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Uses of 4, 5, 6, 7-tetrahydrobenzo[b]thiophene Derivatives in Heterocyclic Synthesis: Synthesis of Pyrazol, Pyrimidine and Pyridazine Derivatives with Antimicrobial Activities

Wagnat W. Wardakhan* and Mastoura M. Edrees
National Organization for Drug Control and Research, P.O. 29, Cairo, Egypt.

THE 2-DAIZO-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide coupled with either malononitrile or ethyl cyanoacetate to give the hydrazo derivatives 4a and 4b, respectively. The latter products underwent hetero-cyclization to give pyrazole, pyrimidine and pyridazine derivatives. The antimicrobial evaluation of the newly synthesized products was measured and most of the products showed interesting activities.

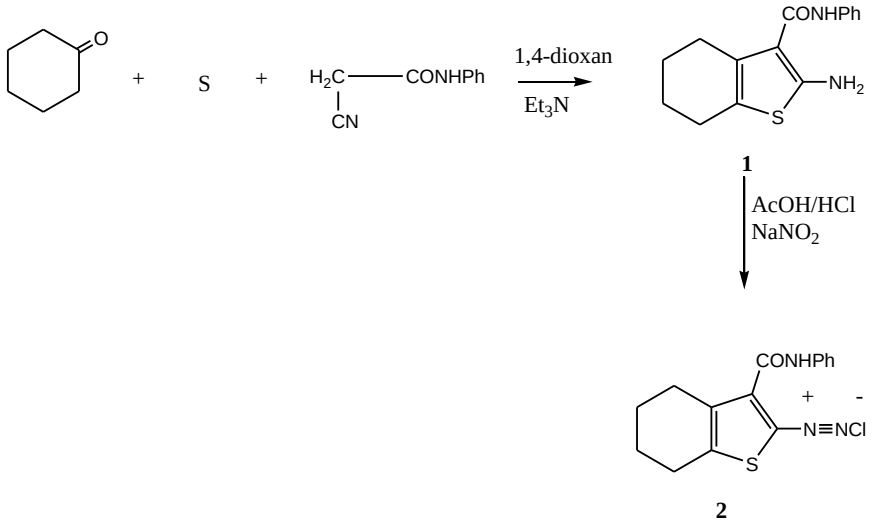
Keywords: Tetrahydrobenzo[b]thiophene, Pyrazole, Pyrimidine and Pyridazine.

Benzothiophenes are one of the most common and consequently the most studied classes of aromatic heterocycles[(1)]. The occurrence of these heterocycles in a significant number of medicinal agents [(2)], active in a variety of disease areas, has led to an enduring interest in the development of new methods for their synthesis[(3–5)]. Methods that utilize new classes of precursors are particularly valuable. Among the many syntheses available, transition metal catalyzed processes[(6)] and palladiummediated methods in particular[(7)] feature heavily. Syntheses based on palladium-catalyzed cyclizations of appropriately substituted alkenyl or alkynyl phenols, or thiophenols, are versatile and have been used on many occasions[(8–10)]. Related tandem processes involving catalyzed C–C bond formation, usually employing Sonogashira-type reactions, before construction of the key C–S bond have also been developed[(11–14)]. The crucial bond-forming event in these processes is intramolecular of a nucleophilic oxygen or sulfur atom onto a palladium-activated C–C multiple bond, resulting in formation of the X–C2 bond of the heterocycle. We aim to develop an alternative method for the synthesis of 2-amino-3-anilido-4,5,6,7-tetrahydrobenzo[b]thiophene derivatives and their uses in heterocyclic synthesis together with their evaluation for antimicrobial and antifungal activities.

Results and Discussions

Chemistry

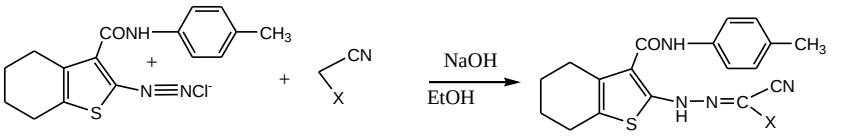
The reaction between cyano acetanilide, cyclohexanone and elemental sulfur in ethanol solution containing triethylamine gave the 2-amino-3-anilido-4,5,6,7-tetrahydrobenzo[b]thiophene (1)[15]. The structure of compound 1 was based on the analytical and spectral data. The 2-amino group present in compound 1 underwent ready diazotization through the reaction of compound 1 with sodium nitrite in an acid medium at 0-5 °C to give the non-isolable intermediate 2-diazo-3-(4-methy)-anilido-4,5,6,7-tetrahydrobenzo[b]thiophene (2). The reaction of the diazonium salt 2a,b with either malononitrile (3a) or ethyl cyanoacetate (3b) in basic ethanol solution at 0 °C gave the hydrazone derivatives 4a,b. The structures of 4a,b were based on analytical and spectral data. Thus, the ^{1}H NMR spectrum of 4a showed the presence of two multiplets at d 1.36-1.60 and 2.62-2.68 for 4 CH_2, a singlet at d 2.88 for CH_3 group, a multiplet at d 7.21-7.35 for C_6H_4, two singlet (D_2O exchangeable) at d 8.80, 9.30 two NH groups.



