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Synthesis and antitumor activity of some fused heterocyclic compounds based on cyclohepta[b]thiophene derivatives

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The reaction of 5,6,7,8-tetrahydro-4H-cyclohepta[b]thiophene derivatives 3a,b with acetic anhydride in presence of glacial acetic acid produced the acetamido derivatives 4a,b. Cyclization of the latter compounds gave the annulated products 5a,b. Compounds 3a,b reacted with one of the activated methylene groups of malononitrile (2a) and afforded compounds 7a,b through internal cyclization of the intermediates of compounds 6a,b. The latter products were reacted with the cyclic ketones 8a,b,c in presence of elemental sulphur and afforded compounds 9a-f. Compounds 3a,b reacted with different types of aldehydes 10a,b,c to produce compounds 11a-f. Finally the products11a-f reacted with hydrazine hydrate (12) affording compounds 14a-f *via* the proposed intermediate formation of compounds 13a-f. The antitumor activities of the synthesized compounds were tested using three different cell lines.

Keywords: cyclohepta[b]thiophene, pyrimidine, pyridine, antitumor activity

INTROUDUCTION

Thiophene and fused thiophene derivatives were studied within the frame of a comprehensive program in the last few years by our research group and others [1-4]. The biological activity of thiophene derivatives as antimicrobial [5] and antifungal agents [6] was investigated.

Cycloalkyl[*b*]thiophene derivatives display cytotoxic activity [7]. The activity of thienopyridine derivatives as antibacterial [8], anti-inflammatory [9], antidiabetic [10] and anti-hepatocellular carcinoma [11] agents was evaluated.

Moreover, thiophene ring fused with other heterocyclic rings like pyrimidine is known to have a wide spectrum of biological and pharmacological activities. Thus, many synthetic thienopyrimidine derivatives are considered as antibacterial [12], analgesic, anti-inflammatory agents [13], protein kinase inhibitors [14], and potential antiviral agents [15].

In this article, considering the above findings and as a continuation of the efforts directed towards the synthesis of new heterocyclic compounds with expected biological activities [16], we herein report the synthesis of some new cyclohepta[*b*]thiophene derivatives containing pyrimidine and pyridine moieties and the screening of their antitumor activity against three different cell lines. The structures of the newly synthesized compounds were established using IR, ^{1}H-NMR and mass spectrometry techniques.

EXPERIMENTAL

All melting points were uncorrected; the IR spectra, expressed in cm^{-1}, were recorded using KBr pellets on a Pa-9721 IR spectrometer. ^{1}H NMR spectra were obtained on a Varian EM-390 90 Hz spectrometer in DMSO-d_6 as solvent and TMS as internal reference. Chemical shifts (δ) are expressed in ppm. Mass spectra were recorded on Kratos (75 ev) Ms Equipment (Germany). Elemental analyses were carried out by the Microanalytical data unit at the National Research Center, Giza, Egypt and the Microanalytical data unit at the Cairo University.

Synthetic pathways are presented in Schemes 1, 2, 3 and cell growth inhibition data are presented in Table 1.

General procedure for the synthesis of: 2-Amino-5,6,7,8-tetrahydro-4H-cyclohepta [b]thiophene-3-carbonitrile (3a) and 2-Amino-5,6,7,8-tetrahydro-4H-cyclohepta[b]thiophene-3-carboxylic acid ethyl ester (3b)

The compounds (3a,b) were obtained *via* reaction of either malononitrile (2a) or ethylcyanoacetate (2b) with cycloheptanone and elemental sulfur according to a former described procedure [17].

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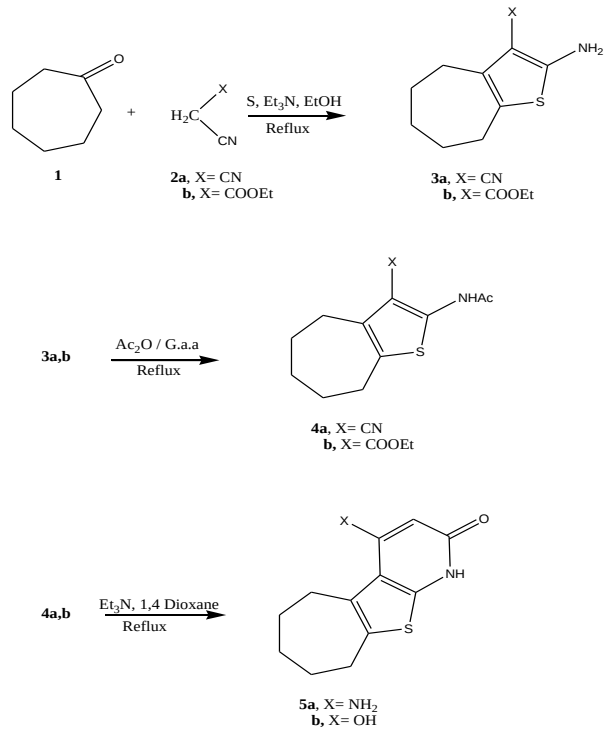
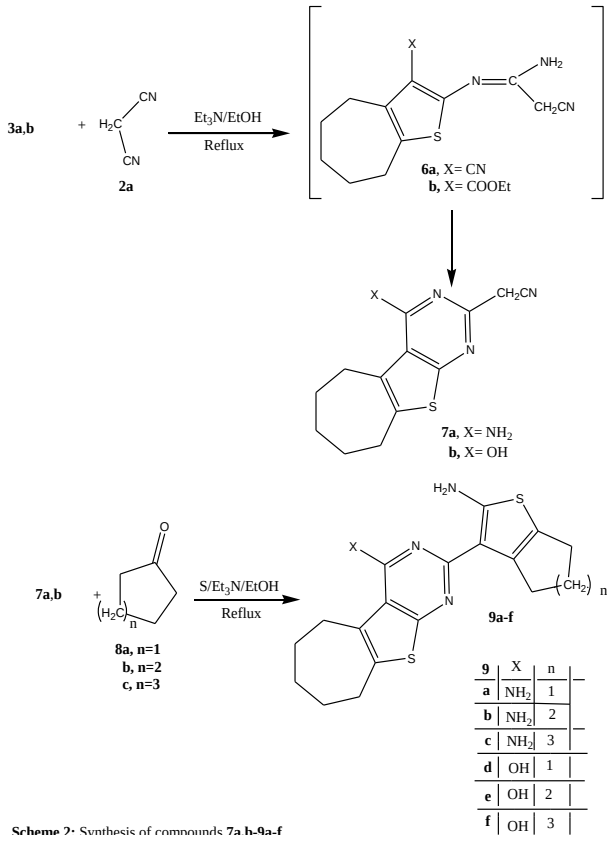
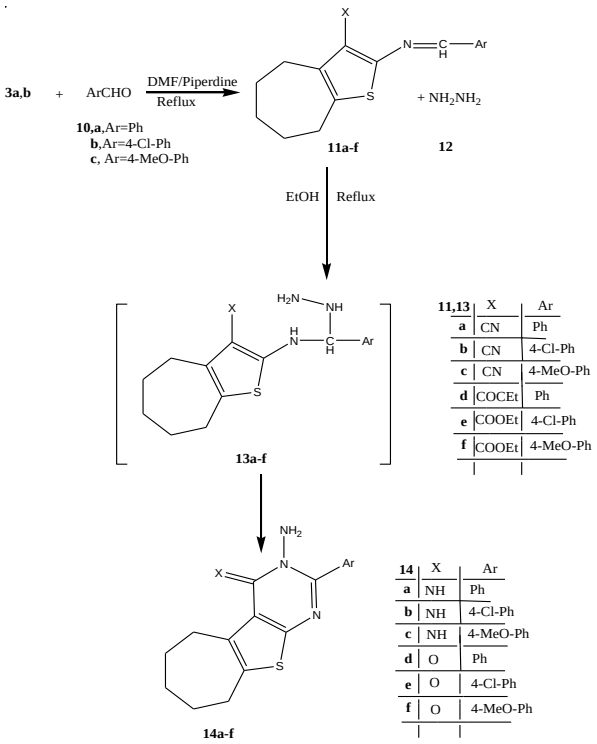


