Synthesis and Pharmacological Activities of Some Thieno Pyridazine Derivatives Using 5-Amino-4-Ethoxycarbonyl Phenanthro[9,10-*e*]Theino[2,3-*c*]Pyridazine as a Starting Material

Saleh A. Bahshwan[1], Atef M. Amer*[2] and Ahmed A. Fayed[3]

[1]Pharmacology Department, Faculty of Health Science, Taibah University, Madinah Munawarra, Saudi Arabia
[2]Chemistry Department, Faculty of Science, Zagazig University, Zagazig, Egypt, [3]National Research Center, Photochemistry Department, Cairo, Egypt
*amer_1eg@yahoo.com

Abstract: 5-amino-4-ethoxycarbonyl-phenanthro [9, 10-*e*]thieno[2,3-*c*]pyridazine 4 was prepared *via* reaction of pyridazine derivative 3 and ethyl chloroacetate. Reaction of 4 with chloroacetyl choride, potassium thiocyanate afforded pyrimidothienopyridazine derivative 6. reaction of 4 with active methylene reagents namely, ethyl acetoacetate, ethyl benzoyl acetate, ethyl phenyl acetate, ethyl cyanoacetate and/or diethyl malonate gave pyridinothienopyridazine derivatives 16a-e respectively. The pharmacological screening should that many of these compounds have good activities. The structure assignments of the new compounds are based on chemical and spectroscopic evidence. The detailed synthesis, spectroscopic data, and pharmacological properties are reported. [Journal of American Science. 2010;6(10):151-159]. (ISSN: 1545-1003).

Keywords: Pyridazines, thienopyridazine, pyrimidine, pyridine, pharmacological activity.

1. Introduction

The biological activities of condensed pyridazine and thienopyridazine derivatives as sedatives, antibacterials, and antimalarials are well documented [1,4] such derivatives have analgesic [5], antipyretic [6] and anti-inflammatory [7,8] activities. Also, in pharmacological studies thieno derivatives have been shown to posses a variety of pharmacological activities including antituberculous [9] and herpes virus inhibitory [10] and antianaphylactine activity [11]. Numerous thieno derivatives have been investigated in relation with their biological and pharmacological activities. Some of them proved antiviral [12], antihypertensive [13], and immunostimulating [14], activities. Also, pyridazine derivatives are currently being developed for the treatment of chromic inflammatory pain associated with csteo arthritis, rheumatoid arthritis and chronic lower back pain [15]. In view of all these facts and as a continuation of work on the synthesis of new condensed thieno[2,3-*c*]pyridazine, which might have shown good biological and pharmacological applications.

2. Experimental

All melting points were taken on electrothermal IA9000 series digital melting point apparatus. Elemental analytical data were obtained from the microahalytical unit, Cairo University, Cairo, Egypt; the results were in favorable agreements with the calculated values. The IR spectra (KBr) were recorded on a PYE UNICAM spectrophotometer. The ^{1}H and ^{13}C-NMR spectra were recorded at 270 MHz on a perkin-Elmer R12B spectrometer using TMS as an internal standard. The mass spectra were performed using VG 2AB-3F spectrometer (70 eV). All reactions were followed by TLC (silica gel,aluminum sheet 60 F_{254}, Merck).

5-Amino-4-ethoxycarbonyl-phenanthro[9,10-*e*]thieno[2,3-*c*]pyridazine 4.

A mixture of 3 (0.28g, 1 mmol), ethylchloroacetate (0.12g, 1 mmol) and few drops of piperidine in ethanol (30 ml) was refluxed for 4h. The solid product was collected and crystallized from ethanol to give 0.32 g 4 (86%), m.p 194°C; IR (film): υ = 3410 (NH_2), 1735 (C=O, ester) cm^{-1}; ^{1}H-NMR (DMSO-d_6); δ = 1.25 (t, 3H, CH_3), 4.31 (q, j = 7.3 H_2, 2H, CH_2), 6.15 (s, 2H. NH_2, D_2O exchangeable), 7.23-7.64 (m, 8H, Ar j = 4.3 H_2, HS) ppm; ^{13}C-NMR (DMSO-d_6); δ= 131.20, 154.51, 162.73, 165.83 (pyridazin-C), 110.95, 113.24, 117.54, 120.74, 121.15, 123.072, 126.53, 132.45, 134.63, 148.37, 148.63, 148.92 (Aromatic-C), 136.21, 147.64 (thiophene-C), 160.62 (C=O), 19.21 (CH_3), 60.91 (CH_2) ppm; MS (El, 70 eV); m/z = 373 (M^+, 16), 242 (100, base peak). Elemental analysis $C_{21}H_{15}N_3O_2S$

calcd: 67.54 C, 4.05 H, 11.25 N; found 67.43 C, 3.91 H, 11.40 N.

5-Chloroacetylamino-4-ethoxycarbonyl phenanthro[9,10-*e*]thieno[2,3-*c*]pyridazine 5

To a solution of compound 4 (0.37g, 1 mmol) in ethanol (20 ml) chloroacetyl chloride (0.11g, 1 mmol) was added, the reaction mixture was refluxed for 5h. The reaction mixture was poured into ice water and the precipitate was filtered off, dried and recrystallized from ethanol to give 0.31g 5 (71%); m.p 226°C; IR (film); ύ = 3341 (NH), 1723 (C=O ester), 1680 (C=O amide) cm^{-1} ^{1}H-NMR (DMSO-d_6); δ = 1.34 (t, j = 7.3 H_2, 3H, CH_3), 2.42 (s, 2H, CH_2), 4.16 (q, j = 7.3 H_2, 2H, CH_2), 6.41 (s, 1H, NH, D_2O exchangeable), 7.18-7.59 (m, 8H, Ar H) ppm; ^{13}C-NMR (DMSO-d_6); δ = 130.26, 157.46, 161.95, 165.48 (pyridazin-C), 111.60, 112.41, 113.56, 119.70, 128.50, 129.31, 134.32, 135.41, 142.61, 143.53, 146.35, 148.64 (aromatic –C), 134.81, 146.32 (thiophene-C), 169.51, (C=O), 172.53 (C=O), 76.13 (CH_2), 65.35 (CH_2), 21.41 (CH_3) ppm; MS (El, 70eV): m/z = 449 (M^+, 21), 297 (100, base peak. Elemental analysis $C_{23}H_{16}N_3O_3SCl$ calcd: 61.40 C, 3.58 H, 9.34 N; found 61.53 C, 3.80 H, 9.71 N.

