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A tandem multi-component synthesis of 5,7-diaryl-5,6,7,8-tetrahydro-1*H*-pyrido[3,4-*b*][1,4]thiazin-2(3*H*)-ones

Velanganni Paul Alex Raja and Subbu Perumal*

School of Chemistry, Madurai Kamaraj University, Madurai 625 021, Tamil Nadu, India

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Abstract—The five-component reaction of ethyl 2-[(2-oxopropyl)sulfanyl]acetate, aromatic aldehydes, and ammonium acetate affords two diastereomers of 5,7-diaryl-5,6,7,8-tetrahydro-1*H*-pyrido[3,4-b][1,4]thiazin-2(3*H*)-ones via a novel tandem Mannich-enamine-substitution sequence. Presumably, they are generated from ethyl 2-[(4-oxo-2,6-diaryl-3-piperidinyl)sulfanyl]acetates. During the formation of the *trans*-5,7-diaryl-5,6,7,8-tetrahydro-1*H*-pyrido[3,4-b][1,4]-thiazin-2(3*H*)-ones from ethyl 2-[(4-oxo-2,6-diaryl-3-piperidinyl)sulfanyl]acetates, the configuration at the carbon bearing an aryl group adjacent to the enamide C=C double bond is inverted via ring opening and closure. When *o*-substituted benzaldehydes were employed in this reaction, 5,7-diaryl-5,6-dihydro-1*H*-pyrido[3,4-b][1,4]thiazin-2(3*H*)-ones were obtained via air oxidation, along with *trans*-5,7-diaryl-5,6,7,8-tetrahydro-1*H*-pyrido[3,4-b][1,4]-thiazin-2(3*H*)-ones.

1. Introduction

Heterocycles containing nitrogen and sulfur possess important biological activities. For instance, the piperidine sub-structure is ubiquitous in nature as it is found in many biologically active compounds such as alkaloids.[1] Compounds incorporating a piperidine ring exhibit biological activities like anti-parkinson,[2] antidepressant[3] and analgesic.[4] Thiazines display many important biological activities such as sedative,[5] neuroleptic,[6] antitussive,[7] anti-fungal, anti-inflammatory and anthelmintic,[8] antipsoriatic[9] and anti-HIV.[10] The derivatives of thiazine act as myocardial calcium channel modulators[11] and also as matrix metalloproteinase inhibitors.[12] Hence, it was considered of interest to synthesis heterocycles comprising these two rings in a one-pot synthesis employing a tandem sequence. Tandem reactions are very useful in constructing molecules of complex structures rapidly with elegance and economy in an eco-friendly manner as wastage is minimised in this protocol.

2. Results and discussion

The synthesis of 5,7-diaryl-5,6,7,8-tetrahydro-1*H*-pyrido [3,4-b][1,4]thiazin-2(3*H*)-ones **5** was planned via a multi-component reaction employing a Mannich-enamine-substitution tandem sequence as depicted in Scheme 1.

Accordingly, a series of 5,7-diaryl-5,6,7,8-tetrahydro-1*H*-pyrido[3,4-b][1,4]thiazin-2(3*H*)-ones **5** (42–74%) were prepared in a one-pot reaction by gently warming the reactants, ethyl 2-[(2-oxopropyl)sulfanyl]acetate **1**, aromatic aldehyde and ammonium acetate in a 1:2:2 molar ratio in ethanol and stirring at ambient temperature for about 5–7 days. When 1 mol of ammonium acetate was used, the reaction was found to afford ethyl 2-[(4-oxo-2,6-diaryl-3-piperidinyl)sulfanyl]acetate **2**, showing that the product-selectivity of the reaction can be tuned statistically. Since, thiazinones were targeted as the final products, only one of the intermediate piperidones was synthesised and the *cis* relationship between the aryl rings in **2** was established.

Ethyl 2-[(2-oxopropyl)sulfanyl]acetate **1** required for the synthesis of the thiazinones was prepared by the reaction of chloroacetone and ethyl 2-sulfanylacetate in presence of potassium carbonate in chloroform medium in 95% yield. In contrast, the preparation of **1** was reported earlier in 62.5% yield from the reaction of chloroacetone and ethyl 2-sulfanylacetate in presence of sodium ethoxide in ethanol under reflux.[13] The ketoester **1** has one active methyl and two active methylene groups. From the structures of **2** and **5**, it follows that the reaction occurs regioselectively, wherein the methylene and methyl adjacent to the keto carbonyl are involved in the reaction, although the methylene adjacent to the sulfur and ester functions should be more acidic relative to the acetyl methyl (Scheme 1). This may probably be ascribed to the greater nucleophilicity of the carbanion formed at the terminal methyl carbon relative to the carbanion generated at the methylene carbon attached to the ester and sulfur functionalities.

Keywords: Piperidine; Thiazine; Ethyl 2-[(2-oxopropyl)sulfanyl]acetate; Tandem; Mannich; Enamine.
* Corresponding author. Tel./fax: +91 452 2459845; e-mail: subbu.perum@gmail.com

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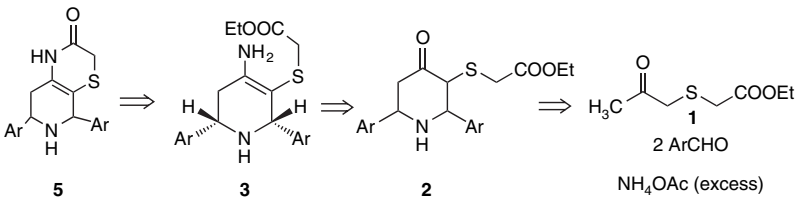


Scheme 1. Retrosynthesis of thiazinones **5**.

