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SYNTHESIS AND ANTIINFLAMMATORY ACTIVITY OF SOME NOVEL THIENOPYRIMIDINE DERIVATIVES

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ABSTRACT

4-Chloro-5,6,7,8-tetrahydrobenzothieno[2,3-d]pyrimidine (**3**) was reacted with 4-aminoacetophenone in ethanol to give 4(4-acetylanilino)5,6,7,8-tetrahydrobenzothieno[2,3-d]pyrimidine (**4**). Compound **4** was used as a key intermediate for the synthesis of several pyrazoles **6-8**, pyridones **13, 14**, thiazoles **15, 17** and thiazolidinones **18, 19**. On the other hand, compound **3** was fused with ethyl 2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate and anthranilic acid to give compound **9** and **10** respectively. Compound **14b** showed the same antiinflammatory activity as that of the reference drug dichlofenac sodium.

INTRODUCTION

Recent investigations have demonstrated biological activity in derivatives of thienopyrimidines such as cardiovascular[1], analgesic and antiinflammatory[2], anxiolytic and antidepressant[3], antihistaminic[4], anticancer[5], antihypertension[6], cercaricidal and miracidicidal activities[7]. Of more particular interest, a variety of pyrazole derivatives showed antiinflammatory[8] and antibacterial activities[9]. Additionally certain substituted pyridones have antiinflammatory[10] and anticonvulsant activities[11]. In an effort to capitalize on the biological potential of these heterocyclic systems as well as exploit the availability of the versatile key intermediate 4-(4-acetylanilino)-5,6,7,8-tetrahydrobenzothieno[2,3-d]pyrimidine (**4**) to provide interesting compounds for testing their antiinflammatory activity, we undertook the synthesis of the compounds herein described.

EXPERIMENTAL

Melting points were determined with a Gallen kamp digital melting point apparatus and are uncorrected. IR spectra (KBr, cm^{-1}) were recorded on Shimadzu FTIR 8000 spectrometers. ^1H NMR spectra were recorded on Varian Gemini 200, 200 MHz spectrometer in DMSO-d_6 or $CDCl_3$ as a solvent and TMS as internal standard (Chemical shift in δ, ppm). Mass spectra were determined on Hewlett Packard 5988 spectrometer. Element analysis were performed at the Microanalytical Center, Faculty of Science, Cairo University, Giza, Egypt. TLC was performed on silica gel G for TLC (Merck) and spot were visualized by iodine vapour or by irradiation with UV light (254 nm).

The sequence of the reactions followed in the synthesis of the target compound is illustrated in schemes (1) and scheme (2).

Ethyl 2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (**1**), 3,4,5,6,7,8-hexahydrobenzothieno-[2,3-d]pyrimidin-4-one (**2**) and 4-chloro-5,6,7,8-tetrahydrobenzothieno[2,3-d]pyrimidine (**3**) were prepared according to reported procedure[12-15].

4-(4-Acetylanilino)-5,6,7,8-tetrahydrobenzothieno-[2,3-d]pyridine (4):

A mixture of **3** (0.01 mole) and 4-aminoacetophenone (0.01 mole) in (30 ml) n-butanol was refluxed for 5 h., until a yellowish crystalline solid separated out. The solid was filtered, dried and crystallized from ethanol in 82% yield, m.p. 182 – 183°C.

Analysis for $C_{18}H_{17}N_3OS$ (323): Calcd.: C, 66.87; H, 5.26; N, 13.00. Found: C, 67.00; H, 4.90; N, 13.20.

MS: m/z = 323 (M^+, 93%)

IR: 3441 (NH), 3046 (CH, aromatic), 2935-2838 (CH, aliphatic), 1671 (C=O) and 1600 (C=N) cm^{-1}.

^1H NMR ($CDCl_3$, δppm) δ: 1.8 – 1.9 (m, 4H, CH_2 at C-6,7), 2.5 (s, 3H, CH_3), 2.9-3.1 (m, 4H at C-5,8), 7.2-8 (m, 4H, ArH), 8.5 (s, 1H, CH of pyrimidine).

4-[4-(2-Arylvinylcarbonyl)anilino]-5,6,7,8-tetrahydrobenzothieno[2,3-d]pyrimidine (5a-d):

A mixture of compound **4** (0.01 mole) and anhydrous K_2CO_3 (0.01 mole) in (20 ml) abs., ethanol was heated for 5 min., and the reaction mixture was filtered. To the stirred filtrate the appropriate aromatic aldehyde (0.01 mole) was added then the mixture was refluxed for 2h. The solid that separated was filtered, washed with ethanol, dried and crystallized from acetic acid:ethanol mixture, to afford compounds **5a-d** (Table 1).