Scheme 1. Synthesis of compounds 3 a, b – 5 a, b



Scheme 2: Synthesis of compounds **7a,b-9a-f**

Scheme 2. Synthesis of compounds 7 a, b – 9 a-f



Scheme 3. Synthesis of compounds 11 a-f – 14 a-f

Table 1. Effect of compounds 3a-14f on the growth of three human tumor cell lines

Compound	GI_{50} (μmol L^{-1})		
	MCF-7	NCI-H460	SF-268
3a	21.0 ± 6.8	12.0 ± 2.4	21.5 ± 5.0
3b	22.0 ± 5.4	14.0 ± 3.6	11.8 ± 4.6
4a	20.6 ± 3.8	17.1 ± 2.9	21.3 ±2.5
4b	41.7 ± 7.9	32.2 ± 4.8	24 ± 2.8
5a	1.2 ± 0.06	0.9 ± 0.08	0.6 ± 0.05
5b	40.7± 7.7	33.2 ± 4.8	28.4 ± 2.8
7a	18.0 ± 1.6	24.0 ± 2.4	22.5 ± 2.5
7b	11.8 ± 2.6	24.5 ± 3.2	16.7 ± 2.4
9a	10.0 ± 1.7	20.6 ± 1.4	22.4 ± 0.8
9b	2.4 ± 0.4	4.1 ± 0.6	4.3 ± 0.4
9c	6.0 ± 0.6	4.0 ± 0.4	2.5 ± 8.0
9d	12.4 ±1.2	11.6 ± 0.9	6.8 ± 0.5
9e	6.6 ± 2.2	4.6 ± 2.6	2.4 ± 1.8
9f	11.4± 1.4	12.6 ±1.6	14.8 ± 2.2
11a	14.0 ± 0.6	12.0 ± 0.4	22.5 ± 8.0
11b	32.7 ± 7.5	40.2 ± 8.8	23.0 ± 5.0
11c	11.0 ± 0.2	16.6 ± 1.6	18.4 ± 0.6
11d	24.0 ± 1.8	24.0 ± 0.8	10.5 ± 1.1
11e	24.2 ± 10.5	20.2 ± 8.8	24.0 ± 8.0
11f	16.6± 2.5	10.05 ± 2.2	8.6 ±1.6
14a	1.0 ± 0.2	3.6 ± 0.4	1.4 ± 0.8
14b	8.2 ± 0.4	6.1 ± 0.6	4.3 ± 0.5
14c	2.0 ± 0.6	1.2 ± 0.4	1.6 ± 8.0
14d	0.2 ± 0.02	0.1 ± 0.02	0.3 ± 0.04
14e	6.6 ± 22.2	4.6 ± 2.6	2.4 ± 1.8
14f	0.01±0.003	0.02 ± 0.001	0.01 ± 0.001
Doxorubicin	0.04 ±0.008	0.09±0.008	0.09±0.007

Results are given as concentrations causing 50 % of cell growth inhibition (GI_{50}) after an exposure of 48 h - means ± SEM of three independent experiments performed in duplicate.

N-(3-Cyano-5,6,7,8-tetrahydro-4H-cyclohepta [*b*]thiophen-2-yl)-acetamide (4a) and 2-Acetyl-amino-5,6,7,8-tetrahydro-4H-cyclohepta [*b*] thiophene-3-carboxylic acid ethyl ester (4b)

To either solution of compound (3a, 1.92 g**,** 0.01 mol) or (3b, 2.39 g, 0.01 mol) in glacial acetic acid (40 mL), acetic anhydride (1.04 g, 0.01 mol) was added at an acetic acid to acetic anhydride ratio of 5:1. The reaction mixture was then refluxed for 3 h, the solution was cooled, poured on an ice/water mixture containing few drops of hydrochloric acid and the formed precipitate was filtered off.