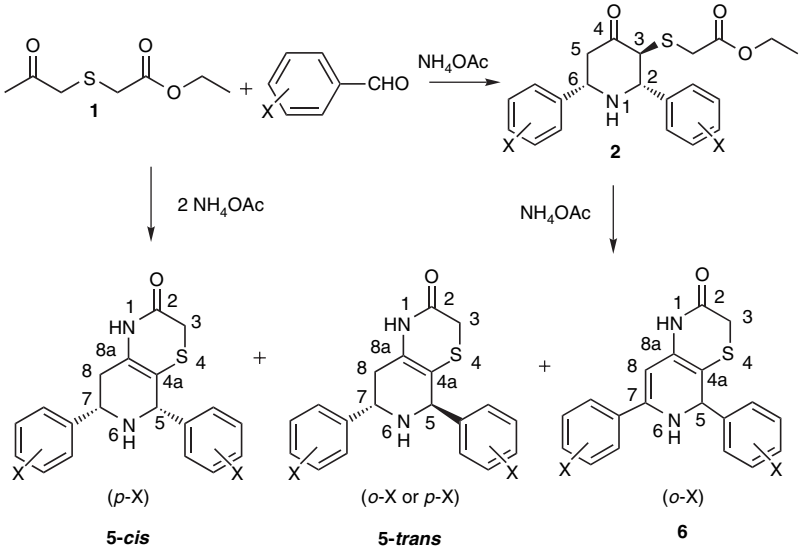
This five-component tandem reaction involving *para*-substituted benzaldehydes affords two diastereomers of thiazinones, **5**-*cis* and **5**-*trans*, which differ in the relative orientations of the aryl rings at C-5 and C-7. The *cis*- and *trans*-isomers of **5a**–**5d** were separated using flash column chromatography. From the ^{1}H NMR spectroscopic data of the reaction mixture, it is found that the ratio of the *trans* and *cis* isomers, **5a**–**5d** is ~0.70:1.00. In the case of *ortho*-substituted benzaldehydes, only the **5**-*trans* and the air-oxidised product, 5,7-diaryl-5,6-dihydro-1*H*-pyrido[3,4-b][1,4]thiazin-2(3*H*)-ones, **6** were obtained (Scheme 2). The yields of **5** and **6** are given in Table 1.

Table 1. Yields of thiazinones, **5a**–**6g**

Comp	X	Yield (%)	Total yield (%)
5a-*cis*	H	38	67
5a-*trans*		29	
5b-*cis*	*p*-Cl	37	63
5b-*trans*		26	
5c-*cis*	*p*-Me	33	54
5c-*trans*		21	
5d-*cis*	*p*-F	32	48
5d-*trans*		16	
5e-*trans*	*o*-Cl	39	49
5f-*trans*	*o*-Me	33	42
5g-*trans*	*o*-MeO	60	74
6e	*o*-Cl	10	
6f	*o*-Me	9	
6g	*o*-MeO	14	

The structure and stereochemistry of **2** was established from ^{1}H, ^{13}C and 2D NMR spectroscopic data. That the ring system in **2f** adopts a chair conformation is evident from the splitting pattern and *J* values of the signals of the ring protons. The proton H-6 gives a doublet of doublets at 4.65 ppm with *J* values of 12 and 3 Hz corresponding to the vicinal diaxial and axial–equatorial couplings, respectively. This points to the equatorial orientation of the *o*-chlorophenyl group at C-6. The axial orientation of the sulfanyl ester side chain at C-3 is inferred from the *J* value of 2 Hz for the protons, H-2 and H-3 giving signals at 4.93 and 3.79 ppm, respectively. The diastereotopic methylene protons, H-5 each appear as a doublet of doublets at 2.60 and 3.62 ppm, respectively, while the diastereotopic methylene protons adjacent to sulfur appear as doublets at 3.01 and 3.12 ppm with a *J* value of 15 Hz. The methyl and the methylenic protons of the ester functionality appear at 1.20 and 4.00 ppm, respectively. The results of X-ray studies are also in accord with the above structure **2f**[14] (Fig. 1).

The *cis*- and *trans*-isomers of **5a**–**5g** were characterised using ^{1}H, ^{13}C and 2D NMR spectroscopic data. The ^{1}H NMR spectrum of **5a**-*cis* gives a doublet of doublets with *J* values of 11 and 4 Hz at 4.20 ppm ascribable to the axial–pseudoaxial and axial–pseudoequatorial couplings of H-7 with the diastereotopic protons at C-8. This points to the equatorial orientation of the phenyl ring at C-7. The diastereotopic methylene protons, H-3 give two doublets at 3.12



Scheme 2. Formation of thiazinones **5** and **6** via tandem reactions.

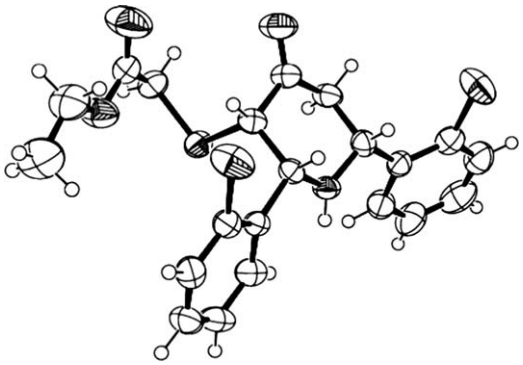


Figure 1. X-ray structure of ethyl 2-[2,6-bis(2-chlorophenyl)-4-oxo-3-piperidinyl]sulfanylacetate **2f**.

and 3.39 ppm with the *J* value of 15 Hz, this assignment being confirmed by a HMBC correlation of these protons with the carbonyl carbon at 164.2 ppm and the C-4a at 111.0 ppm. One of the two protons of 8-CH_2 appears as a doublet of doublets of doublets at 2.37 ppm with *J* values of 16, 4 and 2 Hz corresponding to the geminal coupling, pseudoequatorial–axial coupling with H-7, and a long range coupling with H-5. Another proton of 8-CH_2 group also appears as a doublet of doublets of doublets at 2.58 ppm with *J* values of 16, 11 and 4 Hz corresponding to the geminal coupling, pseudoaxial–axial coupling with H-7 and a long range coupling with H-5. The benzylic proton H-5 appears at 4.75 ppm as a doublet of doublets with *J* values of 4 and 2 Hz resulting from the long range coupling with the allylic protons at C-8, which is evident from H,H-COSY spectroscopic data. The aromatic protons appear in the region of 7.27–7.46 ppm, while the amine and amide protons appear at 1.65 and 7.65 ppm, respectively.