6-Carbethoxymethylemercaptophenanthro[9,10-*e*]pyrimido[4',5':4,5]thieno[2,3-*c*]pyridazin-4-(5H)one 6

A suspension of 5 (0.45g, 1 mmol) and potassium thiocyanate (0.09g, 1 mmol) in *n*-butanol (20 ml) was heated to reflux for 6h. After cooling, the precipitate was separated, washed with water several times, dried and recrystallized from *n*-butanol to give 0.32g 6 (69%); m.p 294°C; IR (film) 3348 (NH), 1735 (C=O ester), 1665 (C=O amide) cm^{-1}, MS (El, 70 eV) m/z = 472 (M^+, 25), 260 (100, base peak). Elemental analysis $C_{24}H_{16}N_4O_3S_2$ calcd: 61.00 C, 3.41 H, 11.86 N; found 61.22 C, 3.50 H, 11.90 N.

6-Hydrazino-phenanthro[9,10-*e*]pyrimido[4',5':4,5]thieno[2,3-*c*]pyridazin-4-(5H)one. 7

To a soluble of compound 6 (0.44g, 1 mmol) in ethanol (20 ml) hydrazine hydrate (0.06g, 1 mmol) was added, the reaction mixture was refluxed for 4h. The solid product was collected and crystallized from ethanol to give 0.25g 7 (65%), m.p > 300°C; IR (film); ύ = 3325-3246 (2NH, NH_2), 1695 (C=O amide) cm^{-1}; ^{1}H-NMR (DMSO-d_6); δ = 5.98 (s, 1H, NH, D_2O exchangeable), 6.84-7.31 (m, 8H, Ar H), 9.63 (s, 1H, NH, D_2O exchangeable), 10.35 (s, 2H, NH_2, D_2O exchangeable) ppm; ^{13}C-NMR (DMSO-d_6); δ = 109.31, 110.53, 112.46, 113.57, 118.53, 120.36, 123.43, 124.75, 135.51, 137.46, 146.27, 147.93 (aromatic-C), 129.35, 141.90, 154.38, 160.74 (pyridazin-C), 132.59, 143.78 (thiophene-C), 146.21 (pyrimidine-C), 162.34 (C=O) ppm; MS (El, 70 eV): m/z = 384 (M^+, 14), 228 (100, base peak). Elemental analysis $C_{20}H_{12}N_6OS$ calcd: 62.49 C, 3.14 H, 21.86 N; found 62.43 C, 3.00 H, 21.90 N.

5-Amino-phenanthro[9,10-*e*]thieno[2,3-*c*]pyridazine-6-carbohydrazide. 8

A mixture of 4 (0.37g, 1 mmol), hydrazinehydrate (0.06g, 1 mmol) in ethanol (20 ml) was refluxed for 3h. The solid product was collected and crystallized from acetic acid to give 0.25g 8 (71%), m.p 279°C; IR (film); ύ = 3360-3275 (NH, $2NH_2$), 1683 (CO amide) cm^{-1}; ^{1}H-NMR (DMSO-d_6); δ = 4.35 (s, 2H, NH_2, D_2O exchangeable), 7.15-7.64 (m, 8H, Ar H), 10.14 (s, 2H, NH_2, D_2O exchangeable), 11.25 (s, 1H, NH, D_2O exchangeable) ppm, ^{13}C-NMR (DMSO-d_6); δ = 110.23, 112.41, 114.18, 118.34, 121.64, 124.34, 125.56, 137.61, 138.25, 147.72, 148.39, 148.78 (aromatic-C), 130.51, 140.36, 152.37, 159.46 (pyridazin-C), 131.95, 142.83 (thiophene-C), 163.12 (C=O) ppm; MS (El, 70 eV): m/z = 359 (M^+, 29), 204 (100, base peak). Elemental analysis $C_{19}H_{13}N_5OS$ calcd: 63.50 C, 3.64 H, 19.49 N; found 63.30 C, 3.80 H, 19.70 N.

5-Amino-6,7-dihydro-phenanthro[9,10-*e*]pyrimido[4',5':4,5]thieno[2,3-*c*]pyridazin-4(5H)one. 9

To solution of 8 (0.36g, 1 mmol) in ethanol (10 ml), formaldehyde (5 ml) was added, the reaction mixture was refluxed for 2h. The solid product was collected and crystallized from ethanol to give 0.28g 9 (75%), m.p > 300°C; IR (film): ύ = 3315-3180 (NH, NH_2), 1678 (C=O amide) cm^{-1}; ^{1}H-NMR (DMSO-d_6); δ = 7.16-7.58 (m, 10H, Ar H and 2H pyrimidine), 9.85 (s, 2H, NH_2, D_2O exchangeable), 10.42 (s, 1H, NH, D_2O exchangeable) ppm; ^{13}C-NMR (DMSO-d_6); δ = 108.92, 110.2, 114.52, 116.34, 119.25, 120.92, 122.30, 125.65, 127.32, 139.14, 146.26, 147.15 (aromatic-C), 132.14, 140.91, 154.73, 158.64 (pyridazin-C), 132.59, 143.28 (thiophene-C), 160.21 (pyrimidine-C), 163.51 (C=O) ppm; MS (El, 70 eV): m/z = 371 (M^+, 32), 260 (100, base peak). Elemental analysis $C_{20}H_{13}N_5OS$ calcd: 64.68 C, 3.53 H, 18.85 N; found 64.60 C, 3.41 H, 18.71 N.

