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Comparative reactivity of N'-(5-benzoyl/ethoxycarbonyl)thiazol-2-yl-*N*,*N*-dimethylformamidines with ketenes

Parvesh Singh, Alka Marwaha, Harmeet Singh and Mohinder P. Mahajan*

Department of Applied Chemistry, Guru Nanak Dev University, Amritsar 143005, Punjab, India

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Abstract—The comparative account of the reactivities of N'-[(5-benzoyl and ethoxycarbonyl)thiazol-2-yl]-*N*,*N*-dimethylformamidines (**1a** and **1b**), tremendously influenced by the electronic nature of the substituents on C-5 of the thiazolic ring with various monosubstituted and conjugated ketenes is reported herein. The DA cycloadditions of the dienyl pyrimidinone **3h** with both symmetrical as well as unsymmetrical dienophiles leading to the formation of various thiazolic pyrimidinone derivatives are also reported.

1. Introduction

The advent of various diazabutadienes as potential 4π components has extended their versatility by allowing easy access to various functionalized six-membered heterocycles.[1] Their cycloaddition reactions with ketenes continue to be an important area of scientific quest because of their synthetic potential and interesting mechanistic features.[2] Considerable attention has also been paid to for the development of suitable synthetic methodologies for efficient synthesis of appropriately substituted diazabutadienes including 1,3-diaza-1,3-butadienes.[3] Recent reports from our laboratory have shown the development of simpler methods for the preparation of various acyclic 1,3-diazabuta-1,3-dienes and their successful utilization in [4+2] cycloaddition reactions with a variety of ketenes[4] yielding a spectrum of biologically and medicinally important pyrimidinones.

In recent years, while in the process of synthesis and cycloadditions of cross-conjugated heterodienes starting from thiourea and its analogues, we came across two reports by Deniaud et al. regarding the synthesis and reactions with α-haloketones/acrylic dienophiles and reactions of the subsequent thiazolic/thiazinic diazadienes with various dienophiles such as acrylates and simple ketenes leading to the formation of various heterobicyclic compounds.[5]

The synthetic versatility of thiazolic diazadienes, despite being excellent synthons, has largely remained unexplored. These have been reported to undergo [4+2] cycloadditions with highly reactive unsubstituted ketenes, generated, in situ, by the cracking of acetone or by treatment of methyl/ethylmalonyl chloride with triethylamine, leading to the formation of thiazolo-pyrimidinone derivatives.[5] Their cycloadditions with other ketenes remained unattempted either because it evaded their attention or the authors failed to obtain any isolable product. Our continued interest in azadiene–ketene cycloadditions, relatively less explored chemistry of these thiazolic diazadienes towards ketenes and the significant pharmacological importance of the functionalized pyrimidinones have prompted us to examine the reactions of these thiazolic diazadienes with various simple and conjugated ketenes.

2. Results and discussion

The treatment of N'-[(5-benzoyl)thiazol-2-yl]-*N*,*N*-dimethylimidoformamide **1a** with monosubstituted ketenes such as phenyl, phenoxy, chloro, bromo, and cyano ketenes, generated, in situ, by the dropwise addition of their corresponding acid chlorides in triethylamine at room temperature. Careful chromatography of the crude adducts resulted in the isolation of the products albeit in yields much lower than (25–36%) normally obtained in other diazadiene–ketene reactions (Scheme 1).

The isolated products were characterized as thiazolo-pyrimidinones **2** on the basis of the available spectral evidences and analytical data (Scheme 2). The detailed spectral features are given in the Section 2; only the salient

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* Corresponding author. Tel.: +91 183 2258802 09x3320; fax: +91 183 2258819 20; e-mail: mahajanmohinderp@yahoo.co.in

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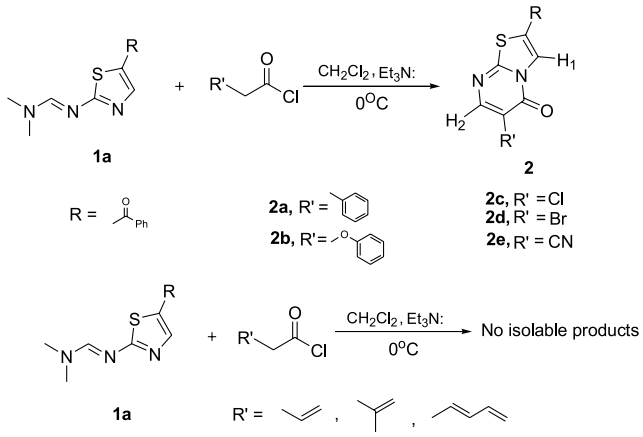
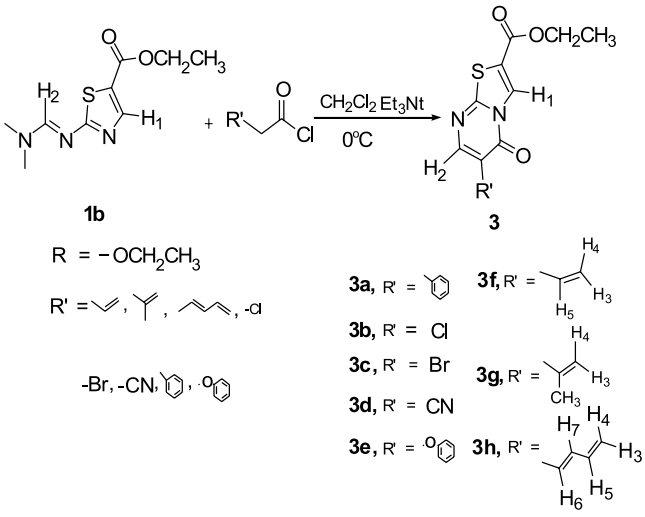