4-[4-(1-Acetyl-5-aryl-4,5-dihydro(1H)pyrazol-3-yl)-anilino]-5,6,7,8-tetrahydrobenzothieno[2,3-d]pyrimidines (6a-d):

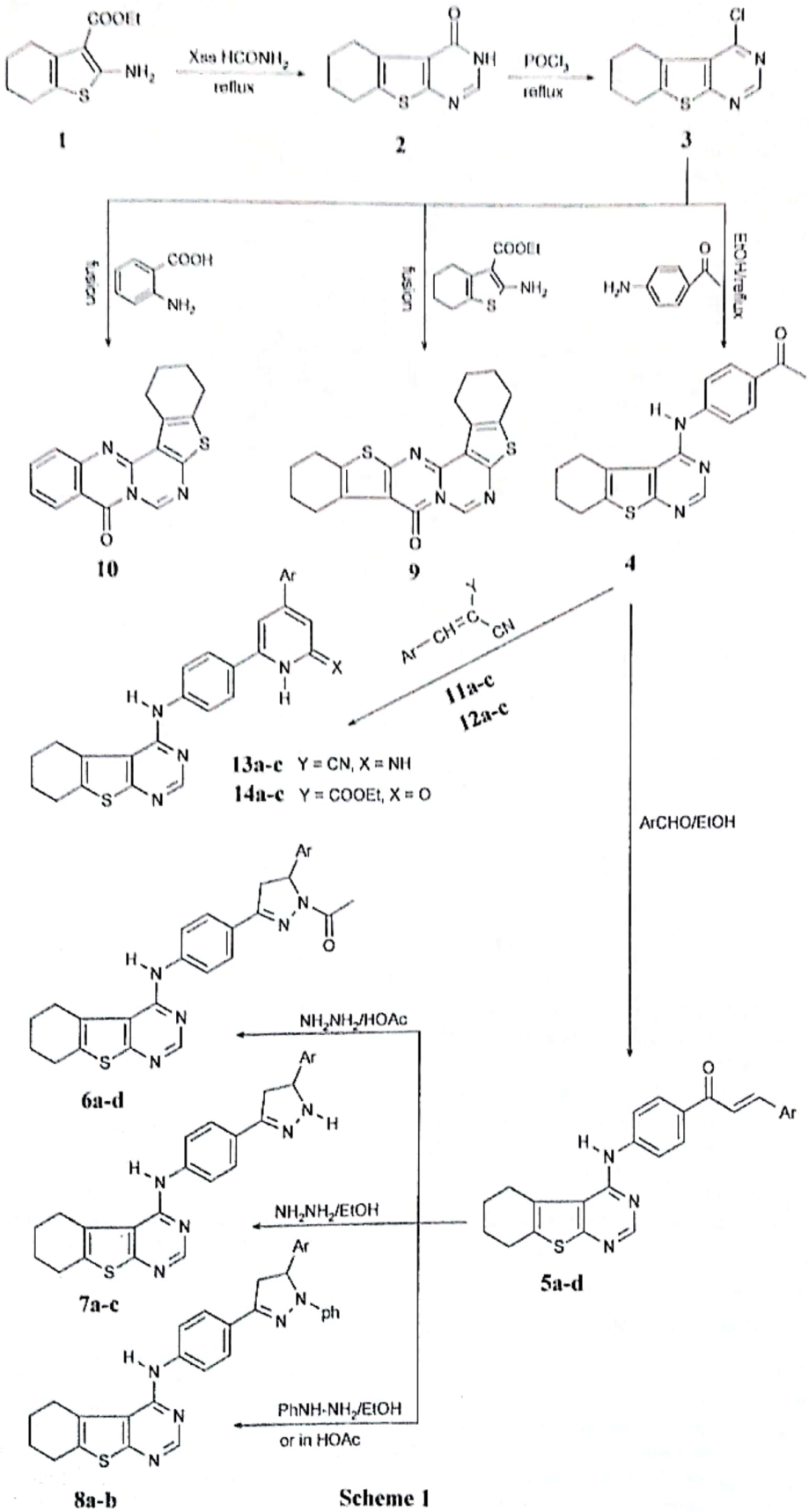
To a solution of hydrazine hydrate 99% (0.002 mole) in glacial acetic acid (5 ml), the appropriate compound **5** (0.001 mol) was added and the reaction mixture was refluxed for 3 h. On cooling, the precipitated solid was filtered, washed with water and crystallization from ethanol afforded compounds **6a-d** (Table 2).

4-[4-(5-Aryl-4,5-dihydro(1H)pyrazole-3-yl)anilino]-5,6,7,8-tetrahydro-benzothieno[2,3-d]pyrimidines (7a-c):

