RSC Advances

PAPER

Cite this: *RSC Adv.*, 2024, **14**, 35585

Reaction of unsymmetrical α-bromo-1,3-diketones with *N*-substituted thioureas: regioselective access to 2-(*N*-arylamino)-5-acyl-4-methylthiazoles and/or rearranged 2-(*N*-acylimino)-3-*N*-aryl-4-methylthiazoles†

Ranjana Aggarwal, *[ab] Shilpa Sharma,[a] Naman Jain,[a] Dionisia Sanz,[c] Rosa M. Claramunt,[c] Patricia Delgado[d] and M. Carmen Torralba[e]

Received 27th July 2024
Accepted 29th August 2024

DOI: 10.1039/d4ra05436a

rsc.li/rsc-advances

The present study reports some fascinating results of Hantzsch's [3 + 2] cyclic condensation of α-bromo-1,3-diketones, a tri-electrophilic synthon generated *in situ* by bromination of 1,3-diketones using the mild brominating reagent NBS with trinucleophilic *N*-substituted thioureas. Interestingly, out of a total of 20 combinations, 10 resulted in the exclusive formation of the desired 2-(*N*-arylamino)-5-acyl-4-methylthiazoles regioselectively, seven led to the formation of unexpected 2-(*N*-acylimino)-3-*N*-aryl-4-methylthiazoles through an interesting C–N acyl migration, and three furnished a mixture consisting of both products. The regioselectivity pattern of the two products may be attributed to a greater electrophilicity of the carbonyl carbon of the acetyl group than that of the acyl group towards both nitrogens of thiourea. The structures of the thiazole derivatives were unambiguously assigned using ^{1}H-NMR, ^{13}C-NMR, and rigorous heteronuclear 2D-NMR [(^{1}H–^{13}C) HMQC and (^{1}H–^{13}C) HMBC] spectroscopic techniques. The outcomes of the spectroscopic experiments were further concurred through X-ray crystallographic studies, and a plausible mechanism for acyl migration was proposed for the formation of the unexpected rearranged product.

Introduction

Among heterocycles, thiazoles are notably important due to their potential as bioactive compounds and versatile building blocks for natural products and pharmaceuticals. 2-Aminothiazoles and 2-iminothiazoles are important sub-units in a number of therapeutically active compounds with a wide range of pharmacological activities, such as antiviral,[1] anticancer,[2] antibacterial,[3] antifungal,[4] anticonvulsant,[5] antimicrobial,[6] anti-parkinsonian[7] and anti-inflammatory activities,[8] which can be illustrated well by the large number of drugs in the market containing this moiety. In this regard, the anticonvulsant riluzole, anti-parkinsonian talipexole, antischistosomal miridazole, anthelmintic tiabendazole, antibacterial sulfathiazole, antidepressant pramipexole, and anti-inflammatory fentiazac and fanetizole are well-cited examples.[9] Moreover, the 2-aminothiazole ring has been applied in other fields, such as polymers,[10] fungicides[11] and antioxidants.[12]

Pertaining to the immense therapeutic eminence, a number of synthetic attempts have been made by various research groups for the synthesis of 2-aminothiazole derivatives, including the cyclocondensation of amidines with phenacyl bromides[13–15] (path I, Chart 1), *N*-substituted thiourea with β-ketoesters[16–18] (path II, Chart 1) and propargyl bromides[19] (path III, Chart 1), potassium thiocyanate with vinyl azides[20] or oximes[21] (path IV, Chart 1), thiourea with phenacyl bromides[22,23] (path V, Chart 1) and aliphatic or aromatic amines with monothiodiketones[24] (path VI, Chart 1). However, only a few reports have cited the use of NBS and *N*-substituted thiourea derivatives. Additionally, although occasionally refined, these methods suffer from demerits such as a longer reaction time, involvement of lachrymatory α-haloketone, low yields, and tedious workup methods.

[a]Department of Chemistry, Kurukshetra University, Kurukshetra, Haryana, India
[b]CSIR-National Institute of Science Communication and Policy Research, New Delhi, India. E-mail: ranjana67in@yahoo.com; ranjanaaggarwal67@gmail.com; Tel: +91 9896740740
[c]Departamento de Química Orgánica y Bio-orgánica, Facultad de Ciencias, UNED, Avenida Esparta s/n, Las Rozas, E-28232, Madrid, Spain
[d]Unidad de Difracción de Rayos X – CAI de Técnicas Químicas, Facultad de Ciencias Químicas, UCM, E-28040 Madrid, Spain
[e]Departamento de Química Inorgánica, Facultad de Ciencias Químicas, UCM, E-28040 Madrid, Spain

† Electronic supplementary information (ESI) available: Additional experimental data (^{1}H, ^{13}C, HMBC, HMQC spectra and X-ray crystallographic studies) for the final compounds. CCDC 2312181–2312183. For ESI and crystallographic data in CIF or other electronic format see DOI: https://doi.org/10.1039/d4ra05436a

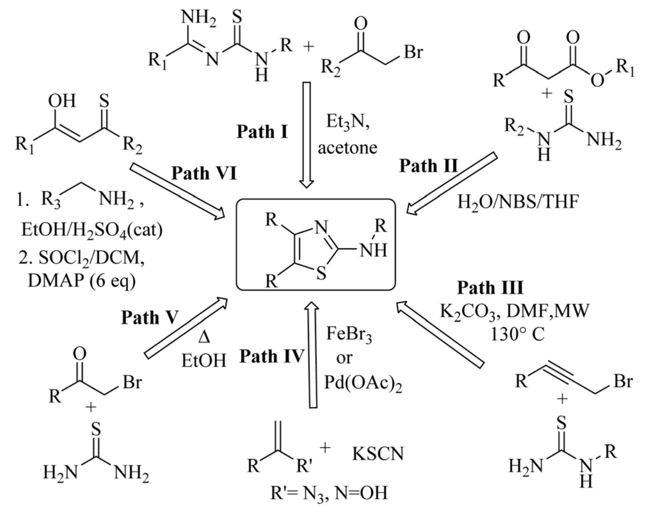


Chart 1 Reported literature methods for 2-aminothiazole derivatives.

Moreover, there is no existing literature report involving a regioselective study of the reaction between the unsymmetrical 1,3-diketones with thiourea derivatives.

However, a careful literature survey revealed that there are some limited methods to synthesis 2-iminothiazole derivatives, mainly dealing with the reaction of 2-chloro carbonyl compounds with aromatic amines and phenacyl bromides in two-step TEBA catalyzed aqueous medium (path I, Chart 2).[25] Other synthetic methods involve the cyclocondensation of amines, and isocyanates with phenacyl bromides (path II, Chart 2),[26,27] nitro epoxides (path III, Chart 2),[28] and β-nitroacrylates (path IV, Chart 2).[29] Additionally, the reaction of tetramethyl guanidine with isocyanate and 2-chloro-1,3-dicarbonyl compounds[30] has been reported to yield a 2-iminothiazole derivative (path V, Chart 2). However, these methods suffer from drawbacks like a multi-step reaction sequence, long reaction time, use of catalysts, and low reaction yields. Also, synthons such as nitro epoxides, β-nitroacrylates and tetramethyl guanidine are not easily accessible, which makes the synthesis of 2-iminothiazole even more challenging.

Our research group has been actively engaged in heterocyclic synthesis using a regioselective reaction between α-bromo-1,3-diketones and various binucleophiles, such as 2-aminopyridine,[31] tetrahydropyrimidine-2-thione,[32] imidazole-2-thione,[33] [1,2,4]triazole-3-thiol,[34] 4-amino-[1,2,4]triazole-3-thiol,[35] thiazole-4-thiocarboxamide[36] and thiosemicarbazide,[37] employing various eco-friendly synthetic routes. Very recently, we have reported the solvent-free regioselective reaction of unsymmetrical diketones **1** with thioamide **3** derivatives, as the binucleophile, for thiazole synthesis,[38] where only one regioisomer is obtained exclusively out of two possible regioisomers (Scheme 1).

This intrigued us to undertake the reaction of trinucleophilic *N*-substituted thiourea derivatives with trielectrophilic α-bromo-1,3-diketone, as regiochemical control of the reaction may generate further complexity in the product formation. α-Bromo-1,3-diketones **6** (generated *in situ* by bromination of 1,3-diketones **1** using the mild brominating reagent NBS **2**) is a potential trielectrophile with sites A_1, A_2 and A_3. In principle, its reaction with *N*-substituted thiourea derivatives **7** (a trinucleophile with reactive sites B_1, B_2 and B_3) may result in the formation of four isomers: 2-(*N*-arylamino)-5-acyl-4-methylthiazoles **8**, 2-(*N*-arylamino)-5-acetyl-4-arylthiazoles **9**, 2-imino-3-(*N*-aryl)-5-acyl-4-methylthiazoles **10**, and 2-imino-3-(*N*-aryl)-5-acetyl-4-arylthiazoles **11**. This would fix the attack of more nucleophilic sulfur (B_2) to displace bromine at A_2 through nucleophilic substitution in the first step (Scheme 2).

Despite the possibility of the insertion of an additional chemical handle, the reaction of α-bromo-1,3-diketones with a trinucleophile (such as substituted thioureas) remains unexplored. Keeping in mind our interest in the synthesis of 2-amino/imino thiazole derivatives,[39–41] along with the quest to study the regioselectivity pattern in the reaction of 1,3-diketones with binucleophiles, we report here the synthesis of 2-(*N*-arylamino)-5-acyl-4-methylthiazole derivatives, along with the

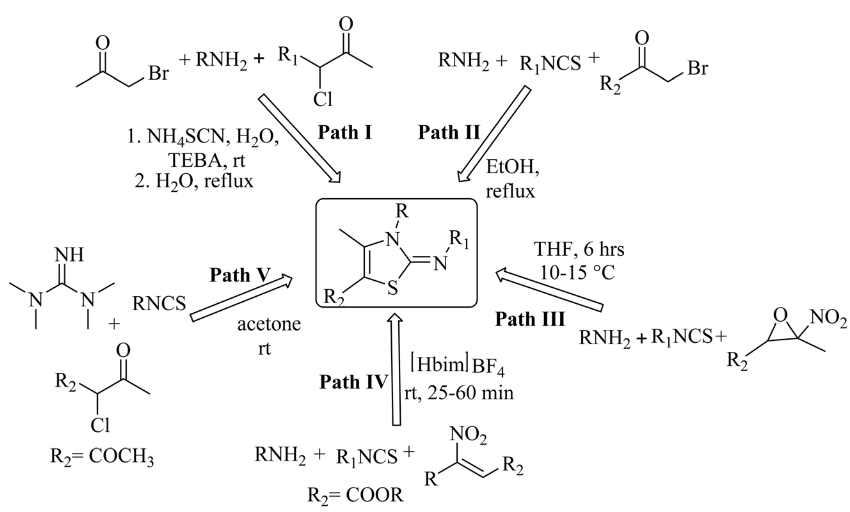
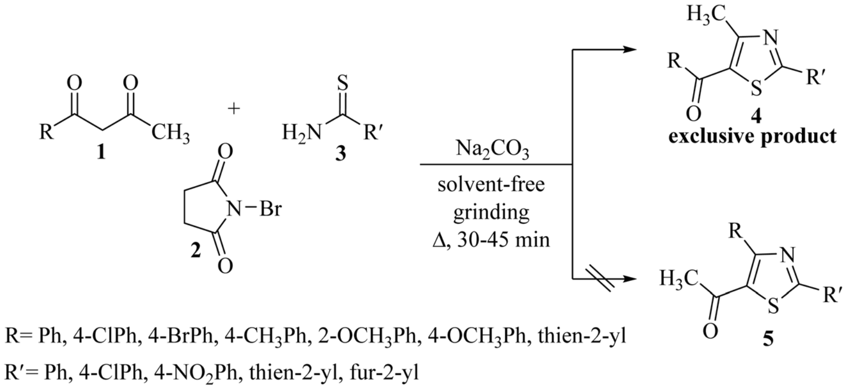
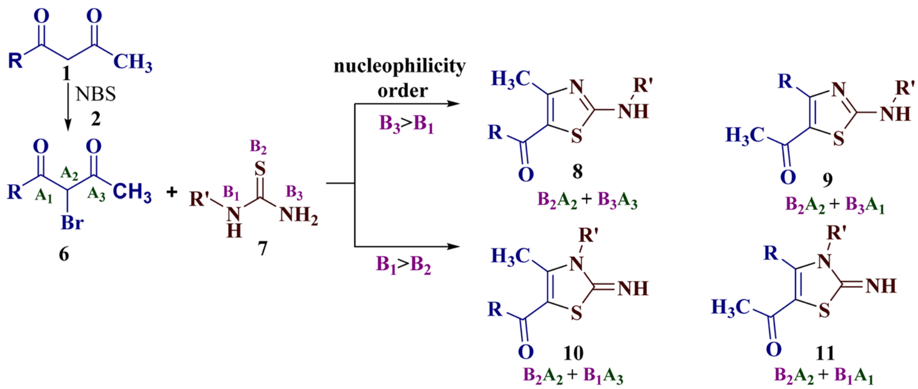


Chart 2 Reported literature methods for 2-iminothiazole derivatives.