Compound 4a: Yellow crystals recrystallized from ethanol, yield 75.6%, 1.76 g, m.p.142-144 ^{o}C. IR (KBr): υ/cm^{-1}= 3321-3290 (NH), 2956 (CH_3), 2890 (CH_2), 2230 (CN), 1675 (CO), 1632 (C=C).^{1}HNMR (DMSO) δ= 2.12-2.21(m, 6H, $3CH_2$), 2.26-2.32 (m, 4H, $2CH_2$), 2.39 (s, 3H, CH_3), 8.84 (s, 1H, NH, D_2O-exchangeable). Calcd. for $C_{12}H_{14}N_2OS$ (234.32): C, 61.51; H, 6.02; N, 11.96; S, 13.68%. Found: C, 61.38; H, 6.24; N, 11.74; S, 13.84 %. MS (relative intensity) m/z: 234 (M^+, 23%), 191 (100%), 176 (48%).

Compound 4b: Pale brown crystals recrystallized from ethanol, yield 81.2%, 1.85 g, m.p. 112-114^{o}C. IR (KBr): υ/cm^{-1}= 3346 (NH), 2977 (CH_3), 2885 (CH_2), 1795 (CO), 1667 (CONH). ^{1}HNMR (DMSO) δ= 1.65 (t, 3H, CH_3), 1.98-2.11(m, 6H, $3CH_2$), 2.14-2.24 (m, 4H, $2CH_2$), 2.63 (s, 3H, CH_3), 4.28 (q, 2H, CH_2), 8.60 (s, 1H, NH, D_2O-exchangeable). Calcd. for $C_{14}H_{19}NO_3S$ (281.37): C, 59.76; H, 6.81; N, 4.98; S, 11.40 %. Found: C, 60.02; H, 6.57; N, 4.86; S, 11.65 %.MS (relative intensity) m/z: 281 (M^+, 16.6%), 252 (33.2%), 236 (100%).

4-Amino-1,5,6,7,8,9-hexahydro-10-thia-1-aza-benzo[α]azulen-2-one (5a) and 4-Hydroxy -1,5, 6,7 ,8,9-hexahydro-10-thia-1-aza-benzo [*α*] -azulen-2-one (5b)

Either compound (4a, 1.17g, 0.005 mol) or (4b, 1.405g**,** 0.005 mol) was dissolved in 50 mL of 1,4-dioxane and 0.5 mL of triethylamine was added. Then the solution was refluxed for 3 h for the formation of the cyclized product. The solution was then cooled, poured on an ice/water mixture containing few drops of hydrochloric acid to enhance precipitate formation and the latter was then collected by filtration.

Compound 5a: Brown crystals recrystallized from ethanol, yield 61%, 0.714 g, m.p. 213-215^{o}C. IR (KBr): υ/cm^{-1}= 3447, 3285, 3219, (NH_2, NH), 2885 (CH_2), 1683 (CO). ^{1}HNMR (DMSO) δ= 1.78-1.94 (m, 6H, $3CH_2$), 1.99-2.08 (m, 4H, $2CH_2$), 5.18 (s, 2H, NH_2, D_2O-exchangeable), 6.75 (s, 1H, pyridine ring), 8.44 (s, 1H, NH, D_2O-exchangeable). Calcd. for $C_{12}H_{14}N_2OS$ (234.32): C, 61.51; H, 6.02; N, 11.96; S, 13.68 %. Found: C, 61.72; H, 6.29; N, 12.14; S, 13.55%.

Compound 5b: Yellowish brown crystals recrystallized from ethanol, yield 72.5%, 0.852 g, m.p.165-167^{o}C. IR (KBr): υ/cm^{-1}= 3485-3380, 3225 (OH, NH), 2890 (CH_2), 1674 (C=O). ^{1}HNMR (DMSO) δ= 1.88-1.97 (m, 6H, $3CH_2$), 2.25-2.33 (m, 4H, $2CH_2$), 6.65 (s, 1H, OH, D_2O-exchangeable), 6.83 (s, 1H, pyridine ring), 8.25 (s, 1H, NH, D_2O-exchangeable) . Calcd. for $C_{12}H_{13}NO_2S$ (235.30): C, 61.25; H, 5.57; N, 5.95; S, 13.63 %. Found: C, 61.50; H, 5.84; N, 6.12; S, 13.86 %. MS (relative intensity) m/z: 235 (M^+, 22.7%).

(4-Amino-6,7,8,9-tetrahydro-5H-10-thia-1,3-diaz - abenzo[*α*]azulen-2-yl)acetonitrile (7a) and (4-Hydroxy-6,7,8,9-tetrahydro-5H-10-thia-1,3-diaza benzo[*α*]azulen-2-yl) acetonitrile (7b)

To either solution of compound (3a, 1.92 g, 0.01 mol) or (3b, 2.39 g, 0.01 mol) in ethanol (50 ml) containing a catalytic amount of triethylamine (0.5 ml), malononitrile (2a) (0.66 g, 0.01 mol) was added. The reaction mixture was refluxed for 8 h and then cooled, poured on an ice/water mixture containing few drops of hydrochloric acid. The solid product formed was collected by filtration.

Compound 7a: Brown crystals recrystallized from ethanol, yield 52%, 1.342 g, m.p. 142-144^{o}C. IR (KBr): υ/cm^{-1}= 3415, 3227 (NH_2), 2882 (CH_2), 2222 (CN). ^{1}HNMR (DMSO) δ= 1.93-1.99 (m, 6H, $3CH_2$), 2.15-2.28 (m., 4H, $2CH_2$), 3.12 (s, 2H, CH_2), 4.58 (s, 2H, NH_2, D_2O-exchangeable). Calcd. for $C_{13}H_{14}N_4S$ (258.34): C, 60.44; H, 5.46; N, 21.69; S, 12.41 %. Found: C, 60.33; H, 5.21; N, 21.88; S, 12.65%.

