Synthesis and characterization of 2-arylidene derivatives of thiazolopyrimidines with potential biological activity

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Abstract

Aryl-3,4-dihydropyrimidinones (DHPM), thiazolopyrimidines and related heteroaromatic compounds are important classes of N-containing fused heterocycles widely used as key building blocks for pharmaceutical agents due to a wide range of biological activities that include antimicrobial and antitumor properties. As part of a program aimed at preparing new bioactive heterocycles, we designed and synthesized a series of thiazolopyrimidines and their 2-arylidene derivatives. The compounds were fully characterized by 1D- and 2D-NMR, high resolution ESI-MS/MS and single crystal X-ray diffraction analysis, which indicated a consistent *Z* configuration at the arylidene double bond. In addition, the ESI-MS fragmentation mechanisms for representatives of the DHPM, thiazolopyrimidine, and 2-arylidene-thiazolopyrimidine classes were elucidated. Studies are underway to assess the biological activities of the new compounds.

Keywords

Aryl-3,4-dihydropyrimidinones; thiazolopyrimidines; biological activity

Introduction

Aryl-3,4-dihydropyrimidinones (DHPM), thiazolopyrimidines and related heteroaromatic compounds are important classes of *N*-containing fused heterocycles widely used as key building blocks for pharmaceutical agents due to a wide range of biological activities that include antimicrobial and antitumor properties. While DHPMs have emerged as potential backbones of several calcium channel blockers, antihypertensive agents and neuropeptide Y antagonists, thiazolopyrimidines and their analogues have raised considerable interest as purine isosteres[1-6].

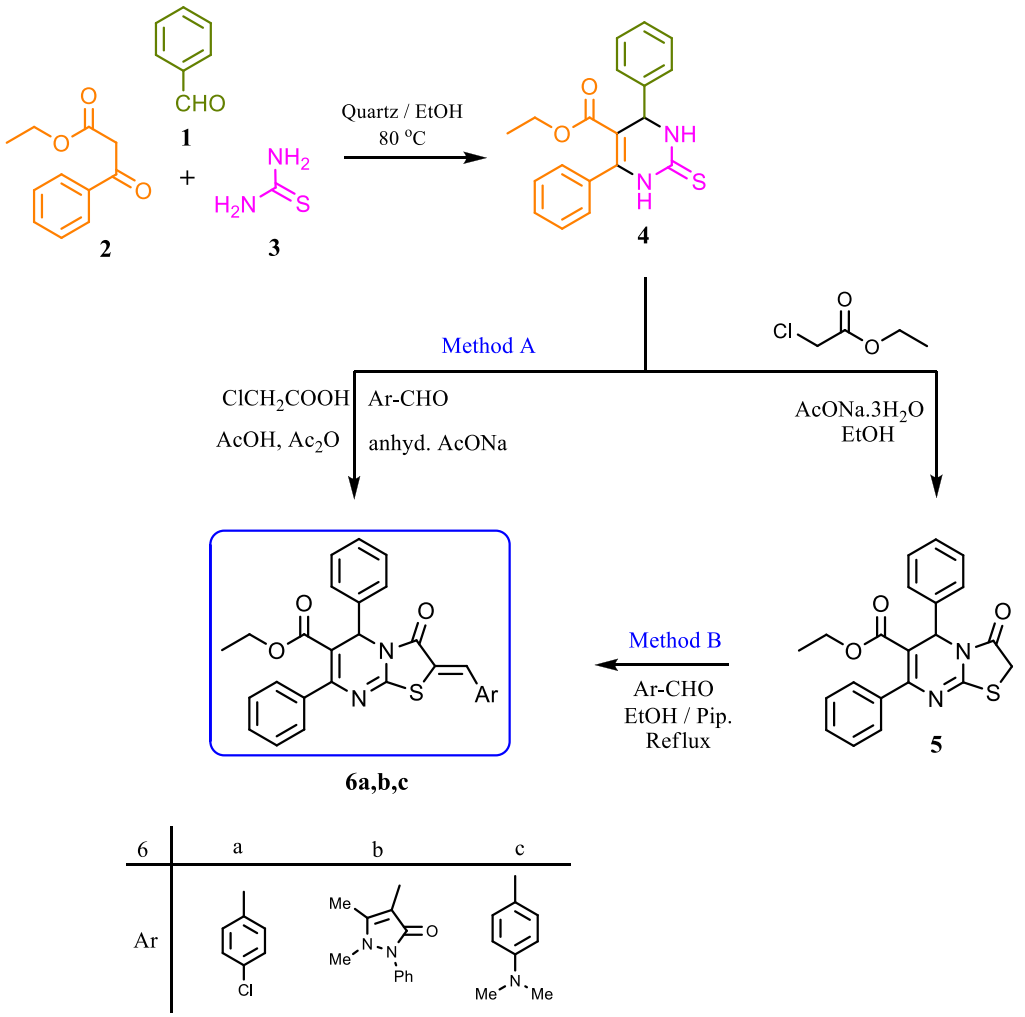
In particular, thiazolo[3,2-*a*]pyrimidine derivatives have been the focus of intense research and several members of this class have been reported to possess analgesic, anti-cancer, anti-microbial, anti-inflammatory and anti-hypertensive activities, as well as inotropic activity; other possible applications include their use as antimalarials, HIV reverse transcriptase inhibitors, and therapeutic agents for neurodegenerative diseases[2,7].