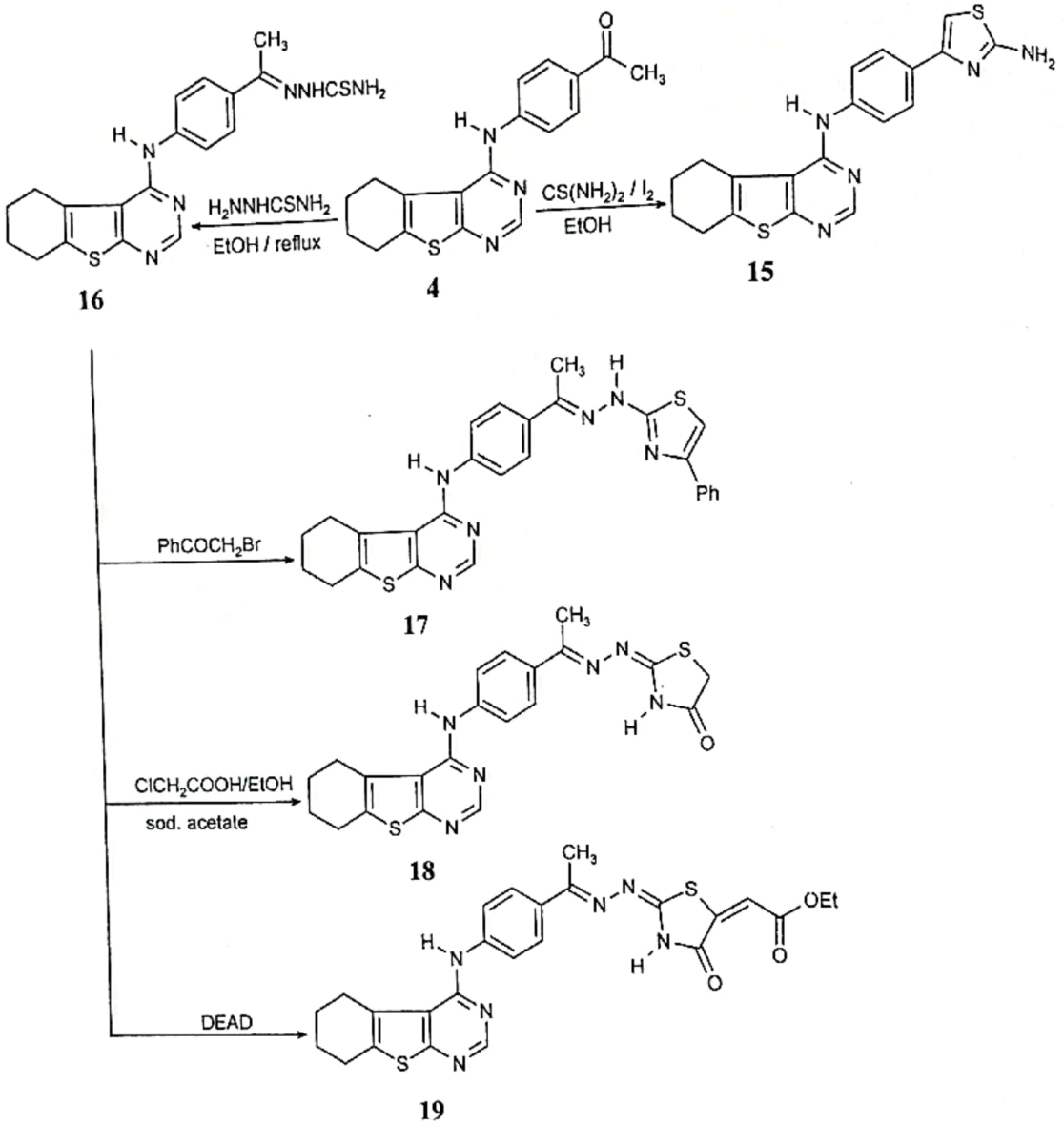
To a suspension of the appropriate **5a-c** (0.001 mol) in abs., ethanol (5 ml), hydrazine hydrate 99% (0.002) was added. The reaction mixture was refluxed for 3-4 h until a crystalline precipitate was separated, the product was filtered, washed and crystallized from ethanol to give compounds **7a-c** in 50-60% yield (Table 3).

4-[4-(5-Aryl-1-phenyl-4,5-dihydro(1H)pyrazol-3-yl)-aniline]-5,6,7,8-tetrahydrobenzothieno[2,3-d]pyrimidines (8a-b):

To a solution of phenyl hydrazine (0.002 mol) in abs., ethanol or glacial acetic acid (5 ml), the appropriate **5a-b** (0.001 mol) was added. The reaction mixture was refluxed for 4-5h., cooled and poured on to ice water. The precipitate was collected by filtration, washed with water and crystallized from ethanol to give compounds **8a-b** in 55-60% yield (Table 4).



Scheme 1



16 4 15

17 18 19

Scheme 2

9-Oxo-1,2,3,4,10,11,12,13-octahydro-9H-1-benzothieno[2``,3``:4,5]pyrimido[1,6-a]-1-benzothieno-[2`,3`-d]pyrimidine (9).

A mixture of compound **3** and **1** in equimolar quantities, was heated in oil bath at 150-160°C for 30 min. The brittle mass that obtained was well powdered, washed with sodium carbonate solution (10%) then crystallized from ethyl acetate/pet. ether (60-80) to give compound **9**, 75% yield, m.p. 243-4°C.

Analysis for $C_{19}H_{17}N_3OS_2$: (367): Calcd.: C, 62.12; H, 4.63; N, 11.44. Found: C, 62.22; H, 4.20; N, 11.72.

IR: 2930, 2838 (CH aliphatic), 1660 (C=O).

9-Oxo-1,2,3,4-tetrahydro-9H-1-benzothieno[2`,3`:4,5]pyrimido[6,1-b]quinazoline (10).

