Synthesis and antimicrobial activity of a novel series of condensed thienopyrimidines

Reda A. Haggam* and Ahmed H. Moustafa**
Department of Chemistry, Faculty of Science, Zagazig University, Zagazig, Egypt

Síntesis y actividad antimicrobiana de una nueva serie de tienopirimidinas condensados

Síntesi i activitat antimicrobiana d'una nova sèrie de tienopirimidines condensades

Recibido: 3 de julio de 2013; aceptado: 13 de noviembre de 2013

RESUMEN

La alquilación de 2-tioxo-5,6,7,8-tetrahidrobenzotieno[2,3-*d*] pirimidin-4 (3H)-ona **(2)** dio los productos S-alquilantes **3-5**. La reacción de 3-carboxamida **1** con tereftaloilo, cloruro de isoftaloílo y benzoína proporcionó las bistienopirimidinas **6,7** y la pirrolopirimidinona **9**, respectivamente. La condensación de **1** con aldehídos aromáticos proporcionó los compuestos **11a-c**. La alquilación de los compuestos **11a-c** con bromuro de alilo dio lugar a los derivados de N-alquil tienopirimidina **12 a-c**. La alquilación de **11 a,b** con acetato de 4-bromobutil dio los derivados de acetato de butilo **13a,b**, que se han desacetilado para proporcionar **14a,b**. Todos los compuestos recién sintetizados se caracterizaron por IR, ^{1}H, ^{13}C NMR y análisis elemental. Algunos de ests compuestos fueron seleccionados para evaluar su actividad antimicrobiana.

Palabras clave: Actividad antimicrobiana, *S*-alquilación, tieno-[2,3-*d*]-pirimidinas, bistienopirimidinas, derivados de pirrol.

SUMMARY

Alkylation of 2-thioxo-5,6,7,8-tetrahydrobenzothieno[2,3-*d*] pyrimidin-4(3)-one (**2**) gave the -alkylating products **3-5**. Reaction of 3-carboxamide **1** with terphthaloyl, isophthaloyl chloride and benzoin afforded bisthienopyrimidines **6**, **7** and pyrrolopyrimidineone **9**, respectively. Condensation of **1** with aromatic aldehydes afforded compounds **11a-c**. Alkylation of compounds **11a–c** with allyl bromide resulted in -alkyl thienopyrimidine derivatives **12a–c**. Alkylation of **11a,b** with 4-bromobutyl acetate gave butylacetate derivatives **13a,b**. which were deacetylated to provide **14a,b**. All the newly synthesized compounds were characterized by the IR, ^{1}H, ^{13}C NMR and elemental analyses. Selected members of these compounds were screened for antimicrobial activity.

Key words: Antimicrobial activity, *S*-alkylation, thieno[2,3-*d*]pyrimidines, bisthienopyrimidines, pyrrol derivatives.

RESUM

La alquilació de 2-tioxo-5, 6,7,8-tetrahidrobenzotié [2,3-*d*] pirimidin-4 (3H)-ona **(2)** va donar els productes S-alquilants **3-5**. La reacció de 3-carboxamida 1 amb tereftaloil, clorur d'isoftaloil i benzoïna va proporcionar les bistienopirimidines **6,7**, i la pyrrolopyrimidinona **9**, respectivament. La condensació de **1** amb aldehids aromàtics proporciona els productes **11 a-c.** L'alquilació dels compostos **11a-c** amb bromur d'al·lil va donar lloc als derivats de N-alquil tienopirimidina **12a-c**. L'alquilació de **11a,b** amb acetat de 4-bromobutil va donar els derivats d'acetat de butil **13a,b,** que s'han desacetilat per proporcionar **14a,b**. Tots els productes sintetitzats es van caracteritzar per IR, ^{1}H i ^{13}C NMR, i anàlisi elemental. Alguns d'aquests compostos van ser seleccionats per avaluar la seva activitat antimicrobiana.

Paraules clau: Activitat antimicrobiana, *S*-alquilació, tieno-[2,3-*d*]-pirimidines, bistienopirimidines, derivats de pirrol.

Corresponding authors:
*rhaggam@yahoo.com, **ah_hu_mostafa@yahoo.com,
Tel.: 00201000960389; fax:0020552308213

INTRODUCTION

Thienopyrimidine derivatives play an essential role in several biological processes and have considerable chemical and pharmacological activities [1–3]. Many of thienopyrimidine derivatives were found to possess avariety of pronounced activities such as ulcerogenic [4] as well as antipsychotic activities [5]. Moreover, some of 2-alkylthio or 2-alkylsubstituted thienopyrimidines show significant antifungal and antibacterial activities [6] whereas others exhibit good anticonvulsant and angiotensin or H^1 receptor antagonistic activities [7]. In view of these observations and in continuation to our previous work on pyrimidine chemistry [8] we synthesized some new compounds containing pyrimidine and pyrrolo--alkylthienopyrimidine moieties and tested some of them for their antimicrobial activities.

MATERIAL AND METHODS

All experiments were carried out using drying solvents. All melting points were determined on a Büchi melting point apparatus B-545 with open capillary tubes and are uncorrected. The IR spectra (KBr disc) were recorded on Perkin-Elmer FTIR 400 Spectrophotometer. The ^{1}H and ^{13}C NMR spectra were recorded on a Varian-300 MHz spectrometer at Al al-Bayt University, Mafraq, Jordan. All chemical shifts were expressed on the δ (ppm) scale using TMS as the standardreference. The coupling constant (*J*) values are given in Hz.