Compound 7b: Brown crystals recrystallized from ethanol, yield 64.5 %, 1.671 g, m.p. 191-193^{o}C. IR (KBr): υ/cm^{-1}= 3498- 3316 (OH), 2873 (CH_2), 2227 (CN).^{1}HNMR (DMSO) δ= 1.78-1.89 (m, 6H, $3CH_2$), 2.05-2.12 (m, 4H, $2CH_2$), 2.98 (s, 2H, CH_2), 7.88 (s, 1H, OH, D_2O-exchangeable). Calcd. for $C_{13}H_{13}N_3OS$ (259.33): C, 60.21; H, 5.05; N, 16.20; S, 12.36 %. Found: C, 60.02; H, 5.30; N, 16.41; S, 12.48%.

2-(2-Amino-5,6-dihydro-4H-cyclopenta[*b*] thiophen-3-yl)-6,7,8,9-tetrahydro-5H-10-thia -1,3-diaza-benzo[*α*]azulen-4-ylamine (9a), 2-(2-Amino-4,5,6,7-tetrahydro-benzo [*b*]- thiophen-3-yl)-6,7, 8,9-tetrahydro-5H-10-thia-1,3-diaza-benzo[*α*] azulen-4-ylamine (9b), 2-(2-Amino-5,6,7 ,8-tetrahydro-4*H*-cyclohepta[*b*]thiophen-3-yl)-6,7,8,9-

tetrahydro-5*H*-10-thia-1,3-diaza-benzo[α]azulen-4-ylamine (9c)

To a mixture of compound (7a, 0.774 g, 0.003 mol) and either cyclopentanone (8a, 0.252g, 0.003 mol), cyclohexanone (8b, 0.294g, 0.003 mol) or cycloheptanone (8c, 0.336g, 0.003 mol) in ethanol (50 ml) containing a catalytic amount of triethylamine (0.5 ml), elemental sulfur (0.096 g, 0.003 mol) was added. The reaction mixture was heated under reflux for 4 h. It was allowed to cool, then poured on an ice/water mixture containing few drops of hydrochloric acid. The reaction mixture was left overnight to settle and the formed solid product was collected by filtration.

Compound 9a: Brown crystals recrystallized from 1,4-dioxane, yield 66%, 0.706 g, m.p.181-183^{o}C. IR (KBr): υ/cm^{-1}= 3442-3180 (2NH_2), 2886-2865 (CH_2), 1658 (C=N). ^{1}HNMR (DMSO) δ= 1.77-1.89 (m, 10H, 5CH_2), 1.98-2.08 (m, 6H, 3CH_2), 3.95, 4.58 (2s, 4H, 2NH_2, D_2O-exchangeable). Calcd. for $C_{18}H_{20}N_4S_2$ (356.51): C, 60.64; H, 5.65; N, 15.72; S, 17.99 %. Found: C, 60.48; H, 5.38; N, 15.97; S, 17.74%.

Compound 9b: Pale brown crystals recrystallized from 1,4-dioxane, yield 63%, 0.7 g, m.p.152-154^{o}C. IR (KBr): υ/cm^{-1}= 3466- 3215 (2NH_2), 2878-2862 (CH_2), 1660 (C=N).^{1}HNMR (DMSO) δ= 1.86-1.93 (m, 10H, 5CH_2), 2.01-2.09 (m, 8H, 4CH_2), 4.47, 4.85 (2s, 4H, 2NH_2, D_2O-exchangeable). Calcd. for $C_{19}H_{22}N_4S_2$ (370.53): C, 61.59; H, 5.98; N, 15.12; S, 17.31 %. Found: C, 61.88; H, 5.77; N, 15.01; S, 17.11%.

Compound 9c: Pale brown crystals recrystallized from 1,4-dioxane, yield 58 %, 0.669 g, m.p.177-179^{o}C. IR (KBr): υ/cm^{-1}= 3427-3263 (2NH_2), 2878-2860 (CH_2), 1657 (C=N), 1646 (C=C).^{1}HNMR (DMSO) δ= 1.72-1.84 (m, 12H, 6CH_2), 2.13-2.22 (m, 8H, 4CH_2), 4.63, 4.98 (2s, 4H, 2NH_2, D_2O-exchangeable). Calcd. for $C_{20}H_{24}N_4S_2$ (384.56): C, 62.46; H, 6.29; N, 14.57; S, 16.68 %. Found: C, 62.19; H, 6.12; N, 14.29; S, 16.42%.

2-(2-Amino-5,6-dihydro-4H-cyclopenta[*b*]-thiophen-3-yl)-6,7,8,9-tetrahydro-*5H*-10-thia-1,3-diaza-benzo[α]azulen-4-ol (9d), 2-(2-Amino-4,5,6,7-tetrahydro-benzo[*b*]-thiophen-3-yl)-6,7,8,9-tetrahydro-*5H*-10-thia-1,3-diaza-benzo[α]azulen-4-ol (9e), 2-(2-Amino-5,6,7,8- tetrahydro-*4H*-cyclohepta [*b*]thiophen-3-yl)-6,7,8,9-tetrahydro-*5H*-10-thia-1,3-di-aza-benzo[α]azulen-4-ol (9f)

To a mixture of compound (7b, 0.778 g, 0.003 mol) and either cyclopentanone (8a, 0.252g, 0.003 mol), cyclohexanone (8b, 0.294g, 0.003 mol) or cycloheptanone (8c, 0.336g, 0.003 mol) in ethanol (50 ml) containing a catalytic amount of triethylamine (0.5 ml), elemental sulfur (0.096 g, 0.003 mol) was added. The reaction mixture was heated under reflux for 3 h. It was allowed to cool then poured on an ice/water mixture containing few drops of hydrochloric acid. The reaction mixture was left overnight to settle and the formed solid product was collected by filtration.

Compound 9d: Pale brown crystals recrystallized from 1,4-dioxane, yield 74%, 0.794 g, m.p.159-161^{o}C. IR (KBr): υ/cm^{-1}= 3485-3194 (OH, NH_2), 2882-2860 (CH_2), 1655 (C=N), 1644 (C=C). ^{1}HNMR (DMSO) δ= 1.66-1.74 (m, 8H, 4CH_2), 1.89-2.06 (m, 8H, 4CH_2), 4.82 (s, 2H, NH_2, D_2O-exchangeable), 8.15 (s, 1H, OH, D_2O-exchangeable). Calcd. for $C_{18}H_{19}N_3OS_2$ (357.49): C, 60.47; H, 5.36; N, 11.75; S, 17.94 %. Found: C, 60.66; H, 5.28; N, 11.95; S, 17.68%.