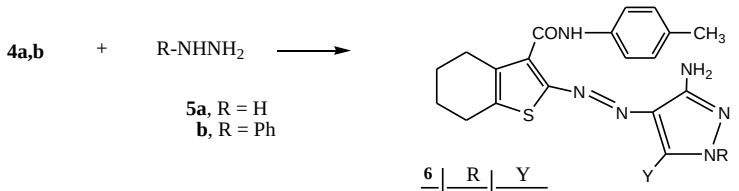
Scheme 1

Compounds 4a,b react with either hydrazine hydrate 5a or phenyl hydrazine 5b to give the pyrazole derivatives 6a-d. Analytical and spectral data of the reaction products are consistent with the assigned structures (see experimental section). On the other hand, the reaction of 4a,b with either urea (7a) or thiourea (7b) gave the pyrimidine derivatives 8a-d. The structures of the latter products were established on the basis of analytical and spectral data. Thus, ^{1}H NMR

spectrum of 8a showed two multiplets at d 1.33-1.49 and 2.60-2.68 for 4 CH_2, a singlet at d 2.86 for CH_3 group, two singlet at d 4.80, 5.41 for two NH_2 groups, a singlet (D_2O exchangeable) at d 8.77 NH groups, a singlet at d 9.73 for OH group. Compound 4b capable for amide formations. Thus, its reaction with aniline in 1,4-dioxan solution gave the anilide derivative 9.

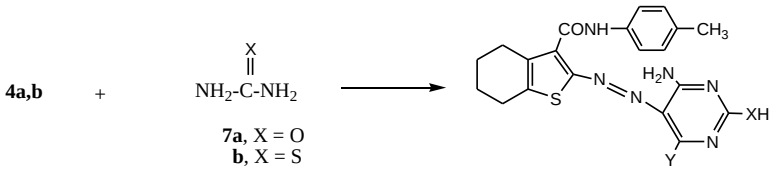


2 **3a**, X = CN; **b**, X = $COOC_2H_5$ **4a**, X = CN; **b**, X = $COOC_2H_5$



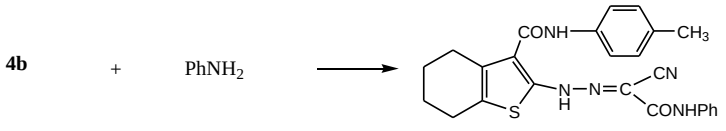
5a, R = H; **b**, R = Ph

6	R	Y
a	H	NH_2
b	H	OH
c	Ph	NH_2
d	Ph	OH



7a, X = O; **b**, X = S

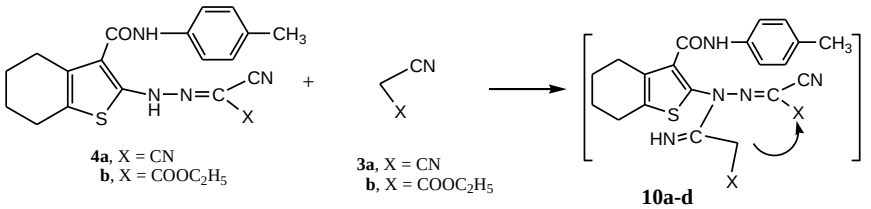
8	Y	X
a	NH2	O
b	OH	O
c	NH_2	S
d	OH	S



9

Scheme 2

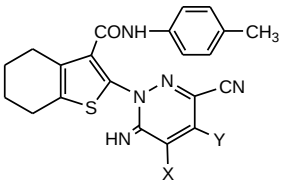
Compounds 4a,b reacted with either malononitrile (3a) or ethyl cyanoacetate (3b) to give the pyridazine derivatives 11a-d. The analytical and spectral data of the reaction products are in analogy with the proposed structures (see experimental section). The reaction of either compound 4a or 4b with phenylisothiocyanate (12) afforded the corresponding 1,2,4-triazine derivatives 13a and 13b, respectively.