In the ^{1}H NMR spectrum of **5a**-*trans*, a doublet of doublets due to H-7 is obtained at 4.08 ppm with *J* values of 10 and 4 Hz, ascribable to pseudoaxial–axial and axial–pseudoequatorial coupling, respectively, with 8-CH_2 protons. This shows that the phenyl ring at C-7 is oriented equatorially. The diastereotopic protons at C-3 give two doublets at 3.31 and 3.44 ppm (J=15 Hz). The two allylic protons at C-8 appear as a multiplet at 2.53 ppm. Unlike in the case of **5a**-*cis*, the proton, H-5 of **5a**-*trans* appears as a singlet at 4.74 ppm, while the amine and amide protons give signals at 1.70 and 7.45 ppm, respectively.

An unambiguous assignment of the heterocyclic ring carbon chemical shifts for **5a**-*cis* and **5a**-*trans* was arrived at from the proton chemical shift values and C,H-COSY correlations. The ^{13}C chemical shifts of 5,7-diaryl-5,6,7,8-tetrahydro-1*H*-pyrido[3,4-b][1,4]thiazin-2(*3H*)-ones show that the carbon signals of **5a**-*trans* isomers appear slightly more shielded than the corresponding carbons of the *cis* isomer (**5a**-*cis*). For instance, the quaternary carbon, C-4a and the homoallylic carbon, C-7 of **5a**-*trans* appear shielded by 3.7 and 6.7 ppm, respectively, compared to the corresponding carbons of the *cis* isomer. Presumably, this is ascribable to the *syn* axial interaction between the C-5 aryl ring and the axial proton H-7 of the **5a**-*trans* isomer. The ratio of the **5**-*trans* to **5**-*cis* isomers ~0.70:1.00 found from the ^{1}H NMR spectrum of the reaction mixture suggests that the **5**-*trans* is slightly less stable than the **5**-*cis* isomer in the case of aryl rings with *p*-substituent. The C-3 of **5a**-*cis* gives a signal at 30.6 ppm, while the quaternary carbon, C-4a appears at 111.0 ppm. The assignment of the chemical shift of C-4a is also further supported by the HMBC spectroscopic data, which shows correlation between C-4a and H-3 proton. The allylic carbons, C-5 and C-8 appear at 62.7 and 36.4 ppm, respectively, the assignments being aided by the C,H-COSY correlations. Similarly, the homoallylic carbon C-7 was assigned to the signal at 57.9 ppm. The signal of another quaternary carbon C-8a appears at 142.6 ppm. The homoallylic proton, H-7 appearing at 4.20 ppm shows a weak correlation with quaternary carbon, C-8a at 142.6 ppm in the HMBC spectrum. The aromatic carbons appear in the region of 126.6–139.7 ppm.

The stereochemistry of the *cis*- and *trans*-isomers of **5** arrived at from NMR studies is also in complete agreement with that determined by the X-ray crystallographic studies of crystals of **5b**-*cis* (Fig. 2), **5e**-*trans* (Fig. 3) and **5g**-*trans* (Fig. 4).

In the thiazinone ring of **5**-*cis* isomers, both six membered rings adopt a half chair conformation and the aryl rings at 5- and 7-positions are oriented equatorially and pseudoequatorially. For the **5**-*trans* isomers, the aryl rings at 5- and 7-positions are oriented equatorially and pseudoaxially in contrast to their *cis* relationship for the aryl rings found in

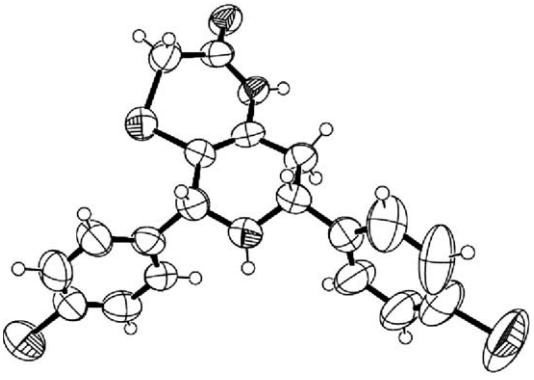


Figure 2. X-ray structure of *cis*-5,7-bis(4-chlorophenyl)-5,6,7,8-tetrahydro-1*H*-pyrido[3,4-*b*][1,4]thiazin-2(3*H*)-one **5b**-*cis*.

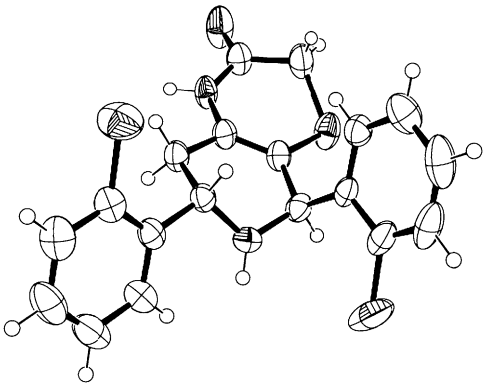


Figure 3. X-ray structure of *trans*-5,7-bis(2-chlorophenyl)-5,6,7,8-tetrahydro-1*H*-pyrido[3,4-*b*][1,4]thiazin-2(3*H*)-one **5e**-*trans*.