A mixture of compound **3** and anthranilic acid in equimolar quantities was heated in oil bath at 150 – 160°C for 30 min. The brittle mass obtained was well powdered and washed with Na_2CO_3 solution (10%) then crystallized from ethyl acetate/petroleum ether (60-80%) to give compound **10** in 65% yield, m.p. 297-8°C.

Analysis for $C_{17}H_{13}N_3OS$ (307): Calcd.: C, 66.44; H, 4.23; N, 13.68. Found: C, 66.23; H, 4.56; N, 13.43.
MS: m/z = 307 (M^+, 75%).
IR: 3092 (CH aromatic), 2931, 2854 (CH aliphatic), 1692 (C=O).

3-Aryl-2-substituted acrylonitriles **11a-c** and **12a-c** were prepared according to reported procedure[16-18].

4-[4-(4-Aryl-3-cyano-2-imino-1,2-dihydropyridin-6-yl)anilino]5,6,7,8-tetrahydrobenzothieno[2,3-d]pyramidines (13a-c) and 4-[4-(4-aryl-3-cyano-2-oxo-(1,2-dihydro)-pyridin-6-yl)anilino]5,6,7,8-tetrahydrobenzothieno[2,3-d]pyrimidines (14a-c).

A mixture of compound **4** (0.01 mol), the appropriate substituted acrylonitriles **11a-c** or **12a-c** (0.01 mol) and ammonium acetate (0.08 mol) in abs. ethanol (40 ml) was refluxed for 1-2 h until a crystalline yellow ppt was separated. The separated solid was filtered, crystallized from ethanol/acetic acid (1:2) to give **13a-c** (Table 5) and **14a-c** (Table 6).

4-[4-(2-Aminothiazol-4-yl)anilino]5,6,7,8,-tetrahydrobenzothieno[2,3-d]pyrimidine (15).

A mixture of compound **4** (0.002 mol), thiourea (0.003 mol) and I_2 (0.003 mol) in abs. ethanol (10 ml) was refluxed for 4h with stirring. After cooling the resulting precipitate was filtered and crystallized from DMF to give compound **15** in 60% yield, m.p. 285-6°C.

Analysis for $C_{19}H_{17}N_5S_2$ (379): Calcd.: C, 60.15; H, 4.48; N, 18.46. Found: C, 59.51; H, 4.88; N, 18.44.

IR: 3448, 3421 (NH_2), 3252 (NH), 3062 (CH aromatic), 2925, 2854 (CH aliphatic), 1620 (C=N) cm^{-1}.

^1H NMR (DMSO-d_6): 1.9-2 (m, 4H, CH_2 at C-6,7), 2.8-3.1 (m, 4H, CH_2 at C-5,8), 6.92 (s, 1H, NH), 7.04 (s, 2H, NH_2), 7.6-7.8 (m, 4H, ArH), 8.1 (s, 1H, C-4 thiazole), 8.49 (s, 1H, CH pyrimidine).

4-[5,6,7,8-Tetrahydrobenzothieno[2,3-d]pyrimidin-4-yl-amino]acetophenone thiosemicarbazone (16).

A mixture of **4** (0.01 mol) and thiosemicarbazide hydrochloride (0.01 mol) in abs. ethanol (20 ml) was refluxed for 1h. The separated solid was filtered and crystallized from ethanol to give compounds **16**, 67% yield, m.p. 228-9°C.

Analysis for $C_{19}H_{20}N_6S_2$ (396); Calcd.,: C, 57.57; H, 5.05; N, 21.21. Found: C, 57.51; H, 5.10; N, 21.12.

IR: 3424 (NH), 3247, 3147 (NH_2), 1596 (C=N), 1556 (C=C) and 1183 (C=S).

^1H NMR, DMSO-d_6: 1.9-2 (m, 4H, CH_2 at $C_{6,7}$), 2.9-3.1 (m, 4H, CH_2 at $C_{5,8}$), 2.5 (s, 3H, CH_3), 7.6-7.8 (m, 4H, ArH), 8.2 (s, 1H, NH) at C-4 of pyrimidine), 8.3 (s, 1H, CH pyrimidine), 10.1 (s, 2H, NH_2), 10.4 (s, 1H, NH).

N^2-(4-Phenyl-2-thiazolyl)-4-[5,6,7,8-tetrahydrobenzothieno[2,3-d]pyrimidin-4-yl-amino]acetophenone-hydrazone (17).

A suspension containing compound **16** (0.001 mol) and phenacyl bromide (0.0015 mol) in abs. ethanol (20 ml) was refluxed for 3 h., then anhydrous sodium acetate (0.0015 mol) was added and the reaction mixture was heated for additional 30 min. It was then cold and poured on to cold water where the yellowish precipitate was filtered and crystallized from ethanol, 64% yield, m.p. 278-9°C.

Analysis for $C_{27}H_{24}N_6S_2$ (496): Calcd.: C, 65.32; H, 4.83; N, 16.93. Found: C, 65.28; H, 4.71; N, 16.91.