Scheme 1 Previous work on the synthesis of thiazole derivatives from thioamides.



Scheme 2 The four possible regioisomers **8**, **9**, **10** and **11** of the reaction of α-bromo-1,3-diketones **6** with *N*-substituted thiourea derivative **7**.

rearranged product 2-(*N*-acylimino)-3-*N*-aryl-4-methylthiazoles under a solvent-free synthetic approach using 1,3-diketones and *N*-substituted thiourea derivatives.

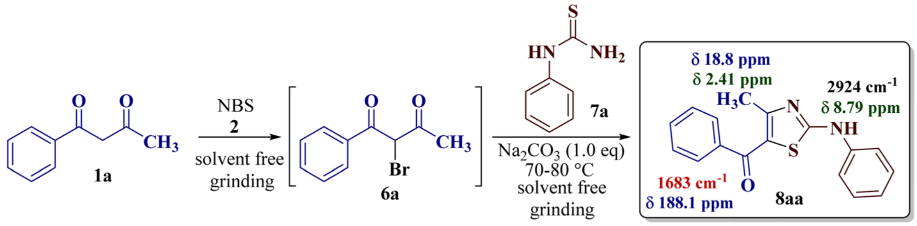
Results and discussion

For the reaction, unsymmetrical 1,3-diketones **1a–e** were prepared by the sodium ethoxide-mediated Claisen condensation reaction of various acetophenones with ethyl acetate, according to the literature method.[42] *N*-Bromosuccinimide **2** was chosen as a brominating agent due to its mild oxidizing ability, easy availability, low cost, and ease of application. *N*-Substituted thioureas **7** were prepared by HCl-catalyzed thiocyanation reaction of different anilines with ammonium thiocyanate in water at 70–80 °C.[43]

In our earlier laboratory studies,[44] the solvent-free organic synthesis has been a matter of practice[45,46] to induce excellent regioselectivity, along with extraction of a considerable product yield (70–80%), ruling out of the possibility of solvolysis. Solid-phase synthesis has emerged as the preferred synthetic route in the last few years due to its associated merits, including a more efficient and regioselective product formation, the avoidance of separating lachrymatory α-halocarbonyl compounds, simple reaction conditions and reduced reaction times, environmentally benign approach, cost-effective method, and reduced or no use of organic solvents.

Exploiting the same synthetic strategy, the present reaction protocol was studied by implementing solid-phase synthesis. In this pretext, 1-phenylbutane-1,3-dione **1a** (1.0 eq.) was pulverized with NBS **2** (1.0 eq.) in a dry mortar using a pestle to form α-bromo-1-phenylbutane-1,3-dione **6a**, according to a literature procedure.[47] The so-formed α-bromo-1-phenylbutane-1,3-dione **6a** was treated with *N*-phenyl thiourea **7a** (1.0 eq.). The resulting mixture was minced well, but the TLC did not confirm the completion of the reaction and the product could be recovered only in 50% yield.

As a mild base, sodium carbonate has been reported to be a good promoter in thiazole synthesis,[38] and is helpful in accelerating the reaction by consuming hydrobromic acid produced within the reaction. Taking the lead, the present reaction protocol was improvised by the addition of an equivalent amount of sodium carbonate and smashing the reaction mixture well using a pestle and mortar at a temperature between 70 and 80 °C. A reaction mass developed into a sticky solid in about an hour, with TLC indicating the complete consumption of reactants **6a** and **9a**, along with the formation of a single product. The reaction content on dilution with water resulted in a fluffy solid formation at ambient temperature. The solid product was filtered, dried, and recrystallized using ethanol to give a thiazole derivative in 77.8% reaction yield. The so-obtained thiazole derivative was later characterized as 2-(*N*-phenylamino)-4-methyl-5-benzoylthiazole **8aa** (Scheme 3).



Scheme 3 Reaction optimization between 1-phenylbutane-1,3-dione **1a** with *N*-phenyl thiourea **7a** to give 2-(*N*-phenylamino)-4-methyl-5-benzoylthiazole **8aa**.

The IR spectrum of compound **8aa** revealed the presence of a strong absorption band at 1683 cm^{-1}, which was attributed to a carbonyl group, and a sharp band corresponding to the N–H group was observed at 2924 cm^{-1}. Also, the presence of a single peak at δ 2.41 ppm integrated to three protons of a methyl group and at δ 8.79 ppm integrated for the N–H proton, along with the multiplet of ten protons of two phenyl rings in region δ 7.16–7.75 ppm, in the ^{1}H-NMR spectrum of compound **8aa** indicated the complete exhaustion of the starting materials. The desired corresponding fourteen peaks in the ^{13}C-NMR spectrum of compound **8aa** demonstrated the successful construction of the thiazole ring. Further, the product formation of **8aa** was established, comparing the melting point and other analytical data with the literature.[19]

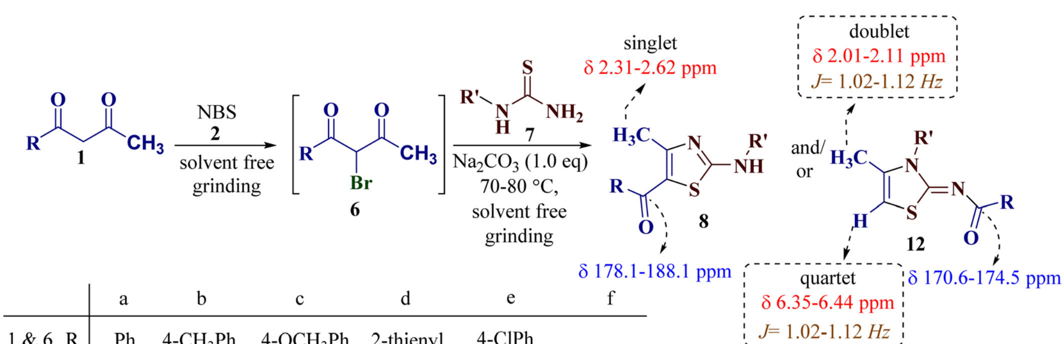
To study the scope of the reaction, differently substituted 1,3-diketones **1a–e** were employed to react with various *N*-substituted thiourea derivatives **7a–f** containing electron-donating and electron-withdrawing groups under identical reaction conditions to obtain regioselective thiazoles (Scheme 4).

Encouraged by the success of the unsubstituted phenyl thiourea **7a** with differently substituted 1,3-diketones **1a–d** to afford 2-(*N*-arylamino)-5-acyl-4-methylthiazoles **8aa–ad**, we envisaged exploring the reaction scope with other *N*-substituted thiourea **7b–f** with 1,3-diketones **1a–e**. It is interesting to note that the reaction outcomes were not uniform as per our expectations. Instead, various combinations resulted in the production of the anticipated product 2-(*N*-arylamino)-4-methyl-5-acyl thiazole **8**, in some cases an unforeseen rearranged product 2-(*N*-acylimino)-4-methyl-3-(*N*-aryl)thiazole **12** and a combination of both in rest (Table 1).

The condensation reaction of *N*-phenyl thiourea **7a** with differently substituted 1,3-diketones **1a–d** was attempted under identical conditions, which resulted in the formation of the corresponding 2-*N*-(4-methylphenyl)amino-5-acyl-4-methyl thiazoles **8aa–ad** in quantitative yields (60–80%).

It is interesting to note that condensation of *p*-chlorophenyl thiourea **7b** with 1-phenylbutane-1,3-dione **6a** led to the formation of an unexpected product with interesting observations. The IR spectrum of the product did not display the significant peak for the NH stretch expected from the desired amino thiazole **8**. Rather, it showed a stretching band at 1599 cm^{-1} corresponding to C=N. The most striking feature in the ^{1}H NMR spectra was a doublet of three proton intensity, which was attributed to the methyl group at δ 2.06 ppm with a coupling constant of J = 1.12 Hz, instead of a sharp peak of three proton intensity at the thiazole derivative with δ 2.67–2.41 ppm, as observed in isomer **8aa–ad**. Also, a quartet of one proton intensity at δ 6.39 ppm was attributed to 5-H with a coupling constant value of J = 1.12 Hz, indicated the allylic cross-coupling of methyl protons with the 5-H in ^{1}H-NMR spectrum. Similarly, the chemical shift of the methyl group shifted upfield to δ 15.1 ppm in the ^{13}C-NMR spectrum, instead of δ 18.8–18.6 ppm in isomers **8aa–ad**. Furthermore, HRMS studies supported thiazole ring formation by displaying the base peak at an *m*/*z* value of 329.8231.

It has been proposed earlier that the reaction between the trielectrophilic α-bromo-1,3-diketone **8** and trinucleophilic *N*-substituted thiourea derivative **7** can lead to the formation of



	a	b	c	d	e	f
1 & 6 R	Ph	4-CH_3Ph	4-OCH_3Ph	2-thienyl	4-ClPh	
7 R′	Ph	4-ClPh	2-ClPh	4-CH_3Ph	4-OCH_3Ph	4-NO_2Ph

Scheme 4 The general synthetic route to thiazole derivatives using 1,3-diketones **1a–e** and *N*-substituted thiourea derivatives **7a–f**.

Table 1 Product ratios of different thiazole derivatives on extending the substrate scope

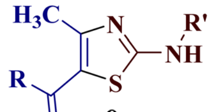
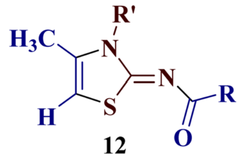
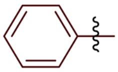
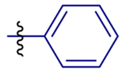
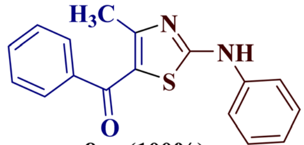
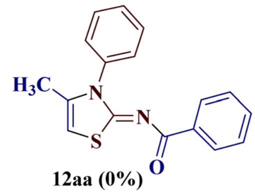
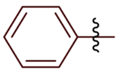
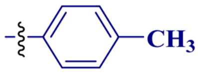
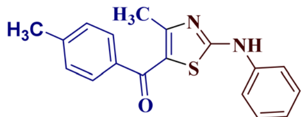
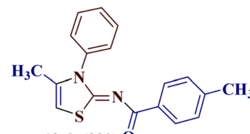
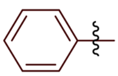
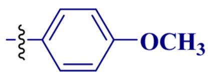
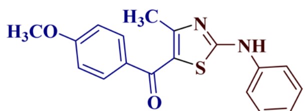
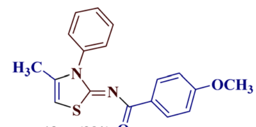
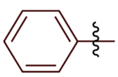
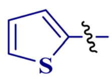
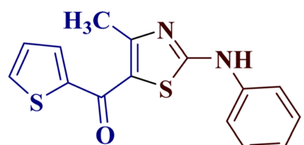
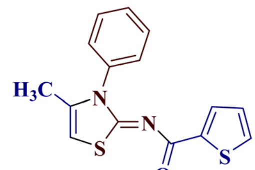
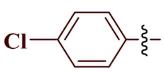
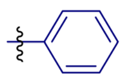
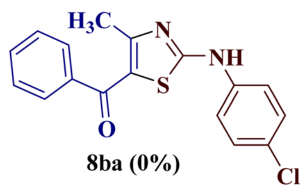
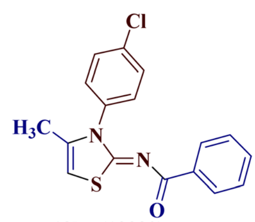
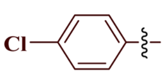
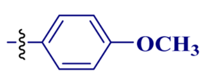
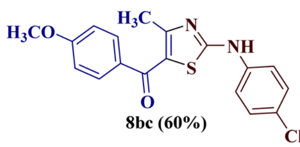
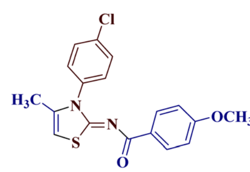
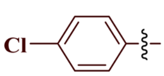
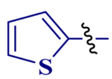
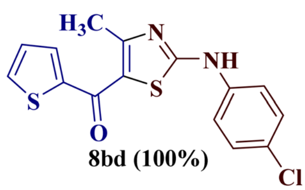
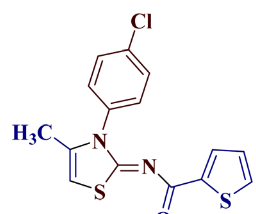
			Ratio[a] of regioisomers	
Compd number	R′ (7)	R (1)	 8	 12
aa			 **8aa (100%)**	 **12aa (0%)**
ab			 **8ab (100%)**	 **12ab (0%)**
ac			 **8ac (100%)**	 **12ac (0%)**
ad			 **8ad (100%)**	 **12ad (0%)**
ba			 **8ba (0%)**	 **12ba (100%)**
bc			 **8bc (60%)**	 **12bc (40%)**
bd			 **8bd (100%)**	 **12bd (0%)**