4a, X = CN
b, X = $COOC_2H_5$

3a, X = CN
b, X = $COOC_2H_5$

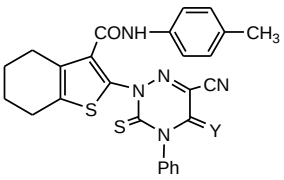
10a-d



11	X	Y
a	CN	NH_2
b	CN	OH
c	$COOC_2H_5$	NH_2
d	COOC2H5	OH

4a,b + PhNCS

12



13a, Y = NH
b, Y = O

Scheme 3

Test solutions were added to the inoculated wells, one control well on each slide being treated with solvent only. The slides were then returned to the incubator until germ tubes 400 mm (±50 mm) long were visible in the control wells. Further growth was arrested by the addition of lactophenol aniline blue to each of the wells. The minimal inhibitory concentration (MIC in mg ml^{-1}) was determined.

Antimicrobial Activity

The *in vitro* antimicrobial activity of the heterocyclic derivatives 1-13b against two strains of Gram positive bacteria (*Bacillus subtilis* CECT 498 and *Bacillus cereus* CECT 148), two strains of Gram negative bacteria (*Escherichia coli* ECT 101 and *Pseudomonas aeruginosa*) and *Candida albicans* CECT 1394 as a representative species of fungi was investigated. The newly synthesized products were dissolved in aqueous ethanol to give a logarithmic series of concentrations from 2 to 256 mg/l upon tenfold dilution with the growth medium and spore suspension of the test fungi. The toxicity of compounds was determined via a pipette additions into the wells of multi-well slides, followed with 25 μl of the culture medium. The inoculated slides were then incubated at 25°C until short germ tubes appeared; approximately 50 mm in length (at 0 hr) was measured. Five μl volumes of the prepared compound adaptation of agar streak dilution method based on radial diffusion[16,17]. Under the same conditions ampicillin (antibacterial) and cycloheximide (antifungal) were used as standards. The MIC was considered to be the lowest concentration of the tested compound (in dimethylformamide) which inhibits growth of bacteria or fungi on the plate (Table 1). The diameters of the inhibition zones corresponding to the MICs are also presented in Table 1.

Experimental

Chemistry

All melting points are uncorrected. IR spectra were recorded for (KBr) discs on a Pye Unicam SP-1000 spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were measured on a Varian EM 390-200 MHz in DMSOd6 as solvent and using TMS as internal standard, and chemical shifts are expressed as δ ppm. Analytical data were recorded at the Micro Analytical Data Unit at Cairo University, Giza, Egypt.

TABLE 1. Antimicrobial activities of the tested compounds .

Compound	MIC gml ($^{-1}$) (zone of inhibition, mm)			
	E. coli ECT	*B. cereus* CECT	*B. subtilis* CECT	*C. albicans* CECT
1	-	6.05 (15)	21.01 (8)	33.23
4a	12.50 (6)	22.52 (8)	20.55(4)	8.65 (4)
4b	-	22.38 (8)	3.72 (6)	16.58 (12)
6b	-	11.32 (3)	18.22 (8)	12.40 (4)
6c	-	19.15 (4)	20.46 (9)	0.40 (10)
6d	-	18.12 (5)	12.25 (2)	23.64 (6)
8a	16.20 (6)	18.23 (5)	22.45 (8)	100.00
8b	-	0.03 (9)	4.13 (10)	0.61 (6)
8c	-	10.05 (6)	16.42 (2)	4.55 (10)
8d	-	18.24 (7)	6.18 (4)	0.40 (5)
9	-	16.22 (3)	18.32 (8)	14.40 (4)
11a	-	10.38 (4)	6.22 (6)	12.55 (12)
11b	-	6.25 (15)	22.01 (8)	30.23 (6)
11c	-	21.15 (4)	23.16 (9)	100.00
11d	-	25.36 (8)	23.63 (6)	26.12 (3)
13a	-	0.08 (9)	2.13 (10)	0.85 (6)
13b	-	12.05 (6)	14.42 (2)	4.66(10)
Ampicillin	6.25	3.13	12.50 (10)	-
Cycloheximide	-	-	-	12.50 (6)

2-Amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-N-phenylcarboxamide (1)

To a solution of cyanoacetanilide (16.0 g, 0.01 mol) in 1,4-dioxan (80 ml) containing triethylamine (1.0 ml) each of cyaclohexanone (9.8 g, 0.01 mol) and elemental sulphur (0.32 g, 0.01 mol) were added. The reaction mixture was heated under reflux for 2 h then poured onto ice/water containing few drops of hydrochloric acid.