As part of a program aimed at obtaining new bioactive heterocycles, we are currently exploring thiazolo[3,2-*a*]pyrimidines and their 2-arylidene derivatives. The combination of potentially significant therapeutic value with simple and efficient synthetic procedures makes this class of compounds very appealing for biological testing. In order to modulate the affinity of these compounds to specific biological targets (*e.g.*, receptors) by rational design it is of utmost importance to obtain a full characterization of their configurational and conformational characteristics. Toward this end, we report herein a comparative characterization, primarily based on X-ray diffraction studies, of selected 2-arylidene thiazolo[3,2-*a*]pyrimidines and their synthetic precursors.

Results and Discussion

Syntheses.

We used a multiple component Biginelli-type reaction between benzaldehyde (**1**), ethyl benzoylacetate (**2**) and thiourea (**3**) to obtain the parent compound, ethyl 4,6-diphenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**4**), essentially as described[8] (**Scheme 1**). The thiazolo[3,2-*a*]pyrimidine **5** was then easily obtained by condensation with either ethyl chloroacetate or chloroacetyl chloride[8]. Although 2-arylidene derivatives of **5** could be synthesized in a one-pot process, directly from **4** (Method A)[9], we obtained better yields and purity using the isolated compound **5** as the starting material for condensation of the corresponding enolate with the appropriate aldehyde in the presence of piperidine (Method B)[8] (**Scheme 1**). The known compound **6a** and its new analogues, **6b** and **6c**, were thus prepared as racemates in good yields.



Scheme 1. Synthetic methodologies used to obtain compounds 4, 5, and 6a-c as racemic mixtures.

NMR and Mass Spectrometry Characterization.

Although compounds **4**, **5**, and **6a** had been reported before[8], the current study provides a more complete characterization. Herein, we have used 1D- and 2D-NMR, as well as mass spectrometry (MS), for the full characterization of all compounds mentioned above (*cf.* the Experimental section for a complete listing of the NMR and MS data). High-resolution electrospray ionization MS, obtained in the positive ionization mode, allowed us to establish unequivocally the molecular composition of each compound. The specific MS/MS fragmentation mechanisms will be discussed elsewhere. Moreover, the NMR spectra were fully consistent with the expected structures. Among the most notable features in these spectra were downfield shifts in the resonances of the tetrahydropyrimidine methine proton and carbon of compound **4** (5.27 and 54.08 ppm to 6.01 and 55.34 ppm, respectively) upon cyclization to compound **5**, presumably reflecting the vicinity of the electrowithdrawing carbonyl group. Further downfield shifts of the same signals occurred upon formation of the 2-arylidene compounds **6a-c**, as a result of the extended conjugation in these compounds. Also noteworthy is the significant magnetic anisotropy of the methylene protons in compound **5**, which were observed as two mutually coupled doublets at 4.14 and 4.20 ppm with a geminal constant of 17.7 Hz and bound to the same carbon at 32.67 ppm in the HSQC spectrum. In addition to the signals from the new aromatic rings, clear evidence for the formation of compounds **6a-c** from **5** stemmed from the presence of an olefinic proton singlet in each instance. However, the NMR data were insufficient to establish the configuration of the olefinic bonds and it was necessary to resort to X-ray crystallography to solve this issue (*cf.* the X-ray diffraction studies section, where data are reported for compounds **4**, **5**, and **6a-b**).

X-ray diffraction studies

Single crystal X-ray diffraction analysis allowed us to confirm the structures of compounds **4**, **5**, **6a**, and **6b** without ambiguity (**Figure 1**). Some of the relevant crystal parameters are reported in **Table 1**, while selected geometrical parameters are presented in **Tables 2** and **3**. For structurally similar fragments, bond lengths and angles are comparable in all four molecules and well within the expected range, as judged from extensive analysis of the values included in the CSD.[10, 11]