Table 1 (*Contd.*)

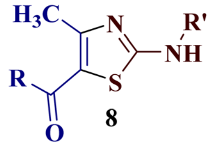
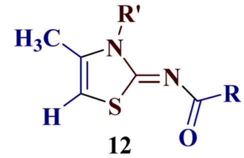
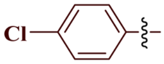
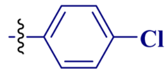
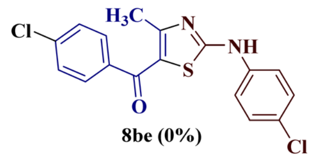
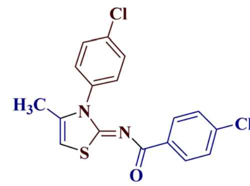
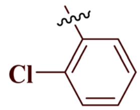
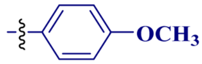
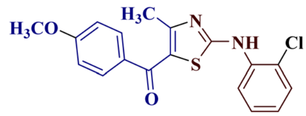
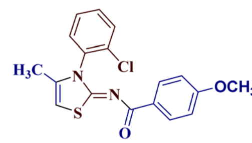
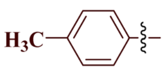
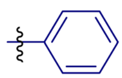
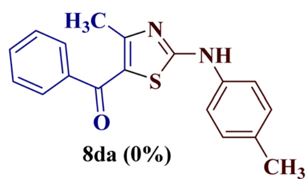
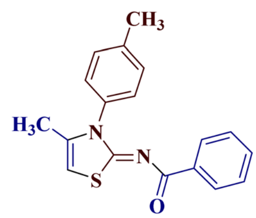
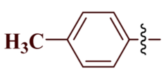
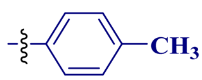
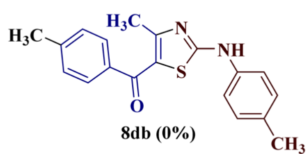
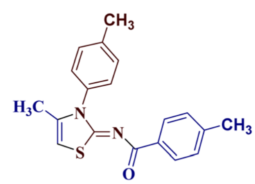
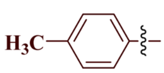
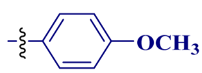
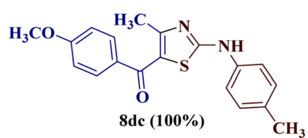
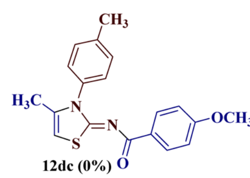
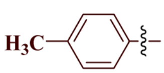
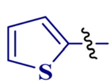
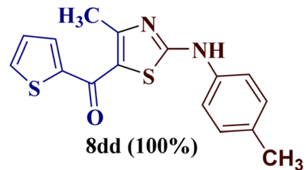
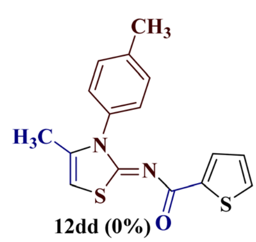
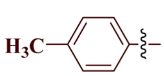
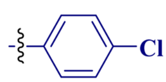
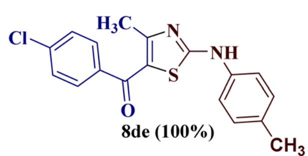
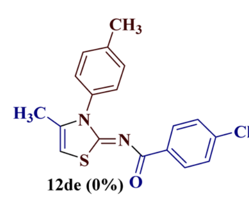
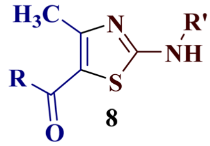
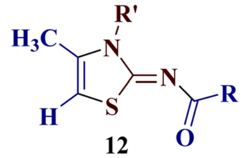
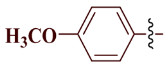
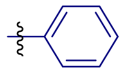
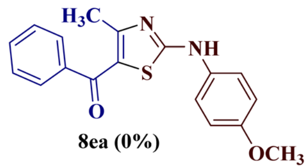
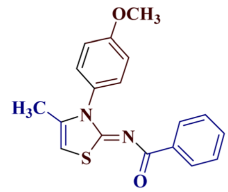
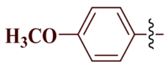
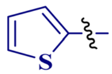
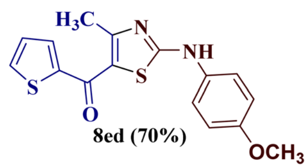
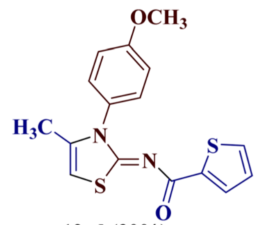
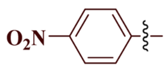
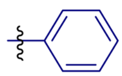
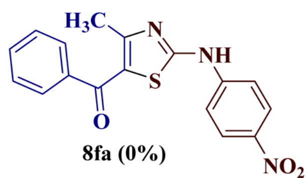
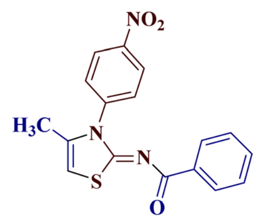
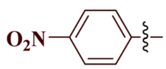
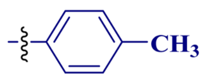
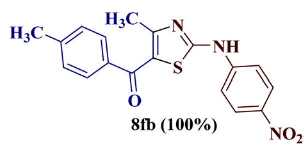
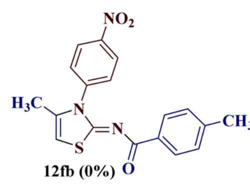
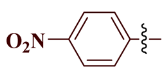
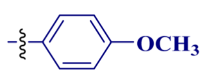
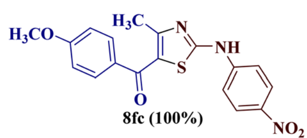
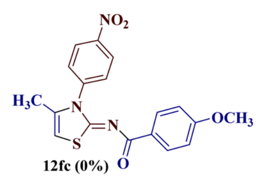
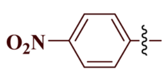
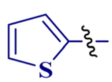
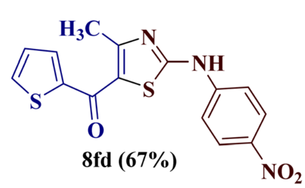
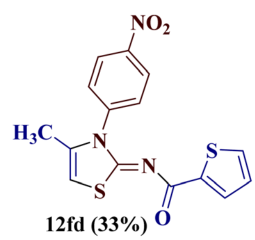
Compd number	R′ (7)	R (1)	Ratio[a] of regioisomers	
			 8	 12
be			 8be (0%)	 12be (100%)
cc			 8cc (0%)	 12cc (100%)
da			 8da (0%)	 12da (100%)
db			 8db (0%)	 12db (100%)
dc			 8dc (100%)	 12dc (0%)
dd			 8dd (100%)	 12dd (0%)
de			 8de (100%)	 12de (0%)

Table 1 (*Contd.*)

			Ratio[a] of regioisomers	
Compd number	R′ (7)	R (1)	 8	 12
ea			 **8ea (0%)**	 **12ea (100%)**
ed			 **8ed (70%)**	 **12ed (30%)**
fa			 **8fa (0%)**	 **12fa (100%)**
fb			 **8fb (100%)**	 **12fb (0%)**
fc			 **8fc (100%)**	 **12fc (0%)**
fd			 **8fd (67%)**	 **12fd (33%)**

[a] The product ratio of two isomers is calculated through the ^{1}H-NMR spectra of the crude reaction mixture.

four closely resembling regioisomers (Scheme 1). However, the combined spectral data did not correspond to either of the proposed thiazole derivatives **8–11**, as none of these justify the presence of the mutually correlated methyl group and vicinal 1-H proton in the product. Therefore, on the basis of the data, the compound was identified as 2-(*N*-benzoylimino)-3-*N*-(*p*-chlorophenyl)-4-methylthiazole **12ba**, which is possible through an intramolecular rearrangement involving C–N acyl migration.

Formation of 2-(*N*-benzoylimino)-3-*N*-(*p*-chlorophenyl)-4-methylthiazole **12ba** has also been reported in the literature through the aqueous mediated reaction of *N*-(4-chlorophenylcarbamothioyl)benzamide with 1-bromopropan-2-one (lit. mp 210 °C) by Wang *et al.*[25] The melting point and the analytical data of the rearranged thiazole derivative were found to be in agreement with 2-(*N*-benzoylimino)-3-*N*-(*p*-chlorophenyl)-4-methylthiazole **12ba**, thereby confirming the proposed structure.

Similar results were obtained for the reaction of **7b** with 1-(*p*-chlorophenyl)butane-1,3-dione **1e**, where a quantitative amount of 2-(*N*-(*p*-chlorobenzoyl)imino)-3-*N*-(*p*-chlorophenyl)-4-methylthiazole **12be** was observed.

However, the reaction of *p*-chlorophenyl thiourea **7b** with 1-(*p*-methylphenyl)butane-1,3-dione **1b** proceeded to give the expected 2-(*N*-(*p*-chlorophenylamino))-4-methyl-5-(*p*-methylbenzoyl)thiazole **8bb** efficiently with a single peak for the three protons of the methyl group (4-CH_3) at δ 2.39 ppm, along with eight aromatic protons of two *p*-substituted phenyl rings.

This type of observation was also consistent for 1-(thiophen-2-yl)butane-1,3-dione **1d** to furnish 2-*N*-(*p*-chlorophenylamino)-4-methyl-5-(2-thienoyl)thiazole **8bd**.

Reaction of *p*-chlorophenyl thiourea **7b** with *p*-methoxyphenylbutane-1,3-dione **1c** yielded a mixture of two products, as evident from TLC (Table 1). The two isomers **8bc** and **12bc** were distinguishable from each other due to the slightly different R_f value on TLC (EtOAc : pet ether, 1 : 4), and existed in a 60 : 40 ratio in a crude mixture, as indicated by the chemical shift values of the methyl group in ^{1}H and ^{13}C-NMR spectroscopy.

For a detailed structural investigation of the two isomers, the product mixture of the reaction between the *N*-(*p*-chlorophenyl) thiourea derivative **7b** and 1-(4-methoxyphenyl)butane-1,3-dione **1c** was separated through column chromatography using pet ether : ethyl acetate (4 : 1) as eluting medium. The two isomers 2-*N*-(*p*-chlorophenylamino)-4-methyl-5-(*p*-methoxybenzoyl)thiazole **8bc** and 2-(*N*-(*p*-methoxybenzoyl)imino)-3-*N*-(*p*-chlorophenyl)-4-methylthiazole **12bc** obtained after separation were individually analyzed through ^{1}H and ^{13}C-NMR spectroscopic techniques.

However, when the reaction was carried out between *N*-(*o*-chlorophenyl)thiourea derivative **7c** and 1-(4-methoxyphenyl) butane-1,3-dione **1c**, 2-imino thiazole derivative **12cc** was obtained exclusively. The reaction of the *N*-(*p*-methylphenyl)thiourea derivative **7d** with unsymmetrical 1,3-diketones **1a–e** furnished 2-amino thiazoles in three combinations (**8dc**, **8dd** and **8de**), while 2-imino thiazoles were used in the remaining two combinations (**12da** and **12db**). Furthermore, the reaction of *N*-(*p*-methylphenyl)thiourea derivative **7e** with unsymmetrical 1,3-diketones **1a** and **1d** furnished 2-imino thiazole derivative exclusively in one case (**12ea**), while a mixture of 2-imino thiazole and 2-amino thiazole was used in the second case (**8ed** and **12ed**). Finally, the reaction of *N*-(*p*-nitrophenyl)thiourea derivative **7f** with unsymmetrical 1,3-diketones **1a–d** lead to the formation of 2-amino thiazoles in two combinations (**8fb** and **8fc**), 2-imino thiazole in one combinations (**12fa**) and a mixture of 2-imino thiazole and 2-amino thiazole in the remaining one case (**8fd** and **12fd**).

Determination of regioisomeric structure by 2D-NMR studies

The chemical shift values obtained by the ^{1}H and ^{13}C spectral studies of the two isomers provided ample information about the structure. However, to gain better insight into the two structures **8bc** and **12bc**, two-dimensional NMR spectroscopic [(^{1}H–^{13}C) HMQC (^{1}H–^{13}C) HMBC and (^{1}H–^{15}N) HMBC] studies of the two isomers were conducted.

The (^{1}H–^{13}C) HMBC of compound 2-(*N*-(*p*-chlorophenyl) amino)-4-methyl-5-(4-methoxybenzoyl)thiazole **8bc** confirmed the direct correlation of the C=O group at δ 186.9 ppm with the 2″,6″-H proton (δ 7.78–7.76 ppm) of the *p*-methoxy phenyl ring, indicating the presence of the (*p*-methoxy)benzoyl group. Also, the correlations between C-4 (δ 157.4 ppm) with C-5 (δ 120.6 ppm) and the methyl protons (δ 2.41 ppm) demonstrated the methyl group presence at the fourth position of the thiazole ring (Fig. 1).

