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SYNTHESIS OF SOME NEW PULVINAMIDES AND THEIR ANTI-INFLAMMATORY ACTIVITY

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ABSTRACT
Reaction of 3,6-diphenylthieno[3,2-*b*]furan-2,5-dione **(1)** with substituted anilines **(2a-g)** in glacial acetic acid afforded 2-(3-hydroxy-5-oxo-4-phenylthiophen-2(5*H*)-ylidene)-*N*,2-diphenylacetamides **(3a-g).** Similarly reaction of 3,6-diphenylthieno[3,2-*b*]thiophene-2,5-dione **(4)** with substituted anilines **(5a-e)** in acidic medium afforded 2-(3-mercapto-5-oxo-4-phenylthiophen-2(5*H*)-ylidene)-*N*,2-diphenylacetamides **(6a-e)**. All the compounds have screened *in vitro* for their anti-inflammatory activity against the carrageenan induced rat paw oedema in albino rats. In the primary screening, some of the compounds **3b**, **3c**, **3e**, **3g** and **6e** exhibited significant activity.

Keywords: 3,6-Diphenyl-thieno[3,2-*b*]furan-2,5-dione, 3,6-diphenyl-thieno[3,2-*b*] thiophene-2,5-dione, substituted anilines, pulvinamides and glacial acetic acid.

1. INTRODUCTION
Naturally occurring pulvinamides[i] are very few and the substituted pulvinic acid derivatives are yet to be isolated from natural sources. Rhizocarpic acid an optically active pulvinamide of phenylalanine methyl ester has been reported from lichens. It was first isolated from *Rhizocarpon geographicum*[ii]. A new pulvinic acid derivative, pulvinamide has been identified as a constitutent of *Pseudocyphellaria crocata*[iii]. Synthetic compounds of pulvinamide class outnumber the naturally occurring ones. These synthetic derivatives are mostly prepared in view of their physiological activities mainly antiinflammatory and antiarthritic properties. The amides include many heterocyclic ones besides a series of derivatives prepared by involving substituted anilines[iv].

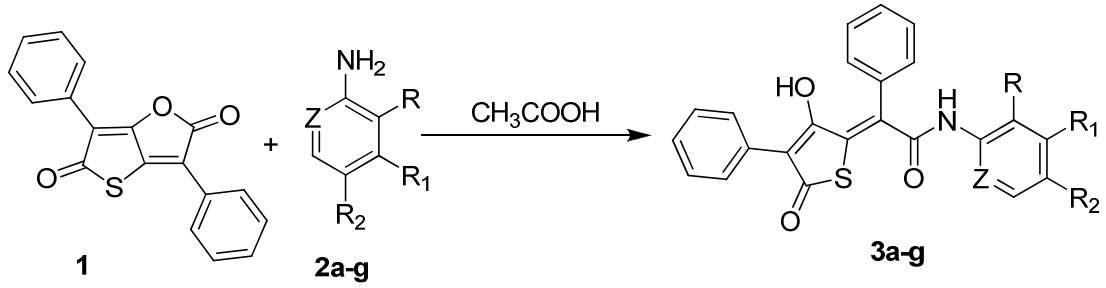
In the present work, it is intended not only to investigate the synthesis of 2-(3-hydroxy-5-oxo-4-phenylthiophen-2(5*H*)-ylidene)-*N*,2-diphenylacetamide analogues and 2-(3-mercapto-5-oxo-4-phenylthiophen-2(5*H*)-ylidene)-*N*,2-diphenylacetamide analogues but also to evaluate their antiinflammatory properties. According to the literature, pulvinic group of compounds possess anti-inflammatory activity[v,vi] and N-heterocyclic pulvinamides also possess the same along with antiarthritic activity[vii,viii]. The interest in this study is originated by the fact

that a limited number of publications reported the synthesis of the target heterocyclic nucleus which prompted the present investigation for establishing novel synthetic approach.