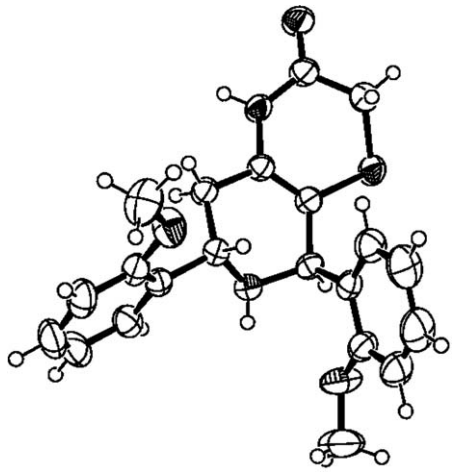
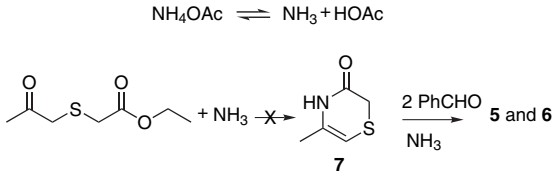


Figure 4. X-ray structure of *trans*-5,7-bis(2-methoxyphenyl)-5,6,7,8-tetrahydro-1*H*-pyrido[3,4-*b*][1,4]thiazin-2(3*H*)-one **5g**-*trans*.

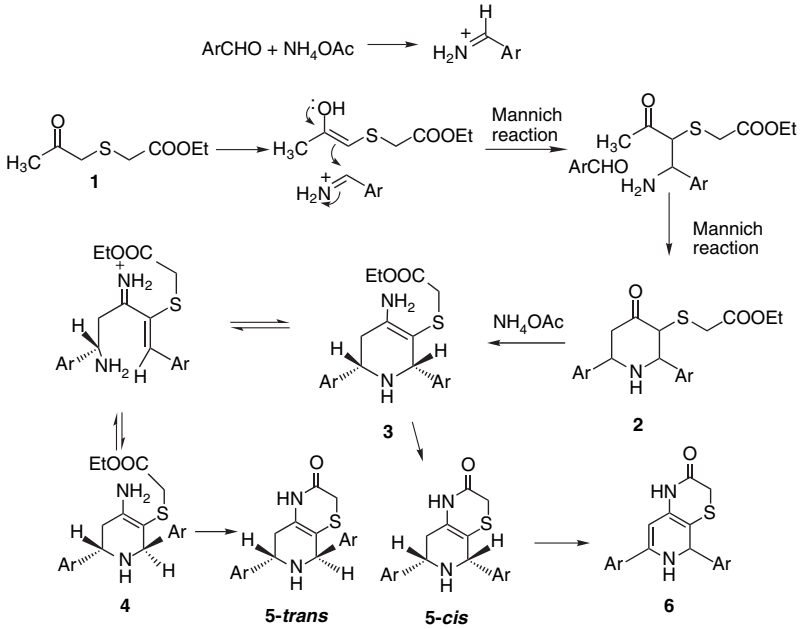
piperidone **2f**, although **2f** is the precursor for **5e**-*trans* as found from the conversion of **2f** into **5e**-*trans* upon treatment of the former with ammonium acetate under the reaction conditions in a separate reaction. This suggests that during the formation of **5e**-*trans* from **2f**, the configuration at C-5 is inverted, presumably via the opening and reformation of the ring with inversion at one of the benzylic positions of the piperidine ring as shown in Scheme 3. The probable mechanism of formation of the thiazinones is given in Scheme 3, wherein two Mannich reactions, enamine formation, ring opening and closure and condensation occur in a tandem sequence. In the case of *o*-substituted benzaldehydes, the *trans*-tetrahydrothiazinones undergo air oxidation to furnish the dihydrothiazinones **6** as minor product, whose structure was elucidated from NMR spectroscopic data. For instance, in the ^{1}H NMR spectrum of **6e**, the two diastereotopic protons at C-3 give two doublets at 3.33 and 3.44 ppm (J=14 Hz). The H-5 appears as a singlet at 4.77 ppm, while the alkenic proton, H-8 appears as a singlet at 5.49 ppm. The amino and the amide protons give broad singlets at 1.70 and 7.76 ppm, respectively. That the reaction proceeding through an alternative mechanistic pathway via an initially formed **7** depicted in Scheme 4 is not involved under the present reaction conditions is evident from the following. The reaction of ethyl 2-[(2-oxopropyl)sulfanyl]acetate **1** with ammonium acetate both under room temperature and at reflux for 8 days in the absence of benzaldehyde and the subsequent examination of the reaction mixture employing ^{1}H NMR, ^{13}C NMR and GC–MS techniques failed to show the formation of even a small amount of the thiazine **7**.



Scheme 4. Mechanism for the formation of thiazinones **5** and **6** through **7**.

3. Conclusion

The present study reports a concise, one-pot, multi-component tandem synthesis of thiazinones, which could possess important biological activities. The complete structure and stereochemistry of the products have been elucidated using NMR spectroscopic and X-ray crystallographic studies. In view of the pharmacophoric nature of the piperidine and thiazine ring systems, investigations are now currently in progress in our group with a view to using the thiazinones as synthons for the construction of more complex molecules and to prepare enantiomerically pure compounds belonging to this class.



Scheme 3. Mechanism of formation of thiazinones.

4. Experimental

4.1. General methods

All melting points reported in this work were measured in open capillaries. Flash chromatography was performed on silica gel (230–400 mesh). The ^{1}H and ^{13}C NMR spectra have been measured at 300 and 75 MHz, respectively, using Bruker 300 MHz (Avance) instrument in $CDCl_3$ solvent using tetramethylsilane as internal standard. Chemical shifts were reported as δ values (ppm). All one- and two-dimensional NMR spectra were obtained using standard Bruker software throughout. IR spectra were recorded on a JASCO FTIR instrument (KBr pellet in case of solids and CH_2Cl_2 in case of liquids). Elemental analysis were done using Vario EL III instrument. Crystals suitable for X-ray analysis were obtained by crystallisation from ethanol and ethyl acetate mixture.