IR: 3455 (NH), 3206 (NH), 3020 (CH aromatic), 2931, 2858 (CH aliphatic), 1556 (C=N), 1504 (C=C), 1052 (C-S-C).

N^2-(4-Oxothiazolidin-2-ylidene)-4-[5,6,7,8-tetrahydrobenzothieno[2,3-d]pyrimidin-4-yl-amino]acetophenone hydrazone (18).

To a suspension of **16** (0.01 mol) in abs. ethanol, monochloro acetic acid (0.01 mol) and anhydrous sodium acetate (0.01 mol) were added. The reaction mixture was refluxed for (2h) cooled and the separated solid was filtered and crystallized from ethanol, 60% yield, m.p. 299 – 300°C.

Analysis for $C_{21}H_{20}N_6S_2O$ (436) : Calcd.: C, 57.79; H, 4.58; N, 19.26. Found: C, 58.26; H, 4.91; N, 19.23.

IR: 3445 (NH), 3051 (CH aromatic), 2933, 2858 (CH aliphatic), 1709 (C=O), 1609 (C=N), 1500 (C=C), 1093 (C-S-C).

^1H NMR: DMSO-d_6: 1.9-2 (m, 4H, CH_2 at $C_{6,7}$), 2.9-3.1 (m, 4H, CH_2 at $C_{5,8}$), 3.3(s, 3H, CH_3), 3.8 (s, 2H, CH_2 thiazolidinone), 7.7-7.9 (m, 4H, ArH), 8.2 (s, 1H, NH), 8.4 (s, 1H, CH-pyrimidine), 11.9 (s, 1H, NH).

N^2-(5-Ethoxycarbonylmethylidene-4-oxothiazolid-ine-2-ylidene)-4-[5,6,7,8-tetrahydrobenzothieno[2,3-d]pyrimidin-4-yl-amino] acetophenonehydrazone (19).

Diethylacetylenedicarboxylate (DEAD) (0.15 mol) was added dropwise at room temperature to a well stirred suspension of compound **16** (0.01 mol) in abs. Ethanol (5 ml). After an additional stirring for 1 h., the separated crystals were collected and washed with methanol, then recrystallized from DMF in 68% yield, m.p. 264-5°C.

Analysis for $C_{25}H_{24}N_6S_2O_3$ (520): Calcd.: C, 57.69; H, 4.61; N, 16.15. Found: C, 57.42; H, 4.80; N, 16.12.

IR: 3451 (NH), 3312 (NH of thiazolidinone), 3061 (CH aromatic), 2929, 2826 (CH aliphatic), 1719 (C=O), 1605 (C=N), 1504 (C=C).

^1H NMR, DMSO-d_6): 1.4 (t, 3H, CH_3), 1.9-2 (m, 4H, CH_2 at $C_{6,7}$), 2.9-3 (m, 4H, CH_2 at $C_{5,8}$), 3.3 (s, 3H, CH_3), 4.3 (q, 2H, CH_2), 6.52 (s, 1H, CH olefenic), 7.7-7.9 (m, 4H, ArH), 8.4 (s, 1H, CH, pyrimidine), 10.7 (s, 1H, NH) and 12.77 (s, 1H, NH).

Screening for antiinflammatory activity:

Ten selected compounds (**6a, 6d, 7a, 7c, 8b, 13a, 13c, 14b, 17 and 19**) were evaluated for their antiinflammatory activity.

This experiment was carried out on 60 mature albino rats of both sex weighing 100-120 g. each. Rats were obtained from Animal Breading House, Faculty of Vet. Med., Zagazig University, fed on a balanced pelleted diet and watered ad-libitum. They were classified into 12 equal groups each of five and housed in separate cages. The tested compounds were dissolved in DMSO as a vehicle.

Diclofenac sodium (Voltarin) was used as a standard antiinflammatory drug. The first group was left as a control group injected only intraperitoneally with 0.2 ml of the vehicle, DMSO, whereas groups from 2-11 where injected with test compounds i.p. in a dose of 7.0 mg/kg (0.2 ml), while the last group (12^{th}) was injected i.p. with diclofenac sodium as a standard antiinflammatory drug in the same dose. The dose of the standard and test compounds was determined by converting human dose into rat dose according to Paget and Bame[19].

One hour later, oedema in the right hind paw was induced by s.c. injection of 0.1 ml of 10% carragenin according to Winter et. al.[20]. The thickness of the rat paw was measured at base line (zero time) and the after one, two, three and four hours after carragenin injection using skin caliber to determine the possible antiinflammatory effect of the test compounds and the standard. The obtained results were statistically analysed using student's (t) test according to Snedecor and Cochran[21].

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Table 1: Spectroscopic analysis and physical properties of 4-[4-(2-arylvinylcarbonyl)anilino]-5.6.7.8-tetrahydro-benzothieno[2.3-d]pyrimidines (**5a-d**).