RESULTS AND DISCUSSION

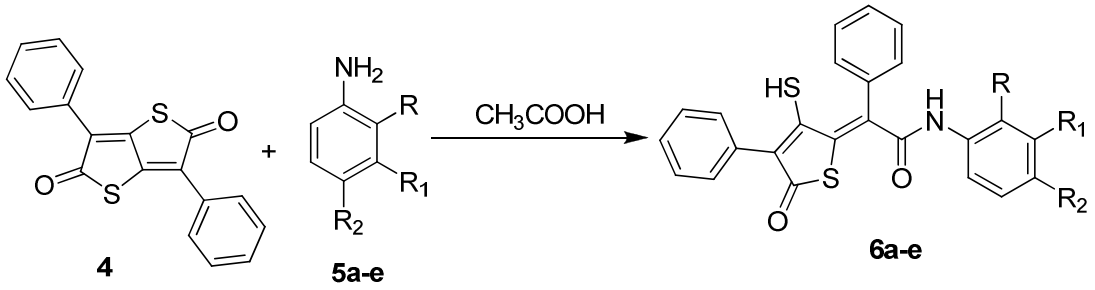
Reaction of 3,6-diphenylthieno[3,2-*b*]furan-2,5-dione **1** and substituted anilines **2a-g** in glacial acetic acid at reflux temperature afforded 2-(3-hydroxy-5-oxo-4-phenylthiophen-2(5*H*)-ylidene)-*N*,2-diphenylacetamides **3a-g** in good yields. The IR spectrum of the product **3a** shows absorption bands at 3452, 3398, 1754 and 1610 cm^{-1}, which are characteristic of OH, NH, C=O (lactone) and C=C aliphatic stretching respectively. The ^1H NMR spectrum of compound **3a** appeared signals at δ 7.10-7.64 (ArH), 8.32 (br, NH) and 13.49 (OH). The mass spectrum of compound **3a** exhibits a molecular ion peak m/z at 399 (M^+) (**Scheme 1**).

Reaction of 3,6-diphenylthieno[3,2-b]thiophene-2,5-dione **4** and different anilines **5a-e** in the same manner provided 2-(3-mercapto-5-oxo-4-phenylthiophen-2(5*H*)-ylidene)-*N*,2-diphenylacetamide analogues **6a-e** in good yields. The IR spectrum of **6a** absorbed bands at 2849, 3401, 1753 and 1612 cm^{-1}, which are characteristic of SH, NH, C=O lactone and C=C aliphatic stretching respectively. The ^1H NMR spectrum exhibited signals at δ 1.32 (SH), 7.09-7.68 (ArH), 8.30 (br, NH) and in the mass spectrum molecular ion peak m/z appeared at 415 (M^+) (**Scheme 2**). The remaining compounds **3b-g** and **6b-e** were obtained in a similar manner, characterized by IR, ^1H NMR, ^{13}C NMR and Mass spectral data and the results are shown in experimental section.



	R	R_1	R_2	Z
a)	H	H	H	C
b)	H	OCH_3	H	C
c)	H	H	Br	N
d)	NO_2	H	H	C
e)	H	H	H	N
f)	NO_2	H	NO_2	C
g)	H	H	CH_3	C

SCHEME 1



4 5a-e 6a-e

	R	R_1	R_2
a)	H	H	H
b)	NO_2	H	H
c)	NO_2	H	NO_2
d)	H	H	CH_3
e)	H	OCH_3	H

SCHEME 2

BIOLOGICAL ACTIVITY

Anti-inflammatory activity: The compounds **3a-g** and **6a-e** were tested *in vitro* for their anti-inflammatory activity using carrageenan-induced in rats paw oedema method of Winter *et. al*[ix], at an oral dose of 50 mg/kg b.w. in albino rats (weighing 80-110g). The percent inhibition of inflammation was calculated by applying Newbould formula[x]. The compounds **3b**, **3c**, **3e**, **3g** and **6e** were shown significant anti-inflammatory activity when compared with that of phenyl butazone. The obtained anti-inflammatory activity results are shown in **Table 1**.