1: Yellow crystals, yield 88% (23.93), m.p. 146-148 ^{o}C, (acetic acid). IR: (υ/cm^{-1}) = 3458-3241 (NH); 3042 (CH), 2899 (CH_2), 1710 (C=O), 1638 (C=C). ^{1}HNMR: δ/ppm: 2.23-2.26, 2.34-2.39 (m, 8H, cyclohexanone), 4.57 (s, 2H, NH_2), 7.28-7.36 (m, 5H, C_6H_5), 8.93 (s, 1H, NH). $C_{15}H_{16}N_2OS$ (272.37), Calcd: C, 66.15; H, 5.92; N, 10.29; S, 11.77. Found: C, 66.01; H, 5.69; N, 10.51; A, 10.94.

2- Hydrazodicyanomethino-3-(4- methylphenyl)- 4,5,6,7- tetrahydrobenzo [b]-thiophene -3-(4-methylphenyl) carboxamide (4a) and 2-Hydrazoethylcyanoacetato-3-(4-methylphenyl)- 4,5,6,7-tetrahydrobenzo[b]-thiophene-3-(4-methylphenyl) carboxamide (4b)

General procedure

To a cold solution (0 ^{o}C) of 1 (2.87 g, 0.01 mol) in acetic acid (20 ml), propanoic acid (5 ml) and hydrochloric acid (5 ml) sodium nitrite solution (1.4 g, 0.02 mol) was added. The reaction mixture was stirred for 10 minutes then added to a solution of either malononitrile (0.66 mol, 0.01 mol) or ethyl cyanoacetate (1.13 g, 0.01 mol) in ethanol (30 ml) containing sodium hydroxide (5 mL, 20 %) with continuous stirring. The formed solid product was collected by filtration and washed several times with water.

4a: Red crystals from ethanol, 70 % yield (2.55 g), mp 154 ^{o} C, IR (u, cm^{-1}): 3460-3341 (2 NH), 2983, 2877 (CH_3, CH_2), 2222, 2220 (2 CN), 1684 (C=O), 1638 (N=C). ^{1}H NMR (d ppm): 1.36-1.60 (m, 4H, $2CH_2$), 2.62-2.68 (m, 4H, $2CH_2$), 2.88 (s, 3H, CH_3), 7.21-7.35 (m, 4H, C_6H_4), 8.80, 9.30 (2s, 2H, 2NH). $C_{19}H_{17}N_5OS$ (363.44): C, 62.79; H, 4.71; N, 19.27; S, 8.82. Found: C, 62.69; H, 4.49; N, 19.05; S, 9.03.

4b: Red crystals from ethanol, 77 % yield (3.15 g), mp 190 ^{o} C, IR (u, cm^{-1}): 3478-3349 (2 NH), 2980, 2892 (CH_3, CH_2), 2223 (CN), 1687, 1682 (2 C=O), 1634 (N=C). ^{1}H NMR (d ppm): 1.13 (t, 3H, J = 7.11 Hz, CH_3), 1.33-1.62 (m, 4H, $2CH_2$), 2.60-2.67 (m, 4H, $2CH_2$), 2.85 (s, 3H, CH_3), 4.23 (q, 2H, J = 7.11 Hz, CH_2), 7.28-7.39 (m, 4H, C_6H_4), 8.83, 9.28 (2s, 2H, 2NH). $C_{21}H_{22}N_4O_3S$ (410.49): C, 61.44; H, 5.40; N, 13.65; S, 7.81. Found: C, 61.79; H, 5.59; N, 13.91; S, 8.03.

2- Azo(3, 5- diaminopyrazolo)-3-(4- methylphenyl) -4,5,6,7- tetrahydrobenzo-[b]-thiophene-3-(4-methylphenyl)carboxamide (6a), 2-azo(3-amino-5-hydroxypyrazolo)-3-(4-methylphenyl)-4,5,6,7- tetrahydrobenzo[b]-thiophene -3- (4-methylphenyl) carboxamide (6b), 2-azo(3,5-diamino-1-phenylpyrazolo)-3-(4-methylphenyl)-4,5,6,7-tetrahydrobenzo[b]-thiophene-3-(4-methylphenyl)carboxamide (6c) and 2-azo(3-amino5-hydroxy-1-phenylpyrazolo)-3-(4-methylphenyl)-4,5,6,7-tetrahydrobenzo [b]-thiophene-3-(4-methylphenyl)carboxamide (6d)

General procedure

To a solution of either 3a (3.63 g, 0.01 mol) or 4b (4.10 g, 0.01 mol) in ethanol (50 ml) either hydrazine hydrate (0.50 g, 0.01 mol) or phenyl hydrazine (1.08 g, 0.01 mol) was added. The reaction mixture was heated under reflux for 2 hr then left to cool. The solid product formed upon pouring onto ice/water containing few drops of hydrochloric acid was collected by filtration.