N-(4-Ethoxycarbonyl-phenanthro [9, 10-*e*]thieno[2,3-*c*]pyridazin-5-yl)-*N*-benzoyl thiourea 10

A mixture of 4 (0.37g, 1 mmol), benzoyl isothiocyanate (0.16g, 1 mmol) in acetone (20 ml) was refluxed for 2h. The solid product was collected and crystallized from methanol to give 0.34g 10 (64%), m.p 243°C; IR (film); ύ = 3326-3254 (2NH), 1725 (C=O ester), 1674 (C=O amide), 1160 (C=S) cm^{-1}; ^{1}H-NMR (DMSO-d_6); δ = 1.35 (t, j = 7.5 H_2, 3H, CH_3), 3.83 (q, j = 7.5 H_2, 2H, CH_2), 6.23 (s, 1H,

NH, D_2O exchangeable, 7.63 (m, 13H, Ar H), 9.17 (s, 1H, NH, D_2O exchangeable) ppm; MS (El, 70eV): m/z = 536 (M^+, 22), 357 (100, base peak). Elemental analysis $C_{29}H_{20}N_4O_3S_2$ calcd: 64.90 C, 3.76 H, 10.45 N; found 64.80 C, 3.91 H, 10.50 N.

5,7-Dihydro-6-thioxo-phenanthro[9,10-*e*]pyrimido[4',5':4,5]thieno[2,3-*c*]pyridazine-4-one 11

A solution of 10 (0.53g, 1 mmol) in 2N methanolic sodium hydroxide (10 ml) was refluxed for 7h then filtered. The clear solution acidified with 10% HCl. The solid product was collected and crystallized from ethanol to give 0.23g 11 (59%), m.p >300°C; IR (film); ύ = 3280-3335 (2NH), 1687 (C=O, amide), 1190 (C=S) cm^{-1}; ^{1}H-NMR (DMSO-d_6); δ = 6.72 (s, 1H, NH, D_2Oexcangeble), 7.31 -7.64 (m, 8H, Ar H), 10.24 (s, 1H, NH, D_2O exchangeble) ppm; ^{13}C-NMR (DMSO-d_6); δ = 111.23, 113.45, 114.51, 116.32, 117.54, 119.61, 120.15, 124.16, 125.24, 134.63, 138.12, 141.32 (aromatic-C), 134.26, 143.51, 152.37, 156.82 (pyridazin-C), 147.13, 149.34 (thiophene-C), 160.21 (C=O), 163.54 (C=O) ppm; MS (El, 70 eV); m/z = 386 (M^+, 43), 210 (100, base peak). Elemental analysis $C_{20}H_{10}N_4OS_2$ calcd: 62.16 C, 2.61 H, 14.50 N; found 62.43 C, 2.80 H, 14.61 N.

N-(4-Ethoxycarbonyl-phenanthro[9,10-*e*]thieno[2,3-*c*]pyridazin-5-yl)-*N'*-phenyl thiourea 12

A mixture of 4 (0.37g, 1 mmol), phenylisocyanate (0.13g, 1 mmol) in pyridine (20 ml) was refluxed for 4h. The reaction mixture was poured into HCl. The solid product was collected and crystallized from ethanol to give 0.34g 12 (66%), m.p 285°C; IR (film); ύ = 3315-3260 (2NH), 1730 (C=O, ester), 121 (C=S) cm^{-1}; ^{1}H-NMR (DMSO-d_6); δ = 1.41 (t, j = 7.5 H_2, 3H, CH_3), 4.23 (q, j = 7.5 H_2, 2H, CH_2), 7.13-7.46 (m, 13H, Ar H), 9.16 (s, 1H, NH, D_2O exchangeable), 10.32 (s, 1H, NH, D_2O exchangeable) ppm; MS (El, 70 eV); m/z = 508 (M^+, 26), 260 (100, base peak). Elemental analysis $C_{28}H_{20}N_4O_2S_2$ calcd: 66.12 C, 3.96 H, 6.29N; found 66.43 C, 4.00 H, 6.85 N.

5-phenyl-6-thioxo-phenanthro[9,10-*e*]pyrimido[4',5':4,5]thieno[2,3-*c*]pyridazin-4-(7*H*) one 13

A solution of 12 (0.51g, 1 mmol) in ethanolic potassium hydroxide 2N (10 mL) was refluxed for 5h Then filtered. The clear solution acidified with 10% HCl. The solid product was collected and crystallized from ethanol to give 0.32g 13 (69%), m.p > 300°C; IR (film); ύ = 3342 (NH), 1680 (C=O, amide), 1160 (C=S) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ = 6.95 – 7.43 (m, 13H, Ar H), 11.24 (s, NH, D_2O exchangeable) ppm; MS (El, 70 eV); m/z = 462 (M^+, 35), 284 (100, base peak). Elemental analysis $C_{26}H_{14}N_4OS_2$ calcd: 66.23 C, 2.99 H, 11.88 N; found 66.43 C, 3.00 H, 11.90 N.

Reaction of thieno[2,3-*c*]pyridazine-4 with active methylene to synthesis compound 14a-e.

A mixture of 4 (0.37g, 1 mmol), active methylene reagents, namely, ethyl acetoacetate, ethyl benzoyl acetate, ethyl phenyl acetate, ethyl cyanoacetate and diethyl malonate respectively, in ploy phosphoric acid (30 ml) were refluxed for 3h. After cooling, water added, neutralized with sodium carbonate. The solid products were collected and crystallized from methanol to give 0.31g 14a (67%), 0.32g 14b (62%), 0.33g 14c (68%), 0.27g 14d (61%) and 0.28g 14e (59%).

Ethyl-5-acetoacetylamino-phenanthro[9,10-*e*]thieno[2,3-*c*]pyridazine-4-carboxylate 14a

m.p 215°C (MeOH), IR (film); ύ = 3310 (NH), 1676 (C=O, amide), 1705 (C=O ketone), 1732 (C=O, ester) cm^{-1}, ^{1}H-MNR (DMSO-d_6); δ = 1.31 (t, j = 7.5 H_2, 3H, CH_3), 2.14 (s, 3H, CH_3), 3.36 (s, 2H, CH_2), 4.12 (q, j = H_2 2H, CH_2), 6.93 – 7.52 (m, 8H, Ar H), 10.35 (s, 1H, NH, D_2O exchangeable) ppm; MS (El, 70 eV): m/z = 457 (M^+, 42), 260 (100, base peak). Elemental analysis $C_{25}H_{19}N_3O_4S$ calcd: 65.63 C, 4.19 H, 9.18 N; found 65.43 C, 4.20 H, 18.21 N.

