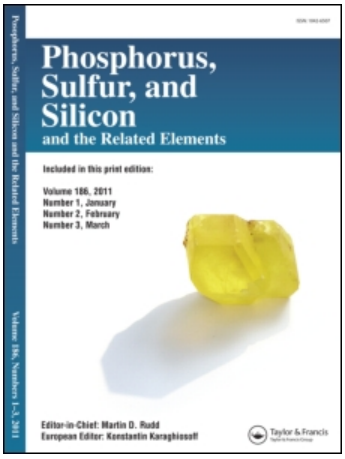

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Novel Synthesis of 2-(2-(3-Hydroxy-5-oxo-4-phenylthiophen-2(5H)-ylidene)-2-phenylacetamido)propanoic Acid Analogues and Their Anti-Inflammatory Properties

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NOVEL SYNTHESIS OF 2-(2-(3-HYDROXY-5-OXO-4-PHENYLTHIOPHEN-2(5H)-YLIDENE)-2-PHENYLACETAMIDO)PROPANOIC ACID ANALOGUES AND THEIR ANTI-INFLAMMATORY PROPERTIES

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This article describes the reaction of 3,6-diphenyl-thieno[3,2-b]furan-2,5-dione 1 with different amino acids 2a–j in glacial acetic acid which afforded the 2-(2-(3-hydroxy-5-oxo-4-phenylthiophen-2(5H)-ylidene)-2-phenylacetamido)propanoic acid analogues 3a–j and also describes the reaction of 3,6-diphenyl-thieno[3,2-b]thiophene-2,5-dione 4 with different amino acids 5a–e in acidic medium to give 2-(2-(3-mercapto-5-oxo-4-phenylthiophen-2(5H)-ylidene)-2-phenylacetamido)propanoic acid analogues 6a–e. All the compounds have been screened for their anti-inflammatory activity against the carrageenan induced rat paw edema in albino rats. In the primary screening, some of the compounds exhibited appreciable activity.

Supplemental materials are available for this article. Go to the publisher's online edition of* Phosphorus, Sulfur, and Silicon and the Related Elements *to view the free supplemental file.

Keywords Amino acids; 3,6-diphenyl-thieno[3,2-b]furan-2,5-dione; 3,6-diphenyl-thieno[3,2-b]thiophene-2,5-dione

INTRODUCTION

The wide range of biological properties and the potency for pharmaceutical applications have attracted considerable interest in the development of general methods for the synthesis of this pulvinamide group of heterocyclic molecules. Inflammation is a normal, essential, protective response to any noxious stimulus that may threaten the host and may vary from a localized reaction to a complex response involving the whole organism. An ideal anti-inflammatory drug should affect only aberrant, uncontrolled inflammation and not interfere with the normal inflammatory response, which is a part of the body's

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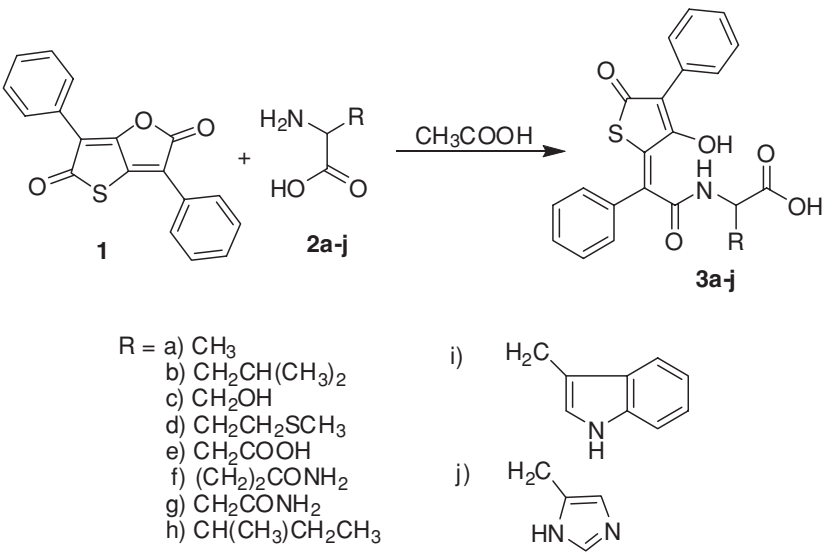
vital defense mechanism to invading microorganisms and other environmental insults.[1] Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used for treatment of pain, pyrexia, inflammation, rheumatoid arthritis, and osteoarthritis. NSAIDs block biosynthesis of prostaglandins by inhibiting enzyme prostaglandin H_2 endoperoxide synthase or cyclooxygenase (COX).[2–6]