6a: Yellow crystals from ethanol, 67 % yield (2.67 g), mp 205 °C, IR (u, cm^{-1}): 3483-3327 (2 NH, $2NH_2$), 2980, 2889 (CH_3, CH_2), 1687 (C=O), 1635 (C=C). ^1H NMR (d ppm): 1.33-1.58 (m, 4H, $2CH_2$), 2.64-2.69 (m, 4H, $2CH_2$), 2.86 (s, 3H, CH_3), 5.20 (s, 4H, $2NH_2$), 7.28-7.39 (m, 4H, C_6H_4), 8.78, 9.87 (2s, 2H, 2NH). $C_{19}H_{21}N_7OS$ (395.48): C, 57.70; H, 5.35; N, 24.79; S, 8.11. Found: C, 57.93; H, 5.76; N, 25.06; S, 7.93.

6b: Pale yellow crystals from ethanol, 55 % yield (2.17 g), mp 204 °C, IR (u, cm^{-1}): 3520-3322 (OH, 2 NH, NH_2), 2983, 2886 (CH_3, CH_2), 1689 (C=O), 1635 (C=C). ^1H NMR (d ppm): 1.34-1.57 (m, 4H, $2CH_2$), 2.63-2.68 (m, 4H, $2CH_2$), 2.87 (s, 3H, CH_3), 5.21 (s, 2H, NH_2)7.30-7.38 (m, 4H, C_6H_4), 8.66, 9.91 (2s, 2H, 2NH), 10.25 (s, br, 1H, OH). $C_{19}H_{20}N_6O_2S$ (396.47): C, 57.56; H, 5.08; N, 21.20; S, 8.09. Found: C, 57.38; H, 5.25; N, 21.05; S, 7.88.

6c: Yellow crystals from 1,4-dioxan, 71 % yield (3.33 g), mp 168-170 °C, IR (u, cm^{-1}): 3486-3352 (NH, $2NH_2$), 2986, 2890 (CH_3, CH_2), 1686 (C=O), 1633 (C=C). ^1H NMR (d ppm): 1.35-1.59 (m, 4H, $2CH_2$), 2.58-2.69 (m, 4H, $2CH_2$), 2.89 (s, 3H, CH_3), 5.34 (s, 4H, $2NH_2$), 7.32-7.36 (m, 9H, C_6H_4), 8.69 (s, H, NH). $C_{25}H_{25}N_7OS$ (471.58): C, 63.67; H, 5.34; N, 20.79; S, 6.80. Found: C, 63.58; H, 5.60; N, 20.94; S, 7.25.

6d: Orange crystals from 1,4-dioxan, 63 % yield (2.99 g), mp 235 °C, IR (u, cm^{-1}): 3520-3324 (OH, NH, NH_2), 2983, 2884 (CH_3, CH_2), 1686 (C=O), 1636 (C=C). ^1H NMR (d ppm): 1.30-1.55 (m, 4H, $2CH_2$), 2.60-2.69 (m, 4H, $2CH_2$), 2.86 (s, 3H, CH_3), 5.34 (s, 2H, NH_2), 7.28-7.39 (m, 9H, C_6H_4), 8.66 (s, H, NH), 10.22 (s, 1H, OH). $C_{25}H_{24}N_6O_2S$ (472.56): C, 63.54; H, 5.12; N, 17.78; S, 6.79. Found: C, 63.64; H, 5.05; N, 17.90; S, 7.03.

2-Azo(4,6-diamino-2-hydroxypyrimidino)-3-(4-methylphenyl)-4,5,6,7-tetrahydrobenzo-[b]-thiophene-3-(4-methylphenyl) carboxamide (8a), 2-azo(4-amino -2,6-dihydroxypyrimidino)-3-(4-methylphenyl)-4,5,6,7-tetrahydrobenzo[b]-thiophene-3-(4-methylphenyl) carboxamide (8b), 2-azo(4,6-diamino-2-mercaptopyrimidino)-3-(4-methylphenyl)-4,5,6,7-tetrahydrobenzo[b]-thiophene-3-(4-methylphenyl) carboxamide (8c) and 2-azo(4-amino-6-hydroxy-2-mercaptopyrimidino)-3-(4-methylphenyl)-4,5,6,7-tetrahydrobenzo[b]-thiophene-3-(4-methylphenyl)carboxamide (8d)

General procedure

To a suspension of either 4a (3.63 g, 0.01 mol) or 4b (4.10 g, 0.01 mol) in sodium ethoxide solution [prepared by dissolving sodium metal (0.46 g, 0.02 mol) in absolue ethanol (30 ml)] either urea (0.60 g, 0.01 mol) or thiourea (0.76 g, 0.01 mol) was added. The reaction mixture was heated in a boiling water bath

for 3 hr then poured onto ice/water then poured onto ice/water and neutralized with a few drops of hydrochloric acid (till pH 6).