Ethyl-5-benzoylacetylamino-phenanthro[9,10-*e*]thieno[2,3-*c*]pyridazine-4-carboxylate 14b

m.p 253°C (MeOH), IR (film); ύ = 3285 (NH), 1682 (C=O, amide), 1715 (C=O ketone), 1730 (C=O, ester) cm^{-1}, MS (El, 70 eV): m/z = 519 (M^+, 42), 291 (100, base peak). Elemental analysis $C_{30}H_{21}N_3O_4S$ calcd: 69.35 C, 4.07 H, 8.09 N; found 69.43 C, 4.10 H, 8.20 N.

Ethyl-5-phenylacetylamino-phenanthro[9,10-*e*]thieno[2,3-*c*]pyridazine-4-carboxylate 14c

m.p 271°C (MeOH), IR (film); ύ = 3314 (NH), 1695 (C=O, amide), 1712 (C=O, ester) cm^{-1}, ^{1}H-MNR (DMSO-d_6); δ = 1.42 (t, j = 7.5 H_2, 3H, CH_3), 2.35 (q, j = 7.5 H_2, 2H, CH_2), 3.82 (q, j = 7.5 H_2, 2H, CH_2), 7.24 – 7.69 (m, 13H, Ar H), 11.13 (s, 1H, NH, D_2O exchangeable) ppm; MS (El, 70 eV): m/z = 491 (M^+, 37), 272 (100, base peak). Elemental analysis $C_{29}H_{21}N_3O_3S$) calcd: 70.68 C, 4.30 H, 8.55 N; found 70.70 C, 4.50 H, 8.62 N.

Ethyl-5-cyanoacetylamino-phenanthro[9,10-*e*]thieno[2,3-*c*]pyridazine-4-carboxylate 14d

m.p 286°C (MeOH), IR (film); ύ = 3311 (NH), 1683 (C=O, amide), 1730 (C=O, ester), 2218 (C≡N) cm^{-1}, MS (El, 70 eV): m/z = 441 (M^+, 42), 275 (100, base peak). Elemental analysis $C_{24}H_{16}N_4O_3S$ calcd: 65.44 C, 3.66 H, 12.72 N; found 65.43 C, 3.70 H, 12.50 N.

Ethyl-5-ethoxycarbonylacetaylamino-phenanthro[9,10-*e*]thieno[2,3-*c*]pyridazine-4-carboxylate 14e

m.p 257°C (ACOH), IR (film); ύ = 3324 (NH), 1681 (C=O, amide), 1725(C=O, ester), cm^{-1}, MS (El, 70 eV): m/z = 487 (M^+, 23), 260 (100, base peak). Elemental analysis $C_{26}H_{21}N_3O_5S$ calcd: 64.00 C, 4.38 H, 9.61 N; found 64.12 C, 4.25 H, 8.73 N.

Synthesis of pyrido-thieno pyridazine derivatives 15a-e

Compounds 14a-e (1 mmol) were boiled under reflux for 2h, with a solution of sodium ethoxide (20 ml), the mixture was evaporated to dryness under reduced pressure, water was added to the residue, the solution was washed with ethanol. The solution was cooled in ice and acidified with conc. HCl. The solid products were collected and crystallized from proper solvents to give 0.28 g 15a (70%), 0.33 g 15b (69%), 0.29 g 15c (65%), 0.25 g 15d (63%), 0.30 g 15e (68%) respectively.

5-Acetyl-4-hydroxy-phenanthro[9,10-e]pyrido[2',3':4.5]thieno[2.3-c]pyridazin-6(5H)-one 15a

Mp>300° C (EtOH);IR (film): ύ = 3410 – 3326 (OH, NH), 1678 (C=O, amide) 1715 (C=O, ketone) cm^{-1}, ^{1}H-NMR(DMSO-d_6): δ = 1.57 (S, 3H, CH), 7.25-7.46(m, 8H, Ar H), 9.56(S, 1H, NH, D_2O exchangeable), 13.21 (S, 1H, OH, D_2O exchangeable) ppm; ^{13}C.NMR (DMSOd_6): δ = 112.06, 112.15, 113.62, 118.17, 119.35, 127.13, 128.46, 129.13, 134.36, 143.54, 145.36, 147.39 (aromatic – C), 134.91, 142.27, 145.37, 149.07 (pyridazin – C), 154.13, 160.25 (thiophene – C), 151.37, 151.54 (pyridine – C), 160.29 (C=O)ppm; MS (EL, 70 eV): m/z = 411, (100, base peake). Elemental analysis $C_{23}H_{13}N_3O_3S$ calcd: 67.14 C, 3.18 H, 10.21 N; found 67.43 C, 3.20 H, 10.30 N.

5-Benzoyl-4-hydroxy-phenanthro[9,10-e]pyrido[2',3':4,5]thieno[2,3-c]pyridazine-6-(5H)-one 15b

m.p 291°C (EtOH); IR film):ύ =3390-3275(OH,NH), 1678(C=O,amide), 1718 (C=O, ketone) cm^{-1},^{1}H-NMR (DMSO-d_6): δ=6.93-7.45 (m, 13H, Ar H), 10.21 (s, 1H, NH, D_2O exchangeable), 13.52 (s, 1H, OH, D_2O exchangeable) ppm; ^{13}C-NMR (DMSO-d_6): δ=109.12, 110.34, 112.51, 113.36, 114.91, 115.84, 117.21, 118.35, 119.45, 120.37, 122.48, 123.54, 127.32, 136.24, 138.36, 140.28, 142.47, 149.35 (aromatic–C), 133.10, 141.52, 146.36, 148.25 (pyridazin – C), 152.31, 154.82 (thiophene – C), 149.13, 153.64 (pyridine – C), 168.13 (C=O), 171.32 (C=O) ppm; MS (El, 70 eV): m/z = 473 (M^+, 18), 284 (100, base peak). Elemental analysis $C_{28}H_{15}N_3O_3S$ calcd: 71.03 C, 3.19 H, 8.87 N; found 71.23 C, 3.20 H, 8.90 N.