The (^{1}H–^{13}C) HMBC of compound 2-(*N*-(*p*-methoxybenzoyl) imino)-3-*N*-(*p*-chlorophenyl)-4-methylthiazole **12bc** showed cross-coupling between the methyl protons at C-4 and vinylic hydrogen at C-5 with a coupling constant of 1.3 Hz, which splits their peaks to doublet and quartet, respectively. Additionally, the cross peak between the carbonyl carbon at 174.0 ppm with 2″,6″-H of the *p*-methoxy phenyl ring (δ 8.01–7.98 ppm) was observed, as in the other isomer **8bc**. This observation confirms the formation of the unexpected 2-(*N*-(*p*-methoxybenzoyl) imino)-3-*N*-(*p*-chlorophenyl)-4-methylthiazole **12bc** as a product. The formation of the rearranged product **12bc** could be attributed to the acyl group cleavage and migration in the transition states of the reaction progression (Fig. 1).

Additionally, 2-(*N*-benzoylimino)-4-methyl-3-*N*-(*p*-methylphenyl)thiazole **12da** and 2-(*N*-(*p*-methylphenyl)amino)-4-methyl-5-(*p*-methoxybenzoyl)thiazole **8dc** were subjected to multinuclear NMR analysis. The combined correlation results, along with the complete assignments of the [(^{1}H–^{13}C) HMQC, (^{1}H–^{13}C) HMBC and (^{1}H–^{15}N) HMBC] experiments, are depicted in Fig. 2.

Conformation of the regioisomeric structure by X-ray crystallographic studies

The structures 2-(*N*-arylamino)-4-methyl-5-acylthiazoles **8** and 2-(*N*-acylimino)-4-methyl-3-(*N*-aryl)thiazoles **12** were finally confirmed by X-ray crystallographic studies. For this, single crystals of compounds **8aa**, **12da** and **12bc** were obtained using gradual dissipation of the solvent at ambient conditions.

On examination, the single crystal structure of compound **8aa** revealed that the compound crystallizes in the monoclinic

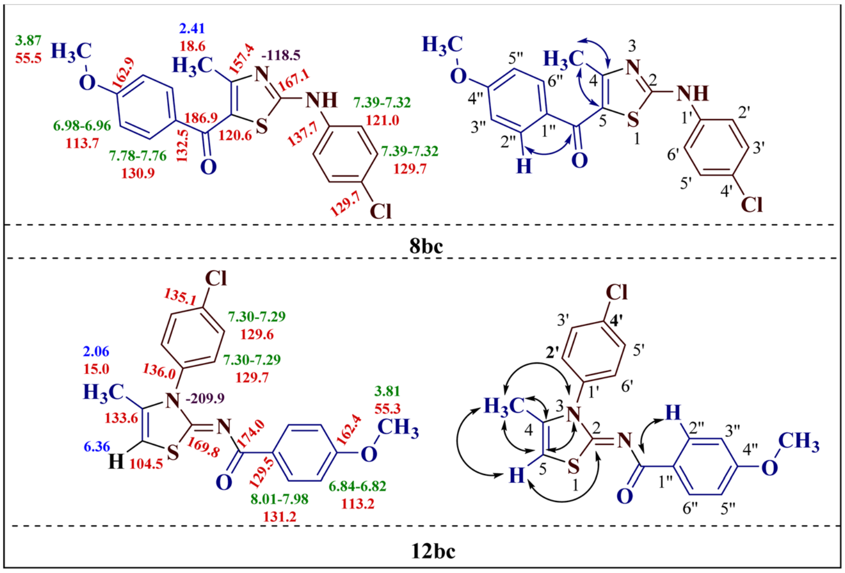


Fig. 1 Important correlations illustrated by (^{1}H–^{13}C) HMQC and (^{1}H–^{13}C) HMBC experiments for compounds **8bc** and **12bc**, along with the ^{1}H (in green), 4-CH_3 and 5-H protons (in blue) and ^{13}C (in red) chemical shifts.

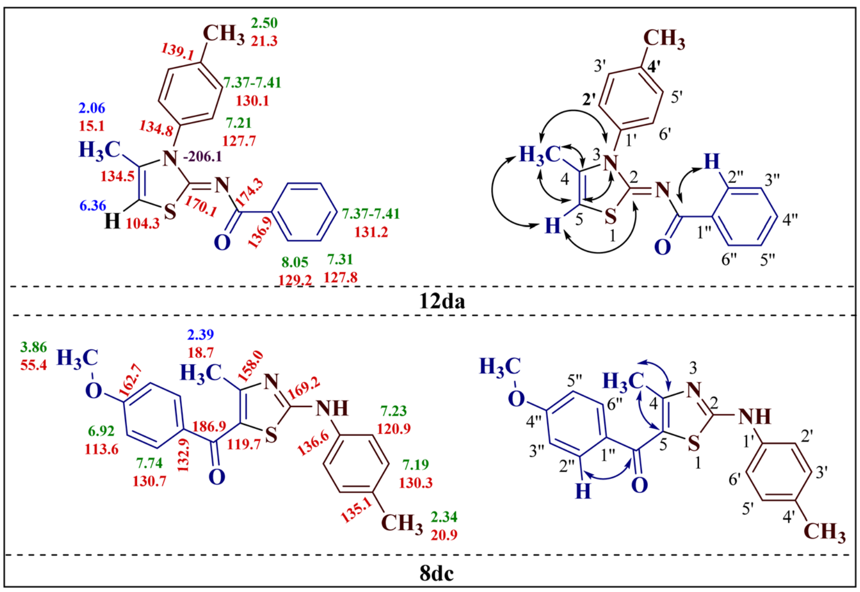


Fig. 2 Important correlations illustrated by (^{1}H–^{13}C) HMQC and (^{1}H–^{13}C) HMBC experiments for compounds **12da** and **8dc**, along with the ^{1}H (in green), 4-CH_3 and 5-H protons (in blue) and ^{13}C (in red) chemical shifts.

*C*2/*c* space group (Fig. 3a) containing one molecule per asymmetric unit, which shows the presence of one ketonic group and one amine group. The ORTEP diagram for compound **8aa** with 20% probability is shown in Fig. 3b.

The electronic delocalization on the main fragment is broken, as evidenced by the bond distances. Hence, the molecule is nonplanar with dihedral angles of 66.2(3)° and 28.9(3)° between the thiazole and both phenyl rings. The lower electronic delocalization induces differences in the thiazole bond distances, with the N3–C2 and C4–C5 bonds having an enhanced double bond character. The loss of electronic delocalization is also observed by the positional disorder found on the benzoyl ring, where the four carbon atoms are distributed over two positions with an occupancy of about 50%.

Further, the crystal packing of **8aa** consists of zigzagged chains formed by intermolecular hydrogen bonds between the amine group (N_6H_6) of one molecule and the thiazole N3 atom of an adjacent molecule with a bond distance of 2.266(4) Å and an angle of 167.3(3)°, as shown in Fig. 4.

This interaction extends along the *b*-axis, and it is strengthened by a partial overlapping of the non-disordered phenyl rings of two neighbouring molecules (shortest C–C distance of about 3.3 Å). Those chains are interconnected through weak contacts between the ketonic groups and

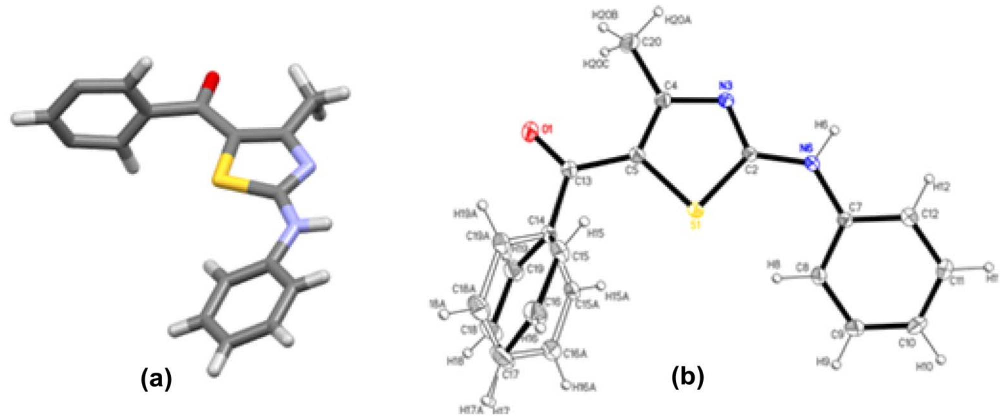


Fig. 3 (a) *C*2/*c* space group for compound **8aa**. (b) ORTEP plot with 20% probability for structure **8aa** with all atoms labelled.

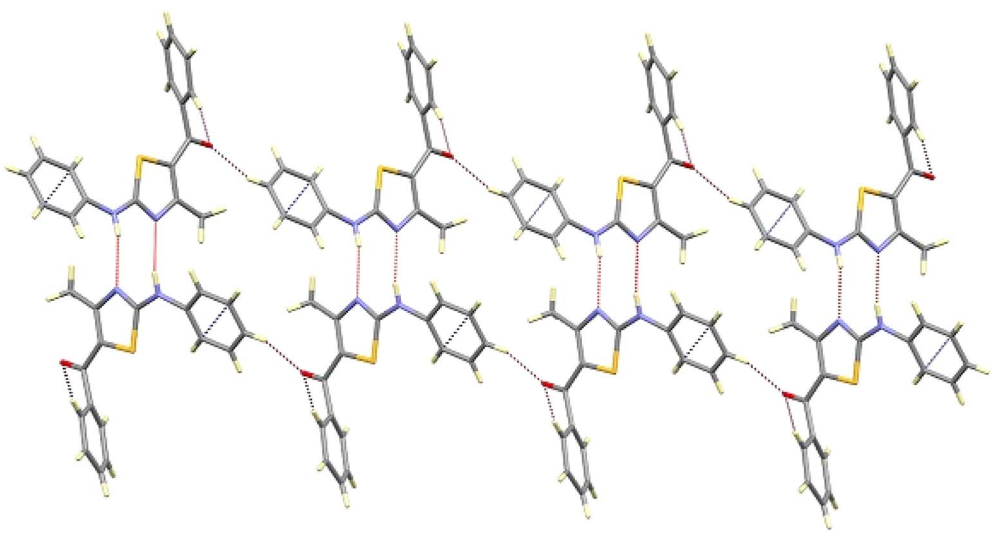


Fig. 4 View of the chain of compound **8aa** along the *b*-axis, showing the intermolecular hydrogen bonding.

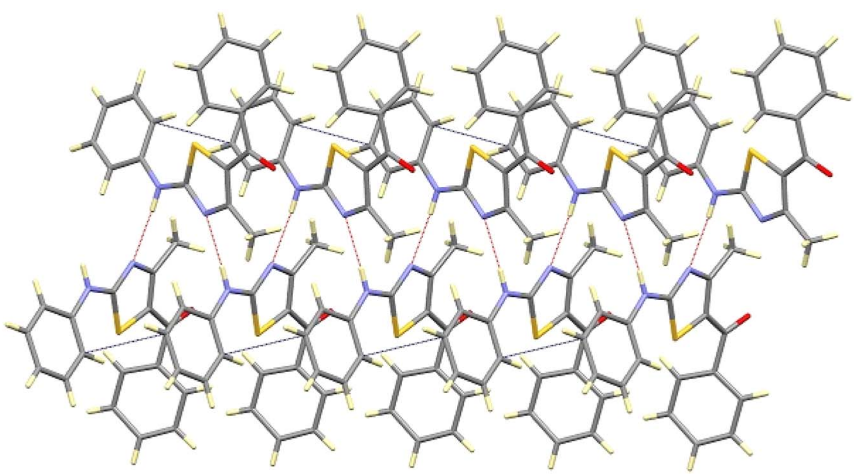
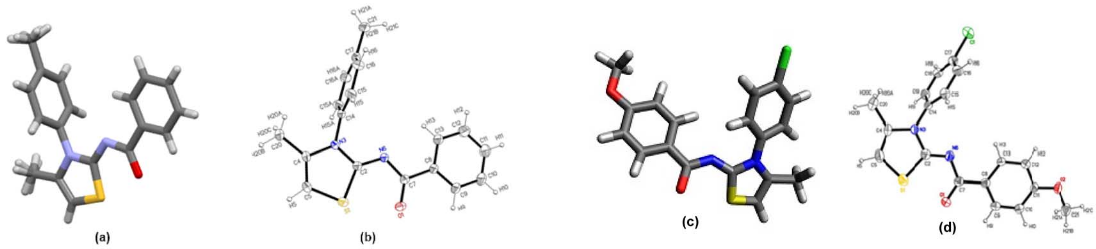


Fig. 5 View of the interaction between the chains along the *b*-axis of compound **8aa**.