4.2. Synthesis of thiazin-2(3*H*)-ones from benzaldehyde and *p*-substituted benzaldehydes—general procedure

Ammonium acetate (0.663 g, 8.4 mmol) was dissolved in ethanol (3 mL) by heating. Benzaldehyde (0.582 mL, 5.7 mmol) and ethyl 2-[(2-oxopropyl)sulfanyl]acetate (0.338 mL, 2.8 mmol) were added to this solution, the mixture heated until the colour of the solution turned yellow and left at room temperature for 5–7 days. After the completion of the reaction, the two diastereomers were separated using flash column chromatography performed on silica gel (230–400 mesh) and petroleum ether and ethyl acetate mixture. The products were further recrystallised from ethanol and ethyl acetate.

4.2.1. *cis*-5,7-Diphenyl-5,6,7,8-tetrahydro-1*H*-pyrido [3,4-*b*][1,4]thiazin-2(3*H*)-one 5a-*cis*. Isolated as colourless solid. (347 mg, 38%) mp=202 °C; υ_{max} (KBr) 3199, 1672 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.65 (1H, s), 2.37 (1H, ddd, *J*=16, 4, 2 Hz), 2.58 (1H, ddd, *J*=16, 11, 4 Hz), 3.12 (1H, d, *J*=15 Hz), 3.39 (1H, d, *J*=15 Hz), 4.20 (1H, dd, *J*=11, 4 Hz), 4.75 (1H, dd, *J*=4, 2 Hz), 7.27–7.46 (10H, m), 7.65 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 30.6, 36.4, 57.9, 62.7, 111.0, 126.6, 127.8, 128.4, 128.5, 128.6, 128.7, 128.8, 139.7, 142.6, 164.2. Anal. Calcd for $C_{19}H_{18}N_2OS$: C, 70.78; H, 5.63; N, 8.69. Found C, 70.73; H, 5.67; N, 8.70.

4.2.2. *trans*-5,7-Diphenyl-5,6,7,8-tetrahydro-1*H*-pyrido[3,4-*b*][1,4]thiazin-2(3*H*)-one 5a-*trans*. Isolated as colourless solid. (265 mg, 29%) mp=199 °C; υ_{max} (KBr) 3430, 1648 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.70 (1H, s), 2.53 (2H, m), 3.31 (1H, d, *J*=15 Hz), 3.44 (1H, d, *J*=15 Hz), 4.08 (1H, dd, *J*=10, 4 Hz), 4.74 (1H, s), 7.22–7.39 (10H, m), 7.45 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 30.4, 36.0, 51.2, 60.1, 107.3, 126.6, 127.7, 128.0, 128.1, 128.6, 128.7, 130.0, 140.8, 142.3, 164.1. Anal. Calcd for $C_{19}H_{18}N_2OS$: C, 70.78; H, 5.63; N, 8.69. Found C, 70.76; H, 5.69; N, 8.60.

4.2.3. *cis*-5,7-Bis(4-chlorophenyl)-5,6,7,8-tetrahydro-1*H*-pyrido[3,4-*b*][1,4]thiazin-2(3*H*)-one 5b-*cis*. Isolated as pale yellow solid. (410 mg, 37%) mp=195 °C; υ_{max} (KBr) 3285, 1671 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.78 (1H, s), 2.34 (1H, ddd, *J*=16, 4, 2 Hz), 2.52 (1H, ddd, *J*=16, 11, 4 Hz), 3.12 (1H, d, *J*=15 Hz), 3.37 (1H, d, *J*=15 Hz), 4.15 (1H, dd, *J*=11, 4 Hz), 4.72 (1H, dd, *J*=4, 2 Hz), 7.28–7.49 (10H, m), 8.18 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 30.5, 36.5, 57.2, 61.9, 110.4, 128.0, 128.6, 128.7, 128.8, 130.2, 133.6, 134.3, 138.2, 141.0, 164.0. Anal. Calcd for $C_{19}H_{16}Cl_2N_2OS$: C, 58.32; H, 4.12; N, 7.16. Found C, 58.29; H, 4.18; N, 7.14.

4.2.4. *trans*-5,7-Bis(4-chlorophenyl)-5,6,7,8-tetrahydro-1*H*-pyrido[3,4-*b*][1,4]thiazin-2(3*H*)-one 5b-*trans*. Isolated as colourless solid. (288 mg, 26%) mp=180 °C; υ_{max} (KBr) 3350, 1681 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 2.33 (1H, m), 3.21 (1H, d, *J*=15 Hz), 3.35 (1H, d, *J*=15 Hz), 4.34 (1H, s), 4.63 (1H, s), 3.97 (1H, m), 7.15–7.27 (10H, m), 8.83 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 30.2, 35.2, 50.6, 59.1, 107.1, 128.1, 128.8, 128.9, 129.5, 130.0, 133.6, 134.1, 140.1. Anal. Calcd for $C_{19}H_{16}Cl_2N_2OS$: C, 58.32; H, 4.12; N, 7.16. Found C, 58.39; H, 4.08; N, 7.21.

4.2.5. *cis*-5,7-Bis(4-methylphenyl)-5,6,7,8-tetrahydro-1*H*-pyrido[3,4-*b*][1,4]thiazin-2(3*H*)-one 5c-*cis*. Isolated as colourless solid. (328 mg, 33%) mp=180 °C; υ_{max} (KBr) 3402, 1675 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 2.1 (1H, s), 2.31 (3H, s), 2.32 (2H, m), 2.34 (3H, s), 2.54 (1H, ddd, *J*=14, 11, 4 Hz), 3.10 (1H, d, *J*=15 Hz), 3.37 (1H, d, *J*=15 Hz), 4.14 (1H, dd, *J*=11, 4 Hz), 4.70 (1H, dd, *J*=4, 2 Hz), 7.11–7.33 (8H, m), 8.9 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 21.1, 21.2, 30.6, 36.5, 57.6, 62.4, 111.1, 126.4, 128.6, 129.1, 129.2, 136.7, 137.4, 138.3, 139.7, 164.1. Anal. Calcd for $C_{21}H_{22}N_2OS$: C, 71.97; H, 6.33; N, 7.99. Found C, 71.90; H, 6.35; N, 8.07.