In this article, we intend not only to investigate the synthesis of 2-(2-(3-hydroxy-5-oxo-4-phenylthiophen-2(5H)-ylidene)-2-phenylacetamido)propanoic acid analogues and 2-(2-(3-mercapto-5-oxo-4-phenylthiophen-2(5H)-ylidene)-2-phenyl acetamido)propanoic acid analogues but also to evaluate their anti-inflammatory properties. According to the literature, the pulvinic group of compounds possesses anti-inflammatory activity,[7,8] and N-heterocyclic pulvinamides also possess anti-inflammatory and anti-arthritic activity.[9,10] The interest in this study is originated by the fact that a limited number of publications have reported the synthesis of the target heterocyclic nucleus, which prompted the present investigation for establishing a novel synthetic approach.

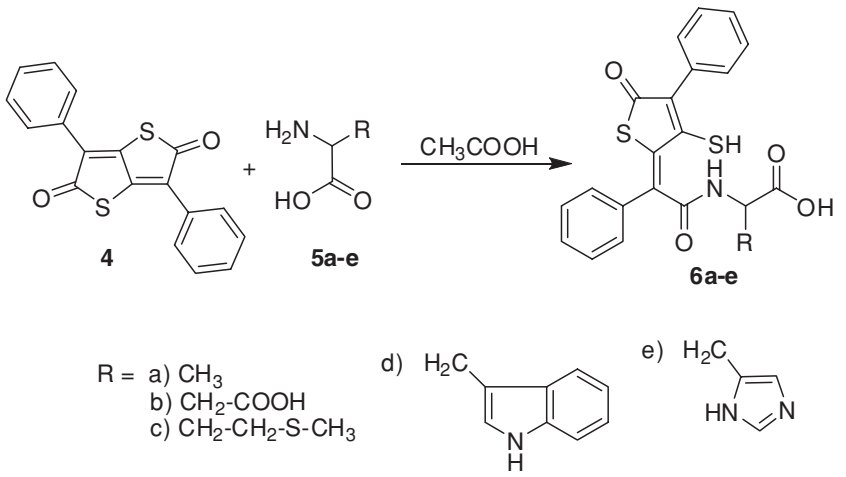
RESULTS AND DISCUSSION

Treatment of 3,6-diphenyl-thieno[3,2-b]furan-2,5-dione **1** with alanine **2a** in refluxing glacial acetic acid for 5 h provided 2-(2-(3-hydroxy-5-oxo-4-phenylthiophen-2(5H)-ylidene)-2-phenylacetamido)propanoic acid **3a** in good yield. The IR spectrum of the product **3a** shows absorbances at 3458, 3380, 1756, 1724, 1652, and 1613 cm^{-1}, which are characteristic of OH, NH, C=O lactone, C=O acid, C=O amide, and C=C aliphatic stretching, respectively. The ^1H NMR spectrum of compound **3a** revealed signals at 1.41 (d, 3H, CH_3), 4.62 (q, 1H, CH), 7.14–7.31 (m, 10H, Ar—H), 8.34 (br s, 1H, NH), 10.25 (s, 1H, COOH), and 13.52 (s, 1H, OH). The mass spectrum of compound **3a** exhibits a molecular ion peak m/z at 395 (M^+) (Scheme 1).



Scheme 1

The treatment of 3,6-diphenyl-thieno[3,2-b]thiophene-2,5-dione **4** with alanine **5a** in the same manner provided 2-(2-(3-mercapto-5-oxo-4-phenylthiophen-2(5H)-ylidene)-2-phenylacetamido) propanoic acid **6a**. The IR spectrum of **6a** revealed bands at 3415 (NH), 2846 (SH), 1753 (C═O lactone), 1710 (C═O acid), 1646 (C═O amide), and 1608 (C═C aliphatic) cm^{-1}. The ^1H NMR spectrum exhibited signals at 1.36 (s, 1H, SH), 1.39 (d, 3H, CH_3), 4.59 (q, 1H, CH), 7.10–7.54 (m, 10H, Ar—H), 8.31 (br s, 1H, NH), 10.36 (s, 1H, COOH), and molecular ion peak m/z at 411 (M^+) (Scheme 2). The remaining compounds **3b**–**3j** and **6b**–**6e** were obtained in a similar manner, characterized by IR, mass, and ^1H NMR spectra, and the results are shown in Tables I–IV.



