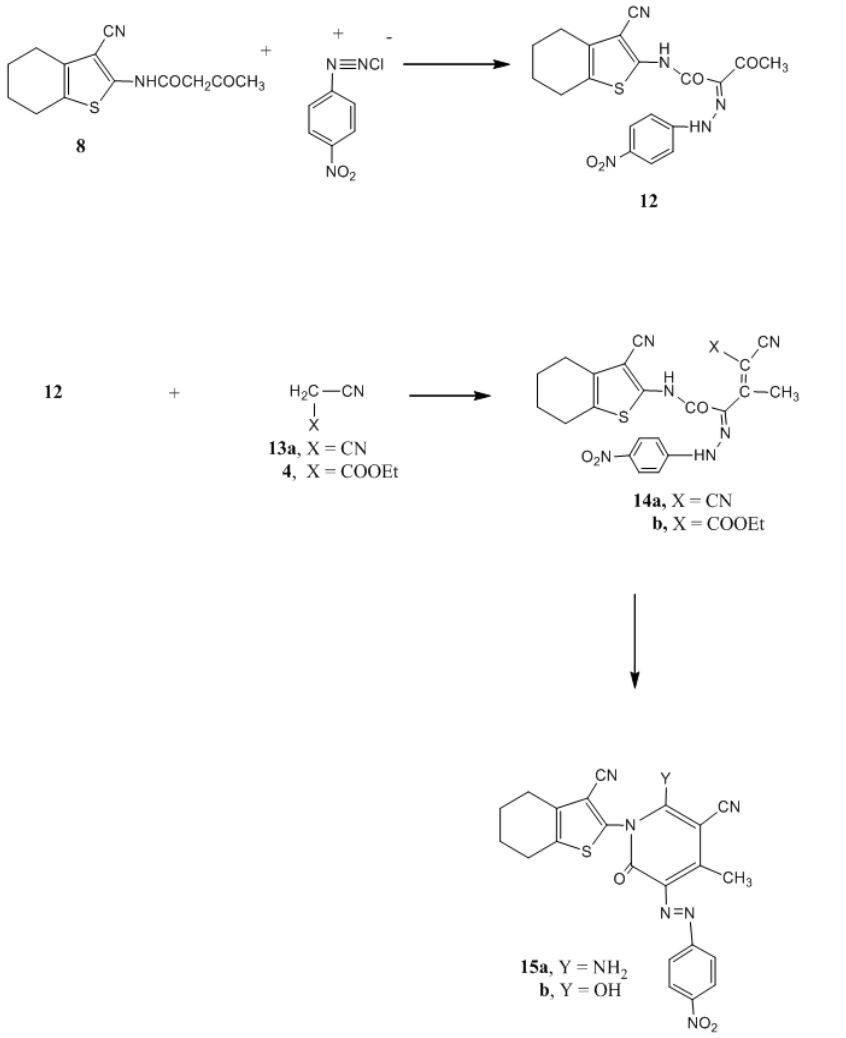
Compound 15a: Yellow crystals from 1,4-dioxane, 76 % (3.49 g) yield; mp. 138-140 ^{o}C, MS: m/z = 459 (M^{+}), IR (KBr): υ/cm^{-1} = 3473-3344 (NH), 3058 (CH_{Ar}), 2228, 2220 (2 CN), 1684 (CO), 1563 (C=N), ^{1}H NMR (DMSO-d_6): δ = 1.71-1.80 (m, 8H, 4CH_2), 2.36 (s. 3H, CH_3), 5.22 (s, 2H, NH_2), 7.22-7.36 (m, 4H, benzene-CH). *Analysis Calcd for* $C_{22}H_{17}N_7O_3S$ (459.48): C, 57.51; H, 3.73; N, 21.34; S, 6.98 %. Found: C, 57.63; H, 4.01; N, 21.29; S, 7.24 %.

Compound 15b: Yellow crystals from ethanol, 80 % (3.68 g) yield; mp. 221-223^{o}C, MS: m/z = 460 (M^{+}), IR (KBr): υ/cm^{-1} = 3436-3325 (NH), 3053 (CH_{Ar}), 2227, 2221 (2CN), 1686 (CO), 1562 (C=N), ^{1}H NMR (DMSO-d_6): δ = 1.77-1.90 (m, 8H, 4CH_2), 2.36 (s, 3H, CH_3), 7.26-7.38 (m, 4H, benzene-CH), 10.22 (s,

1H,OH, D_2O-exchangeable). *Analysis Calcd for* $C_{22}H_{16}N_6O_4S$ (460.47): C, 57.38; H, 3.50; N, 18.25; S, 6.96 %. Found: C, 57.48; H, 3,79; N, 17.94; S, 6.73 %.



Scheme 1.



Scheme 2.

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نهج جديد لتخليق مشتقات ثيوفين مع الأنشطة الضد سرطانية

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تم تخليق مشتقات التيتراهايدروبنزو - ب- ثيوفين 3 أ،ب و 5 أ،ب ثم تلاها ألكلة بعض المشتقات الأخرى.

وسجلت تقييم انتيتومور من المواد المخلقة حديثا ضد ثلاثة خطوط الخلايا السرطانية و هى الأدينوكارسينوما الثديية و الخلايا الغير صغيرة لسرطان الرئة و سرطان الجهاز العصبى المركزى و وجد أن بعض المركبات المخلقة تظهر أثار مثبطة عالية.