Compound 9e: Yellowish brown crystals recrystallized from 1,4-dioxane, yield 71%, 0.791 g, m.p. 205-207^{o}C. IR (KBr): υ/cm^{-1}= 3438- 3155 (OH, NH_2), 2878-2857 (CH_2), 1652 (C=N), 1640 (C=C). ^{1}HNMR (DMSO) δ= 1.88-1.97 (m, 10H, 5CH_2), 2.15-2.26 (m, 8H, 4CH_2), 5.11 (s, 2H, NH_2, D_2O-exchangeable), 7.85 (s, 1H, OH, D_2O-exchangeable). Calcd. for $C_{19}H_{21}N_3OS_2$ (371.52): C, 61.42; H, 5.70; N, 11.31; S, 17.26 %. Found: C, 61.68; H, 5.44; N, 11.52; S, 17.43%.

Compound 9f: Brown crystals recrystallized from 1,4-dioxane, yield 63 %, 0.729 g, m.p. 217-219^{o}C. IR (KBr): υ/cm^{-1}= 3398-3165 (OH, NH_2), 2875-2862 (CH_2), 1653 (C=N), 1641 (C=C). ^{1}HNMR (DMSO) δ= 1.95-2.11 (m, 12H, 6CH_2), 2.17-2.24 (m, 8H, 4CH_2),4.91 (s, 2H, NH_2, D_2O-exchangeable), 8.36 (s, 1H, OH, D_2O-exchangeable). Calcd. for $C_{20}H_{23}N_3OS_2$ (385.55): C, 62.30; H, 6.01; N, 10.90; S, 16.63 %. Found: C, 62.47; H, 5.87; N, 11.12; S, 16.86%.

2-(Benzylidene-amino)-5,6,7,8-tetrahydro-4H-cyclohepta[b]thiophene-3-carbonitrile (11a), 2-(4-Chloro-benzylidene-amino)-5,6,7,8-tetrahydro-4H-cyclohepta[b]thiophen-3-carbonitrile (11b), 2-[(4-Methoxy-benzylidene)-amino]-5,6,7,8-tetrahydro-4H-cyclo- hepta[b]thiophene-3-carbonitrile (11c)

A mixture of compound (3a, 0.96 g, 0.005mol) and either benzaldehyde (10a, 0.53 g, 0.005mol), 4-chlorobenzaldehyde (10b, 0.71 g, 0.005 mol) or 4-methoxy-benzaldehyde (10c, 0.68 g, 0.005 mol) in dry dimethylformamide (40 ml) containing a catalytic amount of piperidine (0.5 ml) was heated under reflux for 3 h, then poured on an ice/water mixture containing few drops of hydrochloric acid. The solid product formed was collected by filtration.

Compound 11a: Pale **y**ellow crystals recrystallized from ethanol, yield 59%, 0.827 g, m.p. 208-210°C. IR (KBr): υ/cm^{-1}=3048 (CH aromatic), 2893-2864 (CH_2), 2225 (CN), 1651 (C=N), 1642 (C=C).^{1}HNMR (DMSO) δ= 2.12-2.18 (m, 6H, $3CH_2$), 2.24-2.32 (m, 4H, $2CH_2$), 6.87 (s, 1H, CH), 7.23-7.55 (m, 5H, C_6H_5). Calcd. for $C_{17}H_{16}N_2S$ (280.39): C, 72.82; H, 5.75; N, 9.99; S, 11.44 %. Found: C, 72.99; H, 5.96; N, 9.67; S, 11.22 %. MS (relative intensity) m/z: 280 (M^+, 21.4%).

Compound 11b: Colorless crystals recrystallized from ethanol, yield 63%, 0.989 g, m.p. 171-173°C. IR (KBr): υ/cm^{-1}= 3043 (CH aromatic), 2881-2862 (CH_2), 2223 (CN), 1655 (C=N), 1644 (C=C). ^{1}HNMR (DMSO) δ= 2.09-2.14 (m, 6H, $3CH_2$), 2.21-2.29 (m, 4H, $2CH_2$), 6.93 (s, 1H, CH), 7.18-7.45 (dd, 4H, C_6H_4). Calcd. for $C_{17}H_{15}ClN_2S$ (314.83): C, 64.85; H, 4.80; N, 8.90; S, 10.18 %. Found: C, 65.12; H, 4.56; N, 8.63; S, 10.01%. MS (relative intensity) m/z: 314 (M^+, 9.8 %), 316 (M^+, 3.5 %).

Compound 11c: Yellowish white crystals recrystallized from ethanol, yield 67%, 1.039 g, m.p. 233-235°C. IR (KBr): υ/cm^{-1}= 3052 (CH aromatic), 2981 (CH_3), 2897-2872 (CH_2), 2220 (CN), 1656 (C=N), 1646 (C=C).^{1}HNMR (DMSO) δ= 1.83-1.89 (m, 6H, $3CH_2$), 1.92-1.97 (m, 4H, $2CH_2$), 3.12 (s, 3H, CH_3), 6.38 (s, 1H, CH), 7.11-7.23 (dd, 4H, C_6H_4). Calcd. for $C_{18}H_{18}N_2OS$ (310.41): C, 69.65; H, 5.84; N, 9.02; S, 10.33 %. Found: C, 69.89; H, 5.98; N, 9.25; S, 10.07%. MS (relative intensity) m/z: 310 (M^+, 19.1%).