Scheme 2

BIOLOGICAL ACTIVITY

Anti-Inflammatory Activity

The compounds **3a–j** and **6a–e** were also tested for their anti-inflammatory activity using the carrageenan-induced in rats paw edema method of Winter et Al.,[11] at an oral dose of 50 mg/kg b.w. in albino rats (weighing 80–110 g). The percent inhibition of inflammation was calculated by applying the Newbould formula.[12] (See the Supplemental Materials, Table 5S, available online.)

EXPERIMENTAL

All the melting points were determined in an open capillary in a liquid paraffin bath and are uncorrected. The purity of the compounds was checked by thin-layer chromatography (TLC). IR spectra (KBr) were recorded on a Shimadzu FTIR model 8010 spectrometer and the ^1H NMR spectra on Varian Gemini 200 MHz spectrometer using TMS as an internal standard. The C, H and N analysis of the compounds was done on a Carlo Erba model EA1108 and mass spectra on a JEOL JMS D-300 spectrometer. The starting compounds **1** and **4** were prepared according to the procedure in the literature.[13]

Table I IR (cm^{-1}) and ^1H NMR (δ ppm) of the compounds **3a–3j**

Compound	OH-str	NH-str	CO lactone	CO acid	CO amide	C=C aliphatic	^1H NMR ($CDCl_3$)
3a	3458	3380	1756	1724	1652	1613	δ 1.41 (d, 3H), 4.62 (q, 1H), 7.14–7.31 (m, 10H), 8.34 (br s, 1H), 10.25 (s, 1H), 13.52 (s, 1H)
3b	3443	3371	1751	1710	1649	1609	δ 0.97 (d, 3H), 0.99 (d, 3H), 1.65 (t, 2H), 1.79 (m, 1H), 4.38 (t, 1H), 7.12–7.58 (m, 10H), 8.32 (br s, 1H), 10.41 (s, 1H), 13.72 (s, 1H)
3c	3434	3381	1748	1703	1641	1605	δ 1.86 (s, 1H),3.98 (d, 2H), 4.46 (t, 1H), 7.09–7.53 (m, 10H), 8.33 (br s, 1H), 10.49 (s, 1H), 13.70 (s, 1H)
3d	3439	3378	1745	1708	1643	1610	δ 2.01 (s, 3H), 2.12 (q, 2H), 2.38 (t, 2H), 4.43 (t, 1H), 7.15–7.63 (m, 10H), 8.30 (br s, 1H), 10.43 (s, 1H), 13.81 (s, 1H),
3e	3451	3372	1753	1720	1651	1611	δ 2.58 (d, 2H), 4.56 (t, 1H), 7.12–7.82 (m, 10H), 8.31 (br s, 1H), 10.32 (s, 1H), 13.56 (s, 1H)
3f	3454	3365	1752	1718	1653	1609	δ 1.98 (q, 2H), 2.12 (t, 2H), 4.38 (t, 1H), 5.72 (s, 2H), 7.10–7.65 (m, 10H), 8.34 (br s, 1H), 10.34 (s, 1H), 13.61 (s, 1H)
3g	3451	3362	1750	1716	1652	1610	δ 1.98 (d, 2H), 4.35 (t, 1H), 5.70 (s, 2H), 7.08–7.56 (m, 10H), 8.32 (br s, 1H), 10.31 (s, 1H), 13.59 (s, 1H)
3h	3453	3364	1748	1712	1650	1609	δ 0.92 (t, 3H), 1.02 (d, 3H), 1.17 (m, 2H), 1.96 (m, 1H), 4.36 (d, 1H), 7.06–7.48 (m, 10H), 8.35 (br s, 1H), 10.30 (s, 1H), 13.52 (s, 1H)
3i	3438	3382	1750	1707	1643	1608	δ 2.90 (d, 2H), 4.68 (t, 1H), 6.76 (s, 1H), 7.13–7.46 (m, 14H), 8.34 (br s, 1H), 9.87 (s, 1H), 10.52 (s, 1H), 13.68 (s, 1H),
3j	3459	3386	1749	1714	1649	1606	δ 2.96 (d, 2H), 4.78 (t, 1H), 6.65 (s, 1H), 7.20 (s, 1H), 7.10–7.56 (m, 10H), 8.33 (br s, 1H), 10.58 (s, 1H), 12.84 (s, 1H), 13.65 (s, 1H)