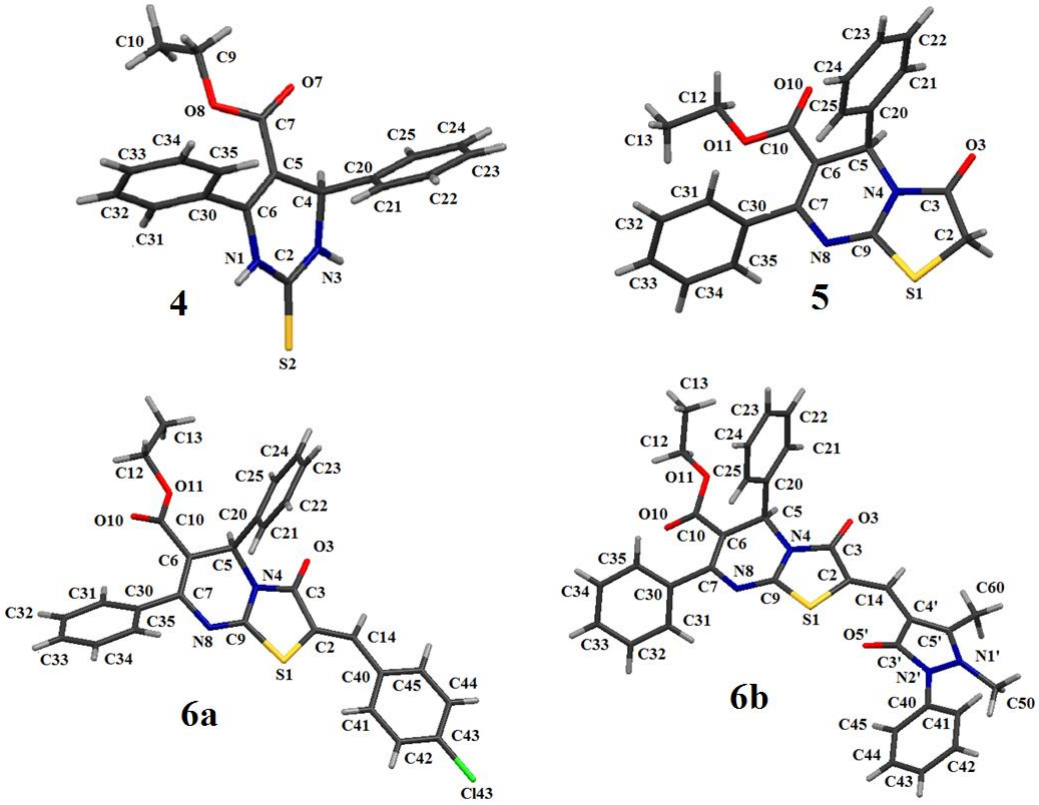


Figure 1. Diagrams of the molecular structures of compounds **4**, **5**, **6a** and **6b**, showing the atomic labelling scheme.

Table 1. Crystal parameters for compounds **4**, **5**, **6a**, and **6b**

Compound	4	5	6a	6b
Empirical formula	$C_{19}H_{18}N_2O_2S$	$C_{42}H_{36}N_4O_6S_2$	$C_{28}H_{21}ClN_2O_3S$	$C_{99}H_{84}N_{12}O_{13}S_3$
Formula weight	338.41	756.87	500.98	1745.96
Crystal system	Monoclinic	Monoclinic	Monoclinic	Triclinic
Space group	P 21/n	P 21/c	P 21/c	P -1
a (Å)	13.511(9).	8.0299(12)	8.6549(8)	11.991(5)
b (Å)	8.255(6)	22.015(3)	12.0701(14).	12.758(5)
c (Å)	16.230(10)	21.508(3)	24.114(3).	31.425(12)
α (°)	90	90	90	94.90(2)
β (°)	99.15(2)	91.461(5)	100.106(5)	97.07(2)
γ (°)	90	90	90	105.11(2)
Volume (Å^3)	1787(2)	3801.0 (1)	2480.0(5)	4571(3)
Z	4	4	4	2
Packing index	64.2	66.2	65.7	63.6

Table 2. Selected geometrical parameters for compound **4**

Bond	Bond length [Å]	Angle	Angle [°]
N(1)-C(2)	1.360(3)	C(2)-N(1)-C(6)	123.1(2)
N(1)-C(6)	1.387(3)	N(3)-C(2)-N(1)	116.4(2)
S(2)-C(2)	1.680(3)	N(3)-C(2)-S(2)	121.9(2)
N(3)-C(2)	1.327(3)	N(1)-C(2)-S(2)	121.70(18)
N(3)-C(4)	1.469(3)	C(2)-N(3)-C(4)	126.8(2)
C(4)-C(5)	1.508(3)	N(3)-C(4)-C(5)	108.95(18)
C(5)-C(6)	1.353(3)	N(3)-C(4)-C(20)	110.4(2)
Torsion angle [(*R*)-molecule]	**Angle [°]**	C(5)-C(4)-C(20)	113.3(2)
O(7)-C(7)-C(5)-C(4)	-11.5(4)	C(6)-C(5)-C(7)	125.1(2)
		C(6)-C(5)-C(4)	120.6(2)
		C(7)-C(5)-C(4)	114.2(2)
		C(5)-C(6)-C(30)	126.6(2)
		N(1)-C(6)-C(30)	113.9(2)
		C(5)-C(6)-N(1)	119.5(2)
Angle between planes		**Angle [°]**	
N1-C2-N3-C4-C5-C6 / C20-…-C25		85.68(13)	
N1-C2-N3-C4-C5-C6 / C30-…-C35		66.15(17)	