2-(Benzylidene-amino)-5,6,7,8-tetrahydro-4H-cyclo -hepta[b]thiophene-3-carboxylic acid ethyl ester (11d), 2-[(4-Chloro-benzylidene)-amino]-5,6,7,8-tetrahydro-4H-cyclo-hepta[b]thiophene-3-carboxylic acid ethyl ester (11e), 2-[(4-Methoxy-benzylidene)-amino]-5,6,7,8-tetrahydro-4H-cyclohepta[b]thiophene-3-carboxylic acid ethyl ester (11f)

A mixture of compound (3b, 1.195 g, 0.005mol) and either benzaldehyde (10a, 0.53 g, 0.005mol), 4-chlorobenzaldehyde (10b, 0.71 g, 0.005mol) or 4-methoxy-benzaldehyde (10c, 0.68 g, 0.005 mol) in dry dimethylformamide (40 ml) containing a catalytic amount of piperdine (0.5 ml) was heated under reflux for 4 h, then poured on an ice/water mixture containing few drops of hydrochloric acid. The solid product formed was collected by filtration.

Compound 11d: Colorless crystals recrystallized from ethanol, yield 52%, 0.851 g, m.p. 222-224°C. IR (KBr): υ/cm^{-1}= 3057 (CH aromatic), 2965 (CH_3), 2866-2854(CH_2), 1774 (C=O), 1661(C=N), 1643 (C=C). ^{1}HNMR (DMSO) δ= 1.28 (t, 3H, J = 6.48 Hz, CH_3), 1.74-1.88 (m, 6H, $3CH_2$), 2.05-2.13 (m, 4H, $2CH_2$), 4.17 (q, 2H, J = 6.48 Hz, CH_2), 6.45 (s, 1H, CH), 7.34-7.53 (m, 5H, C_6H_5). Calcd. for $C_{19}H_{21}NO_2S$ (327.44): C, 69.69; H, 6.46; N, 4.28; S, 9.79 %. Found: C, 69.42; H, 6.25; N, 4.47; S, 10.02 %. MS (relative intensity) m/z: 327 (M^+, 23.3%).

Compound 11e: Pale **y**ellow crystals recrystallized from ethanol, yield 60 %, 1.086 g, m.p. 238-240°C. IR (KBr): υ/cm^{-1}= 3060 (CH aromatic), 2973 (CH_3), 2870 (CH_2), 1781 (C=O), 1663 (C=N), 1646 (C=C). ^{1}HNMR (DMSO) δ= 1.44 (t, 3H, J = 7.18 Hz, CH_3), 1.84-1.89 (m, 6H, $3CH_2$), 2.11-2.19 (m, 4H, $2CH_2$), 4.41 (q, 2H, J = 7.18 Hz, CH_2), 6.33 (s, 1H, CH), 7.41-7.56 (dd, 4H, C_6H_4). Calcd. for $C_{19}H_{20}ClNO_2S$ (361.89): C, 63.06; H, 5.57; N, 3.87; S, 8.86 %. Found: C, 63.33; H, 5.76; N, 3.57; S, 9.07%. MS (relative intensity) m/z: 361 (M^+, 12.7 %), 363 (M^+, 4.6 %).

Compound 11f: Brownish white crystals recrystallized from ethanol, yield 46 %, 0.822 g, m.p. 219-221°C. IR (KBr): υ/cm^{-1}= 3055 (CH aromatic), 2988 (CH_3), 2878 (CH_2), 1786 (C=O), 1652 (C=N), 1641 (C=C). ^{1}HNMR (DMSO) δ= 1.49 (t, 3H, J = 8.06 Hz, CH_3), 1.87-1.94 (m, 6H, $3CH_2$), 1.98-2.07 (m, 4H, $2CH_2$), 2.96 (s, 3H, CH_3), 4.52 (q, 2H, J = 8.06 Hz, CH_2), 6.24 (s, 1H, CH), 7.14-7.28 (dd, 4H, C_6H_4). Calcd. for $C_{20}H_{23}NO_3S$ (357.47): C, 67.20; H, 6.49; N, 3.92; S, 8.97 %. Found: C, 67.48; H, 6.19; N, 4.21; S, 8.68%. MS (relative intensity) m/z: 357 (M^+, 19.8 %).

4-Imino-2-phenyl-6,7,8,9-tetrahydro-4H,5H-10-thia-1,3-diaza-benzo[α]azulen-3-yl-amine (14a), 2-(4-Chloro-phenyl)-4-imino-6,7,8,9-tetrahydro-4H, 5H-10-thia-1,3-diaza-benzo [α] azulen-3-ylamine (14b), 4-Imino-2-(4-methoxy-phenyl)-6,7,8,9-tetrahydro-4H,5H-10-thia-1,3-diaza-benzo[α] - azulen-3-ylamine (14c)

To either solution of compound (11a, 0.56 g, 0.002 mol), (11b, 0.63 g, 0.002 mol) or (11c, 0.62 g, 0.002 mol) in ethanol (50 ml), hydrazine hydrate (12, 0.1 ml, 0.002 mol) was added. The reaction mixture was heated under reflux for 6 h, left to cool at room temperature, then poured on an ice/water mixture containing few drops of hydrochloric acid. The solid product formed was collected by filtration.

Compound 14a: Yellow crystals recrystallized from ethanol, yield 52%, 0.323 g, m.p. 252-254°C. IR (KBr): υ/cm^{-1}= 3454-3211 (NH_2, NH), 3043 (CH aromatic), 2881 (CH_2), 1647 (C=N), 1641 (C=C).^{1}HNMR (DMSO) δ= 1.91-2.08 (m, 6H,

$3CH_2$), 2.11-2.15 (m, 4H, $2CH_2$), 4.81 (s, 2H, NH_2, D_2O-exchangeable), 7.29-7.38 (m, 5H, C_6H_5), 8.63 (s, 1H, NH, D_2O-exchangeable). Calcd. for $C_{17}H_{18}N_4S$ (310.42): C, 65.78; H, 5.84; N, 18.05; S, 10.33 %. Found: C, 65.55; H, 5.99; N, 18.33; S, 10.52%. MS (relative intensity) m/z: 310 (M^+, 26.8 %).