8a: Orange crystals from acetic acid, 70 % yield (2.96 g), mp 172 °C, IR (u, cm^{-1}): 3490-3342 (OH, NH, $2NH_2$), 2977, 2890 (CH_3, CH_2), 1689 (C=O), 1638 (C=C). ^{1}H NMR (d ppm): 1.35-1.59 (m, 4H, $2CH_2$), 2.62-2.68 (m, 4H, $2CH_2$), 2.90 (s, 3H, CH_3), 4.72, 5.07 (2s, 4H, $2NH_2$), 7.32-7.36 (m, 4H, C_6H_4), 8.80 (s, 1H, NH), 9.02 (s, 1H, OH). $C_{20}H_{21}N_7O_2S$ (423.49): C, 56.72; H, 5.00; N, 23.15; S, 7.57. Found: C, 56.79; H, 4.83; N, 23.07; S, 7.80.

8b: Yellow crystals from ethanol, 66 % yield (2.79 g), mp 215 °C, IR (u, cm^{-1}): 3538-3356 (2OH, NH, NH_2), 2978, 2889 (CH_3, CH_2), 1683 (C=O), 1638 (C=C). ^{1}H NMR (d ppm): 1.36-1.60 (m, 4H, $2CH_2$), 2.62-2.66 (m, 4H, $2CH_2$), 2.90 (s, 3H, CH_3), 5.08 (s, 2H, NH_2)7.29-7.36 (m, 4H, C_6H_4), 8.68 (s, 1H, NH), 9.68, 10.22 (2s, 2H, 2OH). $C_{20}H_{20}N_6O_3S$ (424.48): C, 56.59; H, 4.75; N, 19.80; S, 7.55. Found: C, 56.84; H, 4.99; N, 20.31; S, 7.70.

8c: Pale brown crystals from acetic acid, 62 % yield (2.72 g), mp 142-148 °C, IR (u, cm^{-1}): 3456-3320 (NH, $2NH_2$), 2982, 2893 (CH_3, CH_2), 1688 (C=O), 1630 (C=C). ^{1}H NMR (d ppm): 1.35-1.60 (m, 4H, $2CH_2$), 2.58-2.66 (m, 4H, $2CH_2$), 2.86 (s, 3H, CH_3), 3.01 (s, br, 1H, SH), 4.86, 5.24 (2s, 4H, $2NH_2$), 7.30-7.38 (m, 4H, C_6H_4), 8.70 (s, H, NH). $C_{20}H_{21}N_7OS_2$ (439.56): C, 54.65; H, 4.82; N, 22.31; S, 14.59. Found: C, 54.82; H, 4.91; N, 22.47; S, 14.89.

8d: Yellow crystals from ethanol, 66 % yield (2.90 g), mp 173 °C, IR (u, cm^{-1}): 3346-3336 (OH, 2 NH, NH_2), 2977, 2892 (CH_3, CH_2), 1688 (C=O), 1634 (C=C). ^{1}H NMR (d ppm): 1.32-1.58 (m, 4H, $2CH_2$), 2.58-2.67 (m, 4H, $2CH_2$), 2.87 (s, 3H, CH_3), 3.31 (s, 1H, SH), 5.23 (s, 2H, NH_2), 7.32-7.38 (m, 4H, C_6H_4), 8.70 (s, H, NH), 10.03 (s, 1H, OH). $C_{20}H_{20}N_6O_2S_2$ (440.54): C, 54.53; H, 4.58; N, 19.08; S, 14.56. Found: C, 54.82; H, 4.80; N, 18.83; S, 14.74.

2- hydrazo(cyanoacetanilide) -3- (4-methylphenyl) -4,5,6,7-tetrahydrobenzo-[b]-thiophene-3-(4-methylphenyl)carboxamide (9)

To a solution 4b (4.10 g, 0.01 mol) in 1,4-dioxan (30 ml), aniline (0.94 g, 0.01 mol) was added. The reaction mixture was heated under reflux for 1 hr then evaporated under vacuum. The remaining product was triturated with ethanol and the formed solid product was collected by filtration.