4.2.6. *trans*-5,7-Bis(4-methylphenyl)-5,6,7,8-tetrahydro-1*H*-pyrido[3,4-*b*][1,4]thiazin-2(3*H*)-one 5c-*trans*. Isolated as paste. (208 mg, 21%); υ_{max} (CH_2Cl_2) 3328, 1675 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 2.53 (2H, m), 3.27 (3H, s), 3.25 (1H, d, *J*=15 Hz), 3.41 (1H, d, *J*=15 Hz), 3.39 (3H, s), 4.07 (1H, m), 4.75 (1H, s), 5.03 (1H, s), 7.08–7.26 (8H, m), 8.50 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 21.0, 21.1, 30.2, 35.4, 50.9, 59.4, 107.2, 126.7, 128.1, 129.3, 129.4, 130.0, 137.1, 137.6, 138.1, 138.6, 164.8. Anal. Calcd for $C_{21}H_{22}N_2OS$: C, 71.97; H, 6.33; N, 7.99. Found C, 71.94; H, 6.25; N, 7.91.

4.2.7. *cis*-5,7-Bis(4-fluorophenyl)-5,6,7,8-tetrahydro-1*H*-pyrido[3,4-*b*][1,4]thiazin-2(3*H*)-one 5d-*cis*. Isolated as colourless solid. (325 mg, 32%) mp=205 °C; υ_{max} (KBr) 3212, 1671 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.83 (1H, s), 2.35 (1H, ddd, *J*=16, 4, 2 Hz), 2.54 (1H, ddd, *J*=16, 11, 4 Hz), 3.10 (1H, d, *J*=15 Hz), 3.37 (1H, d, *J*=15 Hz), 4.16 (1H, dd, *J*=11, 4 Hz), 4.73 (1H, dd, *J*=4, 2 Hz), 6.98–7.43 (8H, m), 8.50 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 30.9, 57.7, 62.3, 36.9, 111.1, 115.6, 115.7, 115.9, 116.0, 128.6, 128.7, 130.8, 130.9, 135.9, 138.8, 164.6. Anal. Calcd for $C_{19}H_{16}F_2N_2OS$: C, 63.67; H, 4.50; N, 7.82. Found C, 63.66; H, 4.57; N, 7.72.

4.2.8. *trans*-5,7-Bis(4-fluorophenyl)-5,6,7,8-tetrahydro-1*H*-pyrido[3,4-*b*][1,4]thiazin-2(3*H*)-one 5d-*trans*. Isolated as colourless solid. (163 mg, 16%) mp=198 °C; υ_{max} (KBr) 3091, 1650 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 2.51 (m), 3.29 (1H, d, *J*=15 Hz), 3.44 (1H, d, *J*=15 Hz), 4.06 (1H, m),

4.70 (1H, s), 6.15 (1H, s), 6.99–7.50 (8H, m), 7.71 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 30.3, 35.7, 50.5, 59.2, 107.6, 115.3, 115.4, 115.6, 115.7, 115.8, 116.1, 128.4, 128.8, 129.7, 129.8, 130.0, 164.6. Anal. Calcd for $C_{19}H_{16}F_2N_2OS$: C, 63.67; H, 4.50; N, 7.82. Found C, 63.64; H, 4.49; N, 7.89.

4.3. Synthesis of thiazin-2(3*H*)-ones from *o*-substituted benzaldehydes—general procedure

The procedure described above for benzaldehyde and *p*-substituted benzaldehydes was used as such here. In these reactions, a mixture of **5**-*trans* and **6** were obtained, which were separated by flash column chromatography using silica gel (230–400 mesh) and petroleum ether and ethyl acetate mixture.

4.3.1. *trans*-5,7-Bis(2-chlorophenyl)-5,6,7,8-tetrahydro-1*H*-pyrido[3,4-*b*][1,4]thiazin-2(3*H*)-one 5e-*trans*. Isolated as colourless solid. (432 mg, 39%) mp=181 °C; υ_{max} (KBr) 3295, 1658 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 2.02 (1H, s), 2.53 (2H, m), 3.33 (1H, d, *J*=15 Hz), 3.44 (1H, d, *J*=15 Hz), 4.38 (1H, dd, *J*=11, 4 Hz), 5.21 (1H, s), 7.16–7.57 (8H, m), 8.49 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 30.3, 34.3, 47.5, 56.9, 106.0, 126.5, 127.3, 127.5, 128.8, 129.3, 129.4, 129.6, 131.0, 130.2, 133.1, 134.2, 137.3, 139.3, 164.3. Anal. Calcd for $C_{19}H_{16}N_2Cl_2OS$: C, 58.32; H, 4.12; N, 7.16. Found C, 58.33; H, 4.10; N, 7.11.

4.3.2. *trans*-5,7-Bis(2-methylphenyl)-5,6,7,8-tetrahydro-1*H*-pyrido[3,4-*b*][1,4]thiazin-2(3*H*)-one 5f-*trans*. Isolated as colourless solid. (328 mg, 33%) mp=141 °C; υ_{max} (KBr) 3420, 1678 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.96 (1H, s), 2.39 (3H, s), 2.42 (3H, s), 2.57 (2H, m), 3.27 (1H, d, *J*=15 Hz), 3.40 (1H, d, *J*=15 Hz), 4.24 (1H, dd, *J*=11, 4 Hz), 4.96 (1H, s), 7.03–7.42 (8H, m), 8.99 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 19.0, 19.4, 30.3, 33.9, 46.7, 56.7, 107.3, 125.4, 125.6, 126.3, 127.4, 127.5, 127.9, 130.5, 130.8, 131.2, 136.0, 136.6, 137.8, 139.7, 164.6. Anal. Calcd for $C_{21}H_{22}N_2OS$: C, 71.97; H, 6.33; N, 7.99. Found C, 71.90; H, 6.31; N, 8.06.