2-Thioxo-5,6,7,8-tetrahydro[1] benzothieno[2,3-*d*]pyrimidin-4(3*H*)one (2)

A mixture of compound **1** (10 mmol), carbon disulphide (10 mL) and potassium hydroxide (12 mmol) in ethanol (50 mL) was heated on a water bath for 24 h. The reaction mixture was acidified with dilute acetic acid. The solid product was filtered off, washed with water and crystallized from ethanol to give compound **2** in 62% yield as yellow crystals. Mp. 259–260°C (lit. 245 °C) [9], IR (KBr): 3436 cm^{-1} (NH), 1666 cm^{-1} (C=O, amide), 1200 cm^{-1} (C=S). ^{1}H NMR (300 MHz, DMSO-d6): δ = 1.73 (m, 4H, 2CH$_2$), 2.64 (t, 2H, J = 5.7 Hz, CH$_2$), 2.75 (t, 2H, J = 5.7 Hz, CH$_2$), 12.21 (s, 1H, NH), 13.21 (s, 1H, SH). ^{13}C NMR (75 MHz, DMSO-d6): δ = 21.9, 22.9, 24.3 and 25.3 (4 CH$_2$-cyclohexane), 116.8, 128.6, 131.2, 150.3, 157.4 and 173.2 (Ar-C, C=O and C=S).

2-(Prop-2-yn-1-ylthio)-5,6,7,8-tetrahydro[1] benzothieno[2,3-*d*]pyrimidin-4(3*H*)-one (3)

Propargyl bromide (11 mmol) was added portion wise to a well stirred mixture of compound **2** (10 mmol) and potassium carbonate (11 mmol) in dry dimethylformamide (15 mL) and then, the reaction mixture was refluxed for 8 h. The solvent was evaporated under reduced pressure and the residue was diluted with water, the solid product was filtered off, dried and crystallized from ethanol to give compound **3** in 60% yield as reddish powder. Mp. 180–181°C, IR (KBr): 3474 cm^{-1} (NH), 1676 cm^{-1} (C=O, amide). ^{1}H NMR (300 MHz, DMSO-d6): δ = 1.78 (m, 4H, 2CH$_2$), 2.70 (t, 2H, J = 5.7 Hz, CH$_2$), 2.85 (t, 2H, J = 5.7 Hz, CH$_2$), 3.28 (s, 1H, $\equiv$CH), 4.82 (s, 2H, SCH$_2$), 12.12 (s, 1H, NH). Anal. Calcd for $C_{13}H_{12}N_2OS_2$ (276.38): C, 56.49; H, 4.38; N, 10.14. Found: C, 56.50; H, 4.38; N, 10.14.

2-(Allylthio)-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*] pyrimidin-4(3*H*)-one (4)

Exp. as in compound **3** by using allyl bromide (11 mmol), the solid product was filtered off, dried and crystallized from ethanol to give compound **4** in 64% yield as brownish powder. Mp. 100–101°C, IR (KBr): 3430 cm^{-1} (NH), 1671 cm^{-1} (C=O, amide). ^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.82 (m, 4H, 2CH$_2$), 2.70 (t, 2H, J = 5.7 Hz, CH$_2$), 2.95 (t, 2H, J = 5.7 Hz, CH$_2$), 3.85 (d, 2H, J = 7.8 Hz, SCH$_2$), 4.69 (d, 1H, J = 4.2 Hz, Ha), 4.87 (d, 1H, J = 15.0 Hz, Ha`), 4.96 (m, 1H, Hb), 12.21(s, 1H, NH). Anal. Calcd for $C_{13}H_{14}N_2OS_2$ (278.39): C, 56.09; H, 5.07; N, 10.06. Found: C, 56.09; H, 5.06; N, 10.05.

2-Oxirane-2-ylmethylthio-5,6,7,8-tetrahydro[1] benzothieno[2,3-*d*]pyrimidin-4(3*H*)-one (5)

Epichlorohydrin (11 mmol) was added to a well stirred mixture of **2** (10 mmol) and potassium carbonate (11 mmol) in dry DMF (15 mL) and stirring was continued 24 h. The reaction mixture was filtered off and the solvent evaporated under reduced pressure. The residue was crystallized from ethanol to give compound **5** in 61% yield as colorless crystals. Mp. 130–131°C, IR (KBr): 3445 cm^{-1} (NH), 1653 cm^{-1} (C=O, amide). ^{1}H NMR (300 MHz, DMSO-d6): δ = 1.72 (m, 4H, 2CH$_2$), 2.65 (t, 2H, J = 5.7 Hz, CH$_2$), 2.79 (t, 2H, J = 5.7 Hz, CH$_2$), 3.25 (d, 2H,J = 6.0 Hz, SCH$_2$), 3.73 (m, 1H, Hb, oxirane), 3.87 (dd, 1H, J = 5.1 Hz,J = 4.9 Hz, Ha`), 4.25 (m, 1H, Ha), 12.14 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d6): δ = 22.0, 23.1, 24.2 and 25.7 (4CH$_2$, cyclohexane), 31.9 (SCH$_2$), 45.2 (OCH$_2$, oxirane), 49.2 (CH, oxirane), 113.1, 126.9, 132.5, 150.6, 152.5 and 158.3 (Ar-C, C=N and C=O). MS (EI): m/z (M$^+$, 294.0).