12da 12bc

Fig. 6 (a) $P\bar{1}$ space group for compound **12da**. (b) ORTEP plot of compound **12da** with 20% probability for the ellipsoids with their labelling scheme. (c) *Pnma* space group for compound **12bc**. (d) ORTEP plot with 20% probability for structure **12bc** with all atoms labelled.

neighbouring aromatic hydrogen atoms, spreading out the interactions along the *a*-axis, as depicted in Fig. 5.

The X-ray studies of the compound **12da** revealed that the compound crystallizes in orthorhombic *Pnma* space group (Fig. 6a) with the asymmetric unit formed by the $C_{18}H_{16}N_2OS$ moiety, being the rest of the molecule generated by symmetry. The ORTEP plot for molecule **12da** is shown in Fig. 6b with 20% probability.

The X-ray studies supported the $P\bar{1}$ space group for compound **12bc** with one molecule per asymmetric unit, and the ORTEP plot for compound **12bc** with labelling scheme is shown in Fig. 6.

The compound **12da** forms a planar fragment formed by the thiazole and phenylamide groups related to the electronic delocalization along them, as deduced by their bond distances and bond angles. The plane containing this fragment acts as a mirror plane that forces the *p*-methylphenyl ring, linked to N3, to be placed perpendicular to the rest of the molecule, as shown in Fig. 7. The molecular packing of compound **12da** is quite similar to that described for **12bc**, arranging the molecules in the *bc* plane too.

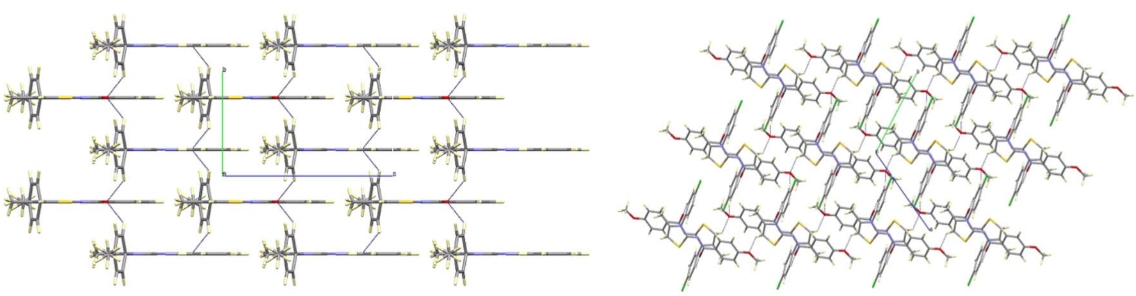
Compound **12bc** exhibits a lower planarity in the main fragment, as indicated by the dihedral angle of about 13° defined by the thiazole and the phenylamide moieties. This bending is attributed to the presence of the *para*-methoxy group. Moreover, the *p*-chlorophenyl substituent present on the N3 atom is found to be twisted 73.5(2)° relative to the thiazole plane. The molecular packing of compounds **12bc** shows only weak contacts between the oxygen atoms and the aromatic rings that arrange the molecules in the *bc* plane, as shown in Fig. 7.

Although the molecular packing of compounds **12da** and **12bc** are similar, the two structures differ only in the weak contacts between the oxygen atoms and the aromatic rings that arrange the molecules in the *bc* plane.

Plausible mechanism

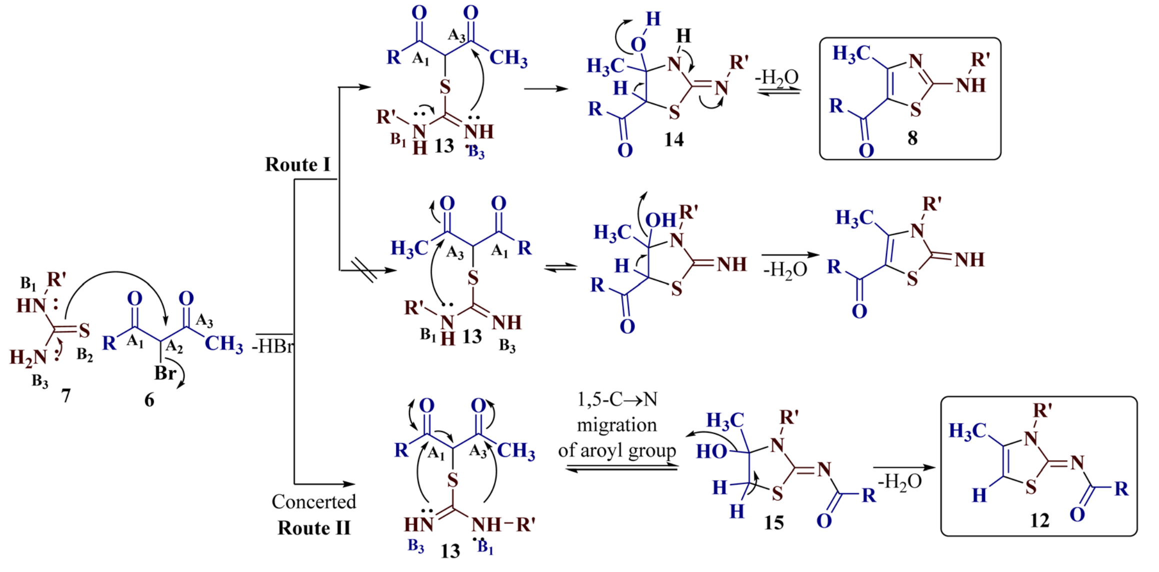
A possible reaction path for the reaction of trielectrophilic α-bromo-1,3-diketones **6** and trinucleophilic *N*-substituted thiourea derivatives **7** to furnish 2-(*N*-arylamino)-4-methyl-5-acylthiazoles **8** and 2-(*N*-acylimino)-3-*N*-aryl-4-methylthiazoles **12** is depicted in Scheme 5. Considering the bromine-bearing methylene carbon (electrophilic centre A_2) of α-bromo-1,3-diketones **6** to be the most electrophilic and sulfur (nucleophilic centre B_2) of the *N*-substituted thiourea derivatives **7** to be the most nucleophilic of all centres, the reaction is assumed to be triggered by the initial nucleophilic displacement of bromine from α-bromo-1,3-diketones **6** by the sulphur of thiourea derivatives **7**, leading to the formation of the *S*-alkylated open chain intermediate **13**. This alkylated open chain structure **13** having two different electrophilic carbonyl carbons from diketone (A_1 and A_3) and two nucleophilic nitrogens (B_1 and B_3) from the thiourea moiety may undergo different routes to ring closure, leading to the formation of **8** and **12**.

Synthesis of 2-(*N*-arylamino)-4-methyl-5-acylthiazoles **8** demands the nucleophilic attack of the unsubstituted imino group (nucleophilic centre B_3) on the less sterically hindered acetyl group (electrophilic centre A_3) to initially produce a cyclic intermediate **14**, which undergoes dehydration to furnish **10** (route I, Scheme 5).



12da 12bc

Fig. 7 View of the crystal packing for compounds **12da** and **12bc**.



Scheme 5

The formation of unexpected 2-(*N*-acylimino)-4-methyl-3-(*N*-aryl)thiazole derivatives **12** may be attributed through participation of a nucleophilic attack of a terminal or substituted amine nitrogen (nucleophilic centre B_1) on the less substituted acetyl group (electrophilic centre A_3), and the nucleophilic addition of an imine nitrogen (nucleophilic centre B_3) to the aroyl group (electrophilic centre A_1) in a concerted manner in the *S*-alkylated open chain structure **13**. During the attack of the amino group (nucleophilic centre B_3) on the acyl group (electrophilic centre A_1), intramolecular C → N acyl migration takes place by C–C bond cleavage to furnish 2-imino-4-hydroxythiazole **15** as an intermediate, which on dehydration, affords **12** as the product (route II, Scheme 5).

It is proposed that competitive reaction routes are operative in cases where a mixture of both regioisomers has been achieved.

Although it is difficult to generalize the influence of a substituent on substituted thiourea on the reactivity pattern, and thus to control the regioselectivity in either direction of **8** or **12**, attempts are underway to conclusively establish the reaction conditions (such as solvents, pH, energy source *etc.*) necessary to uniformly obtain **8** or **12**.

Conclusion

In summary, the novel synthesis of 2-(*N*-arylamino)-5-acyl-4-methylthiazoles along with 2-(*N*-acylimino)-3-*N*-aryl-4-methylthiazoles has been achieved using a simple green protocol involving a sodium carbonate-mediated, one-pot, solvent-free synthetic approach. The present protocol offers a wide substrate scope, as differently substituted 2-aminothiazoles and 2-iminothiazoles were obtained in good to excellent yields with remarkable regioselectivity for the substrates substituted with electron-donating and -withdrawing groups. It was very interesting to observe that the reaction of *N*-substituted thioureas with differently substituted diketones did not follow any pattern to uniformly yield 2-aminothiazoles or 2-iminothiazoles, even upon repeating the reaction. Rather, different combinations abruptly led to the formation of the expected product 2-(*N*-arylamino)-4-methyl-5-acyl thiazole and/or an unexpected rearranged product 2-(*N*-acylimino)-4-methyl-3-(*N*-aryl)thiazole. The formation of the unexpected product has been supported by 1,5-C → N acyl group migration in the *S*-alkylated open chain transition state, as depicted in the proposed mechanism. The structures of the regioisomers have been established by intensive multinuclear NMR [(^1H–^{13}C) HMBC and (^1H–^{13}C) HMQC] spectroscopy and X-ray crystallographic studies.

Experimental

General information

Commercial solvents and reagents were used as purchased. Melting points were determined in open capillaries on a digital melting point apparatus (MEPA), and were uncorrected. IR spectra were recorded on a Buck Scientific IR M-500 spectrophotometer using KBr pellets (ν_{max} in cm^{-1}). Analytical TLC was performed using Merck Kieselgel 60 F254 silica gel plates. Visualization was performed by UV light (254 nm). Elemental analysis was performed at the Sophisticated Analytical Instrumentation Facility, Panjab University, Chandigarh. All compounds gave C, H and N analysis results within ±0.5 of the theoretical values.

NMR experiments

^1H and ^{13}C NMR spectra were recorded on a Bruker instrument at 400 and 100 MHz, respectively, using deuterochloroform and deuterodimethyl sulphoxide as solvents, and chemical shifts were recorded in ppm (δ) downfield from the internal standard tetramethylsilane (δ 0.00 ppm). The 2D correlation spectra,

(^{1}H–^{13}C) gs-HMQC and (^{1}H–^{13}C) gs-HMBC were acquired on a Bruker DRX 400 (9.4 tesla, 400.13 MHz for ^{1}H, 100.62 MHz for ^{13}C, and 40.56 MHz for the ^{15}N spectrometer with a 5-mm inverse-detection H–X probe equipped with a *z*-gradient coil, at 300 K), and processed using standard Bruker NMR software and in the non-phase-sensitive mode. Gradient selection was achieved through a 5% sine truncated shaped pulse gradient of 1 ms.

Single crystal X-ray diffraction

X-ray data collection for compounds **8aa**, **12bc** and **12da** were carried out at room temperature on a Bruker Smart CCD diffractometer using graphite-monochromated Mo-Kα radiation ($\lambda = 0.71073$ Å) operating at 50 kV and 40 mA. Data were collected over a sphere of the reciprocal space by combination of five exposure sets. Each exposure was of 30 s covered 0.3 in ω. The cell parameters were determined, and refinement was performed by least-squares fit of all reflections. The 50 frames were recollected at the end of the data collections to monitor crystal decay, and no appreciable decay was observed.

The structures were solved by direct methods and refined by full-matrix least-square procedures on F^2 (SHELXL-97).[1] All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were included in their calculated positions and refined on the respective carbon atoms. Compound **8aa** shows a positional disorder for the C atoms of the benzoyl ring over two positions. This disorder was modeled and refined with occupancies of about 50%. Mercury CSD 4.0[2] was used for molecular graphics.

CCDC 2312181–2312183 deposition numbers for compounds **8aa**, **12bc** and **12da** contain the supplementary crystallographic data for this paper.

Synthesis

Unsymmetrical 1,3-diketones[47] **1a–e** and *N*-substituted thioureas **7a–f** were synthesized employing the literal cited approach, and NBS **2** was procured commercially.

General method for the synthesis

1,3-Diketone **1a–e** (1.0 mmol) was ground with *N*-bromo succinimide **2** (0.177 g, 1.0 mmol) with a dry pestle mortar until a thick paste was formed, and the reaction mass was subsequently combined with *N*-substituted thiourea derivative **7a–f** (1.0 mmol) and sodium carbonate (0.108 g, 1.0 mmol). The reaction mixture was homogenized properly at room temperature for 5 min, transferred to a conical flask and heated to a temperature of 80 °C. The reaction progress was monitored with TLC. On completion of the reaction, water was added to the reaction mixture and filtered to get the coarse product, which was recrystallized from boiling ethanol.