Table 3. Selected geometrical parameters for compound **5, 6a and 6b**

Molecule	5	6a	6b		5	6a	6b
	Bond length [Å]				**Angle [°]**		
S(1)-C(2)	1.798(6)	1.752(3)	1.761(9)	C(9)-S(1)-C(2)	92.1(2)	91.58(12)	90.7(4)
S(1)-C(9)	1.746(4)	1.754(3)	1.746(9)	C(3)-C(2)-S(1)	107.8(3)	110.13(18)	109.7(7)
C(3)-C(2)	1.510(8)	1.481(3)	1.460(12)	C(14)-C(2)-C(3)		120.5(2)	119.8(8)
O(3)-C(3)	1.198(6)	1.210(3)	1.205(10)	C(14)-C(2)-S(1)		129.34(19)	130.3(7)
N(4)-C(3)	1.383(6)	1.382(3)	1.380(11)	N(4)-C(3)-C(2)	110.7(5)	110.6(2)	111.2(8)
N(4)-C(5)	1.484(5)	1.478(3)	1.464(10)	O(3)-C(3)-N(4)	123.8(5)	122.6(2)	122.2(8)
C(5)-C(6)	1.516(5)	1.522(3)	1.516(12)	O(3)-C(3)-C(2)	125.5(5)	126.8(2)	126.7(9)
C(6)-C(7)	1.352(6)	1.339(3)	1.339(12)	C(3)-N(4)-C(5)	121.1(4)	122.0(2)	122.8(7)
N(8)-C(7)	1.415(5)	1.420(3)	1.420(11)	C(9)-N(4)-C(3)	117.4(4)	116.2(2)	115.7(7)
N(8)-C(9)	1.292(6)	1.276(3)	1.280(10)	C(9)-N(4)-C(5)	121.4(3)	120.8(2)	120.6(7)
N(4)-C(9)	1.361(6)	1.373(3)	1.345(10)	N(4)-C(5)-C(6)	107.8(3)	108.2(2)	108.0(6)
				N(4)-C(5)-C(20)	109.4(3)	109.80(18)	111.0(6)
				C(6)-C(5)-C(20)	113.3(3)	112.1(2)	111.2(7)
				C(7)-C(6)-C(10)	125.8(4)	122.6(2)	129.3(9)
				C(7)-C(6)-C(5)	122.2(4)	122.2(2)	120.9(8)
				C(10)-C(6)-C(5)	112.0(3)	114.9(2)	109.8(8)
				C(6)-C(7)-N(8)	122.3(4)	122.5(2)	120.9(8)
				C(6)-C(7)-C(30)	126.8(4)	126.7(2)	126.0(8)
				N(8)-C(7)-C(30)	110.9(4)	110.8(2)	113.1(8)
				C(9)-N(8)-C(7)	115.9(4)	116.2(2)	117.7(7)
				N(8)-C(9)-N(4)	127.2(4)	126.4(2)	125.0(8)
				N(8)-C(9)-S(1)	120.9(4)	122.2(2)	122.4(7)
				N(4)-C(9)-S(1)	111.9(3)	111.48(18)	112.5(6)
Torsion Angle [(*R*)- molecules]		**Angle [°]**					
O(10)-C(10)-C(6)-C(5	-1.6(6)	-149.0(3)	-2.9(14)				
Angle between planes		**Angle [°]**					
Center ring[a] / C20-25	84.40(13)	90.60(8)	85.4(3)				
Center ring[a] / C30-35	58.38(16)	127.95(8)	49.5(3)				
Center ring[a] / C40-45		5.86(6)					
Center ring[a] / N ring[b]			9.5(3)				
N ring[b] / C40-45			48.8(4)				

[a]S1-C2-C3-N4-C5-C6-C7-N8-C9
[b]N1'-N2'-C3'-C4'-C5'

All four compounds have two phenyl groups bonded to a quasi-planar (see **Figure 1** and **Tables 2**, **and 3**) dihydropyrimidine-containing central ring. The dihedral angles that these substituents form with the central ring are very similar, with the exception of the one involving the phenyl C30-35 group in **6a** (S1,C2,C3,N4,C5,C6,C7,N8,C9 / C30-35). This difference can be attributed to the packing in compound **6a** that places the ester group of a second molecule very close to the C30-C35 phenyl ring, forcing it to rotate to the opposite direction of the ester group of its own molecule (*see **Figure 3***). Apart from this difference, and despite not presenting large values of packing indexes, it is

possible to attribute the main geometrical features in these compounds to an attempt to achieve the most compact structures possible.[12] Another fragment whose orientation is affected by this trend is the ester group itself (*see the torsion angles in* ***Tables 1 and 2***).

Regarding compound **4,** it is noteworthy that S(2)-C(2) has all the characteristics of a double bond. Indeed, the angles around C(2) are in the range 116.4-121.9° and the bond length is 1.680 Å. Carbon-sulfur double bonds usually display values between 1.630 and 1.720 Å while, as expected, single bonds are longer (1.749 – 1.856 Å).[10]

In compounds **6a** and **6b** there is a third substituent bound to C(2) of the central thiazolopyrimidinone ring by a carbon-carbon double bond. Importantly, single crystal X-ray diffraction allows the unequivocal confirmation that this double bond displays a *Z* configuration in both molecules. Moreover, the decreased lengths of the C(2)-C(3) and S(1)-C(2) bonds (*e.g.*, compared to compound **5**, **Table 3**), are consistent with an extended electron delocalization, spanning from these substituents to the carbonyl group and the sulphur atom of the central ring. Interestingly, the remarkable stereoselectivity observed in the formation of compounds **6a-c** is consistent with a few other reports[7, 13-17], though most studies have left the configuration of the olefinic bond undetermined.

Supramolecular interactions

Analysis of the crystal packing for compounds **4**-**6b** confirms that they are all racemic mixtures, as expected from the lack of stereoselectivity of the reaction conditions involved in their synthesis.