2,2'-(1,4-Phenylene)bis(5,6,7,8-tetrahydro[1] benzothieno[2,3-*d*]pyrimidin-4(3*H*)-one (6)

Thionyl chloride (20 mmol) was added to (10 mmol) of terphthalic acid in dry round flask and heated on water bath for 2 h. The excess of thionyl chloride was removed under reduced pressure then compound **1** (20 mmol) dissolved in (15 mL) of dry pyridine was added. The reaction mixture was refluxed for 6 h. After cooling, the mixture was poured on ice-cold hydrochloric acid. The solid product was filtered off, dried and crystallized from dimethyformamide to give compound **6** in 67% yield as dark green crystals. Mp. > 360–361 °C, IR (KBr): 3432 and 3198 cm^{-1} (2NH), 1654 cm^{-1} (C=O, amide). ^{1}H NMR (300 MHz, DMSO-d6): δ = 1.77 (m, 8H, 4CH$_2$), 2.67 (t, 4H, J = 5.7 Hz, 2CH$_2$), 2.76 (t, 4H,J = 5.7 Hz, 2CH$_2$), 7.26 (br, 1H, NH), 8.04 (m, 4H, Ar-H), 13.08 (s, 1H, NH). MS (EI): m/z (M$^+$, 487.0). Anal. Calcd for $C_{26}H_{22}N_4O_2S_2$ (486.61): C, 64.17; H, 4.56; N, 11.51. Found: C, 64.16; H, 4.55; N, 11.50.

2,2'-(1,3-Phenylene)bis(5,6,7,8-tetrahydro[1] benzothieno[2,3-*d*]pyrimidin-4(3*H*)-one) (7)

Exp. as in **6**; the solid product was filtered off, dried and crystallized from DMF to give compound **7** in 55% yield as gray crystals. Mp. > 360–362 °C, IR (KBr): 3417 and 3171 cm^{-1} (2NH), 1639 cm^{-1} (C=O, amide). ^{1}H NMR (300 MHz, DMSO-d6): δ = 1.76 (m, 8H, 4CH$_2$), 2.67 (t, 4 H, J = 5.7 Hz, 2CH$_2$), 2.76 (t, 4H, J = 5.7 Hz, 2CH$_2$), 7.31 (br, 1H, NH), 7.71 (t, 1H, J = 7.8 Hz, Ar-H), 8.12 (m, 2H, Ar-H), 8.46 (s, 1H, Ar-H), 13.19 (s, 1H, NH). MS (EI): m/z (M^{+1}, 488.0).

1,2-Diphenyl-6,7,8,9-tetrahydro[1]benzothieno[3,2-e]-pyrrolo[1,2-*a*]pyrimidin-5(4*H*)-one (9)

Compound **1** (10 mmol) was heated under reflux for 2 h in the presence of acetic acid/acetic anhydride (30 mL) (1:1). The reaction mixture was cooled and poured into ice-cod water. The precipitated solid was filtered off to obtain the crude product of the acetylated compound **8**. A mixture of compound **8** (10 mmol) and benzoin (10 mmol) in ethanol was heated under reflux for 1 h. The reaction mixture was concentrated and cooled. The separated solid was filtered off and crystallized from toluene to give compound **9** in 55% yield as colorless crystals. Mp. > 220–222 °C, IR (KBr): 3218 cm^{-1} (NH), 1693 cm^{-1} (C=O, amide). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.82 (m, 4H, $2CH_2$), 2.28 (t, 2H,J = 5.8 Hz, CH_2), 2.62 (t, 2H, J = 5.8 Hz, CH_2), 6.87 (s, 1H, pyrrole), 7.27–7.94 (m, 10H, Ar-H), 9.16 (s, 1H, NH). MS (EI): m/z (M^+, 397.0).

4-Allyl-1,2-diphenyl-6,7,8,9-tetrahydro[1]benzothieno[3,2-e]pyrrolo[1,2-*a*]pyrimidin-5(4*H*)-one (10)

Exp. as in **3**; using allyl bromide, (11 mmol), the solid product was filtered off, dried and crystallized from ethanol to give compound **10** in 45% yield as colorless crystals. Mp. 164–165°C, IR (KBr): 1693 cm^{-1} (C=O, amide). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.77 (m, 4H, $2CH_2$), 2.54 (t, 2H, J = 5.6 Hz, CH_2), 2.62 (t, 2H,J = 5.6 Hz, CH_2), 4.20 (d, 2H, J = 6.0 Hz, SCH_2), 5.05–5.22 (m, 2H, Ha and Ha`), 5.81 (m, 1H, Hb), 6.76 (s, 1H, pyrrole), 7.24–7.95 (m, 10H, Ar-H). Anal. Calcd for $C_{28}H_{24}N_2OS$ (436.57): C, 77.03; H, 5.54; N, 6.42. Found: C, 77.02; H, 5.54; N, 6.43.

General procedure for synthesis of compounds (11a–c)

A mixture of compound **1** (10 mmol) and aromatic aldehyde, namely, benzaldehyde, anisaldehyde and -chlorobenzaldehyde (10 mmol) was heated under reflux for 10 h in the presence of -butanol and chlorine water (1 mL) as a catalyst. The precipitated product was filtered off, dried and crystallized from proper solvent.

2-Phenyl-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidin-4(3*H*)-one (11a)

The formed precipitate was crystallized from glacial acetic acid to give compound **11a** in 77% yield as yellow crystals. Mp. 320–321°C, IR (KBr): 2924 cm^{-1} (NH), 1660 cm^{-1} (C=O, amide). ^1H NMR (300 MHz, DMSO-d6): δ = 1.91 (m, 4H, $2CH_2$), 2.27 (t, 2H, J = 5.7 Hz, CH_2), 2.92 (t, 2H, J = 5.7 Hz, CH_2), 7.49–8.08 (m, 5H, Ar-H), 12.52 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d6): δ = 22.2, 22.8, 25.4, and 25.7 ($4CH_2$, cyclohexane), 116.8, 127.3, 128.2, 129.0, 131.0, 135.0, 137.1, 157.9, 162.2 and 168.3 (Ar-C, C=N and C=O). Anal. Calcd for $C_{16}H_{14}N_2OS$ (282.36): C, 68.06; H, 5.00; N, 9.92. Found: C, 68.05; H, 5.02; N, 9.91.