Table 1: Anti-inflammatory activity of compounds **3a-g** and **6a-e**

Compound	Volume of paw (mL) after drug administration (mean ± SE)		Total increase in paw volume after	Percent inhibition
	0 hr	5 hr		
3a	0.69±0.02	0.86±0.03	0.27±0.02	25.10
3b	0.68±0.03	0.90±0.02	0.22±0.01	38.88
3c	0.63±0.02	0.88±0.03	0.25±0.02	30.55
3d	0.59±0.01	0.85±0.03	0.26±0.02	27.77
3e	0.65±0.04	0.89±0.02	0.24±0.01	33.33
3f	0.66±0.03	0.96±0.03	0.30±0.02	16.67
3g	0.76±0.03	0.86±0.03	0.20±0.02	44.44
6a	0.61±0.03	0.89±0.02	0.28±0.02	22.22
6b	0.60±0.04	0.89±0.02	0.29±0.01	19.44
6c	0.63±0.02	0.94±0.02	0.31±0.03	13.88
6d	0.50±0.03	0.76±0.02	0.26±0.02	27.77
6e	0.57±0.02	0.79±0.02	0.22±0.03	38.88
Phenyl butazone	0.75±0.02	0.91±0.02	0.16±0.03	55.55
Control	0.62±0.02	0.98±0.03	0.36±0.02	-

EXPERIMENTAL

Melting points were uncorrected. IR spectra were recorded (KBr) on a Perkin Elmer 1650 spectrophotometer. ^{1}H NMR spectra were recorded on Varian Gemini spectrometer (200 MHz) using DMSO-d_6 as a solvent, and TMS as internal standard. Chemical shifts were expressed as δ ppm units. Mass spectra were recorded on a V.G. Micromass 7070H. The starting compounds **1**, **4** are prepared according to literature procedure[xi].

General procedure for the synthesis of 3a-g:

A mixture of 3,6-diphenyl-thieno[3,2-b]furan-2,5-dione (**1)** (0.01 mol) and substituted anilines **(2a-g)** (0.01 mol) in glacial acetic acid (25 mL) was refluxed for 4 h. The completion of the reaction was monitored by TLC and then the reaction mixture was poured over crushed ice. The precipitated solid was separated by filtration, washed free of acid and crystallized from glacial acetic acid to get **3a-g**.

2-(3-Hydroxy-5-oxo-4-phenyl-5*H*-thiophen-2-ylidene)-2,*N*-diphenyl-acetamide (3a)

Yellow solid; mp 133-135°C; Yield 89%; IR ν (cm^{-1}): 3452 (OH), 3398 (NH), 1754 (CO lactone), 1649 (CO amide), 1610 (C=C aliphatic); ^{1}H NMR: δ 13.49 (s, 1H, OH enolic), 8.32 (br s, 1H, NH) and 7.10-7.64 (m, 15H, phenyl H); ^{13}C NMR: δ 191.1, 186.3, 171.5, 135.8, 135.3, 134.6, 133.7, 133.1, 130.3, 128.8, 128.2, 127.9, 127.7, 127.2, 126.8, 125.3, 122.3, 121.9, 109.8; MS: 399 (M^+); Anal. Calcd. for $C_{24}H_{17}NO_3S$: C, 72.18; H, 4.26; N, 3.51; S, 8.02 %; Found: C, 71.89; H, 4.31; N, 3.59; S, 7.98 %.

2-(3-hydroxy-5-oxo-4-phenylthiophen-2(5*H*)-ylidene)-*N*-(3-methoxyphenyl)-2-phenylacetamide (3b)

Yellow solid; mp 129-131°C; Yield 91%; IR ν (cm^{-1}): 3450 (OH), 3396 (NH), 1752 (CO lactone), 1646 (C=O amide), 1608 (C=C aliphatic) 1125 (Ph-O-CH_3); ^{1}H NMR δ 13.52 (s, 1H, OH enolic), 8.30 (br s, 1H, NH), 7.12-7.59 (m, 14H, phenyl H), and 3.67 (s, 3H, OCH_3); ^{13}C NMR: δ 191.4, 187.6, 174.3, 159.6, 137.7, 136.4, 133.7, 133.1, 131.2, 127.5, 127.6, 127.3, 126.9, 125.9, 114.8, 111.3, 108.7, 105.6, 54.7; MS: 429 (M^+); Anal. Calcd. for $C_{25}H_{19}NO_4S$: C, 69.93; H, 4.43; N, 3.26; S, 7.46 %; Found: C, 69.86; H, 4.41; N, 3.31; S, 7.43 %.