Comp. No.	Ar	Yield (%)	m.p. (°C)	Mol. Form. (M.Wt.)	Analysis (%) calcd/found			IR (KBr) (cm^{-1})	^{1}H-NMR (δ, ppm)
5a	4-(NO_2)C_6H_4-	85	264-5	$C_{25}H_{20}N_4O_3S$ (456)	C H N	65.78 4.38 12.28	65.64 4.82 12.52	3421 (NH), 3039 (CH, aromatic), 2932, 2856 (CH, aliphatic), 1553, 1342 (NO_2), 1658 (C=O), 1598 (C=N)	
5b	4-(Cl)C_6H_4-	84	243-4	$C_{25}H_{20}ClN_3OS$ (445.5)	C H N	67.34 4.48 9.42	67.45 4.74 9.67	3423 (NH), 3035 (CH, aromatic), 2930, 2843 (CH, aliphatic), 1656 (C=O) and 1600 (C=N)	(DMSO), 1.8-1.9 (m, 4H, CH_2 at C-6, 7), 2.8-3.1 (m, 4H, CH_2 at C-5, 8), 7.5-7.8 (m, 8H, ArH), 7.9-8.1 (dd, 2H, vinylic CH=CH), 8.5 (s, 1H, CH pyrimidine) and 8.6 (s, 1H, NH)
5c	4-(OCH_3)C_6H_4-	80	232-3	$C_{26}H_{23}N_3O_2S$ (441)	C H N	70.74 5.21 9.52	70.59 5.66 9.60		($CDCl_3$), 1.8-1.9 (m, 4H, CH_2 at 6, 7), 2.9-3.1 (m, 4H, CH_2 at 5, 8), 3.8 (s, 3H, OCH_3), 6.9-7.8 (m, 8H, ArH), 7.8-8.1 (dd, 2H vinylic CH=CH), and 8.5 (s, 1H, CH of pyrimidine)
5d	2-(Cl)C_6H_4-	83	234-5	$C_{25}H_{20}ClN_3OS$ (445.5)	C H N	67.34 4.48 9.42	67.22 4.17 9.23		

Table 2: Spectroscopic analysis and physical properties of 4-[4-(1-acetyl-5-aryl-4,5-dihydro-(1H)-pyrazol-3-yl)-anilino]-5,6,7,8-tetrahydrobenzothieno[2,3-d]pyrimidine (**6a-d**).

Comp. No.	Ar	Yield (%)	m.p. (°C)	Mol. Form. (M.Wt.)	Analysis (%) calcd/found			IR (KBr) (cm^{-1})	^{1}H-NMR (δ, ppm)
6a	4-(NO_2)C_6H_4-	65	284-6	$C_{27}H_{24}N_6O_3S$ (512)	C H N	63.28 4.68 16.40	62.80 5.03 16.41	3448 (NH), 3042 (CH, aromatic), 2934, 2860 (CH, aliphatic), 1664 (C=O), 1602 (C=N) and 1505, 1361 (NO_2)	
6b	4-(Cl)C_6H_4-	60	220-1	$C_{27}H_{24}ClN_5OS$ (501.5)	C H N	64.60 4.78 13.95	64.67 5.53 13.85		(DMSO-d_6), 1.8-1.9 (m, 4H, CH_2 at 6, 7), 2.4 (s, 3H of CH_3CO-), 2.9-3.1 (m, 4H, CH_2 at 5, 8), 3.8-3.95 (dd, 2H, CH_2 pyrazoline), 5.52-5.60 (dd, 1H, CH pyrazoline), 7.22-7.26 (d, 2H, ArH, J 8), 7.4-7.44 (d, 2H, ArH, J 8), 7.26-7.7 (m, 4H, ArH), 8.4 (s, 1H, CH pyrimidine) and 8.5 (s, 1H, NH)
6c	4-(OCH_3)C_6H_4-	55	197-8	$C_{28}H_{27}N_5O_2S$ (497)	C H N	67.60 5.43 14.08	67.69 5.49 14.10	3446 (NH), 3038, (CH, aromatic), 2924, 2838 (CH, aliphatic), 1665 (C=O) and 1606 (C=N)	($CDCl_3$), 1.8-1.9 (m, 4H, CH_2 at C-6, 7), 2.4 (s, 3H, CH_3CO-), 2.9-3.1 (m, 4H, CH_2 at 5, 8), 3.7 (dd, 2H, CH_2, pyrazoline), 3.8 (s, 3H, OCH_3), 5.56 (dd, H, CH pyrazoline), 6.82-6.86 (d, 2H, ArH, J 8), 7.15-7.19 (d, 2H, ArH, J 8), 7.26-7.7 (m, 5H, ArH, NH) and 8.5 (s, 1H, CH, pyrimidine)
6d	2-(Cl)C_6H_4-	63	282-3	$C_{27}H_{24}ClN_5OS$ (501.5)	C H N	64.60 4.78 13.95	64.52 5.00 13.87		

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Table 3: Spectroscopic analysis and physical properties of 4-[4-(5-aryl-4,5-dihyydro-(1H)-pyrazol-3-yl)anilino]-5,6,7,8-tetrahydrobenzothieno[2,3-d]pyrimidines (7a-c).