Table II IR (cm^{-1}) and ^1H NMR (δ ppm) of the compounds **6a–6e**

Compound	SH-str	NH-str	CO lactone	CO acid	CO amide	C=C aliphatic	^1H NMR ($CDCl_3$)
6a	2846	3415	1753	1710	1646	1608	δ 1.36 (s, 1H), 1.39 (d, 3H), 4.59 (q, 1H), 7.10–7.54 (m, 10H), 8.31 (br s, 1H), 10.36 (s, 1H)
6b	2852	3412	1750	1705	1637	1606	δ 1.38 (s, 1H), 2.68 (d, 2H), 4.71 (t, 1H), 7.08–7.57 (m, 10H), 8.30 (br s, 1H), 10.49 (s, 1H)
6c	2854	3405	1752	1708	1639	1607	δ 1.37 (s, 1H), 1.97 (s, 3H), 2.10 (q, 2H), 2.38 (t, 2H), 4.43 (t, 1H), 7.10–7.65 (m, 10H), 8.34 (br s, 1H), 10.52 (s, 1H)
6d	2856	3410	1750	1706	1643	1608	δ 1.35 (s, 1H), 2.91 (d, 2H), 4.66 (t, 1H), 6.75 (s, 1H), 7.11–7.53 (m, 14H), 8.32 (br s, 1H), 9.84 (s, 1H), 10.52 (s, 1H)
6e	2849	3414	1749	1711	1640	1610	δ 1.34 (s, 1H), 2.96 (d, 2H), 4.78 (t, 1H), 6.62 (s, 1H), 7.19 (s, 1H), 7.10–7.61 (m, 10H), 8.35 (br s, 1H), 10.52 (s, 1H), 12.79 (s, 1H)

Table III Physical and analytical data of the newly synthesized compounds **3a–3j** and **6a–6e**

Compound	Mp [°C]	Yield [%]	Mol. Formula (Mol.Wt.)	Analyses % Require (Found) C	H	N	S
3a	140–142	91	$C_{21}H_{17}NO_5S$	63.80 (63.72)	4.30 (4.32)	3.54 (3.53)	8.10 (8.08)
3b	169–171	72	$C_{24}H_{23}NO_5S$	65.87 (65.91)	5.31 (5.25)	3.19 (3.22)	7.34 (7.32)
3c	150–152	78	$C_{21}H_{17}NO_6S$	61.31 (61.42)	4.14 (4.13)	3.41 (3.43)	7.79 (7.83)
3d	147–149	76	$C_{23}H_{21}NO_5S_2$	60.66 (60.56)	4.62 (4.61)	3.08 (3.06)	14.07 (14.04)
3e	151–153	82	$C_{22}H_{17}NO_7S$	60.14 (60.25)	3.87 (3.86)	3.19 (3.21)	7.29 (7.32)
3f	165–167	86	$C_{23}H_{20}N_2O_6S$	61.06 (61.11)	4.42 (4.41)	6.19 (6.17)	7.08 (7.05)
3g	155–156	82	$C_{22}H_{18}N_2O_6S$	60.27 (60.32)	4.11 (4.16)	6.39 (6.42)	7.31 (7.28)
3h	146–148	79	$C_{24}H_{23}NO_5S$	65.90 (65.86)	5.26 (5.25)	3.20 (3.26)	7.32 (7.30)
3i	149–151	68	$C_{29}H_{22}N_2O_5S$	68.24 (68.16)	4.31 (4.36)	5.49 (5.48)	6.27 (7.32)
3j	178–180	75	$C_{24}H_{19}N_3O_5S$	62.47 (62.51)	4.12 (4.10)	9.11 (9.13)	6.94 (6.93)
6a	210–212	82	$C_{21}H_{17}NO_4S_2$	61.31 (61.17)	4.14 (4.13)	3.41 (3.45)	15.57 (15.53)
6b	205–207	84	$C_{22}H_{17}NO_6S_2$	58.02 (58.13)	3.74 (4.73)	3.08 (3.07)	14.07 (14.09)
6c	198–200	72	$C_{23}H_{21}NO_4S_3$	58.60 (58.49)	4.46 (4.44)	2.97 (2.97)	20.38 (20.35)
6d	179–181	65	$C_{29}H_{22}N_2O_4S_2$	66.16 (66.21)	4.18 (4.23)	5.32 (5.30)	12.17 (12.15)
6e	203–205	62	$C_{24}H_{19}N_3O_4S_2$	60.38 (60.29)	3.98 (3.96)	8.81 (8.79)	13.42 (13.40)