***N*-(5-bromopyridin-2-yl)-2-(3-hydroxy-5-oxo-4-phenylthiophen-2(5*H*)-ylidene)-2-phenylacetamide (3c)**

Yellow solid; mp 151-153°C; Yield 86%; IR ν (cm^{-1}): 3453 (OH), 3398 (NH), 1756 (CO lactone), 1647 (CO amide), 1609 (C=C aliphatic), 670 (C-Br); ^{1}H NMR δ 13.57 (s, 1H, OH enolic), 8.36 (br s, 1H, NH), 8.26 (s, 1H, pyridine ring), 7.81 (d, 1H, pyridine ring), 7.10-7.55 (m, 10H, phenyl H) and 6.98 (d, 1H, pyridine ring); ^{13}C NMR: δ 192.2, 188.1, 171.3, 158.6, 153.1, 146.8, 133.4, 133.1, 132.1, 131.4, 129.5, 127.2, 126.8, 110.7, 110.1, 103.8; MS: 478 (M^+); Anal. Calcd. for $C_{23}H_{15}N_2O_3SBr$: C, 57.62; H, 3.13; N, 5.85; S, 6.69 %; found: C, 57.71; H, 3.16; N, 5.89; S, 6.73 %.

2-(3-hydroxy-5-oxo-4-phenylthiophen-2(5*H*)-ylidene)-*N*-(2-nitrophenyl)-2-phenyl acetamide (3d)

Yellow solid; mp 160-162°C; Yield 65%; IR ν (cm^{-1}): 3456 (OH), 3401 (NH), 1757 (CO lactone), 1653 (CO amide), 1624 (NO_2), 1613 (C=C aliphatic); ^{1}H NMR δ 13.39 (s, 1H, OH enolic), 8.38 (br s, 1H, NH) and 7.10-8.25 (m, 14H, phenyl H); ^{13}C NMR: δ 192.4, 186.9, 171.9, 143.8, 135.3, 134.2, 133.8, 133.2, 131.3, 131.1, 127.8, 127.3, 127.1, 126.8, 124.9, 121.5, 119.4, 108.6; MS: 444 (M^+); Anal. Calcd. for $C_{24}H_{16}N_2O_5S$: C, 64.86; H, 3.60; N, 6.09; S, 7.21 %; Found: C, 64.73; H, 3.58; N, 6.05; S, 7.19 %.

2-(3-hydroxy-5-oxo-4-phenylthiophen-2(5*H*)-ylidene)-2-phenyl-*N*-(pyridin-2-yl) acetamide (3e)

Yellow solid; mp 175-177°C; Yield 79%; IR ν (cm^{-1}): 3450 (OH), 3395 (NH), 1756 (CO lactone), 1647 (CO amide), 1610 (C=C aliphatic); ^{1}H NMR δ 13.56 (s, 1H, OH enolic), 8.37 (br s, 1H, NH) and 6.12-8.21 (m, 14H, phenyl H); ^{13}C NMR: δ 192.9, 186.3, 169.1, 159.4, 149.5, 137.7, 136.0, 133.4, 132.7, 129.1, 128.3, 127.2, 114.6, 111.6, 108.8; MS: 400 (M^{+}); Anal. Calcd. for $C_{23}H_{16}N_2O_3S$: C, 69.00; H, 4.01; N, 7.01; S, 8.00 %; Found: C, 69.12; H, 3.93; N, 7.05; S, 8.15 %.