4-Hydroxy-5-phenyl-phenanthro[9,10-e]pyrido[2',3':4.5]thieno[2,3-c]pyridazin-6(5H)-one 15c

m.p>300°C (MeOH); IR (film):ύ = 3405 – 3328 (OH, NH), 1684 (C=O, amide)cm^{-1}, ^{1}H-NMR (DMSO-d_6): δ = 6.54 (5, 1H, NH, D_2O exchangeable), 6.97 – 7.35 (m, 13 H, ArH's), 13.42 (s, 1H, OH, D_2O exchangeable) ppm; MS (El, 70 eV): m/z = 445 (M^+, 19), 284 (100, base peak). Elemental analysis $C_{27}H_{15}N_3O_2S$ calcd: 72.79 C, 3.39 H, 9.43 N; found 72.80 C, 3.40 H, 9.50 N.

5-cyano-4-hydroxy-phenanthro[9,10-*e*]pyrido[2',3':4,5]thieno[2,3-*c*]pyridazine-6(5*H*)-one 15d

m.p 298°C (pet. Ether); IR (film): ύ = 3387 – 3295 (OH, NH), 1687 (C=O amide), 2225 (C≡N) cm^{-1}, ^{1}H-NMR (DMSO-d_6): δ = 6.51 (s, 1H, NH, D_2O exchangeable), 7.15 – 7.49 (m, 8H, Ar H), 13.57 (s, 1H, OH, D_2O exchangeable) ppm; ^{13}C-NMR (DMSO-d_6): δ = 112.34, 113.54, 114.16, 115.82, 116.17, 119.32, 121.45, 122.37, 127.15, 129.32, 131.43, 134.81 (aromatic-C), 134.21, 135.45, 148.32, 149.17 (pyridazine-C), 149.05, 151.37 (thiophene-C), 158.12,160.30 (pyridine-C), 165.32 (C≡N), 168.41 (C=O) ppm; MS (El,70 eV): m/z = 394 (M^+, 29), 260 (100, base peak). Elemental analysis $C_{22}H_{10}N_4O_2S$ calcd: 67.00 C, 2.55 H, 14.20 N; found 67.20 C, 2.70 H, 14.31 N.

5-Ethoxycarbonyl-4-hydroxy-phenanthro[9,10-*e*]pyrido[2',3':4,5]thieno[2,3-*c*]pyridazine-6(5*H*)-one 15e

m.p 300°C (benzene); IR (film): ύ = 3420 – 3285 (OH, NH), 1675 (C=O amide), 1725 (C=O ester) cm^{-1}, ^{1}H-NMR (DMSO-d_6): δ = 1.19 (t, j = 7.5 H_2, 3H, CH_3), 3.57 (q, j = 7.5 H_2, 2H, CH_2), 7.23 – 7.59 (m, 8H, Ar H), 9.72 (s, 1H, NH, D_2O exchangeable), 13.65 (s, 1H, OH, D_2O exchangeable) ppm; MS (El,70 eV): m/z = 441 (M^+, 12), 244 (100, base peak). Elemental analysis $C_{24}H_{15}N_3O_4S$ calcd: 65.30 C, 3.42 H, 9.52 N; found 65.43 C, 3.50 H, 9.50 N.

5-Amino-phenanthro[9,10-*e*]thieno[2,3-*c*]pyridazine-4-carboxylic acid 16

A suspension of 4 (0.37g, 1 mmol), in ethanolic sodium hysroxide solution 10% (50 ml) was heated under reflux for 4h. The alkaline solution

was acidified with diluted acetic acid and extracted with ether. The solid product was collected and crystallized from ethanol to give 0.24g 16 (69%), m.p 213°C; IR (film): ύ = 3392 – 3247 (OH,NH_2), 1730 (C=O, acid) cm^{-1}, ^{1}H-NMR (DMNSO-d_6): δ = 7.14 – 7.63 (m, 8H, Ar H), 10.24 (s, 2H, NH_2, D_2O exchangeable), 13.15 (s, 1H, OH, D_2O exchangeable) ppm; ^{13}C-NMR (DMSO-d_6): δ = 108.12, 110.30, 111.92, 112.53, 114.71, 118.65, 119.22, 120.08, 122.43, 129.50, 137.16, 142.31 (aromatic-C), 131.24, 135.63, 147.25, 151.17 (pyridazine-C), 135.13, 143.34 (thiophene-C), 162.09 (C=O) ppm; MS (El, 70 eV): m/z = 345 (M^+, 16), 300 (100, base peak). Elemental analysis $C_{19}H_{11}N_3O_2S$ calcd: 66.08 C, 3.21 H, 12.17 N; found 66.20 C, 3.30 H, 12.33 N.

Phenanthro[9,10-*e*]thieno[2,3-*c*]pyridazine-5(4*H*)one 17

A solution of 16 (0.34g, 1 mmol) in orthophosphoric acid 85% (30 ml) was heated on a water bath for 8h. The reaction mixture was pourd into ice-water. The solid product was collected and crystallized from toluene to give 0.20g 17 (65%), m.p 241°C; IR (film): ύ = 1721 (C=O, ketone) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ = 3.85 (s, 2H, CH_2), 7.13 – 7.52 (m, 8H, Ar H) ppm; ^{13}C-NMR (DMSO-d_6): δ = 109.23, 110.63, 112.29, 112.84, 114.19, 117.42, 118.90, 121.13, 122.35, 128.41, 136.61, 145.12 (aromatic-C), 132.35, 136.31, 146.51,154.26 (pyriazine-C) 148.32 (thiophene-C), 167.24 (C=O) ppm; MS (El,70 eV): m/z = 302 (M^+,29), 206 (100, base peak). Elemental analysis $C_{18}H_{10}N_2OS$ calcd: 71.51 C, 3.33 H, 9.26 N; found 71.43 C, 3.40 H, 9.32 N.