9: Orange crystals from acetic acid, 50 % yield (2.28 g), mp 207 °C, IR (u, cm^{-1}): 3432-3338 (3NH), 2978, 2890 (CH_3, CH_2), 2222 CN, 1691, 1688 (2 C=O), 1633 (C=C). ^{1}H NMR (d ppm): 1.33-1.60 (m, 4H, $2CH_2$), 2.56-2.67 (m, 4H, $2CH_2$), 2.87 (s, 3H, CH_3), 7.28-7.38 (m, 9H, C_6H_4, C_6H_5), 8.68, 8.88-9.02 (3s, 3H, 3NH).

$C_{25}H_{23}N_5O_2S$ (457.55): C, 65.63; H, 5.07; N, 15.31; S, 7.01. Found: C, 65.93; H, 4.91; N, 15.03; S, 6.88.

2-(4-Amino-3,5-dicyano-6-iminopyridazino)-3-(4-methylphenyl)-4,5,6,7-tetrahydrobenzo -[b]-thiophene-3-(4-methylphenyl)carboxamide (11a), 2-(3,5-dicyano-3-hydroxy-6-iminopyridazino) -3-(4-methylphenyl) -4,5,6,7- tetrahydrobenzo [b]- thiophene-3-(4-methylphenyl) carboxamide (11b), 2- (4-amino -3- cyano -5- ethoxycarbonyl-6-iminopyridazino)-3- (4-methylphenyl) -4, 5, 6, 7- tetrahydrobenzo [b]- thiophene -3-(4-methylphenyl)carboxamide (11c) and 2-(3-cyano-4-hydroxy-5-hydroxycarbonyl-6-iminopyridazino)-3-(4-methylphenyl)-4,5,6,7-tetrahydrobenzo[b]-thiophene-3-(4-methylphenyl)carboxamide (11d)

General procedure

To a solution of either 4a (3.63 g, 0.01 mol) or 4b (4.10 g, 0.01 mol) in 1,4-dioxan (40 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 2 h then left to cool. The solid product formed upon pouring onto ice/water was collected by filtration.

11a: Buff crystals from acetic acid, 80 % yield (3.43 g), mp 207 ^{o}C, IR (u, cm^{-1}): 3466-3352 (2 NH, NH_2), 2980, 2877 (CH_3, CH_2), 2220, 2222 (2CN), 1687 (C=O), 1666 (C=N), 1634 (C=C). ^{1}H NMR (d ppm): 1.32-1.59 (m, 4H, $2CH_2$), 2.60-2.67 (m, 4H, $2CH_2$), 2.87 (s, 3H, CH_3), 4.70 (s, 2H, NH_2), 7.28-7.38 (m, 4H, C_6H_4), 8.23, 8.76 (2s, 2H, 2NH). $C_{22}H_{19}N_7OS$ (429.50): C, 61.52; H, 4.46; N, 22.83; S, 7.47. Found: C, 61.49; H, 4.51; N, 23.02; S, 7.65.

11b: Orange crystals from ethanol, 89 % yield (3.81 g), mp 148 ^{o}C, IR (u, cm^{-1}): 3530-3321(OH, 2NH), 2983, 2891 (CH_3, CH_2), 2225, 00 (2CN), 1677 (C=O), 1635 (C=C). ^{1}H NMR (d ppm): 1.33-1.58 (m, 4H, $2CH_2$), 2.63-2.69 (m, 4H, $2CH_2$), 2.92 (s, 3H, CH_3), 7.32-7.38 (m, 4H, C_6H_4), 8.58, 9.04 (2s, 2H, 2NH), 10.20 (s, 1H, OH). $C_{22}H_{18}N_6O_2S$ (430.48): C, 61.38; H, 4.21; N, 19.52; S, 7.45. Found: C, 61.47; H, 4.37; N, 19.84; S, 7.52.

11c: Brown crystals from acetic acid, 77 % yield (3.66 g), mp 187 ^{o}C, IR (u, cm^{-1}): 3444-3329 (2NH, NH_2), 2986, 2890 (CH_3, CH_2), 2222 (CN), 1692, 1687 (2C=O), 1629 (C=C). ^{1}H NMR (d ppm): 1.13 (t, 3H, J = 7.02 Hz, CH_3), 1.33-1.58 (m, 4H, $2CH_2$), 2.49-2.63 (m, 4H, $2CH_2$), 2.89 (s, 3H, CH_3), 4.22 (q, 2H, J= 7.02 Hz, CH_2), 4.89 (s, 2H, NH_2), 7.29-7.36 (m, 4H, C_6H_4), 8.68, 9.06 (2s, 2H, 2NH). $C_{24}H_{24}N_6O_3S$ (476.55): C, 60.49; H, 5.08; N, 17.64; S, 6.73. Found: C, 60.53; H, 4.88; N, 17.47; S, 6.99.