2-(4-Methoxyphenyl)-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidin-4(3*H*)-one (11b)

The formed precipitate was crystallized from glacial acetic acid to give compound **11b** in 72% yield as pale brown crystals. Mp. 295–296°C, IR (KBr): 2925 cm^{-1} (NH), 1653 cm^{-1} (C=O, amide). ^1H NMR (300 MHz, DMSO-d6): δ = 1.78 (m, 4H, $2CH_2$), 2.72 (t, 2H,J = 5.7 Hz, CH_2), 2.88 (t, 2H,J = 5.7 Hz, CH_2), 3.82 (s, 3H, OCH_3), 7.02 (d, 2H, J = 8.7 Hz, Ar-H), 8.08 (d, 2H, J = 8.7 Hz, Ar-H), 12.29 (s, 1H, NH). MS (EI): m/z (M^+, 312.0).

2-(4-Chlorophenyl)-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidin-4(3*H*)-one (11c)

The formed precipitate was crystallized from glacial acetic acid to give compound **11a** in 63% yield as colorless crystals. Mp. 341–342°C, IR (KBr): 2927 cm^{-1} (NH), 1653 cm^{-1} (C=O, amide). ^1H NMR (300 MHz, DMSO-d6): δ = 1.79 (m, 4H, $2CH_2$), 2.76 (t, 2H,J = 5.7 Hz, CH_2), 2.09 (t, 2H, J = 5.7 Hz, CH_2), 7.57 (d, 2H, J = 8.4 Hz, Ar-H), 8.12 (d, 2H, J = 8.4 Hz, Ar-H), 12.54 (s, 1H, NH). Anal. Calcd for $C_{16}H_{13}ClN_2OS$ (316.81): C, 60.66; H, 4.14; N, 8.84. Found: C, 60.66; H, 4.15; N, 8.85.

2-Phenyl-3-(prop-2-en-1-yl)-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidin-4(3*H*)-one (12a)

Exp. as **4**; using allyl bromide (11 mmol), the solid product was filtered off, dried and crystallized from ethanol to give compound **12a** in 56% yield as pale yellow crystals. Mp. 101–102°C, IR (KBr): 1647 cm^{-1} (C=O, amide). ^1H NMR (300 MHz, DMSO-d6): δ = 1.81 (m, 4H, $2CH_2$), 2.79 (t, 2H, J = 5.7 Hz, CH_2), 2.88 (t, 2H, J = 5.7 Hz, CH_2), 5.11 (d, 2H, J = 5.1 Hz, N-CH_2), 5.29 (dd, 1H, J = 1.2 Hz, J = 1.5 Hz, Ha), 5.46 (dd, 1H, J = 1.2 Hz, J = 1.5 Hz, Ha`), 6.12 (m, 1H, Hb), 7.49–8.39 (m, 5H, Ar-H). ^{13}C NMR (75 MHz, DMSO-d6): δ = 22.6, 22.8, 25.4 and 25.9 ($4CH_2$, cyclohexane), 66.9 (NCH_2), 116.9, 118.1, 127.5, 128.1, 128.5, 129.0, 129.5, 130.9, 133.4, 135.1, 137.2 and 163.1 (Ar-C, C=C, C=N and C=O). MS (EI): m/z (M^+, 322.0).

2-(4-Methoxyphenyl)-3-(prop-2-en-1-yl)-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidin-4(3*H*)-one (12b)

Exp. as **4**; by using allyl bromide (11 mmol), the solid product was filtered off, dried and recrystallized from ethanol to give compound **12b** in 55% yield as colorless crystals. Mp. 131–132°C, IR (KBr): 1646 cm^{-1} (C=O, amide). ^1H NMR (300 MHz, DMSO-d6): δ = 1.82 (m, 4H, $2CH_2$), 2.82 (t, 2H, J = 5.8 Hz, CH_2), 2.95 (t, 2H,J = 5.8 Hz, CH_2), 3.18 (s, 3H, OCH_3), 5.11 (d, 2H, J = 5.1 Hz, NCH_2), 5.29 (dd, 1H, J = 1.2 Hz, J = 1.5 Hz, Ha), 5.46 (dd, 1H, = 1.2 Hz, J = 1.5 Hz, Ha`), 6.12 (m, 1H, Hb), 7.06 (d, 2H, J = 8.7 Hz, Ar-H), 8.10 (d, 1H, J = 8.7 Hz, Ar-H), 8.32 (d, 1H, J = 8.7 Hz, Ar-H). ^{13}C NMR (75 MHz, DMSO-d6): δ = 22.4, 22.8, 25.3 and 25.9 ($4CH_2$, cyclohexane), 55.7 (OCH_3), 66.8 (NCH_2), 114.3, 116.3, 118.1, 124.5, 129.7, 129.8, 131.2, 132.1, 133.5, 134.3, 159.2 and 163.0 (Ar-C, C=C, C=N and C=O). Anal. Calcd for $C_{20}H_{20}N_2O_2S$ (352.45): C, 68.16; H, 5.72; N, 7.95. Found: C, 68.15; H, 5.73; N, 7.96.