Comp. No.	Ar	m.p. (°C)	Mol. Form. (M.Wt.)	Analysis (%) calcd/found			IR (KBr) (cm^{-1})	^{1}H-NMR (δ, ppm)
7a	4-(NO_2)C_6H_4-	157-8	$C_{25}H_{22}N_6O_2S$ (470)	C H N	63.82 4.68 17.87	63.46 4.90 17.85	3444, 3339, 2(NH), 3065 (CH aromatic), 2930, 2855 (CH aliphatic), 1602 (C=N), 1342, 1506 (NO_2)	
7b	4-(Cl)C_6H_4-	195-6	$C_{25}H_{22}ClN_5S$ (459.5)	C H N	65.28 4.78 15.23	65.06 5.04 15.12	3451, 3256 (2NH), 3057 (CH aromatic), 2939, 2862 (CH aliphatic) and 1603 (C=N)	($CDCl_3$), 1.8-1.9 (m, 4H, CH_2 at 6 and 7), 2.9-3.1 (m, 4H, CH_2 at 5, 8), 3.7 (dd, 2H, CH_2 pyrazoline)), 5.3 (t, 1H, CH of pyrazoline), 6.01 (s, 1H, NH), 7-7.6 (m, 9H, ArH, NH), 8.5 (s, 1H of pyrimidine)
7c	4-(OCH_3)C_6H_4-	130-1	$C_{26}H_{25}N_5OS$ (455)	C H N	68.57 5.49 15.38	68.20 5.39 15.42		

Table 4: Spectroscopic analysis and physical properties of 4[4-(5-aryl-1-phenyl-4,5-dihydro(1H)pyrazol-3-yl)anilino]5,6,7,8-tetrahydrothieno[2,3-d]pyrimidines (8a-b).

Comp. No.	Ar	m.p. (°C)	Mol. Form. (M.Wt.)	Analysis (%) calcd/found			IR (KBr) (cm^{-1})
8a	4-(NO_2)C_6H_4-	162-3	$C_{31}H_{26}N_6O_2S$ (546)	C H N	68.13 4.76 15.38	68.00 4.67 15.33	3442 (NH), 3097 (CH aromatic), 2936, 2838 (CH aliphatic), 1598 (C=N), 1505, 1361 (NO_2)
8b	4-(Cl)C_6H_4-	150-1	$C_{31}H_{26}ClN_5S$ (535.5)	C H N	69.46 4.85 13.07	68.69 4.12 13.13	3447 (NH), 3033 (CH aromatic), 2930, 2856 (CH aliphatic), 1598 (C=N)

Table 5: Spectroscopic analysis and physical properties of 4-[4-(4-aryl-3-cyano-2-imino-1,2-dihydropyridine-6-yl)anilino]5,6,7,8-tetrahydrobenzothieno[2,3-d]pyrimidines (13a-c).

Comp. No.	Ar	Yield (%)	m.p. (°C)	Mol. Form. (M.Wt.)	Analysis (%) calcd/found			IR (KBr) (cm^{-1})	^{1}H-NMR (δ, ppm)
13a	4-(Cl)C_6H_4-	73	297-8	$C_{28}H_{21}ClN_6S$ (508.5)	C H N	66.07 4.12 16.51	66.22 4.33 16.51	3448 (NH), 3416 (NH), 3060 (CH aromatic), 2939, 2850 (CH aliphatic), 2205 (CN), 1601 (C=N)	
13b	2-(Cl)C_6H_4-	70	295-6	$C_{28}H_{21}ClN_6S$ (508.5)	C H N	66.07 4.12 16.51	66.12 4.22 16.50		
13c	4(OCH_3)C_6H_4-	73	286-7	$C_{29}H_{24}N_6OS$ (504)	C H N	69.04 4.76 16.66	69.14 4.75 16.67	3450 (NH), 3409 (NH), 3050 (CH aromatic), 2939, 2837 (CH aliphatic), 2216 (CN), 1601 (C=N)	$CDCl_3$: 1.9-2 (m, 4H, CH_2 at $C_{6,7}$), 2.9-3.1 (m, 4H, CH_2 at $C_{5,8}$), 3.8 (s, 3H, OCH_3), 6.9-8 (m, 11H, ArH, 3NH), 8.5 (s, 1H, CH pyrimidine)

Table 6: Spectroscopic analysis and physical properties of 4-[4-(4-aryl-3-cyano-2-oxo-1,2-dihydropyridine-6-yl)anilino]5,6,7,8-tetrahydrobenzothieno[2,3-d]pyrimidines (14a-c).