2-(2-(3-Hydroxy-5-oxo-4-phenylthiophen-2(5H)-ylidene)-2-phenylacetamido)propanoic Acid Analogues 3a–j

A mixture of 3,6-diphenyl-thieno[3,2-b]furan-2,5-dione **1** (0.01 mol), amino acids **2a–j** (0.01 mol), and glacial acetic acid (25 mL) was heated to reflux temperature. The reaction mixture was maintained under reflux conditions for 5 h. After completion of the reaction (TLC), the reaction mixture was cooled to room temperature and then poured over crushed ice. The precipitated solid was separated by filtration, washed free of acid, and crystallized from the appropriate solvent to give (**3a–j**)**,** respectively (see Tables I, III, and IV).

Table IV Mass spectral fragmentation of compounds **3a–3j** and **6a–6e**

Compound	Mass spectral fragmentation
3a	395 (M^+), 377, 367, 363, 349, 335, 321, 317, 307, 306, 278, 250, 178, 134, 88
3b	437 (M^+), 419, 409, 405, 391, 377, 363, 359, 306, 250, 178, 161, 130
3c	411 (M^+), 393, 383, 379, 365, 351, 337, 333, 307, 278, 134, 104
3d	455 (M^+), 437, 427, 423, 409, 395, 381, 377, 307, 306, 278, 178, 148, 134
3e	439 (M^+), 421, 411, 407, 393, 379, 365, 361, 306, 250, 178, 161, 134, 132
3f	452 (M^+), 434, 424, 420, 406, 392, 378, 374, 307, 306, 250, 178, 145, 134
3g	438 (M^+), 420, 410, 406, 392, 378, 364, 360, 307, 306, 278, 250, 178, 145, 131
3h	437 (M^+), 419, 409, 405, 391, 377, 363, 359, 307, 306, 278, 130
3i	510 (M^+), 492, 482, 478, 464, 450, 432, 359, 306, 250, 134
3j	461 (M^+), 443, 433, 429, 415, 401, 383, 310, 307, 306, 250, 154, 130
6a	411 (M^+), 383, 379, 377, 351, 349, 323, 321, 294, 161, 88
6b	455 (M^+),427, 423, 421, 395, 393, 365, 361, 321, 266, 134
6c	471 (M^+), 443, 439, 437, 411, 409, 377, 322, 321, 304, 294, 148
6d	526 (M^+), 498, 494, 492, 466, 462, 432, 359, 322, 266, 148, 134
6e	477 (M^+), 449, 445, 443, 417, 415, 383, 322, 310, 203, 178, 154

2-(2-(3-Mercapto-5-oxo-4-phenylthiophen-2(5H)-ylidene)-2-phenylacetamido)propanoic Acid Analogues 6a–e

A mixture of 3,6-diphenyl-thieno[3,2-b]thiophene-2,5-dione **4** (0.01 mol), amino acids **5a–e** (0.01 mol), and glacial acetic acid (25 mL) was heated to reflux temperature. The reaction mixture was maintained under reflux conditions for 5 h. After completion of the reaction (TLC), the reaction mixture was cooled to room temperature and then poured over crushed ice. The precipitated solid was separated by filtration, washed free of acid, and crystallized from the appropriate solvent to give (**6a–e**), respectively (Tables II–IV).

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