Compound **4** has four molecules in the unit cell, two of isomer *R* and two of isomer *S*. Since it is the only molecule in this study with good hydrogen donors, it is the only one that forms classical hydrogen bonds: N(3)-H(3N)···O(7) between molecules of the same configuration within the unit cell, and an $R^2_2(8)$ synthon involving N(1)-H(1N)···S(2) interactions with molecules outside the unit cell (*see* ***Figure 2*** *and* ***Table 4***)

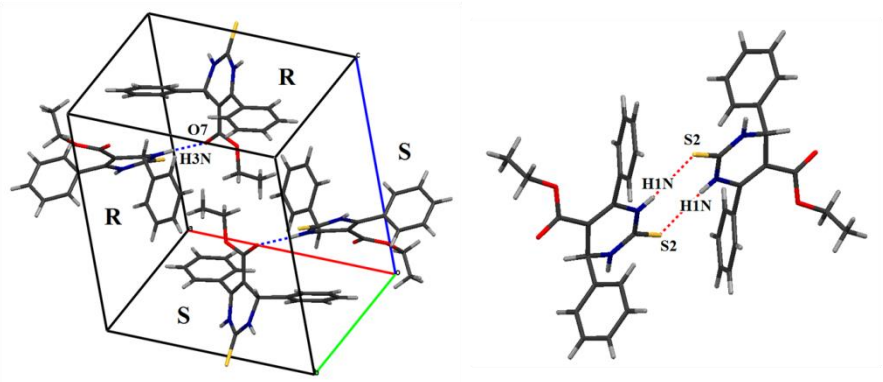


Figure 2. Hydrogen bonds in compound **4**: inside the unit cell (left) and with other molecules outside the unit cell (right).

The other molecules analyzed in the current study present weak short range C-H···X (X = O, N, S) interactions only. **Figure 3** displays the packing inside the unit cells of **5**, **6a** and **6b**. Since the 3D supramolecular structures of these compounds are very complex, only the interactions between molecules within the unit cell of compound **5** are included in this figure. The complete list of supramolecular interactions for these molecules can be found in **Table 4**.

It is noteworthy that the packing of compound **6a** results in a short distance between the ester group of an *R* molecule and the C30-35 phenyl substituent of an *S* molecule (≈ 3.00 Å between H(12A) and the phenyl plane). This value suggests the existence of a C-H···π interaction, which is consistent with the above mentioned rotation of the phenyl away from the ester group.

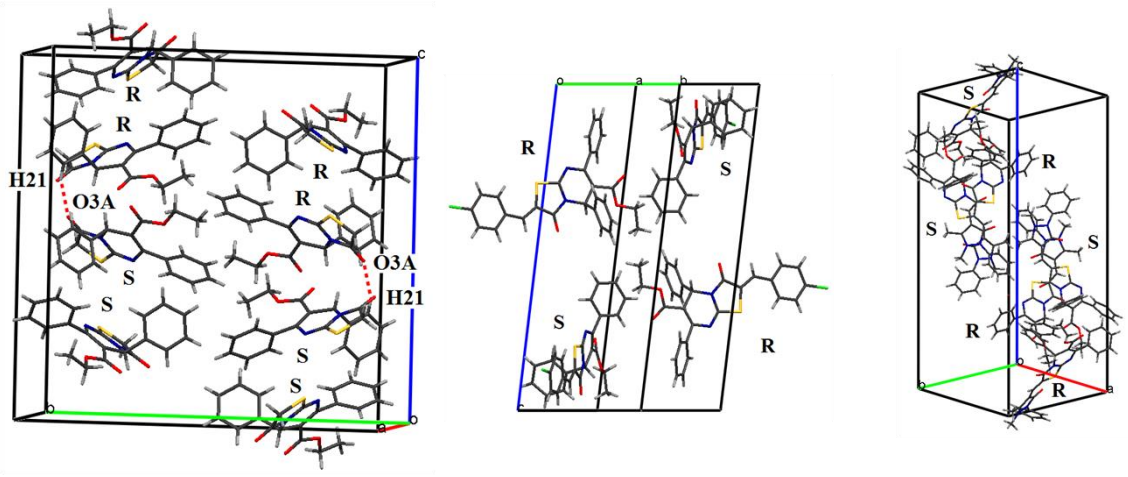


Figure 3. Packing of compounds **5** (left), **6a** (center), and **6b** (right) within their respective unit cells.