11d: Orange crystals from 1,4-dioxan, 50 % yield (2.38 g), mp 195 °C, IR (u, cm^{-1}): 3365-3324 (OH, 2 NH), 2982, 2888 (CH_3, CH_2), 2220 (CN), 1689, 1680 (2 C=O), 1636 (C=C). ^{1}H NMR (d ppm): 1.12 (t, 3H, J= 6.73 Hz, CH_3), 1.32-1.61 (m, 4H, $2CH_2$), 2.55-2.66 (m, 4H, $2CH_2$), 2.89 (s, 3H, CH_3), 4.22 (q, 2H, J= 7.02 Hz, CH_2), 7.30-7.39 (m, 4H, C_6H_4), 8.79, 9.05 (2s, 2H, 2NH), 10.06 (s, 1H, OH). $C_{24}H_{23}N_5O_4S$ (477.54): C, 60.36; H, 4.85; N, 14.67; S, 6.71. Found: C, 60.51; H, 4.89; N, 14.85; S, 6.90.

2-(6-cyano-5-imino-3-thiono- 1-pheny-1,2,3- triazin- 2-yl)-4,5,6,7- tetrahydro-benzo-[b]-thiophene-3-(4-methylphenyl) carboxamide (13a) and 2-(6-cyano-5-imino-3-thiono-1-pheny-1,2,3-triazin-2-yl)-4,5,6,7-tetrahydro-benzo-[b]- thiophene -3- (4-methylphenyl) carboxamide (13b)

General procedure

To a solution of either 4a (3.63 g, 0.01 mol) or 4b (4.10 g, 0.01 mol) in 1,4-dioxan (40 ml) containing triethylamine (0.5 ml) phenylisothiocyanate (1.30 g, 0.01 mol) was added. The whole mixture was heated under reflux for 4hr then poured onto ice/water containing few drops of hydrochloric acid and the formed solid product was collected by filtration.

13a: Yellow crystals from ethanol, 50 % yield (2.49 g), mp 160 °C, IR (u, cm^{-1}): 3443-3329 (2NH), 2980, 2864 (CH_3, CH_2), 2227 (CN), 1688 (C=O), 1641 (C=C), 1205-1190 (C=S). ^{1}H NMR (d ppm): 1.38-1.60 (m, 4H, $2CH_2$), 2.48-2.66 (m, 4H, $2CH_2$), 2.83 (s, 3H, CH_3), 7.27-7.33 (m, 9H, C_6H_5, C_6H_4), 8.83, 9.32 (2s, 2H, 2NH). $C_{26}H_{22}N_6OS_2$ (498.62): C, 62.63; H, 4.45; N, 16.85; S, 12.86. Found: C, 62.41; H, 4.61; N, 17.15; S, 13.09.

13b: Yellow crystals from ethanol, 50 % yield (2.49 g), mp 135 °C, IR (u, cm^{-1}): 3448-3326 (NH), 2980, 2893 (CH_3, CH_2), 2227 (CN), 1689, 1683 (2C=O), 1636 (C=C), 1203-1194 (C=S). ^{1}H NMR (d ppm): 1.28-1.55 (m, 4H, $2CH_2$), 2.60-2.68 (m, 4H, $2CH_2$), 2.88 (s, 3H, CH_3), 7.24-7.36 (m, 9H, C_6H_5, C_6H_4), 8.90 (s, 1H, NH). $C_{26}H_{21}N_5O_2S_2$ (499.61): C, 62.50; H, 4.24; N, 14.02; S, 12.84. Found: C, 62.74; H, 4.49; N, 13.93; S, 13.21.

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وجنات وهبة وردخان و مستورة محمد أدريس
الهيئة القومية للرقابة والبحوث الدوائية – ص.ب. 29 القاهرة – مصر.

تناول هذا البحث تحضير مشتقات الثيوفين عن طريق استخدام مشتقات الديازو ثيوفين والتى تتفاعل مع كل من كاشف المالونو نيتريل و الأيثيل سيانوأسيتات لتعطى مشتقات الهيدرازون. تم استخدام المركبات الأخيرة لتحضير العديد من الكواشف الكيميائية ليعطى مشتقات مختلفة من الثيوفين.
تم فى هذا البحث اجراء درجة النشاط البيكتيرى لجميع المركبات المحضرة وأثبتت الدراسة درجة نشاط عالية.