4.3.3. *trans*-5,7-Bis(2-methoxyphenyl)-5,6,7,8-tetrahydro-1*H*-pyrido[3,4-*b*][1,4]thiazin-2(3*H*)-one 5g-*trans*. Isolated as colourless solid. (651 mg, 60%) mp=161 °C; υ_{max} (KBr) 3442, 1679 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.92 (1H, s), 2.46 (2H, m), 3.32 (1H, d, *J*=15 Hz), 3.43 (1H, d, *J*=15 Hz), 3.62 (3H, s), 3.83 (3H, s), 4.24 (1H, dd, *J*=11, 4 Hz), 5.16 (1H, s), 6.76–7.42 (8H, m), 7.93 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 30.4, 34.4, 45.2, 54.4, 55.1, 55.2, 106.5, 110.3, 110.4, 120.0, 120.8, 126.2, 128.3, 128.4, 128.9, 129.0, 130.8, 131.0, 156.7, 157.4, 164.2. Anal. Calcd for $C_{21}H_{22}N_2O_3S$: C, 65.95; H, 5.80; N, 7.32. Found C, 65.86; H, 5.75; N, 7.34.

4.3.4. 5,7-Bis(2-chlorophenyl)-5,6-dihydro-1*H*-pyrido[3,4-*b*][1,4]thiazin-2(3*H*)-one 6e. Isolated as colourless solid. (111 mg, 10%) mp=136 °C; υ_{max} (KBr) 3307, 1680 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.70 (1H, s), 3.33 (1H, d, *J*=14 Hz), 3.44 (1H, d, *J*=14 Hz), 4.77 (1H, s), 5.49 (1H, s), 6.75–7.53 (9H, m), 7.76 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 30.9, 48.5, 110.2, 118.9, 120.3, 126.5, 126.8, 127.3, 128.7, 129.0, 129.3, 129.6, 129.8, 130.2, 130.6, 133.4, 134.5, 136.5, 163.5. Anal. Calcd for $C_{19}H_{14}Cl_2N_2OS$: C, 58.62; H, 3.62; N, 7.20. Found C, 58.58; H, 3.60; N, 7.23.

4.3.5. 5,7-Bis(2-methylphenyl)-5,6-dihydro-1*H*-pyrido[3,4-*b*][1,4]thiazin-2(3*H*)-one 6f. Isolated as colourless solid. (90 mg, 9%) mp=155 °C; υ_{max} (KBr) 3400, 1670 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.7 (1H, s), 2.26 (3H, s), 2.29 (3H, s), 3.25 (1H, d, *J*=14 Hz), 3.45 (1H, d, *J*=14 Hz), 4.44 (1H, s), 5.20 (1H, s), 6.64–7.25 (9H, m), 8.60 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 18.7, 19.1, 30.7, 54.5, 119.8, 120.0, 125.5, 126.2, 127.1, 128.1, 128.3, 130.0, 130.4, 131.3, 134.8, 136.9, 137.2, 137.3, 137.7, 138.3, 164.6. Anal. Calcd for $C_{21}H_{20}N_2OS$: C, 72.38; H, 5.79; N, 8.04. Found C, 72.39; H, 5.75; N, 8.00.

4.3.6. 5,7-Bis(2-methoxyphenyl)-5,6-dihydro-1*H*-pyrido[3,4-*b*][1,4]thiazin-2(3*H*)-one 6g. Isolated as paste. (151 mg, 10%); υ_{max} (CH_2Cl_2) 3425, 1665 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.7 (1H, s), 3.10 (1H, d, *J*=15 Hz), 3.27 (1H, d, *J*=15 Hz), 3.80 (3H, s), 3.85 (3H, s), 4.81(1H, s), 5.60 (1H, s), 6.64–7.53 (9H, m), 8.00 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 33.0, 49.7, 55.1, 55.4, 109.8, 111.4, 111.1, 119.8, 120.1, 120.4, 124.0, 127.6, 127.9, 128.2, 128.8, 129.6, 129.8, 133.2, 133.6, 170.0. Anal. Calcd for $C_{21}H_{20}N_2O_3S$: C, 66.29; H, 5.30; N, 7.36. Found C, 66.27; H, 5.26; N, 7.38.

4.4. Synthesis of ethyl 2-[2,6-bis(2-chlorophenyl)-4-oxo-3-piperidinyl]sulfanylacetate 2f

Ammonium acetate (0.215 g, 2.8 mol) was dissolved in ethanol (3 mL) by heating. *ortho*-Chlorobenzaldehyde (0.630 mL, 5.7 mol) and ethyl 2-[(2-oxopropyl)sulfanyl] acetate (0.338 mL, 2.8 mmol) were added to this solution and the mixture was heated until the colour of the solution turned yellow. The solution was kept at room temperature for 4 days. The solid precipitated was filtered off, washed with ethanol, and recrystallised from ethanol and ethyl acetate as colourless solid. (597 mg, 49%) mp=178 °C; υ_{max} (CH_2Cl_2) 3307, 1731, 1706 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.20 (3H, t, *J*=7 Hz), 1.65 (1H, s), 2.60 (1H, dd, *J*=15, 3 Hz), 3.01 (1H, d, *J*=15 Hz), 3.12 (1H, d, *J*=15 Hz), 3.62 (1H, dd, *J*=15, 12 Hz), 3.79 (1H, d, *J*=2 Hz), 4.00 (2H, m), 4.65 (1H, dd, *J*=12, 3 Hz), 4.93 (1H, d, *J*=2 Hz), 7.23–7.90 (8H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 13.9, 33.5, 42.3, 55.2, 56.4, 59.3, 61.5, 126.5, 127.6, 127.8, 129.0, 129.1, 129.5, 129.6, 129.7, 132.2, 132.4, 136.0, 139.5, 169.4, 203.6. Anal. Calcd for $C_{21}H_{21}Cl_2NO_3S$: C, 57.54; H, 4.83; N, 3.20. Found C, 57.49; H, 4.88; N, 3.13.