Table 4. Interaction parameters for compounds **4**, **5**, **6a**, and **6b**

D-H···A	H···A [Å]	D···A [Å]	D-H···A [°]	Symmetry operation
Compound 4				
N(3)-H(3N)···O(7)	2.02	2.872(2)	159	1/2-x,1/2+y,1/2-z
N(1)-H(1N)···S(2)	2.52	3.337(2)	173	-x,1-y,1-z
Compound 5				
C(21)-H(21)···O(3A)	2.51	3.2810(5)	140	x,1/2-y,1/2+z
C(2)-H(2A)···O(10)	2.52	3.3549(5)	144	-1+x,y,z
C(2A)-H(2D)···O(10A)	2.56	3.3677(5)	141	-1+x,y,z
Compound 6a				
C(14) --H(14) ..O(3)	2.55	3.3969(4)	152	-x,-y,1-z
C(45) --H(45) ..O(3)	2.57	3.3767(4)	146	-x,-y,1-z
C(42) --H(42) ..O(10)	2.45	3.1349(4)	130	-x,-1/2+y,1/2-z
C(22) --H(22) ..N(8)	2.62	3.5066(4)	160	-x,1/2+y,1/2-z
C(35) --H(35) ..Cl(43)	2.83	3.7226(5)	161	-1-x,1/2+y,1/2-z
C(41) --H(41) ..S(1)	2.56	3.2611(4)	133	Possible Intramolecular
Compound 6b				
C41A --H41A ..O3A	2.48	3.3477(14)	155	2-x,1-y,1-z
C41B --H41B ..O3B	2.33	3.1531(13)	147	1-x,1-y,-z
C50B --H50G ..O10A	2.55	3.4719(14)	162	1-x,1-y,-z
C44B --H44B ..O5'B	2.50	3.3503(14)	153	2-x,1-y,-z
C44B --H44B ..S1B	2.78	3.5336(15)	139	2-x,1-y,-z

Conclusions

We have characterized a set of selected racemic 2-arylidene thiazolo[3,2-*a*]pyrimidines of potential interest for therapeutic uses. By using X-ray diffraction studies, we were able to establish that formation of the olefinic double bond was stereoselective for the *Z* configuration, which is consistent with a few other literature reports for analogous compounds. The compounds reported herein are currently undergoing biological testing.

Experimental

Chemicals and general procedures. All reagents were purchased from commercial sources and used without further purification, unless stated otherwise. Whenever necessary, solvents were dried by standard methods[18].

Melting temperatures were measured with a Leica Galen III hot stage apparatus and are uncorrected.

^{1}H NMR spectra were recorded on a Bruker Avance III 400 spectrometer, operating at 400 MHz. ^{13}C NMR spectra were recorded on the same instrument, operating at 100.62 MHz. Chemical shifts are

reported in ppm downfield from tetramethylsilane and coupling constants (*J*) are reported in Hz; the subscript *gem* indicates a *geminal* coupling of enantiotopic protons. Resonance and structural assignments (indicated using the IUPAC nomenclature system) were based on the analysis of coupling patterns, including the ^{13}C-^{1}H coupling profiles obtained from heteronuclear single quantum coherence (HSQC) and heteronuclear multiple bond correlation (HMBC) experiments, performed with standard pulse programs. The abbreviations Ph and Ar represent phenyl and aryl groups, respectively.

Low resolution mass spectra (MS) were recorded on an LCQ Fleet ion trap mass spectrometer equipped with an electrospray (ESI) ion source (Thermo Scientific). The mass spectrometer was operated in the ESI positive ion mode, with the following optimized parameters: ion spray voltage, ± 4.5 kV; capillary voltage, 16 V; tube lens offset, −63 V; sheath gas (N_2), 80 arbitrary units; auxiliary gas (N_2), 5 arbitrary units; capillary temperature, 300 °C. Spectra typically correspond to the average of 20−35 scans and were recorded in the range between 100 and 1500 Da. Tandem mass spectra (collision-induced dissociation experiments) were obtained with an isolation window of 4−9 Da, a 20−30% relative collision energy, and an activation energy of 30 ms. Data acquisition and processing were performed using the Xcalibur software.

High-resolution mass spectra (HRMS) were obtained on a Bruker Impact II quadrupole time-of-flight mass spectrometer (Bruker Daltoniks). The MS source parameters were set as follows: dry gas heater temperature, 150 °C; dry gas flow, 3 L/min; capillary voltage, 1600 V.

Syntheses

Ethyl 4,6-diphenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4). Compound **4** was synthesized as previously described.[8] Briefly, a mixture of benzaldehyde (1 mmol), ethyl benzoylacetate (1 mmol), thiourea (1 mmol) and quartz (0.5 g) in ethanol (15 mL) was refluxed for 3h. After completion of the reaction, as monitored by thin layer chromatography (tlc), the catalyst was filtered off and the solution was kept overnight. The precipitate formed on setting was filtered under suction and then recrystallized from ethanol to afford the pure product **4**.

Yield 85%; R_f 0.54 (tlc, silica, 2/1 hexane/ethyl acetate); **mp** 193-195 °C (lit[9], 192 °C); **^{1}H NMR (DMSO-d_6)** δ 0.73 (t, 3H, *J* 7.0, C**H$_3$**CH$_2$O), 3.74 (q, 2H, *J* 7.1, CH$_3$C**H$_2$**O), 5.27 (d, 1H, *J* 3.4, C$_4$-**H**), 7.30-7.41 (m, 10 H, Ph-**H**), 9.75 (s, 1H, exchangeable, N3-**H**), 10.47 (s, 1H, exchangeable, N1-**H**); **^{13}C NMR (DMSO-d_6)** δ 13.31 (**C**H$_3$), 54.08 (**C4**), 59.44 (**C**H$_2$), 101.82 (**C5**), 126.38, 127.68, 127.78, 128.63, 128.66, 129.08 (Ph-**C**H), 133.98, 143.00 (Ph-**C$_{quat}$**), 145.79 (**C6**), 164.87 (**C**=O), 174.51 (**C**=S); **ESI-MS**

m/z 339 $[MH]^+$; **ESI-MS/MS** (339) *m/z* 322, 280, 276, 263, 234, 219; **HRMS (ESI-TOF) Calcd for** $C_{19}H_{19}N_2O_2S$, *m/z* 339.1162 ($[MH]^+$), **Found** 339.1154 (Δ= -2.4 ppm).