6-Amino-4-phenyl-phenanthro[9,10-*e*]oxino[3,2-*b*]thieno[2,3-*c*]pyridazine-5-carbonitrile 18

A mixture 17 (0.30g, 1 mmol), benzylidine malonitrile (0.15g, 1 mmol) in ethanol (30 ml) and few drops of piperdine was refluxed for 3h. The solid product was collected and crystallized from methanol to give 0.27g 18 (61%); m.p > 300°C,IR (film): ύ = 3245 (NH_2), 2223 (C≡N) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ = 6.92 – 7.64 (m, 14H, 13Ar H and 1H oxine), 11.32 (s, 2H, NH_2, D_2O exchangeble) ppm; MS (El, 70 eV): m/z = 455 (M^+, 31), 260 (100, base peak). Elemental analysis $C_{28}H_{15}N_4OS$ calcd: 73.83 C, 3.32 H, 12.30 N; found 73.90 C, 3.32 H, 12.11 N.

6-Methyl-phenanthro[9,10-*e*]pyridazino[4',3':4,5]thieno[3,2-*d*]-1,3-oxazin-4-one 19

A mixture of 16 (0.34g, 1 mmol) and acetic anhydride (10 ml) was refluxed for 3h. The mixture was pourd into water. The solid product was collected and crystallized from ethanol to give 0.26g 19 (72%), m.p > 300°C, IR (film): ύ = 1710 (C=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ = 1.41 (s, 3H, CH_3), 7.24 – 7.86 (m, 8H, Ar H) ppm; ^{13}C-NMR, 119.15, 120.17, 122.34, 127.64, 135.25, 143.28 (aromatic-C), 133.61, 137.53, 147.37, 151.18 (pyridazine-C), 136.37, 145.27 (thiophene-C), 149.24 (oxazine-C), 165.10 (C=O), 23.65 (CH_3) ppm; MS (El, 70 eV): m/z = 369 (M^+, 19), 228 (100, base peak). Elemental analysis $C_{21}H_{11}N_3O_2S$ calcd: 68.28 C, 3.00 H, 11.37 N; found 68.33 C, 3.23 H, 11.35 N.

Anti-inflammatory Activity [16, 17]

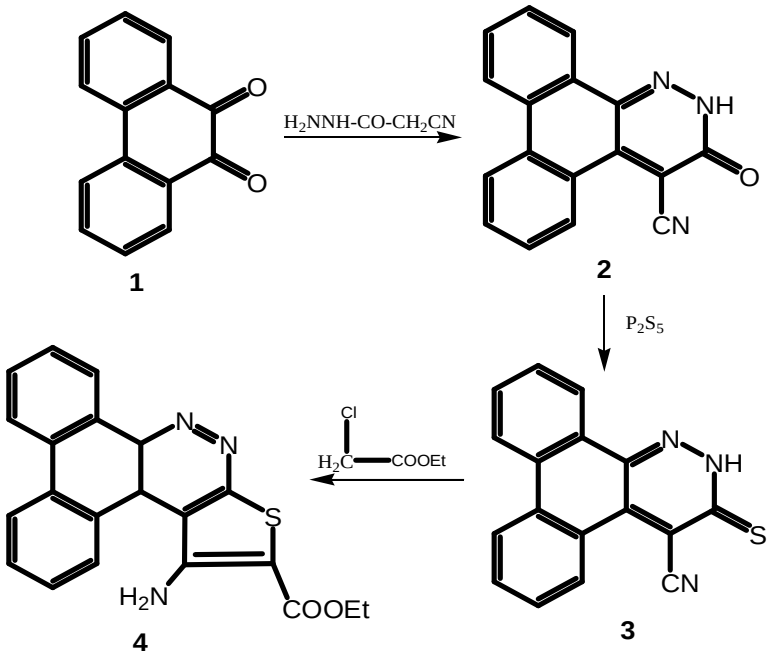
Ten compounds 4, 7, 9, 11, 13, 15a, 15d, 15e, 16 and 18 were evaluated for their anti-inflammatory activity. Mature albino rats (95) of both sexes weighing 50-200g divided into nineteen equal groups was used. Oedema in the rate paw induced by injection of 0.1 cm^3 of 20% Brewer's yeast suspended in physiological saline solution in the paw skin of the hind limb. After 4h, the thickness of the paw was measured using a skin caliber to detect the inflammation induced by the yeast. The first group was left as control while the second group was injected intrapretenoal (I.P) with dimethyl sulfoxide (DMSO) and the third group was injected (I.P) with flurbiprofen (20 mg/kg). the remaining groups were treated with the tested compounds dissolved in DMSO in a dose of 100 mg/kg. The paw thickness was measured after Scand 6h post injection (Table 1).

Analgesic Activity

Sixty mice of both sexes weighting from 20 to 25g were divided into 10 groups. One group was kept as control (received saline), the second group received vehicle (gum acacia), and the third one received voltarene® as a reference drug where the other groups received 4, 7, 9, 11, 13, 15a, 15d, 15e, 16 and 18 (scadministration). Plasma of mice was dropped gently in a dry glass beaker of 1 cm^3 capacity maintained at 55-55.5°C. normal reaction time in second for all animals were determined at time intervals of 10, 30 and 60 min. this is the interval extending from the instant the mouse reaches the hot beaker till the animal licks its feet or jamb out of the beaker (does 5 mg/kg) [18]. Relative potencies to voltarene® were determined (table 2).