4.5. Synthesis of ethyl 2-[(2-oxopropyl)sulfanyl]acetate 1

Ethyl 2-sulfanylacetate (0.912 mL, 5.6 mmol) was dissolved in chloroform (10 mL). To this solution, chloroacetone (0.451 mL, 5.6 mmol) and potassium carbonate (0.392 g, 2.8 mmol) were added. The mixture was stirred under cold condition for 4–5 h. After the completion of the reaction, the product was extracted with chloroform, washed with water, dried over anhydrous calcium chloride and the solvent evaporated in vacuo. The pure product was obtained as a pale yellow liquid (0.936 g, 95%) bp 97 °C, density

1.4760 mg m^{-3}. υ_{max} (CH_2Cl_2) 1725, 1649, 1203; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.29 (3H, t, J=7 Hz), 2.30 (2H, s), 3.25 (2H, s), 3.46 (1H, s), 4.17 (2H, q, J=7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 13.7, 27.8, 32.9, 41.7, 61.0, 169.3, 202.5. Anal. Calcd for $C_7H_{12}O_3S$: C, 47.71; H, 6.86. Found C, 47.68; H, 6.81.

4.6. X-ray crystallographic determination of compounds of 2f, 5b-*cis*, 5e-*trans* and 5g-*trans*

Data were collected at room temperature on an Enraf-Nonius MACH 3 four-circle diffractometer (Mo Kα radiation, λ=0.71073 Å) for compounds **2f**, **5b**-*cis*, **5e**-*trans* and **5g**-*trans*. The data collection, integration, and data reduction for **2f**, **5b**-*cis*, **5e**-*trans*, and **5g**-*trans* were performed using CAD-4 EXPRESS[15] and XCAD4[16] programmes and an empirical absorption correction was applied using ψ scan method.[17] The unit cell parameters were determined by a least square fitting of 25 randomly selected strong reflections and an empirical absorption correction was applied using the azimuthal scan method. The structures were solved by direct methods (SHELXS 97)[18] and subsequent Fourier synthesis and refined by full matrix least squares on SHELXL 97[19] for all non-hydrogen atoms for **2f**, **5b**-*cis*, **5e**-*trans* and **5g**-*trans*. All hydrogen atoms were placed in calculated positions.

4.6.1. Compound 2f. $C_{21}H_{21}Cl_2NO_3S$, M=438.35, monoclinic, space group $Pccn$, a=25.5182(15) Å, b=19.3676(11) Å, c=8.3266(5) Å, V=4115(3) Å^3, Z=8, F(000)=1824, μ=0.439 mm^{-1}, D_c=1.415 mg m^{-3}. The reflections collected were 3845 of which 3594 unique [$R_{(int)}$=0.0459]; 1664 reflections $I>2\sigma(I)$, R_1=0.0677 and wR_2=0.1772 for 1664 [$I>2\sigma(I)$] and R_1=0.1731 and wR_2=0.2397 for all (3594) intensity data. Goodness of fit=1.027, residual electron density in the final Fourier map was 0.372 and −0.637 eÅ^{-3}. CCDC number is 290756.

4.6.2. Compound 5b-*cis*. $C_{19}H_{16}C_{l2}N_2OS$, M=391.31, monoclinic, space group $P2_1/n$, a=17.891(4) Å, b=5.052(6) Å, c=24.603(5) Å, V=4115(3) Å^3, Z=4, F(000)=808, μ=0.402 mm^{-1}, D_c=1.195 mg m^{-3}. The reflections collected were 4179 of which 3792 unique [$R_{(int)}$=0.0334]; 1114 reflections $I>2\sigma(I)$, R_1=0.0661 and wR_2=0.1873 for 1664 [$I>2\sigma(I)$] and R_1=0.1882 and wR_2=0.2241 for all (3792) intensity data. Goodness of fit=0.752, residual electron density in the final Fourier map was 0.453 and −0.271 eÅ^{-3}. CCDC number is 290758.

4.6.3. Compound 5e-*trans*. $C_{19}H_{16}C_{l2}N_2OS$, M=391.31, monoclinic, space group $P2_1/c$, a=7.1010(4) Å, b=26.6410(14) Å, c=9.8301(8) Å, V=1789.7 Å^3, Z=4, F(000)=808, μ=0.489 mm^{-1}, D_c=1.452 mg m^{-3}. The reflections collected were 3893 of which 3157 unique [$R_{(int)}$=0.0118]; 2128 reflections $I>2\sigma(I)$, R_1=0.0355 and wR_2=0.0912 for 2128 [$I>2\sigma(I)$] and R_1=0.0729 and wR_2=0.1200 for all (3157) intensity data. Goodness of fit=1.053, residual electron density in the final Fourier map was 0.463 and −0.455 eÅ^{-3}. CCDC number is 290757.

4.6.4. Compound 5g-*trans*. $C_{21}H_{22}N_2O_3S$, M=382.47, monoclinic, space group P-1, a=9.764 Å, b=10.972 Å, c=11.061 Å, V=965.3 Å^3, Z=2, F(000)=404, μ=0.191 mm^{-1}, D_c=1.316 mg m^{-3}. The reflections collected were 4046 of which 3392 unique [$R_{(int)}$=0.0110]; 2694 reflections $I>2\sigma(I)$, R_1=0.0347 and wR_2=0.0970 for 2694 [$I>2\sigma(I)$] and R_1=0.0492 and wR_2=0.1062 for all (3392) intensity data. Goodness of fit=1.037, residual electron density in the final Fourier map was 0.261 and −0.215 eÅ^{-3}. CCDC number is 290759.

5. Supplementary material

Crystal data and structure refinement for **2f**, **5b**-*cis*, **5e**-*trans* and **5g**-*trans*. Atomic coordinates ($\times 10^4$) and equivalent isotopic displacement parameters (Å$^2\times 10^3$) for **2f**, **5b**-*cis*, **5e**-*trans* and **5g**-*trans*.

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14. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the

Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 290756–290759. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK, +44 1223 336408 or e-mail: deposit@ccdc.cam.ac.uk).

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