Compound 14b: Pale yellow crystals recrystallized from ethanol, yield 59%, 0.371 g, m.p.277-279°C. IR (KBr): υ/cm^{-1}= 3378- 3235 (NH_2, NH), 3052 (CH aromatic), 2888 (CH_2), 1650 (C=N), 1643 (C=C). ^{1}HNMR (DMSO) δ= 1.73-1.84 (m, 6H, $3CH_2$), 1.95-2.12 (m, 4H, $2CH_2$), 4.42 (s, 2H, NH_2, D_2O-exchangeable), 7.46-7.62 (dd, 4H, C_6H_4), 9.35 (s, 1H, NH, D_2O-exchangeable). Calcd. for $C_{17}H_{17}ClN_4S$ (344.86): C, 59.21; H, 4.97; N, 16.25; S, 9.30 %. Found: C, 59.47; H, 5.19; N, 16.39; S, 9.56%. MS (relative intensity) m/z: 344 (M^+, 17.3 %), 346 (M^+, 6.2 %).

Compound 14c: Colorless crystals recrystallized from ethanol, yield 47%, 0.32 g, m.p. 211-213°C. IR (KBr): υ/cm^{-1}= 3426-3212 (NH_2, NH), 3056 (CH aromatic), 2945 (CH_3), 2871 (CH_2), 1653 (C=N), 1644 (C=C). ^{1}HNMR (DMSO) δ= 1.98-2.06 (m, 6H, $3CH_2$), 2.14-2.23 (m, 4H, $2CH_2$), 3.27 (s, 3H, CH_3), 4.61 (s, 2H, NH_2, D_2O-exchangeable), 7.12-7.43 (dd, 4H, C_6H_4), 9.46 (s, 1H, NH, D_2O-exchangeable). Calcd. for $C_{18}H_{20}N_4OS$ (340.44): C, 63.50; H, 5.92; N, 16.46; S, 9.42 %. Found: C, 63.74; H, 5.64; N, 16.19; S, 9.67%. MS (relative intensity) m/z: 340 (M^+, 33.6%).

3-Amino-2-phenyl-3,5,6,7,8,9-hexahydro-10-thia-1,3-diaza-benzo[α]azulen-4-one (14d), 3-Amino-2-(4-chloro-phenyl)-3,5,6,7,8,9-hexahydro-10-thia-1,3-diaza-benzo[α]azulen-4-one (14e), 3-Amino-2-(4-methoxy-phenyl)-3,5,6,7,8,9-hexahydro-10-thia-1,3-diaza-benzo[α]azulen-4-one (14f)

To either solution of compound (11d, 0.492 g, 0.0015 mol), (11e, 0.543 g, 0.0015 mol) or (11f, 0.536 g, 0.0015 mol) in ethanol (40 ml), hydrazine hydrate (12, 0.08 ml, 0.0015 mol) was added. The reaction mixture was heated under reflux for 8 h, left to cool at room temperature, then poured on an ice/water mixture containing few drops of hydrochloric acid. The solid product formed was collected by filtration.

Compound 14d: Colorless crystals recrystallized from ethanol, yield 63 %, 0.295 g, m.p. 233-235°C. IR (KBr): υ/cm^{-1}= 3437-3266 (NH_2), 3053 (CH aromatic), 2865 (CH_2),1672 (C=O), 1643 (C=N), 1640 (C=C). ^{1}HNMR (DMSO) δ= 1.80-1.87 (m, 6H, $3CH_2$), 1.96-2.07 (m, 4H, $2CH_2$), 4.66 (s, 2H, NH_2, D_2O-exchangeable), 7.22-7.36 (m, 5H, C_6H_5). Calcd. for $C_{17}H_{17}N_3OS$ (311.40): C, 65.57; H, 5.50; N, 13.49; S, 10.30 %. Found: C, 65.82; H, 5.79; N, 13.31; S, 10.57%. MS (relative intensity) m/z: 311 (M^+, 41.4 %).

Compound 14e: Yellow crystals recrystallized from ethanol, yield 66 %, 0.342 g, m.p. 203-205°C. IR (KBr): υ/cm^{-1}= 3385-3248 (NH_2), 3056 (CH aromatic), 2873 (CH_2), 1677 (C=O), 1648 (C=N), 1642 (C=C).^{1}HNMR (DMSO) δ= 1.92-1.99 (m, 6H, $3CH_2$), 2.12-2.24 (m, 4H, $2CH_2$), 5.13 (s, 2H, NH_2, D_2O-exchangeable),7.31-7.52 (dd, 4H, C_6H_4). Calcd. for $C_{17}H_{16}ClN_3OS$ (345.85): C, 59.04; H, 4.66; N, 12.15; S, 9.27 %. Found: C, 59.31; H, 4.89; N, 12.34; S, 9.52%. MS (relative intensity) m/z: 345 (M^+, 24.3 %), 347 (M^+, 8.8 %).

Compound 14f: Pale brown crystals recrystallized from ethanol, yield 71 %, 0.364 g, m.p. 247-249°C. IR (KBr): υ/cm^{-1}= 3338-3215 (NH_2), 3057 (CH aromatic), 2976 (CH_3), 2883 (CH_2), 1678 (C=O), 1657 (C=N), 1644 (C=C).^{1}HNMR (DMSO) δ= 2.09-2.15 (m, 6H, $3CH_2$), 2.23-2.28 (m, 4H, $2CH_2$), 3.22 (s, 3H, CH_3), 5.40 (s, 2H, NH_2, D_2O-exchangeable), 7.14-7.23 (dd, 4H, C_6H_4). Calcd. for $C_{18}H_{19}N_3O_2S$ (341.43): C, 63.32; H, 5.61; N, 12.31; S, 9.39 %. Found: C, 63.09; H, 5.39; N, 12.59; S, 9.56%. MS (relative intensity) m/z: 341 (M^+, 30.3 %).