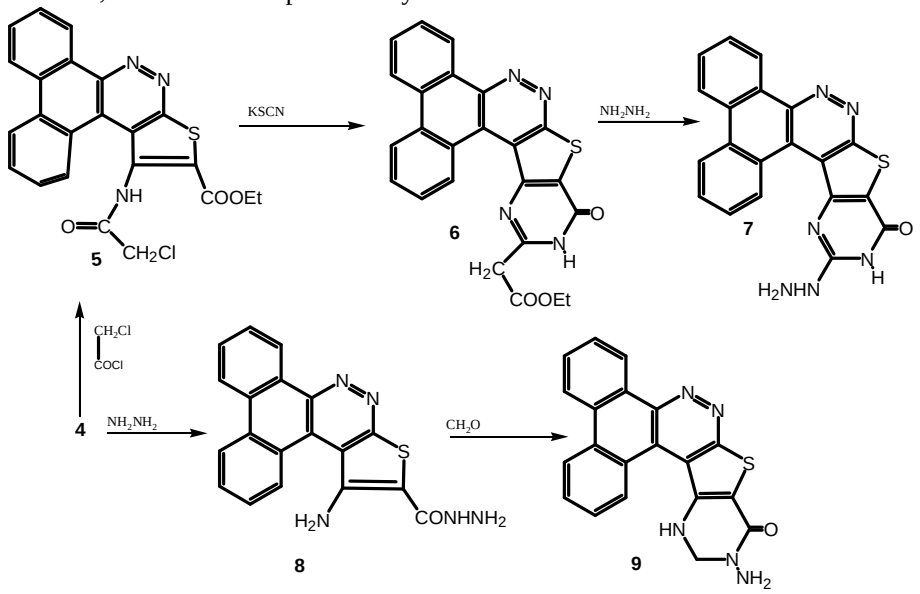
3. Results and Discussion

The starting material 5-amino-4-ethoxycarbonyl phenanthro[9,10-*e*]thieno[2,3-*c*]pyridazine 4 was prepared by the reaction of phenanthroquinone 1 with acyl cyanohydrazine 2, which reacted with P_2S_5 to give 3 [16]. Cyclization of 3 using ethyl chloroacetate in presence of ethanol gave the starting material 4 (scheme 1).



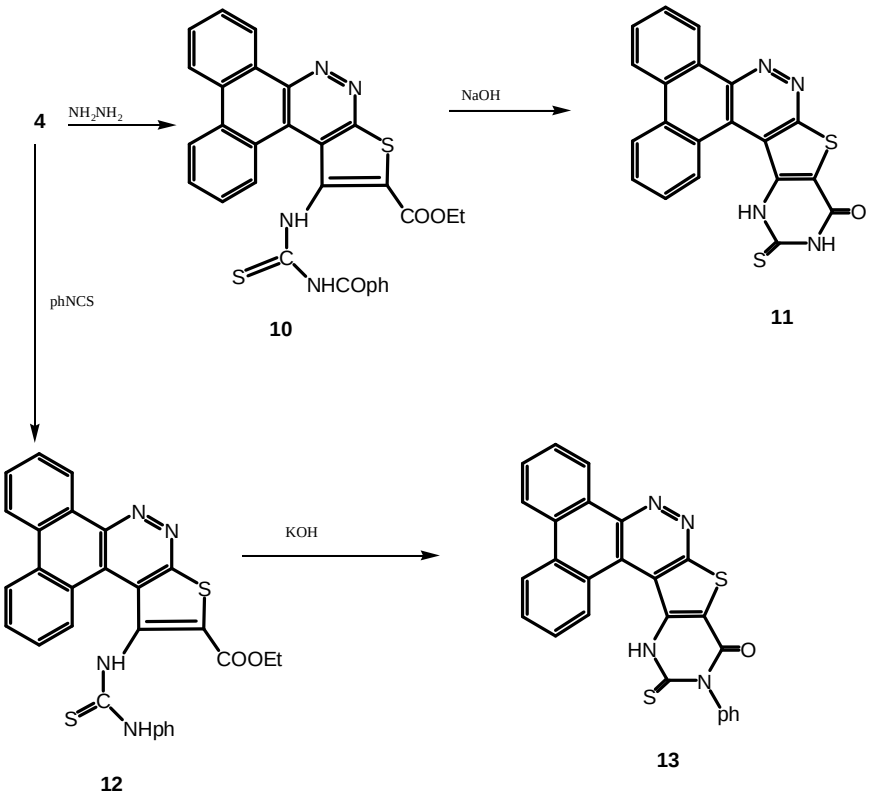
Scheme 1

Amino ester **4** reacted with chloroacetyl chloride to give **5**. Treatment of **5** with potassium thiocyanate afforded pyrimidothienopyridazine derivative **6**, which reacted with hydrazine to give hydrazine derivative **7**, the reaction procced by elimination of thioaceto acid. Also compound **4** reacted with hydrazine to give **6**. Then compound 8 reacted with formaldehyde in refluxing methanol to afford pyrimidothienopyridazine **9** (scheme 2).



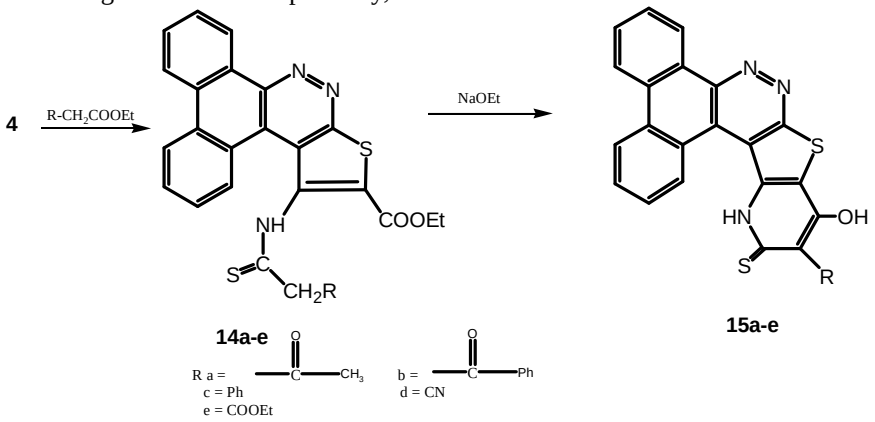
Scheme 2

Reaction of aminoester **4** with benzoyl isothiocyanate in boiling acetone led to formation of benzoyl thiourea derivative **10** which cyclized by alkaline to give pyrimido derivative **11**. Also, compound **4** reacted with phenyl isothiocyanate in refluxing pyridine to give thiourea derivative **12**. Treatment of **12** with ethanolic potassium hydroxide afforded the cyclized product **13** (scheme 3).