8aa: 2-(*N*-phenylamino)-4-methyl-5-benzoylthiazole. Brown crystals; mp 164 °C; mp (lit. [19]) 172 °C; yield 77.8%; IR (KBr) ν_{max} (cm^{-1}); 1683 (C═O); ^{1}H NMR (400 MHz, CDCl$_3$) δ: 8.79 (s, 1H, N–H), 7.75–7.16 (m, 10H, 2′,3′,4′,5′,6′,2″,3″,4″,5″,6″-H), 2.41 (s, 3H, 4-CH$_3$); ^{13}C-NMR (100 MHz, CDCl$_3$) δ: 188.1, 168.4, 158.9, 140.4, 138.9, 131.7, 129.8, 128.4, 128.2, 124.9, 120.4, 120, 18.8; HRMS (ESI): *m*/*z* calcd for $C_{17}H_{14}N_2OS$: 294.0827; found: 295.0914 [M + 1]$^+$; elemental analysis: calcd for $C_{17}H_{14}N_2OS$: C, 69.36; H, 4.79; N, 9.52% found: C, 69.35; H, 4.75; N, 9.49%.

8ab: 2-(*N*-phenylamino)-4-methyl-5-(*p*-methylbenzoyl)thiazole. White solid; mp 207 °C; yield 78.6%; IR; (KBr) ν_{max} (cm^{-1}); 1680 (C═O); ^{1}H NMR (400 MHz, CDCl$_3$) δ: 8.48 (s, 1H, N–H), 7.65–7.63 (d, 2H, J = 8.12 Hz, 2″,6″-H), 7.41–7.37 (t, 2H, J = 8.48 Hz, 2′,6′-H), 7.34–7.32 (d, 2H, J = 7.62 Hz, 3″,5″-H), 7.26–7.24 (d, 2H, J = 8.72 Hz, 3′,5′-H), 7.18–7.14 (t, 1H, J = 7.32 Hz, 4′-H), 2.41 (s, 6H, 4″-CH$_3$, 4-CH$_3$); ^{13}C NMR (100 MHz, CDCl$_3$) δ: 187.9, 167.9, 158.5, 142.5, 139.1, 137.6, 129.7, 129.1, 128.5, 124.7, 120.4, 119.8, 21.6, 18.8; HRMS (ESI): *m*/*z* calcd for $C_{18}H_{16}N_2OS$: 308.0893; found: 309.0952 [M + 1]$^+$; elemental analysis: calcd for $C_{18}H_{16}N_2OS$: C, 70.10; H, 5.23; N, 9.08% found: C, 70.05; H, 5.19; N, 9.05%.

8ac: 2-(*N*-phenylamino)-4-methyl-5-(*p*-methoxybenzoyl)thiazole. Cream solid; mp 202 °C; yield 60.8%; IR; (KBr) ν_{max} (cm^{-1}); 1658 (C═O); ^{1}H NMR (400 MHz, CDCl$_3$) δ: 8.91 (s, 1H, N–H), 7.76–7.74 (d, 2H, J = 9.32 Hz, 2″,6″-H), 7.41–7.33 (m, 4H, 2′,3′,5′,6′-H), 7.15–7.13 (t, 1H, J = 7.64 Hz, 4′-H), 6.94–6.92 (d, 2H, J = 9.24 Hz, 3″,5″-H), 3.86 (s, 3H, 4″-OCH$_3$), 2.41 (s, 3H, 4-CH$_3$); ^{13}C NMR (100 MHz, CDCl$_3$) δ: 186.9, 167.9, 162.7, 157.9, 139.1, 132.8, 130.8, 129.7, 124.7, 120.1, 119.9, 113.6, 55.5, 18.7; HRMS (ESI): calcd for $C_{18}H_{16}N_2O_2S$: 324.0932; found: 325.0812 [M + 1]$^+$; elemental analysis: calcd for $C_{18}H_{16}N_2O_2S$: C, 66.65; H, 4.97; N, 8.64% found: C, 66.61; H, 4.93; N, 8.61%.

8ad: 2-(*N*-phenylamino)-4-methyl-5-(2-thienoyl)thiazole. Black solid; mp 201 °C; yield 79.5%; IR; (KBr) ν_{max} (cm^{-1}); 1693 (C═O); ^{1}H NMR (400 MHz, CDCl$_3$) δ: 8.56 (s, 1H, NH), 7.78–7.77 (d, 1H, J = 3.6 Hz, 5″-H), 7.64–7.62 (d, 1H, J = 4.8 Hz, 3″-H), 7.44–7.40 (m, 2H, 2′,6′-H), 7.37–7.35 (d, 2H, J = 7.6 Hz, 3′,5′-H), 7.20–7.16 (t, 1H, J = 7.2 Hz, 4′-H), 7.14–7.11 (t, 1H, J = 4.8 Hz, 4″-H), 2.67 (s, 3H, 4-CH$_3$); ^{13}C NMR (100 MHz, CDCl$_3$) δ: 178.1, 167.3, 159.9, 145.6, 138.9, 132.8, 131.8, 129.8, 127.7, 124.7, 119.6, 117.1, 18.6; HRMS (ESI): calcd for $C_{15}H_{12}N_2OS_2$: 300.0391; found: 301.0405 [M + 1]$^+$; elemental analysis: calcd for $C_{15}H_{12}N_2OS_2$: C, 59.98; H, 4.03; N, 9.33% found: C, 59.93; H, 3.99; N, 9.00%.

8bd: 2-(*N*-(*p*-chlorophenyl)amino)-4-methyl-5-(2-thienoyl)thiazole. Yellow solid; mp 189 °C; yield 87%; IR; (KBr, cm^{-1}); 1685 (C═O); ^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.76–7.75 (d, 1H, J = 3.32 Hz, 5″-H), 7.65–7.63 (d, 1H, J = 4.56 Hz, 3″-H), 7.38–7.32 (m, 4H, 2′,6′,3′,5′-H), 7.14–7.12 (t, 1H, J = 4.12 Hz, 2″-H), 2.60 (s, 3H, 4-CH$_3$); ^{13}C NMR (100 MHz, CDCl$_3$) δ: 178.1, 167.4, 158.4, 145.2, 137.5, 133.5, 132.3, 130.4, 129.9, 128.0, 121.6, 117.1, 18.5; HRMS (ESI): calcd for $C_{15}H_{11}ClN_2OS_2$: 334.8360, found: 335.8432 [M + 1]$^+$; elemental analysis: calcd for $C_{15}H_{11}ClN_2OS_2$: C, 53.81; H, 3.31; N, 8.37% found: C, 53.76; H, 3.26; N, 8.34%.

8dc: 2-(*N*-(*p*-methylphenyl)amino)-4-methyl-5-(*p*-methoxybenzoyl)thiazole. Cream solid; mp 203 °C; yield 57.5%; IR; (KBr) ν_{max} (cm^{-1}); 1685 (C═O); ^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.75–7.73 (d, 2H, J = 8.68 Hz, 2″,6″-H), 7.23–7.17 (m, 4H, 2′,6′,3′,5′-H), 6.93–6.91 (d, 2H, J = 8.68 Hz, 3″,5″-H), 3.86 (s, 3H, 4″-OCH$_3$), 2.40 (s, 3H, 4-CH$_3$), 2.34 (s, 3H, 4′-CH$_3$); ^{13}C NMR (100 MHz, CDCl$_3$) δ: 186.9, 169.2, 162.6, 158.1, 136.6, 135.1, 132.8, 130.8, 130.3, 120.8, 119.8, 113.6, 55.4, 20.9, 18.7; HRMS (ESI): calcd for $C_{19}H_{18}N_2O_2S$: 338.1089; found: 339.2143 [M + 1]$^+$;

elemental analysis: calcd for $C_{19}H_{18}N_2O_2S$: C, 67.43; H, 5.36; N, 8.28% found: C, 67.38; H, 5.32; N, 8.25%.

8dd: 2-(*N*-(*p*-methylphenyl)amino)-4-methyl-5-(2-thienoyl) thiazole. Black solid; mp 170 °C; yield 69.5%; IR; (KBr) ν_{max} (cm^{-1}); 1623 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.86 (s, 1H, N–H), 7.76–7.74 (d, 1H, J = 3.82 Hz, 5″-H), 7.62–7.60 (d, 1H, J = 4.72 Hz, 3″-H), 7.27–7.21 (m, 4H, 2′,6′,3′,5′-H), 7.12–7.09 (t, 1H, J = 4.38 Hz, 4″-H), 2.59 (s, 3H, 4-CH_3), 2.37 (s, 3H, 4′-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 178.1, 169.4, 160.3, 145.8, 136.6, 135.5, 132.7, 131.7, 130.4, 127.7, 121.4, 116.4, 21.1, 18.9; HRMS (ESI): calcd for $C_{16}H_{14}N_2OS_2$: 314.0548, found: 315.1478 $[M+1]^+$; elemental analysis: calcd for $C_{16}H_{14}N_2OS_2$: C, 61.12; H, 4.49; N, 8.91% found: C, 60.92; H, 4.44; N, 8.77%.

8de: 2-(*N*-(*p*-methylbenzyl)amino)-4-methyl-5-(*p*-chlorobenzoyl)thiazole. Brown solid; mp 210 °C; yield 76.6%; IR; (KBr) ν_{max} (cm^{-1}); 1652 (C=O); ^{1}H NMR (400 MHz, DMSO, d_6) δ: 10.46 (s, 1H, N–H), 7.68–7.66 (d, 2H, J = 7.6 Hz, 2″,6″-H), 7.47–7.41 (m, 4H, 2′,6′,3″,5″-H), 7.14–7.12 (d, 2H, J = 8.32 Hz, 3′,5′-H), 2.37 (s, 3H, 4′-CH_3), 2.31 (s, 3H, 4-CH_3); ^{13}C NMR (100 MHz, DMSO, d_6) δ: 185.6, 166.7, 159.3, 138.9, 137.3, 136.5, 132.1, 129.4, 129.3, 128.3, 118.8, 118.5, 20.4, 18.7; HRMS (ESI): calcd for $C_{18}H_{15}ClN_2OS$: 342.8410, found: 343.8121 $[M+1]^+$, 345.9112 $[M+1+2]^+$ (3 : 1); elemental analysis: calcd for $C_{18}H_{15}ClN_2OS$: C, 63.06; H, 4.41; N, 8.17% found: C, 63.01; H, 4.37; N, 5.14.

8fb: 2-(*N*-(*p*-nitrophenyl)amino)-4-methyl-5-(*p*-methylbenzoyl)thiazole. Brown solid; mp 193.5 °C; yield 85%; IR; (KBr) ν_{max} (cm^{-1}); 1682 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.30–8.28 (d, 2H, J = 7.2 Hz, 3′,5′-H), 7.71–7.69 (d, 2H, J = 8.0 Hz, 2″,6″-H), 7.59–7.57 (d, 2H, J = 7.0 Hz, 2′,6′-H), 7.32–7.30 (d, 2H, J = 7.0 Hz, 3″,5″-H), 2.49 (s, 3H, 4″-CH_3), 2.47 (s, 3H, 4-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 187.9, 163.8, 158.0, 144.5, 143.2, 142.9, 136.9, 129.2, 128.7, 125.7, 117.1, 95.7, 21.7, 18.7; HRMS (ESI): calcd for $C_{18}H_{15}N_3O_3S$: 353.083, found: 354.0914 $[M+1]^+$; elemental analysis: calcd for $C_{18}H_{15}N_3O_3S$: C, 61.18; H, 4.28; N, 11.89% found: C, 61.13; H, 4.24; N, 11.86%.

8fc: 2-(*N*-(*p*-nitrophenyl)amino)-4-methyl-5-(*p*-methoxybenzoyl)thiazole. Dark brown solid; mp 203.5 °C; yield 86.5%; IR; (KBr) ν_{max} (cm^{-1}); 1679 (C=O); ^{1}H NMR (400 MHz, DMSO, d_6) δ: 10.39 (s, 1H, N–H), 7.75–7.73 (d, 2H, J = 7.88 Hz, 3′,5′-H), 7.60–7.58 (d, 2H, J = 6.94 Hz, 2″,6″-H), 7.27–7.25 (d, 2H, J = 6.90 Hz, 2′,6′-H), 6.97–6.95 (d, 2H, J = 7.86 Hz, 3″,5″-H), 3.89 (s, 3H, 4″-OCH_3), 2.41 (s, 3H, 4-CH_3); ^{13}C NMR (100 MHz, DMSO, d_6) δ: 186.9, 167.1, 162.9, 157.4, 137.7, 132.5, 130.9, 129.7, 121.0, 120.6, 113.7, 55.5, 18.6; HRMS (ESI): calcd for $C_{18}H_{15}N_3O_4S$: 369.0783, found: 370.0865 $[M+1]^+$; elemental analysis: calcd for $C_{18}H_{15}N_3O_4S$: C, 58.53; H, 4.09; N, 11.38% found: C, 58.47; H, 4.05; N, 11.35%.