Ethyl 3-oxo-5,7-diphenyl-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-6-carboxylate (5). Compound **5** was synthesized from **4**, essentially as described[8]. Comparable results were obtained by reacting **4** (10 mmol) with either *a)* ethyl chloroacetate (20 mmol) and sodium acetate trihydrate (15 mmol) under reflux in ethanol (30 mL) for 7hr or *b)* with chloroacetyl chloride (10 mmol) in dry dioxane at room temperature. In both instances the product precipitated and was filtered off. Following recrystallization from ethanol, the pure compound was obtained quantitatively.
Yield 90%; R_f 0.49 (tlc, silica, 2/1 hexane/ethyl acetate); **mp** 139-140 °C (lit[8], 136-138 °C); **^{1}H NMR (DMSO-d_6)** δ 0.77 (t, 3H, *J* 7.1, C**H$_3$**CH_2O), 3.80 (q, 2H, *J* 6.9, CH_3C**H$_2$**O), 4.14 (d, 1H, J_{gem} 17.7, C2-**Ha**), 4.20 (d, 1H, J_{gem} 17.8 C2-**Hb**), 6.01 (s, 1H, C5-**H**), 7.31-7.41 (m, 10 H, Ph-**H**); **^{13}C NMR (DMSO-d_6)** δ 13.27 (**C**H_3), 32.67 (**C2**), 55.34 (**C**5), 60.00 (**C**H_2), 108.77 (**C6**), 127.37, 127.60, 128.20, 128.55, 128.62, 128.80 (Ph-**C**H), 138.74, 140.11 (Ph-**C$_{quat}$**), 149.99 (**C7**), 160.73 (**C9**), 165.53 (O-**C**=O), 171.02 (**C3**); **ESI-MS** *m/z* 379 $[MH]^+$; **ESI-MS/MS** (379) *m/z* 333, 305, 263, 219; **HRMS (ESI-TOF) Calcd for** $C_{21}H_{19}N_2O_3S$, *m/z* 379.1111 ($[MH]^+$), **Found** 379.1111 (Δ = 0.0 ppm).

General procedure for the preparation of 2-arylidene derivatives (6) of thiazolopyrimidine 5.
Although 2-arylidene derivatives of **5** can be synthesized in a one-pot process, directly from **4**, [9] we obtained better yields and purity using the isolated compound **5** as the starting material[8]. Briefly, a mixture of **5** (1 mmol), the appropriate aromatic aldehyde (1 mmol) and piperidine (80 µL, 0.8 mmol) was refluxed in ethanol. After completion of the reaction (*ca.* 3h), as monitored by tlc, the mixture was kept overnight, upon which the solid precipitate was filtered off and crystallized from ethanol.

Ethyl (2*Z*)-2-(4-chlorobenzylidene)-3-oxo-5,7-diphenyl-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-6-carboxylate (6a).
Yield 88%; R_f 0.64 (tlc, silica, 2/1 hexane/ethyl acetate); **mp** 175-177 °C (lit[8], 164-166 °C; lit[9], 164 °C); **^{1}H NMR ($CDCl_3$)** δ 0.87 (t, 3H, *J* 7.2, C**H$_3$**CH_2O), 3.90 (q, 2H, *J* 7.03, CH_3C**H$_2$**O), 6.32 (s, 1H, C_5-**H**), , 7.31-7.54 (m, 14H, Ar-**H**), 7.70 (s, 1H, C2=C**H**); **^{13}C NMR ($CDCl_3$)** δ 13.60 (**C**H_3), 56.41 (**C**5), 60.80 (**C**H_2), 110.66 (**C6**), 121.09 (**C2**), 128.09, 128.17, 128.36, 129.01, 129.07, 129.11, 129.72, 131.26 (Ar-**C**H), 131.81 (Ar-**C$_{quat}$**), 132.06 (C2=**C**H), 136.68, 138.89, 139.56 (Ar-**C$_{quat}$**), 151.09 (**C7**), 155.69 (**C9**), 165.13

(**C3**), 165.92 (O-**C**=O); **ESI-MS** *m/z* 501 [^{35}Cl-MH]$^+$, **ESI-MS/MS** (501) *m/z* 473, 455, 440, 423, 377, 263, 219; **HRMS Calcd for** $C_{28}H_{22}{}^{35}ClN_2O_3S$, *m/z* 501.1034 ([MH]$^+$), **Found** 501.1042 (Δ = 1.6 ppm).

Ethyl (2*Z*)-2-[(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)methylidene]-3-oxo-5,7-diphenyl-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-6-carboxylate (6b).