RESULTS AND DISCUSSION

The reaction of 3a,b with acetic anhydride gave the acetamido derivatives 4a,b. The structures of compounds 4a,b were based on analytical and spectral data. Thus, for example, the ^{1}H NMR spectrum of 4a showed besides the expected regular data for the cycloheptenyl moiety, two multiplets at δ= 2.12-2.21(6H, $3CH_2$), δ= 2.26-2.32 (4H, $2CH_2$), a singlet at δ= 2.39 (3H, CH_3) and a singlet at δ= (1H, NH). The structure of compounds 4a,b was confirmed through internal cyclization on heating in a basic catalyst to give 4-amino-1,5,6,7,8,9-hexahydro-10-thia-1-aza-benzo[α]azulen-2-one (5a) and 4-hydroxy-1,5,6,7,8,9-hexahydro-10-thia-1-aza-benzo[α]azulen-2-one (5b), respectively (scheme 1). Compounds 3a,b reacted with malononitrile (2a) in Et_3N/ethanol followed by internal cyclization through the proposed intermediate formation of imines 6a,b to form thieno-pyrimidine derivatives 7a,b. The structures of the latter products were based on analytical and spectral data. The products 7a,b readily reacted with the cyclic ketones 8a-c in presence of elemental sulfur, triethylamine and ethanol as solvent to give fused thiophene derivatives 9a-f (scheme 2). The ^{1}HNMR spectrum of each compound revealed, in case of 9a, two multiplets at

δ= 1.77-1.89 (10H, $5CH_2$), δ= 1.98-2.08 (6H, $3CH_2$) and two singlets at 3.95, 4.58 (4H, $2NH_2$).

Furthermore, the reaction of compounds 3a,b with different aryl aldehydes 10a-c in DMF/piperidine gave the corresponding imines 11a-f which were directed toward reaction with hydrazine hydrate (12). The final products 14a-f were obtained through internal cyclization of the proposed intermediates 13a-f (scheme 3). The structures of compounds 14a-f were based on analytical and spectral data. Thus, for example, the ^{1}H NMR spectrum of 14a showed besides the expected regular data for the cycloheptenyl moiety, two multiplets at δ= 1.91-2.08 (6H, $3CH_2$), δ= 2.11-2.15 (4H, $2CH_2$), a singlet at δ= (2H, NH_2), a multiplet at δ= 7.29-7.38 (5H) corresponding to aromatic protons and a singlet at δ= (1H, NH).

Antitumor activity tests

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 a monolayer and are routinely maintained in RPMI-1640 medium supplemented with 5% heat-inactivated FBS, 2 mM glutamine and antibiotics (penicillin 100 U/mL, streptomycin 100 µg/mL), at 37^{o}C in a humidified atmosphere containing 5% CO_2. Exponentially growing cells were obtained by plating 1.5×10^5 cells/mL for MCF-7 and SF-268 and 0.75×10^4 cells/mL for NCI-H460, followed by 24 h of incubation. The effect of the vehicle solvent (DMSO) on the growth of these cell lines was evaluated in all experiments by exposing untreated control cells to the maximum concentration (0.5%) of DMSO used in each assay.

Tumor cell growth assay: The effect of 3a–14f on the *in vitro* growth of human tumor cell lines was 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, cells growing in 96-wellplates were then exposed for 48 h to five serial concentrations of each compound [18], 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., Power wave 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 [19]**.** 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 3a-14f 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 an exposure for 48 h. All tested compounds inhibited the growth of the tested human tumor cell lines in a dose-dependent manner (data not shown). The results presented in Table 1 revealed that the thieno-pyrimidine derivatives 14d and 14f showed the highest inhibitory effect against all three tumor cell lines corresponding to the reference standard material (Doxorubicin); the compounds 5a, 9b, 14a and 14c showed the highest inhibitory effect against all three tumor cell lines. On the other hand, the compounds 9a, 9c, 9e, 14b and 14e showed moderate inhibitory effects against the three cancer cell lines. The rest of the compounds 3a, b, 4a, b, 5b, 7a, b, 9d, f, 11a, b, c, d, e and f showed a low growth-inhibitory effect.

Comparing the thieno-pyridone derivatives 5a and 5b it was found that compound 5a with X = NH_2 showed a higher inhibitory effect than compound 5b, with X=OH. Comparing the cycloalkylthieno derivatives 9a, b, c, d, e, and f it was found that compound 9b with X = NH_2 and n = 2 showed the highest inhibitory effect among the six compounds, while compounds 9a, c and 9e with X = NH_2, NH_2, OH and n = 1,3,2, respectively, showed a moderate inhibitory effect. The comparison of compounds 14a, b, c, d, e and f revealed that the presence of O instead of NH group and Ar=Ph or 4-Meo-Ph only in compounds 14d and 14f increased the inhibitory effect stronger than in compounds 14a, b, c and 14e, while the presence of NH group and 4-Cl-Ph in compound 14b may be the cause for the decrease in inhibitory effect against the three tumor cell lines.

CONCLUSIONS

In this work fused heterocyclic compounds based on cyclohepta[*b*]thiophene derivatives were synthesized and screened for their antitumor activity against three different cell lines in comparison with the reference standard "doxorubicin". Among the newly synthesized products, the thienopyrimidine derivatives 14d and 14f showed the highest inhibitory effect against all three tumor cell lines. Compounds 5a, 9b, 14a and 14c showed the highest inhibitory effect against all three tumor cell lines in comparison with the other synthesized compounds.

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Synthesis and antitumor activity of some fused heterocyclic compounds based on cyclohepta[b]thiophene derivatives

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The reaction of 5,6,7,8-tetrahydro-4H-cyclohepta[b]thiophene derivatives 3a,b with acetic anhydride in presence of glacial acetic acid produced the acetamido derivatives 4a,b. Cyclization of the latter compounds gave the annulated products 5a,b. Compounds 3a,b reacted with one of the activated methylene groups of malononitrile (2a) and afforded compounds 7a,b through internal cyclization of the intermediates of compounds 6a,b. The latter products were reacted with the cyclic ketones 8a,b,c in presence of elemental sulphur and afforded compounds 9a-f. Compounds 3a,b reacted with different types of aldehydes 10a,b,c to produce compounds 11a-f. Finally the products11a-f reacted with hydrazine hydrate (12) affording compounds 14a-f *via* the proposed intermediate formation of compounds 13a-f. The antitumor activities of the synthesized compounds were tested using three different cell lines.