12ba: 2-(*N*-benzoylimino)-3-*N*-(*p*-chlorophenyl)-4-methylthiazole. White solid; mp 193 °C; yield 86.5%; IR; (KBr) ν_{max} (cm^{-1}); 1623 (C=O), 1599 (C=N); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.05–8.02 (d, 2H, J = 8.48 Hz, 2″,6″-H), 7.58–7.55 (d, 2H, J = 9.52 Hz, 3″,5″-H), 7.43–7.39 (m, 1H, 4″-H), 7.35–7.26 (m, 4H, 2′,6′,3′,5′-H), 6.39 (q, 1H, J = 1.12 Hz, 5-H), 2.06 (d, 3H, J = 1.12 Hz, 4-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.1, 170.6, 136.6, 135.8, 135.2, 133.8, 131.5, 129.8, 129.5, 129.2, 127.9, 104.8, 15.1; HRMS (ESI): calcd for $C_{17}H_{13}ClN_2OS$: 328.8140, found: 329.8231 $[M+1]^+$, 331.9750 $[M+1+2]^+$ (3 : 1); elemental analysis: calcd for $C_{17}H_{13}ClN_2OS$: C, 62.10; H, 3.99; N, 8.52% found: C, 61.9; H, 3.94; N, 8.52%.

12be: 2-(*N*-(*p*-chlorobenzoyl)imino)-3-*N*-(*p*-chlorophenyl)-4-methylthiazole. Brown crystals, mp 195.5 °C; yield 86.5%; IR; (KBr) ν_{max} (cm^{-1}); 1617 (C=O), 1582 (C=N); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.97–7.95 (d, 2H, J = 6.72 Hz, 2″,6″-H), 7.59–7.57 (d, 2H, J = 6.6 Hz, 3″,5″-H), 7.31–7.27 (m, 4H, 2′,6′,3′,5′-H), 6.43 (q, 1H, J = 1.08 Hz, 5-H), 2.08 (d, 3H, J = 1.04 Hz, 4-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.4, 170.2, 137.6, 135.7, 135.3, 134.0, 130.6, 129.8, 129.4, 128.2, 104.9, 15.0; HRMS (ESI): calcd for $C_{17}H_{12}Cl_2N_2OS$: 362.0067, found: 363.1058 $[M+1]^+$, 364.0078 $[M+1+2]^+$, 367.0098 $[M+1+4]^+$ (9 : 6 : 1); Elemental analysis: calcd for $C_{17}H_{12}Cl_2N_2OS$: C, 56.21; H, 3.33; N, 7.71% found: C, 56.01; H, 3.28; N, 7.58%.

12cc: 2-(*N*-*p*-methoxybenzoylimino)-3-*N*-(*o*-chlorophenyl)-4-methylthiazole. Mp 146 °C; yield 75%; IR; (KBr, cm^{-1}); 1605 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.96 (d, 2H, J = 11.0 Hz, 2″,6″-H), 7.65–7.63 (m, 1H, 3′-H), 7.54–7.47 (m, 2H, 4′,5′-H), 7.40–7.38 (m, 1H, 3′-H), 6.80 (d, 2H, J = 11 Hz, 3″,5″-H), 6.38 (q, 1H, J = 1.5 Hz, 5-H), 3.79 (s, 3H, 4″-OCH_3), 2.01 (d, 3H, J = 1.5 Hz, 4-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 174.1, 169.4, 162.4, 135.3, 133.6, 132.9, 131.3, 130.9, 130.6, 130.3, 129.6, 128.0, 113.1, 104.2, 55.3, 14.4; elemental analysis: calcd for $C_{18}H_{15}ClN_2O_2S$: C, 60.25; H, 4.21; N, 7.81% found: C, 60.23; H, 4.18; N, 7.80%.

12da: 2-(*N*-benzoylimino)-3-*N*-(*p*-methylphenyl)-4-methylthiazole. Colourless needles; mp 105 °C; mp (lit. [48]) 106–107 °C; yield 94.2%; IR (KBr) ν_{max} (cm^{-1}); 1684 (C=O), 1597(C=N); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.06–8.04 (d, 2H, J = 7.62 Hz, 2″,6″-H), 7.41–7.37 (m, 3H, 3′,5′,4″-H), 7.33–7.29 (m, 2H, 3″,5″-H), 7.22–7.21 (d, 2H, J = 6.46 Hz, 2′,6′-H), 6.38 (q, 1H, J = 1.2 Hz, 5-H), 2.50 (s, 3H, 4′-CH_3), 2.06 (d, 3H, J = 1.2 Hz, 4-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.4, 170.2, 139.2, 136.9, 134.8, 134.5, 131.3, 130.1, 129.3, 127.8, 127.7, 104.4, 21.4, 15.1; HRMS (ESI): calcd for $C_{18}H_{16}N_2OS$: 309.0983, found: 310.0997 $[M+1]^+$; elemental analysis: calcd for $C_{18}H_{16}N_2OS$: C, 70.10; H, 5.23; N, 9.08% found: C, 69.90; H, 5.17; N, 8.84%.

12db: 2-(*N*-(*p*-methylbenzoyl)imino)-3-*N*-(*p*-methylphenyl)-4-methylthiazole. Yellow solid; mp 205 °C; yield 27.3%; IR; (KBr) ν_{max} (cm^{-1}); 1635 (C=O), 1589 (C=N); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.94–7.92 (d, 2H, J = 8.08 Hz, 2″,6″-H), 7.37–7.35 (d, 2H, J = 8.0 Hz, 3″,5″-H), 7.21–7.19 (d, 2H, J = 8.2 Hz, 3′,5′-H), 7.12–7.10 (d, 2H, J = 7.92 Hz, 2′,6′-H), 6.35 (q, 1H, J = 1.04 Hz, 5-H), 2.49 (s, 3H, 4″-CH_3), 2.33 (s, 3H, 4′-CH_3), 2.05 (d, 3H, J = 0.96 Hz, 4-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.9, 157.2, 141.6, 139.1, 134.4, 130.1, 129.3, 128.6, 127.8, 104.2, 21.6, 21.4, 15.1; HRMS (ESI): calcd for $C_{19}H_{18}N_2OS$: 322.1140, found: 323.2149 $[M+1]^+$; elemental analysis: calcd for $C_{19}H_{18}N_2OS$: C, 70.78; H, 5.63; N, 8.69% found: C, 70.6; H, 5.58; N, 8.55%.

12ea: 2-(*N*-benzoylimino)-3-*N*-(*p*-methoxyphenyl)-4-methylthiazole. White crystals; mp 189 °C; yield 86.5%; IR; (KBr) ν_{max} (cm^{-1}); 1651 (C=O), 1597 (C=N); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.07–8.04 (d, 2H, J = 7.44 Hz, 2″,6″-H), 7.39–7.37 (m, 1H, 4″-H), 7.33–7.29 (m, 2H, 3″,5″-H), 7.25–7.24 (d, 2H, J = 5.76 Hz, 2′,6′-H), 7.09–7.06 (d, 2H, J = 6.76 Hz, 3′,5′-H), 6.37 (q, 1H, J = 1.08 Hz, 5-H), 3.92 (s, 3H, 4′-OCH_3), 2.07 (d, 3H, J = 1.08 Hz, 4-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.5, 170.4, 159.9, 136.9, 134.8, 131.4, 130.1, 129.3, 129.2, 127.9, 114.7, 104.3, 55.7, 15.2; HRMS (ESI): calcd for $C_{18}H_{16}N_2O_2S$: 324.0932, found: 325.0954 $[M + 1]^+$; elemental analysis: calcd for $C_{18}H_{16}N_2O_2S$: C, 66.65; H, 4.97; N, 8.64% found: C, 66.59; H, 4.94; N, 8.59%.

12fa: 2-(*N*-benzoylimino)-3-*N*-(*p*-nitrophenyl)-4-methylthiazole. Brown solid; mp 203.5 °C; yield 86.5%; IR; (KBr) ν_{max} (cm^{-1}); 1633 (C═O), 1573 (C═N); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.49–8.46 (d, 2H, J = 7.26 Hz, 3′,5′-H), 8.01–7.99 (d, 2H, J = 7.8 Hz, 2″,6″-H), 7.61–7.58 (d, 2H, J = 8.15 Hz, 3″,5″-H), 7.44–7.41 (m, 1H, 4″-H), 7.35–7.31 (m, 2H, 2′,6′-H), 6.44 (q, 1H, J = 1.08 Hz, 5-H), 2.09 (d, 3H, J = 0.84 Hz, 4-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.5, 170.1, 147.9, 142.7, 136.3, 132.9, 131.8, 129.6, 129.2, 128.1, 124.8, 105.6, 15.1; HRMS (ESI): calcd for $C_{17}H_{13}N_3O_3S$: 339.0678, found: 340.0754 $[M + 1]^+$; elemental analysis: calcd for $C_{17}H_{13}N_3O_3S$: C, 60.17; H, 3.86; N, 12.38% found: C, 60.12; H, 3.82; N, 12.35%.

8bc: 2-(*N*-(*p*-chlorophenyl)amino)-4-methyl-5-(*p*-methoxybenzoyl)thiazole. White crystal; mp 178 °C; yield 89%; IR; (KBr) ν_{max} (cm^{-1}); 1658 (C═O); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.78–7.76 (d, 2H, J = 6.82 Hz, 2″,6″-H), 7.39–7.32 (m, 4H, 2′,6′,3′,5′-H), 6.98–6.96 (d, 2H, J = 8.11 Hz, 3″,5″-H), 3.87 (s, 3H, 4″-OCH_3), 2.42 (s, 3H, 4-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 186.9, 167.1, 162.9, 157.4, 137.7, 132.5, 130.9, 129.7, 121.0, 120.6, 113.7, 55.5, 18.6; HRMS (ESI): calcd for $C_{18}H_{15}ClN_2O_2S$: 358.8400, found: 359.9975 $[M + 1]^+$, 361.0876 $[M + 1 + 2]^+$ (3 : 1); elemental analysis: calcd for $C_{18}H_{15}ClN_2O_2S$: C, 60.25; H, 4.21; N, 7.81% found: C, 60.05; H, 4.16; N, 7.67%.

12bc: 2-(*N*-(*p*-methoxybenzoyl)imino)-3-*N*-(*p*-chlorophenyl)-4-methylthiazole. Cream solid; mp 200.5 °C; yield 86.5%; IR; (KBr, cm^{-1}); 1686 (C═O), 1528 (C═N); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.01–7.98 (d, 2H, J = 8.88 Hz, 2″,6″-H), 7.57–7.56 (d, 2H, J = 7.62 Hz, 2′,6′-H), 7.30–7.28 (d, 2H, J = 7.6 Hz, 3′,5′-H), 6.84–6.82 (d, 2H, J = 8.92 Hz, 3″,5″-H), 6.36 (q, 1H, J = 1.3 Hz, 5-H), 3.81 (s, 3H, 4″-OCH_3), 2.06 (d, 3H, J = 1.3 Hz, 4-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.0, 169.8, 162.4, 136.0, 135.1, 133.6, 131.2, 129.7, 129.6, 129.5, 113.2, 104.5, 55.3, 15.0; HRMS (ESI): calcd for $C_{18}H_{15}ClN_2O_2S$: 358.5769, found: 359.5876 $[M + 1]^+$, 361.5768 $[M + 1 + 2]^+$ (3 : 1); elemental analysis: calcd for $C_{18}H_{15}ClN_2O_2S$: C, 60.25; H, 4.21; N, 7.81% found: C, 60.05; H, 4.16; N, 7.67%.

8ed: 2-(*N*-(*p*-methoxyphenyl)amino)-4-methyl-5-(2-thienoyl)thiazole. Black solid; mp 175 °C; yield 70%; IR; (KBr) ν_{max} (cm^{-1}); 1636 (C═O); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.73–7.72 (d, 1H, J = 3.76 Hz, 5″-H), 7.61–7.59 (d, 1H, J = 4.94 Hz, 3″-H), 7.32–7.30 (d, 2H, J = 6.72 Hz, 2′,6′-H), 7.10–7.07 (m, 1H, 4″-H), 6.98–6.96 (d, 2H, J = 6.74 Hz, 3′,5′-H), 3.83 (s, 3H, 4′-OCH_3), 2.57 (s, 3H, 4-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 178.1, 160.3, 157.8, 145.8, 132.8, 132.1, 131.7, 129.2, 127.8, 123.9, 115.1, 114.5, 55.6, 18.8; HRMS (ESI): calcd for $C_{16}H_{14}N_2O_2S_2$: 330.0497, found: 331.2567 $[M + 1]^+$; elemental analysis: calcd for $C_{16}H_{14}N_2O_2S_2$: C, 58.16; H, 4.27; N, 8.48% found: C, 57.96; H, 4.22; N, 8.35%.