Comp. No.	Ar	Yield (%)	m.p. (°C)	Mol. Form. (M.Wt.)	Analysis (%) calcd/found			IR (KBr) (cm^{-1})	^{1}H-NMR (δ, ppm)
14a	4-(Cl)C_6H_4-	70	300	$C_{28}H_{20}ClN_5OS$ (509.5)	C H N	65.94 3.92 13.73	65.82 3.82 13.75		
14b	2-(Cl)C_6H_4-	73	293	$C_{28}H_{20}ClN_5OS$ (509.5)	C H N	65.94 3.92 13.73	65.91 3.91 13.62	3345 (NH), 3032 (CH aromatic), 2929, 2855 (CH aliphatic), 2221 (CN), 1636 (C=O), 1604 (C=N)	$CDCl_3$: 1.9-2 (m, 4H, CH_2 at $C_{6,7}$), 2.9-3.1 (m, 4H, CH_2 at $C_{5,8}$), 5.2 (s, 2H at C-5 pyrimidine, NH), 7-8.1 (m, 9H, ArH, NH), 8.5 (s, 1H, CH pyrimidine)
14c	4(OCH_3)C_6H_4-	73	286	$C_{29}H_{23}N_5O_2S$ (505)	C H N	68.91 4.55 13.86	68.93 4.53 13.81	3347 (NH), 3025 (CH aromatic), 2929, 2838 (CH aliphatic), 2214 (CN), 1640 (C=O), 1601(C=N)	

(14b) MS: m/z = 509 (M^+, 20.24%).

RESULTS AND DISCUSSION

4-(4-Acetylanilino)-5,6,7,8-tetrahydrobenzothieno-[2,3-d]pyrimidine (**4**) the key intermediate was prepared according to the reported procedure[12] Scheme (1). Condensation of **4** with various aromatic aldehydes afforded the corresponding 4-[4-(2-arylvinyl-carbonyl)anilino]-5,6,7,8-tetrahydrobenzothieno[2,3-d]pyrimidines (**5a-d**). Cyclocondensation of **5a-d** with hydrazine hydrate and phenylhydrazine in glacial acetic acid or ethanol gave pyrazoline derivatives **6a-d**, **7a-c** and **8a-b**.

Compound **4** was also condensed with the appropriate a substituted acrylonitrile **11a-c** or **12a-c** in the presence of excess ammonium acetate to give **13a-c**, **14a-c** with a high yield. On the other hand, fusion of equimolar quantities of **3** with ethyl 2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate or anthranilic acid afforded **9** or **10**, respectively. The aminothiazole derivative **15** was obtained by the action of thiourea and iodine on **4** in ethanol as reported[22].

Compound **4** was also used as a precursor for the synthesis of thiazoles and thiazolidinone derivatives. Compound **4** was condensed with thiosemicarbazide to give the thiosemicarbazone **16**. Compound **16** was cyclized to the thiazole derivative **17** by its reaction with phenacyl bromide or to the thiazolidinone derivatives **18** and **19** by its reaction with chloroacetic acid or diethylacetylene dicarboxylate (DEAD) respectively.

Results of Anti-inflammatory Activity:

Table (7) showed that compounds **6a, 8b, 13a, 13c** and **14b** have a marked antiinflammatory activity when compared with the control group starting after one hour till the end of the experiment (4 hours). Whereas the antiinflammatory activity of compound **17** started after two hours and lasted for one hour.

The rank order of potency as antiinflammatory activity was as follows: Compound **14b > 13a > 13c > 8b > 6a > 17**.

The antiinflammatory activity of the compound **14b** was nearly equal to that of diclofenac sodium. On the other hand. Compounds **6d, 7a, 7c** and **19** showed no antiinflammatory activity when compared with control group.

Table 7: The antiinflammatory activity of the test compounds and diclofenac sodium in rats.

Group	Initial Thickness	Thickness of paw skin in mm after			
		1 hour	2 hours	3 hours	4 hours
Carragenin	2.0	7.0	13.0	15.0	17.0
6a	2.4	5.0	7.0	9.5	11
8b	2.2	4.5	6.0	8.0	9.5
13a	2.0	3.6	4.5	5.5	6.8
13c	2.4	4.2	5.6	8.3	9.2
14b	2.5	3.5	4.0	4.7	5.8
17	2.5	5.5	9.0	12	15
Diclofenac sodium	2.0	2.9	3.5	4.7	5.3

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تشييد بعض مشتقات الثينوبيرميدين الجديدة كمضادات للإلتهابات

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قسم الكيمياء العضوية الصيدلية – كلية الصيدلة – جامعة الزقازيق – الزقازيق – مصر

تم فى هذا البحث تحضير ٤-[٤-(أستيل أنيلينو)- ٥،٦،٧،٨-رباعى هيدروبنزوثينو(٢،٣-د)بيرميدين (٤) والذى تم تحويله إلى ألفا-بيتا الكيتونات الغير مشبعة ٥(أ-د) التى استخدمت كمركبات وسيطة لتحضير بعض مشتقات البيرازولين ٦(أ-د) ، ٧(أ-د) ، ٨(أ-ب). تم تحويل مركب (٤) إلى مشتقات جديدة للبيريدون وأمينوبيريدين ١٣(أ-ج) ، ١٤(أ-ج) وأيضاً تم تحضير مركبات الأمينوثيازول (١٥) والثيوسيميكربازون (١٦) . وعلاوة على ذلك تم تحويل الأخير (١٦) إلى مشتقات الثيازول (١٧) الثيازوليدنيون (١٨ ، ١٩) بتفاعله مع بروميد الفناسيل وكلورو حمض الخليك ، ثنائى إيثيل أستيلين ثنائى كربوكسيلات وقد وجد أن بعض المركبات الجديدة لها فاعلية عالية كمضادات للالتهابات .