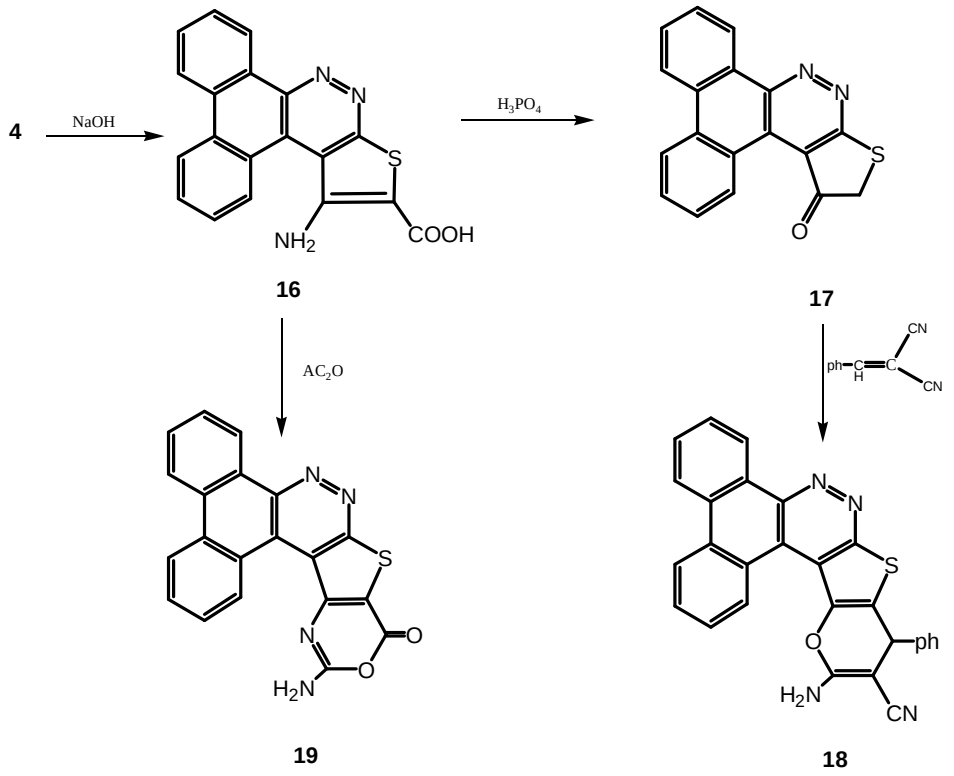
Scheme 3

Reaction of compound **4** with active methylene reagents, namely, ethyl acetoacetate,ethyl benzoyl acetate, ethyl phenyl acetate, ethyl cyanoacetate and/or diethyl malonate gave **14 a-e** respectively, which cyclized by sodium ethoxide to give pyridinothienopyridazine derivatives **15a-e** respectively (scheme 4).



Scheme 4

Hydrolysis of amino ester 4 afforded amino acid 16 which upon treatment with orthophosphoric acid at 100°C, efforded thienopyridazine-5one 17. The condensation of 17 with benzylidine malononitrile in refluxing ethanol afforded 18. Also, reaction of amino acid 16 with acetic anhydride under reflux gave oxazine derivative 19 (scheme 5).



Scheme 5

Pharmacological Screening

Two pharmacological activities namely, anti-inflammatory and analgesic were tested despite their different biological receptors. Yet both are of neurological origin. Ten representative compounds 4, 7, 9, 11, 13, 15a, 15d, 15e, 16 and 18 were studied with respect to their anti-inflammatory and analgesic activities.

Anti-inflammatory activity

From table 1 it appeared that the compounds 4, 7, 9, 11, 13, 15a, 15d, 15e, 16 and 18 have significant anti-inflammatory activities. Among the compounds 4, 9 and 16 have anti-inflammatory activities higher than that of 7, 11, 13, 15d and 15e. The compounds 15a and 18 were found to have lower anti-inflammatory activities. The most active compounds 4, 16 and the standard drug flurbiprofen were found to exhibit essentially equipotent anti-inflammatory activity.

Analgesic activity

All tested compounds exhibited analgesic activities (table 2) the most potent one is 9 that should the same activity as voltarene® after 30 min. Also, the analgesic activities of 4, 13, 15e and 16 approached those of voltarine®, and the other compounds are weak activity.

Table 1. Anti-inflammatory activity of some synthesized (% reduction in edema induced by yeast)

Compound	Post treatment 3h%	Post treatment 6h%
Flurbiprofen	100	100
4	25.4	33.5
7	18.3	21.4
9	22.6	28.3
11	16.1	25.6
13	17.4	31.5
15a	6.5	23.1
15d	14.3	34.5
15e	18.7	27.7
16	24.8	35.3
18	8.6	17.4

Table 2. Analgesic activity of several compounds as compound with Voltarene® in mice

Compound No.	Analgesic activity after		
	10 min	30 min	60 min
Voltarene®	1	1	1
4	0.85	0.87	0.91
7	0.54	0.57	0.62
9	0.95	1.03	1.05
11	0.63	0.65	0.69
13	0.81	0.83	0.87
15a	0.34	0.42	0.49
15d	0.68	0.71	0.75
15e	0.79	0.80	0.82
16	0.84	0.87	0.89
18	0.41	0.45	0.47

Corresponding author
Atef M. Amer
[2]Chemistry Department, Faculty of Science, Zagazig University, Zagazig, Egypt.
E-mail: amer_1eg@yahoo.com

Acknowledgement:
Part from this work was supported by Research Garnt from the Zagazig University.

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5/7/2010