12ed: 2-(*N*-(2-thienoyl)imino)-3-*N*-(*p*-methoxyphenyl)-4-methylthiazole. Black solid; yield 30%; IR; (KBr, cm^{-1}); 1643 (C═O), 1585 (C═N); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.66–7.63 (m, 1H, 5″-H), 7.41–7.39 (m, 1H, 3″-H), 7.24–7.22 (m, 1H, 4″-H), 7.08–7.05 (m, 2H, 3′,5′-H), 7.00–6.97 (m, 2H, 2′,6′-H), 6.35 (q, 1H, J = 1.16 Hz, 5-H), 3.83 (s, 3H, 4′-OCH_3), 2.06 (d, 3H, J = 1.12 Hz, 4-CH_3); HRMS (ESI): calcd for $C_{16}H_{14}N_2O_2S_2$: 330.0497, found: 331.2564 $[M + 1]^+$; elemental analysis: calcd for $C_{16}H_{14}N_2O_2S_2$: C, 58.16; H, 4.27; N, 8.48% found: C, 57.96; H, 4.22; N, 8.35%.

8fd: 2-(*N*-(*p*-nitrophenyl)amino)-4-methyl-5-(2-thienoyl)thiazole. Dark brown solid; mp 175 °C; yield 67%; IR; (KBr) ν_{max} (cm^{-1}); 1634 (C═O); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.32–8.30 (d, 2H, J = 7.6 Hz, 3′,5′-H), 7.84–7.83 (d, 1H, J = 3.8 Hz, 5″-H), 7.72–7.71 (d, 1H, J = 5.0 Hz, 3″-H), 7.63–7.61 (d, 2H, J = 7.2 Hz, 2″,6″-H), 7.21–7.18 (t, 1H, J = 4.6 Hz, 4″-H), 2.69 (s, 3H, 4-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 186.3, 167.4, 158.4, 143.4, 132.7, 131.5, 126.9, 124.8, 116.2, 17.6; HRMS (ESI): calcd for $C_{15}H_{11}N_3O_3S_2$: 345.0242, found: 346.1254 $[M + 1]^+$; elemental analysis: calcd for $C_{15}H_{11}N_3O_3S_2$: C, 52.16; H, 3.21; N, 12.17% found: C, 51.96; H, 3.16; N, 12.04%.

12fd: 2-(*N*-(2-thienoyl)imino)-3-*N*-(*p*-nitrophenyl)-4-methylthiazole. Brown solid; mp 175 °C; yield 33%; IR; (KBr) ν_{max} (cm^{-1}); 1630 (C═O), 1590 (C═N); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.48–8.45 (d, 2H, J = 9.38 Hz, 3′,5′-H), 7.64–7.62 (d, 1H, J = 4.7 Hz, 5″-H), 7.60–7.57 (d, 2H, J = 8.18 Hz, 2′,6′-H), 7.40–7.38 (d, 1H, J = 4.96 Hz, 3″-H), 7.02–6.99 (m, 1H, 4″-H), 6.44 (q, 1H, J = 1.28 Hz, 5-H), 2.11 (d, 3H, J = 1.02 Hz, 4-CH_3); HRMS (ESI): calcd for $C_{15}H_{11}N_3O_3S_2$: 345.0242, found: 346.1254 $[M + 1]^+$; elemental analysis: calcd for $C_{15}H_{11}N_3O_3S_2$: C, 52.16; H, 3.21; N, 12.17% found: C, 51.96; H, 3.16; N, 12.04%.

Data availability

The analytical data (^{1}H-NMR, ^{13}C-NMR, HMQC and HMBC) of all compounds supporting the research have been included in the ESI. CCDC 2312181–2312183 deposition numbers for compounds **8aa**, **12bc** and **12da** contain the supplementary crystallographic data for this paper. The X-ray crystallographic data CIF files in the pdf format have been uploaded separately.

Conflicts of interest

The authors declare no competing interest.

Acknowledgements

We are grateful to the Council of Scientific and Industrial Research (CSIR), New Delhi, India for providing financial assistance through a Senior Research Fellowship (SRF) to Shilpa Sharma. We are also grateful to the Haryana State Council for Science and Technology (HSCST) for providing financial help to Project Fellow Naman Jain. We would like to thank the Spanish Ministerio de Economia, Industria y Competitividad (Ministerio de Economia, Industria y Competitividad, Gobierno de Espana) [CTQ2014-56833-R] for financial support to Dionisia Sanz and Rosa M. Claramunt.

References

1 K. M. Dawood, T. M. Eldebss, H. S. El-Zahabi and M. H. Yousef, *Eur. J. Med. Chem.*, 2015, **102**, 266–276.

2 G. Turan-Zitouni, M. D. Altintop, A. Ozdemir, Z. A. Kaplancıklı, G. A. Çiftçi and H. E. Temel, *Eur. J. Med. Chem.*, 2016, **107**, 288–294.
3 J. R. Li, D. D. Li, R. R. Wang, J. Sun, J. J. Dong, Q. R. Du, F. Fang, W. M. Zhang and H. L. Zhu, *Eur. J. Med. Chem.*, 2014, **75**, 438–447.
4 C. B. Mishra, S. Kumari and M. Tiwari, *Eur. J. Med. Chem.*, 2015, **92**, 1–34.
5 H. A. Ghabbour, A. A. Kadi, K. E. H. El-Tahir, R. F. Angawi and H. El-Subbagh, *Med. Chem. Res.*, 2015, **24**, 3194–3211.
6 S. Bondock, T. Naser and Y. A. Ammar, *Eur. J. Med. Chem.*, 2013, **62**, 270–279.
7 S. Carradori, F. Ortuso, A. Petzer, D. Bagetta, C. De Monte, D. Secci, D. De Vita, P. Guglielmi, G. Zengin, A. Aktumsek, S. Alcaro and J. P. Petzer, *Eur. J. Med. Chem.*, 2018, **143**, 1543–1552.
8 S. Koppireddi, J. R. Komsani, S. Avula, S. Pombala, S. Vasamsetti, S. Kotamraju and R. Yadla, *Eur. J. Med. Chem.*, 2013, **66**, 305–313.
9 M. V. N. de Souza, *J. Sulfur Chem.*, 2005, **26**, 429–449.
10 L. Y. Wang, C. X. Zhang, Z. Q. Liu, D. Z. Liao, Z. H. Jiang and S. P. Yan, *Inorg. Chem. Commun.*, 2003, **6**, 1255–1258.
11 Z. Yan, A. Liu, M. Huang, M. Liu, H. Pei, L. Huang, H. Yi, W. Liu and A. Hu, *Eur. J. Med. Chem.*, 2018, **149**, 170–181.
12 I. Parasotas, K. Anusevicius, R. Vaickelioniene, I. Jonuskiene, M. Stasevych, V. Zvarych, O. Komarovska-Porokhnyavets, V. Novikov, S. Belyakov and V. Mickevicius, *Arkivoc*, 2018, (iii), 240–256.
13 M. Romero-Ortega, A. Aviles, R. Cruz, A. Fuentes, R. M. Gomez and A. Plata, *J. Org. Chem.*, 2000, **65**, 7244–7247.
14 P. Yogil, M. Ashid, N. Hussain, S. Khan and A. Joshi, *Asian J. Chem.*, 2016, **28**, 927–932.
15 V. Facchinettia, M. M. Avellar, A. C. S. Nery, C. R. B. Gomes, T. R. A. Vasconcelos and M. V. N. de Souza, *Synthesis*, 2016, **48**, 437–440.
16 M. Narender, M. S. Reddy, V. P. Kumar, B. Srinivas, R. Sridhar, Y. V. D. Nageswar and K. R. Rao, *Synthesis*, 2007, **22**, 3469–3472.
17 G. Meng, M. Wang, A. Zheng, J. Dou and Z. Guo, *Green Chem. Lett. Rev.*, 2014, **7**, 46–49.
18 C. L. Liu, Z. M. Lia and B. Zhonga, *J. Fluorine Chem.*, 2004, **125**, 1287–1290.
19 D. Castagnolo, M. Pagano, M. Bernardinia and M. Botta, *Synlett*, 2009, **13**, 2093–2096.
20 B. Chen, S. Guo, X. Guo, G. Zhang and Y. Yun, *Org. Lett.*, 2015, **17**, 4698–4701.
21 X. Tang, J. Yang, Z. Zhu, M. Zheng, W. Wu and H. Jiang, *J. Org. Chem.*, 2016, **81**, 11461–11466.
22 F. Rahim, M. T. Javeda, H. Ullaha, A. Wadood, M. Taha, M. Ashraf, Q. ul-Ain, M. A. Khan, F. Khan, S. Mirza and K. M. Khan, *Bioorg. Chem.*, 2015, **62**, 106–116.
23 H. Bouherrou, A. Saidoun, A. Abderrahmani, L. Abdellaziz, Y. Rachedi, F. Dumas and A. Demenceau, *Molecules*, 2017, **22**, 757–769.
24 T. R. Swaroop, H. Ila and K. S. Rangappa, *Tetrahedron Lett.*, 2013, **54**, 5288–5292.
25 X. Wang, F. Wang, Z. Quan, Z. Zhan and M. G. Wang, *Synth. Commun.*, 2006, **36**, 2453–2460.
26 (*a*) R. Raja, D. Murugan, A. Sivasubramaniyan, J. George, P. Sakhtivel, P. Alagusundaram, M. R. Jayakumar and M. Saminathan, *Synth. Commun.*, 2016, **46**, 942–948; (*b*) J. A. Shiran, A. Yahyazadeh, M. Mamaghani and R. Mehdi, *J. Mol. Struct.*, 2013, **1039**, 113–118.
27 I. J. Barve, W. J. Chang, Y. T. Lin, T. U. Thikekar and C. M. Sun, *ACS Comb. Sci.*, 2019, **21**, 269–275.
28 E. Badali, A. Z. Halimehjani and A. Habibi, *Sci. Rep.*, 2023, **13**, 3079–3087.
29 G. S. Kumar, S. P. Ragini and H. Meshram, *Tetrahedron Lett.*, 2003, **54**, 5974–5978.
30 I. Yavari, A. Malekafzali and S. Seyfi, *J. Iran. Chem. Soc.*, 2014, **11**, 285–288.
31 R. Aggarwal, G. Singh, D. Sanz, R. M. Claramunt, M. C. Torralba and M. R. Torres, *Tetrahedron*, 2016, **72**, 3832–3838.
32 R. Aggarwal, N. Jain, S. Sharma, P. Kumar, G. P. Dubey, H. Chugh and R. Chandra, *Sci. Rep.*, 2021, **11**, 22135–22153.
33 R. Aggarwal, M. Hooda, P. Kumar, N. Jain, G. P. Dubey, H. Chugh and R. Chandra, *J. Org. Chem.*, 2022, **87**, 3952–3966.
34 R. Aggarwal, M. Hooda, P. Kumar and M. C. Torralba, *Org. Biomol. Chem.*, 2022, **20**, 584–595.
35 R. Aggarwal, S. Sharma, M. Hooda, D. Sanz, R. M. Claramunt, B. Twamley and I. Rozas, *Tetrahedron*, 2019, **75**, 130728.
36 R. Aggarwal, N. Jain, G. P. Dubey, S. Singh and R. Chandra, *Biomacromolecules*, 2023, **24**, 4798–4818.
37 R. Aggarwal, M. Hooda, P. Kumar, S. Kumar, S. Singh and R. Chandra, *Bioorg. Chem.*, 2023, **136**, 106524.
38 R. Aggarwal, M. Hooda, N. Jain, D. Sanz, R. M. Claramunt, B. Twamley and I. Rozas, *J. Sulfur Chem.*, 2022, **43**, 12–21.
39 R. Aggarwal R, R. Kumar, D. Sanz and R. M. Claramunt, *J. Heterocycl. Chem.*, 2014, **51**, 598–603.
40 N. Aggarwal, R. Kumar, P. Dureja and J. M. Khurana, *Eur. J. Med. Chem.*, 2011, **46**, 4089–4099.
41 G. Sumran and R. Aggarwal, *J. Sulfur Chem.*, 2015, **36**, 170–177.
42 B. S. Furniss, A. J. Hannaford, P. W. G. Smith and A. R. Tatchell, in *Vogel's Textbook of Practical Organic Chemistry*, Longman Scientific and Technical, England, 1991, pp. 634–635.
43 K. P. Bhusari, N. D. Amnerkar, P. B. Khedekar, M. K. Kale and R. Bhole, *Asian J. Res. Chem.*, 2008, **1**, 53–58.
44 R. Aggarwal, S. Kumar, R. Sadana, A. Guzman and V. Kumar, *Synth. Commun.*, 2021, **51**, 3308–3324.
45 (*a*) R. Aggarwal, R. Kumar and V. Kumar, *J. Sulfur Chem.*, 2007, **28**, 617–623; (*b*) R. Aggarwal, S. Kumar and S. P. Singh, *J. Sulfur Chem.*, 2012, **33**, 521–525.
46 S. Kumar, R. Aggarwal, V. Kumar, R. Sadana, B. Patel, P. Kaushik and D. Kaushik, *Eur. J. Med. Chem.*, 2016, **123**, 718–726.
47 I. Pravst, M. Zupan and S. Stavber, *Green Chem.*, 2006, **8**, 1001–1005.
48 S. Murru, C. B. Singh, V. Kavala and B. K. Patel, *Tetrahedron*, 2008, **64**, 1931–1942.