2-(4-Chlorophenyl)-3-(prop-2-en-1-yl)-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidin-4(3*H*)-one (12c)

Exp. as in **4**, by using allyl bromide (11 mmol), the solid product was filtered off, dried and crystallized from ethanol to give compound **12c** in 61% yield as buff crystals. Mp. 136–137°C, IR (KBr): 1653 cm^{-1} (C=O, amide). ^1H NMR (300 MHz, DMSO-): δ = 1.91 (m, 4H, $2CH_2$), 2.85 (t, 2H, J = 5.6 Hz,CH_2), 3.0 (t, 2H,J = 5.6 Hz, CH_2), 5.12 (d, 2H, J = 5.1 Hz, NCH_2), 5.31 (dd, 1H, J = 1.2 Hz, = 1.4 Hz, Ha), 5.46 (dd, 1H, J = 1.2 Hz,J = 1.4 Hz, Ha`), 6.17 (m, 1H, Hb), 7.42 (d, 2H, J = 8.1 Hz, Ar-H), 8.40 (d, 2H, J = 8.1 Hz, Ar-H). MS (EI): m/z (M^+, 357.0).

General procedure for synthesis of compounds (13a,b)

4-Bromobutylacetate (10 mmol) was added to a well stirred mixture of **11a,b** (10 mmol) and potassium carbonate (11 mmol) in dry DMF (15 mL). The reaction mixture was stirred under reflux for 2 h. The precipitate was filtered off and the solvent was evaporated under reduced pressure. The product was crystallized from proper solvent.

4-[(2-Phenyl-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidin-4-yl)oxy]butyl acetate (13a)

The formed precipitate was crystallized from ethanol to give compound **13a** in 85% yield as buff crystals. Mp. 165–166°C, IR (KBr): 1739 cm^{-1} (C=O, ester). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.58 (m, 2H, CH_2(b)), 1.79–1.99 (m, 6H, $2CH_2$, cyclohexane, CH_2(c)), 2.06 (s, 3H, CH_3CO), 2.84 (t, 2H, J = 5.7 Hz, CH_2, cyclohexane), 2.97 (t, 2H,J = 5.7 Hz, CH_2, cyclohexane), 3.77 (t, 2H, J = 6.3 Hz, OCH_2(d)), 4.67 (t, 2H, J = 6.3 Hz, CH_2OAC(a)), 7.48–8.48 (m, 5H, Ar-H). MS (EI): m/z (M^+, 397.0).

4-{[2-(4-Methoxyphenyl)-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidin-4-yl]oxy}butyl acetate (13b)

The formed precipitate was crystallized from ethanol to give compound **13b** in 83% yield as brown crystals. Mp. 101–102°C, IR (KBr): 1739 cm^{-1} (C=O, acetoxy). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.64 (m, 2H, CH_2(b)), 1.90–1.96 (m, 6H, $2CH_2$, cyclohexane and CH_2(c)), 2.06 (s, 3H, CH_3CO), 2.82 (t, 2H,J = 5.6 Hz, CH_2, cyclohexane), 2.95 (t, 2H, J = 5.6 Hz, CH_2, cyclohexane), 3.88 (s, 3H, OCH_3), 4.18 (t, 2H, J = 6.3 Hz, OCH_2(d)), 4.65 (t, 2H, J = 6.3 Hz, CH_2OAC(a)), 6.97 (d, 2H, J = 8.7 Hz, Ar-H), 8.40 (d, 2H, J = 8.7 Hz, Ar-H). Anal. Calcd for $C_{23}H_{26}N_2O_4S$ (426.53): C, 64.77; H, 6.14; N, 6.57. Found: C, 64.77; H, 6.15; N, 6.58.

General procedure for deprotection (14a,b)

A mixture of compound **13a,b** (10 mmol) in methanol (20 mL), triethylamine (1 mL) and few drops of water was stirred 24 h at room temperature and then the solvent was removed under reduced pressure. The solid was crystallized from proper solvent.

4-[(2-Phenyl-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidin-4-yl)oxy]butan-1-ol (14a)

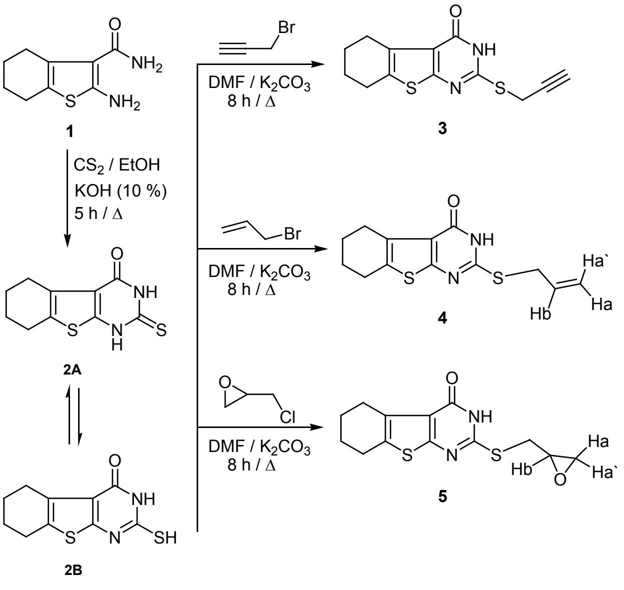
The formed precipitate was crystallized from ethanol to give compound **14a** in 86% yield as brown crystals. Mp. 181–182°C, IR (KBr): 3415 cm^{-1} (br, 1H, OH). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.26 (m, 2H, CH_2(b)), 1.58 (br, 1H, OH, exchange with D_2O), 1.79–2.01 (m, 6H, $2CH_2$, cyclohexane and CH_2(c)), 2.84 (t, 2H, J = 5.7 Hz, CH_2, cyclohexane), 2.97 (t, 2H, J = 5.7 Hz, CH_2, cyclohexane), 3.77 (t, 2H, J = 6.3 Hz, CH_2OH(a)), 4.67 (t, 2H, J = 6.3 Hz, OCH_2 (d)), 7.45–8.49 (m, 5H, Ar-H). MS (EI): m/z (M^{+1}, 355.0).