2-(3-hydroxy-5-oxo-4-phenylthiophen-2(5*H*)-ylidene)-*N*-(2,4-dinitrophenyl)-2-phenylacetamide (3f)

Yellow solid; mp 158-160°C; Yield 73%; IR ν (cm^{-1}): 3456 (OH), 3398 (NH), 1759 (CO lactone), 1650 (CO amide), 1620 (NO_2), 1612 (C=C aliphatic); ^{1}H NMR δ 13.59 (s, 1H, OH enolic), 8.40 (br s, 1H, NH) and 7.21-9.10 (m, 13H, phenyl H); ^{13}C NMR: δ 192.5, 188.1, 171.7, 145.2, 142.1, 138.7, 136.8, 134.1, 133.1, 129.9, 129.1, 128.3, 127.6, 124.5, 119.7, 108.9; MS: 489 (M^{+}); Anal. Calcd. for $C_{24}H_{15}N_3O_7S$: C, 58.90; H, 3.07; N, 8.59; S, 6.54 %; Found: C, 58.75; H, 3.04; N, 8.56; S, 6.63 %.

2-(3-hydroxy-5-oxo-4-phenylthiophen-2(5*H*)-ylidene)-2-phenyl-*N*-p-tolylacetamide (3g)

Yellow solid; mp 122-124°C; Yield 87%; IR ν (cm^{-1}): 3449 (OH), 3396 (NH), 1750 (CO lactone), 1648 (CO amide), 1611 (C=C aliphatic); ^{1}H NMR δ 13.51 (s, 1H, OH enolic), 8.32 (br s, 1H, NH), 7.10-7.65 (m, 14H, phenyl H), and 2.21 (s, 3H, CH_3); ^{13}C NMR: δ 191.9, 188.1, 170.1, 137.1, 135.2, 133.4, 133.1, 132.8, 131.2, 129.4, 128.9, 128.5, 127.5, 124.0, 109.8, 25.1; MS: 413 (M^{+}); Anal. Calcd. for $C_{25}H_{19}NO_3S$: C, 72.64; H, 4.60; N, 3.39; S, 7.75 %; Found: C, 72.76; H, 4.68; N, 3.42; S, 7.71 %.

General procedure for the synthesis of 6a-e:

A mixture of 3,6-diphenyl-thieno[3,2-b]thiophene-2,5-dione **(4)** (0.01 mol) and substituted anilines **(5a-e)** (0.01 mol) in glacial acetic acid (25 mL) was refluxed for 4 h. The completion of reaction was confirmed by TLC and then the reaction mixture was poured over crushed ice, the precipitated solid was separated by filtration, washed free of acid and crystallized from glacial acetic acid to afford **6a-e**.

2-(3-mercapto-5-oxo-4-phenylthiophen-2(5*H*)-ylidene)-*N*,2-diphenylacetamide (6a)

Yellow solid; mp 149-151°C; Yield 81%; IR ν (cm^{-1}): 3401 (NH), 2849 (SH), 1753 (CO lactone), 1652 (CO amide), 1612 (C=C aliphatic); ^{1}H NMR δ 8.30 (br s, 1H, NH), 7.09-7.68 (m, 15H, phenyl H) and 1.32 (s, 1H, SH); ^{13}C NMR: δ 189.7, 171.6, 147.2, 141.2, 135.7, 135.4, 133.3, 131.8, 129.5, 127.9, 126.9, 126.0, 125.4, 123.8, 121.5; MS: 415 (M^{+}); Anal. Calcd. for $C_{24}H_{17}NO_2S_2$: C, 69.40; H, 4.10; N, 3.37; S, 15.42 %; found: C, 69.28; H, 4.15; N, 3.41; S, 15.52 %.