Yield 72 %; ***R*$_f$** 0.55 (tlc, silica, ethyl acetate); **mp** 170-2 °C; **^{1}H NMR ($CDCl_3$)** δ 0.86 (t, 3H, *J* 7.1, C**H$_3$**CH$_2$O), 2.31 (s, 3H, pyrazole-C5-C**H$_3$**), 3.24 (s, 3H, pyrazole-N1-C**H$_3$**), 3.87 (q, 2H, *J* 7.1, CH$_3$C**H$_2$**O), 6.24 (s, 1H, thiazolopyrimidine-C5-**H**), 7.42 (s, 1H, C2=C**H**), 7.26-7.52 (m, 15H, Ph-**H**); **^{13}C NMR ($CDCl_3$)** δ 10.99 (pyrazole-C5-**C**H$_3$), 13.63 (**C**H$_3$CH$_2$O), 34.77 (pyrazole-N1-**C**H$_3$), 55.95 (thiazolopyrimidine-**C5**), 60.40 (CH$_3$**C**H$_2$O), 103.02 (pyrazole-**C4**), 108.70 (thiazolopyrimidine-**C6**), 116.65 (thiazolopyrimidine-**C2**), 123.55 (C2=**C**H), 126.27, 127.81, 128.03, 128.56, 128.61, 128.66, 128.73, 128.78, 129.73 (Ph-**C**H), 133.58, 139.66, 140.74 (Ph-**C**), 152.52 (thiazolopyrimidine-**C7**), 153.22 (pyrazole-**C5**.), 159.08 (thiazolopyrimidine-**C9**), 162.54 (pyrazole-**C3**), 166.40 (thiazolopyrimidine-**C3**), 166.64 (O-**C**=O); **ESI-MS** *m/z* 577 [MH]$^+$, **ESI-MS/MS** (577) *m/z* 549, 531, 505, 273, 245, 239; **HRMS Calcd for** $C_{33}H_{29}N_4O_4S$, *m/z* 577.1904 ([MH]$^+$), **Found** 577.1902 (Δ = -0.3 ppm).

Ethyl (2*Z*)-2-[4-(dimethylamino)benzylidene]-3-oxo-5,7-diphenyl-2,3-dihydro-5*H*-1,3]thiazolo [3,2-*a*]pyrimidine-6-carboxylate (6c).

Yield 75%; ***R*$_f$** 0.71 (tlc, silica, 2/1 hexane/ethyl acetate); **mp** 236-238 °C; **^{1}H NMR ($CDCl_3$)** δ 0.87 (t, 3H, *J* 7.1, C**H$_3$**CH$_2$O), 3.05 (s, 6H, -N(C**H$_3$**)$_2$), 3.89 (q, 2H, *J* 7.0, CH$_3$C**H$_2$**O), 6.32 (s, 1H, C$_5$-**H**), 6.70 (d, 2H, J_{ortho} 8.9, Ar-**H**), 7.28-7.55 (m, 12H, Ar-**H**), 7.69 (s, 1H, C2=C**H**); **^{13}C NMR ($CDCl_3$)** δ 13.65 (**C**H$_3$CH$_2$O), 40.15 (-N(**C**H$_3$)$_2$), 55.99 (**C5**), 60.55 (CH$_3$**C**H$_2$O), 109.48 (**C6**), 112.08 (Ar-**C**H), 113.24 (**C2**), 120.71 (Ar-**C$_{quat}$**), 128.01, 128.13, 128.34, 128.81, 128.87, 132.57 (Ar-**C**H), 134.87 (C2=**C**H), 139.51, 140.37, 151.72 (Ar-**C$_{quat}$**), 152.14 (**C7**), 157.58 (**C9**), 165.83 (**C3**), 166.07 (O-**C**=O); **ESI-MS** *m/z* 510 [MH]$^+$, **ESI-MS/MS** (510) *m/z* 482, 464, 432, 405, 358, 219, 206, 191; **HRMS Calcd for** $C_{30}H_{28}N_3O_3S$, *m/z* 510.1846 ([MH]$^+$), **Found** 510.1858 (Δ 2.4 ppm).

X-Ray crystallographic analysis

X-ray crystallographic data for compounds **4**, **5**, **6a**, and **6b** were collected from single crystals using an area detector diffractometer (Bruker AXS-KAPPA APEX II) at room temperature and graphite-monochromated Mo Kα (λ = 0.71073 Å) radiation. Cell parameters were retrieved using Bruker SMART software and refined with Bruker SAINT[19] on all observed reflections. Absorption

corrections were applied using SADABS.[20] The structures were solved by direct methods using SHELXT[21] and refined with full-matrix least-squares refinement against F^2 using SHELXL.[22] All the programs are included in the WINGX package (version 2014.01).[23] All non-hydrogen atoms were refined anisotropically, and the hydrogen atoms were inserted in idealized positions, riding on the parent C atom, except for those connected to nitrogen atoms, which were placed according to the electron density maps. Drawings were made using Mercury CSD 3.8 (Build RC2).[24] Geometrical parameters such as angles between planes and ring planarity were calculated using Olex^2 – 1.2.7,[25] while intermolecular interactions were determined using Platon 111114[26] and visualized using Mercury. Despite several attempts, good quality crystals of compound **6b** could not be obtained, a circumstance that is reflected in the refinement of the crystal structure. Crystallographic data for compounds **4**, **5**, **6a**, and **6b** were deposited with the Cambridge Crystallographic Data Centre (CCDC 1496341-1496344) and can be obtained free of charge from: CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: 44-1223-226033; e-mail: deposit@ccdc.cam.ac.uk) or http://www.ccdc.cam.ac.uk/deposit.

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