4-{[2-(4-Methoxyphenyl)-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]pyrimidin-4-yl]oxy}butan-1-ol (14b)

The formed precipitate was crystallized from ethanol to give compound **14a** in 80% yield as buff crystals. Mp. 130–132°C, IR (KBr): 3302 cm^{-1} (br, OH). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.26 (m, 2H, CH_2(b)), 1.57 (br, 1H, OH, exchange with D_2O), 1.76–2.01 (m, 6H, $2CH_2$, cyclohexane and CH_2(c)), 2.83 (t, 2H, CH_2, cyclohexane), 2.96 (t, 2H, CH_2, cyclohexane), 3.75 (t, 2H, J = 6.3 Hz, CH_2OH(a)), 3.88 (s, 3H, OCH_3), 4.65 (t, 2H, J = 6.3 Hz, OCH_2(d)), 6.97 (d, 2H, J = 8.7 Hz, Ar-H), 8.41 (d, 2H, J = 8.7 Hz, Ar-H). Anal. Calcd for $C_{21}H_{24}N_2O_3S$ (384.49): C, 65.60; H, 6.29; N, 7.29. Found: C, 65.61; H, 6.28; N, 7.28.

RESULTS AND DISCUSSION

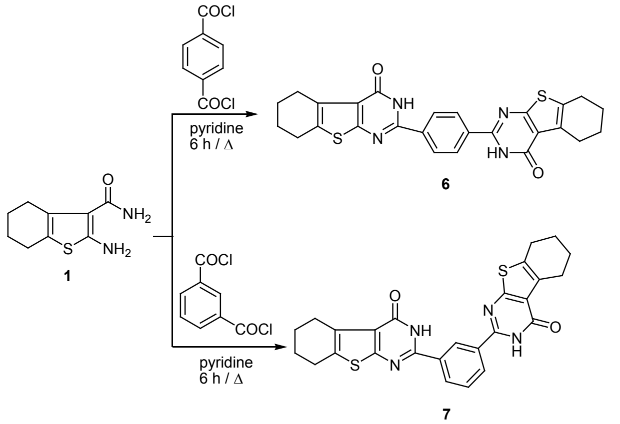
In this investigation, a series of novel tetrahydrobenzothienopyrimidine derivatives were designed and synthesized. The starting material (**2A**) was prepared from the reaction of 4,5,6,7-tetrahydrobenzothieno-3-carboxamide (**1**) [9] with carbon disulphide. The reaction afforded either **2A** or another possible isomer **2B** according to the citations [10]. The IR, ^1H, ^{13}C NMR spectra and m.p. of compound **2** are in agreement with the data mentioned in the previous literatures. Alkylation of compound **2** was achieved by refluxing in dry dimethylformamide in the presence of anhydrous potassium carbonate followed by addition of alkylating agents namely, propargyl, allyl bromide and epichlorohydrin to give the corresponding -alkylating derivatives **3**–**5**, respectively (Scheme 1).



Scheme 1

The alkylated derivatives **3**–**5** were established and confirmed on the basis of their analyses and spectral data. The IR spectra showed bands between 3430–3474 and 1653–1676 cm^{-1} with disappearance of (C=S) bands which confirm the presence of (NH) and (C=O) amides and -alkyl derivatives not - or -alkyl derivatives. ^1H NMR spectrum of **3** showed two singlets at δ 3.28, 4.82 ppm characterized for acetylenic and SCH_2 groups, in addition to signal at δ 12.12 ppm for NH group. While, ^1H NMR spectrum of compound **4** revealed the presence of signal at δ 3.85 ppm as a doublet with J = 7.8 Hz for SCH_2 group, in addition to different signals for olefenic protons (Ha, Ha` and Hb), respectively (see the experimental section). In the $^1H$ NMR spectrum of compound **5** there are signals at $\delta$ 3.25, 3.73 , 3.87, 4.25, and ppm characteristic for $SCH_2$ group, Hb, Ha` and Ha, respectively. Its ^{13}C NMR spectrum showed characteristic signals at δ 31.9, 45.2 and 49.2 ppm responsible for SCH_2, OCH_2 and CH of the oxirane carbon atoms.

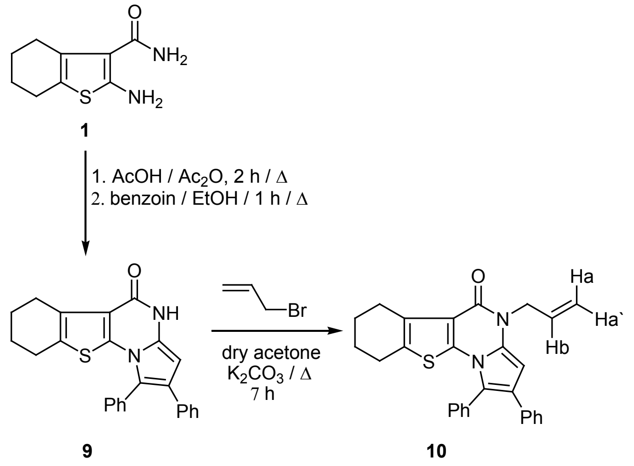
Reaction of the carboxamide **1** with terphthaloyl and isophthaloyl chloride under reflux in dry pyridine resulted in bisthienopyrimidine derivatives **6** and **7** (Scheme 2).