2-(3-mercapto-5-oxo-4-phenylthiophen-2(5*H*)-ylidene)-N-(2-nitrophenyl)-2-phenylacetamide (6b)

Yellow solid; mp 212-214°C; Yield 72%; IR ν (cm^{-1}): 3403 (NH), 2852 (SH), 1756 (CO lactone),1654 (CO amide),1623 (NO_2), 1613 (C=C aliphatic); ^{1}H NMR δ 8.28 (br s, 1H, NH), 7.12-8.10 (m, 14H, phenyl H) and 1.35 (s, 1H, SH); ^{13}C NMR: δ 190.1, 173.2, 146.8, 141.1, 140.8, 135.8, 134.9, 134.1, 133.1, 132.1, 131.5, 129.1, 128.3, 127.1, 126.3, 123.7, 122.4; MS: (460) (M^{+}); Anal. Calcd. for $C_{24}H_{16}N_2O_4S_2$: C, 62.61; H, 3.48; N, 6.09; S, 13.91 %; found: C, 62.73; H, 3.52; N, 6.05; S, 13.88 %.

2-(3-mercapto-5-oxo-4-phenylthiophen-2(5*H*)-ylidene)-N-(2,4-dinitrophenyl)-2-phenylacetamide (6c)

Yellow solid; mp 160-162°C; Yield 70%; IR ν (cm^{-1}): 3398 (NH), 2855 (SH), 1753 (CO lactone), 1675 (CO amide), 1625 (NO_2), 1610 (C=C aliphatic); ^{1}H NMR δ 8.34 (br s, 1H, NH), 7.20-9.26 (m, 13H, phenyl H) and 1.59 (s, 1H, SH); ^{13}C NMR: δ 189.7, 173.3, 147.1, 145.1, 142.1, 141.1, 139.8, 137.2, 133.9, 133.1, 132.7, 129.3, 128.6, 127.8, 126.8, 124.8, 119.1; MS: 505 (M^+); Anal. Calcd. for $C_{24}H_{15}N_3O_6S_2$: C,57.03; H, 2.97; N, 8.32; S, 12.67 %; found: C, 57.16; H, 2.95; N, 8.35; S, 12.64 %.

2-(3-mercapto-5-oxo-4-phenylthiophen-2(5*H*)-ylidene)-2-phenyl-N-p-tolyl acetamide (6d)

Yellow solid; mp 146-147°C; Yield 80%; IR ν (cm^{-1}): 3394 (NH), 2849 (SH), 1748 (CO lactone), 1650 (CO amide), 1608 (C=C aliphatic); ^{1}H NMR δ 8.31 (br s, 1H, NH), 7.08-7.56 (m, 14H, phenyl H), 2.15 (s, 3H, CH_3) and 1.51 (s, 1H, SH); ^{13}C NMR: δ 188.9, 173.8, 147.1, 141.4, 137.1, 134.5, 133.1($C1^{III}$), 132.8, 132.5, 132.3, 130.1, 129.6, 127.5, 122.2, 25.1; MS: 429 (M^+); Anal. Calcd. for $C_{25}H_{19}NO_2S_2$: C, 69.93; H, 4.43; N, 3.26 %; S, 14.92; found: C, 69.86; H, 4.52; N, 3.29; S, 14.95 %.

2-(3-mercapto-5-oxo-4-phenylthiophen-2(5*H*)-ylidene)-*N*-(4-methoxyphenyl)-2-phenyl acetamide (6e)

Yellow solid; mp 156-158°C; Yield 85%; IR ν (cm^{-1}): 3392 (NH), 2845 (SH), 1741 (CO lactone), 1647 (CO amide), 1612 (C=C aliphatic), 1148 (Ph-O-CH_3); ^{1}H NMR δ 8.29 (br s, 1H, NH), 6.56-7.68 (m, 14H, phenyl H), 3.56 (s, 3H, OCH_3) and 1.48 (s, 1H, SH); ^{13}C NMR: δ 189.0, 173.3, 147.1, 161.2, 140.5, 137.1, 135.1, 133.2, 132.1, 131.3, 129.2, 128.4, 127.3, 114.5, 110.8, 105.6, 56.4; MS: 445 (M^+); Anal. Calcd. for $C_{25}H_{19}NO_3S_2$: C, 67.42; H, 4.27; N, 3.15; S, 14.38 %; found: C, 67.26; H, 4.25; N, 3.12; S, 14.43 %.

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