Scheme 2

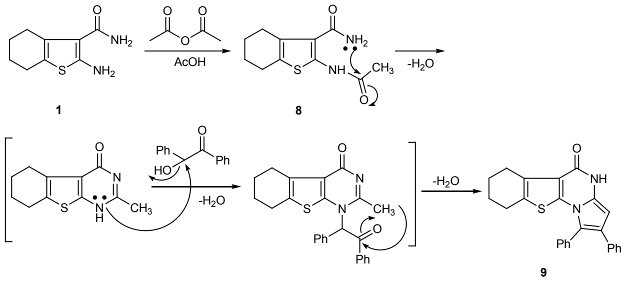
The IR and ^1H NMR spectra of **6** and **7** are in agreement with the structures **6** and **7** (see the experimental section).

Upon reaction of the carboxamid **1** with acetic anhydride in acetic acid the acetylated product **8** (Scheme 4) was synthesized. Reflux of compound **8** with benzoin in ethanol for 1 h afforded the benzothieno[3,2-*e*]pyrrolo[1,2-*a*] pyrimidinone **9** with 65% yield, which on heating under reflux in dry acetone with anhydrous potassium carbonate and allyl bromide resulted in the allyl derivative **10** with 59% yield (Scheme 3).



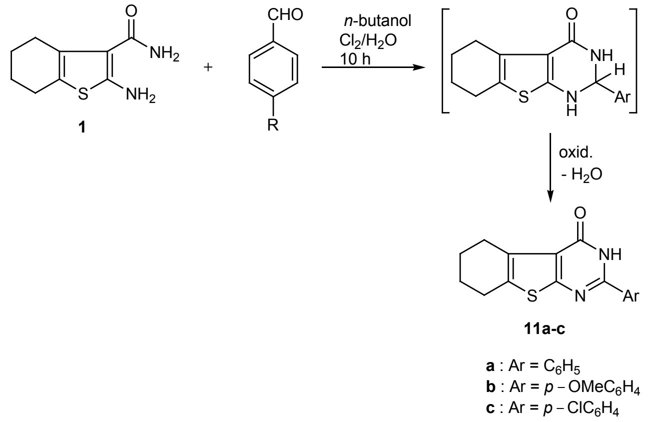
Scheme 3

Structures of compounds **9** and **10** were confirmed by their spectroscopic studies see the experimental section. The formation of compound **9** proceeds via the expected mechanism [11] which occurs through the following steps: firstly acetylation of NH_2 group followed by intramolecular cyclization to form pyrimidine derivative, secondly intermolecular nucleophilic attack via nitrogen atom of pyrimidine on the benzoin carbon with removal of water molecule, and finally elimination of water molecule through condensation to form the pyrrolo derivative **9** (Scheme 4).



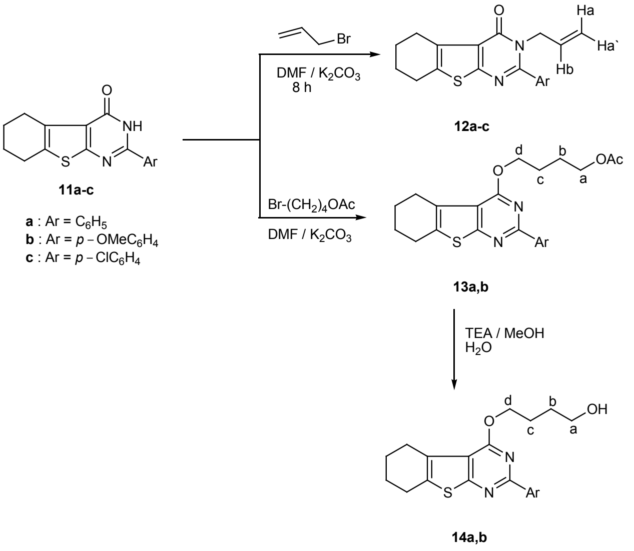
Scheme 4

Condensation of the carboxamide **1** with aromatic aldehydes such as benzaldehyde, 4-methoxybenzaldehyde and 4-chlorobenzaldehyde in the presence of -butanol and chlorine water afforded an intermediate that was oxidized to form benzothieno[2,3-*d*]pyrimidines **11a–c** with good yields 63–77%. The ^1H NMR exhibited that, presence of signal at δ 12.29–12.54 ppm corresponding to one NH group. This indicates that, formation of compound **11a-c** was accompanied by oxidative dehydrogenation for the hydrogen of CHAr group and that of the NH group of the intermediate as water molecule by hypochlorous acid. (Scheme 5).



Scheme 5

Alkylation of compounds **11a–c** with allyl bromide under reflux in dimethylformamide and dry potassium carbonate resulted in alkylation on the nitrogen not the oxygen atom forming -alkyl thienopyrimidine derivatives **12a–c** (Scheme 6). The chemical structures of -alkyl thienopyrimidines **12a–c** were established according to the spectral data. In the IR spectra of compounds **12a–c** there are absorptions bands between 1647–1653 cm^{-1} for (C=O) amide groups, this indicated that the -alkyl derivative was formed. Alkylation of pyrimidin-4(3)-one **11 a,b** with 4-bromobutyl acetate [12] in dimethylformamide and dry potassium carbonate afforded butylacetate derivatives **13a,b**. Deacetylation of **13a,b** in the presence of methanol with triethylamine and few drops of water [13] provided the deprotected benzothieno[2,3-*d*]-pyrimidin-4-yl)oxy]butan-1-ol (**14a,b**) with high yields 83–87%, respectively (Scheme 6).



Scheme 6

The IR spectrum of **14a,b** revealed the absence of carbonyl of acetoxy and amide groups, this assigned the alkylation at oxygen not nitrogen and presence of absorption band at 3402–3463 cm^{-1} for free (OH) groups. ^1H NMR spectrum of **14a** showed a characteristic signals at δ 1.26 (CH_2b), 1.58 (OH, exchange with D_2O), 3.77 (CH_2OH(a)) and 4.67 ppm for (CH_2OH(a)), respectively. The analytical spectra for **14b**

Table (1): *Antifungal and antibacterial activities of some synthesized compounds:*

Comp. No	Inhibation zones (cm)				
	fungi		Gram (+ve)		Gram (-ve)
	Aspergillus sp.	*Penicillium sp.*	*B. cereus*	*S. aureus*	*P. aeruginosa*
4	-	+	-	+++	+++
6	-	-	++++	++++	+++
9	-	+	++	-	+++
10	+	+++	+++	+++	+++
Griseofulvin	++	+++			
Ampicillin			++	+++++	++++

are in agreement with the its structure and were written in the experimental section.

PHARMACOLOGICAL STUDIES

1. Antifungal Activity

The antifungal activity of some synthetic compounds were evaluated against fungi as (,) as stock cultures in Mycology Lab., Faculty of Science, Zagazig University. After seeding of the cooled–solid medium by the microbial suspension (10 mL/250 medium) and pouring in sterile plates, the cultures were incubated overnight for pre-germination, then 500µl of each tested compound was pipetted to the wells of the plate cultures. Blanks of dissolving solvent were made. The cultures were incubated for 7 days at 30°C for fungal growth. The antifungal activity was expressed by the diameter of inhibitory zone [14] comparing to griseofulvin and ampicillin as standard antifungal. It clearly observed from the obtained data in Table 1, compound **10** was the potent agent against the growth of Penicillium sp. comparing with griseofulvin. Compounds **4**, **9** have a relative inhibitory effect towards the growth of tested fungi. However, compound **6** has no antifungal activity.

2. ANTIBACTERIAL ACTIVITY

The antibacterial activity of some selected compounds were evaluated against , (Gram +ve) and (Gram -ve). The cultures were incubated for 7 days at 30°C for fungal growth and for 2 days at 37°C for bacterial growth. The antibacterial activity was expressed by the diameter of inhibitory zone [14] comparing to ampicillin as standard antibacterial agent. The result of antibacterial activity in Table 1 indicated that, strain was sensitive to all synthetic compounds in concenteration (0.2 mL), While, and strains were sensitive to compounds **6** and **10** at concenteration (0.2 mL). Also, the results revealed that was more resistant to compound **9** than and strains.

CONCLUSION

In summary, we report on the alkylation of tetrahydrobenzothienopyrimidines with several alkylating agents aiming at preparation some new *S*-alkyl and *N*-alkyl thienopyrimidine derivatives with high yields. The synthesis of *S*-alkyl and *N*-alkyl products depends upon the reaction conditions and the nature of the alkylating agents. Some novel bisthienopyrimidines, pyrrolopyrimidineones and butylacetate derivatives were synthesized. The structures of the compounds prepared have been elucidated unambiguously by analytical and spectroscopic methods including ^{1}H, ^{13}C NMR spectroscopy, IR spectroscopy and elemental analysis. The antimicrobial activity of some selected compounds was studied.

BIBLIOGRAPHY

1. D.J. Brown, pyrimidine and their benzo derivatives, in Comperhensive Heterocyclic Chemistry (Ed. Katritsy, A. R.; Rees, C. W.), vol 3, pergamon Press, Oxford, p. 443, (1984).
2. B.V. Ashalatha, B. Narayana, K.K. Vijayaraj, S. Kumari, Eur. J. Med. Chem. 719, , (2007)
3. S.K. Jain, J. Bariwal, M. Kathiravan, M. Phoujdar, R. Shane, B. Chauhan, A. Shah, M. Yadav, Bioorg. Med. Chem. 4759, , (2008)
4. A.B.A. El-Gazzar, H.A.R. Hussein, H.N. Hafez, Acta Pharm. 395, , (2007)
5. C. Sharma, S. Yerande, R. Chavan, A.V E. Bhosale, E-Journal of Chem. 655, , (2010)
6. R.V. Chambhare, B.G. Khadse, A.S. Bobde and R.H. Bahekar, Eur. J. Med. Chem. 89, , (2003)
7. C.J. Shishoo, V.S. Shirsath, I.S. Rathod, V.D. Yande, Eur. J. Med. Chem. 351, , (2000)
8. A.H. Moustafa, M.G. Assy, A.E. Amr, R.M. Saber, Current Organic Chem. 1661, , (2011)
9. K. Gewald, Z. Chem. 305, , (1962)
10. L.M. Break, N.A.M.M. Shmiss, M.A N. Mosselhi, Phosphorus, Sulfur and Silicon 1615, , (2010)
11. A.F.A. Harb, H.H. Abbas, F.H. Mostafa, J. of the Iranian Chem. Soc. 115, , (2005)
12. H.B. Lazrek, M. Taourite, J.L. Barascut, J.L. Imbach, Bull. Soc. Chem. Belg. 391, 105, (1996)
13. A.H. Moustafa, H.A. Morsy, M.G. Assy and A.Z. Haikal, Nucleosides, Nucleotides & Nucleic Acids 835, 28, (2009)
14. A.L. Barry, procedures of testing antimicrobial agents in agar media. Baltimore, USA. 1, (1980)