Scheme 1.



Scheme 2.

features being mentioned here. The compound 2-benzoyl-6-phenyl-thiazolo[3,2-*a*]pyrimidin-5-one **2a**, for example, analyzed for $C_{19}H_{12}N_2O_2S$, exhibited a molecular ion peak at *m/z* 332 (M^+) in the mass spectrum and the IR spectrum (KBr) showed a strong absorption peak at 1685 cm^{-1} due to α,β-unsaturated carbonyl group. The ^1H spectrum showed characteristic two singlets for deshielded olefinic protons H_1 and H_2 at δ 8.24 and 8.53, respectively. The structure of the compound **2a** was further corroborated by the ^{13}C spectrum, which showed characteristic peaks at δ 119.4, 128.0, 128.2, 128.4, 128.6, 129.0, 129.2, 130.1, 132.7, 133.9, 135.7, 152.0, 157.7, 161.5 and 186.4.

However, the reactions of **1a** with conjugated ketenes, such as vinyl, isopropenyl and butadienyl, generated, in situ, from the corresponding acid halides and triethyl amine, were found to be very sluggish and all attempts, by varying the reaction conditions, invariably resulted in an intractable mixture, from which no pure product could be isolated. It was felt that it may probably be the result of lower nucleophilicity of the thiazolic nitrogen of **1a** resulting, in turn, in its lower reactivity, largely being attributed to the extended conjugation of the π-electrons across the carbonyl group as shown in Figure 1.

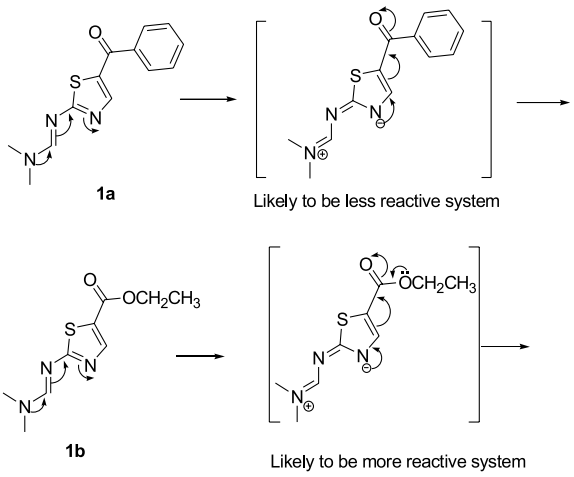


Figure 1.

Keeping this rationale in mind, it was thought that the nature of the substituents (withdrawing or donating) on carbonyl carbon may alter the nucleophilicity and hence the reactivity of the thiazolic nitrogen of such diaza-1,3-dienes. It was believed that the substitution of the phenyl on the carbonyl carbon by an alkoxy group might result in its lower electrophilicity and in turn higher nucleophilicity of thiazolic nitrogen of these thiazolic dienes. Keeping this in view, the desired system *N′*-[(5-ethoxycarbonyl)thiazol-2-yl]-*N*,*N*-diethylimidoformamide (**1b**) was prepared according to the reported procedure and its reactions with monosubstituted and conjugated ketenes were examined. As expected, the reactions of **1b** with monosubstituted ketenes such as phenyl, chloro, bromo, cyano and phenoxyketenes, generated in situ, from the corresponding acid chlorides in the presence of triethylamine in dry dichloromethane at 0 °C, were found to be very neat and yielded a variety of substituted thiazolo-pyrimidinone derivatives **3** in good yields (72–88%)

The isolated compounds **3** were characterized on the basis of available spectral evidences and analytical data. The compound **3a**, characterized as 6-phenyl-5-oxo-5*H*-thiazolo[3,2-a]pyrimidine-2-carboxylic acid ethyl ester, showed in its ^1H NMR spectrum a triplet at δ 1.41 for $-CH_3$, a quartet at δ 4.40 for $-CH_2$ and two characteristic singlets at δ 7.98 and 8.57 for protons H_1 and H_2, respectively, along with the multiplets for aromatic protons. Also a molecular ion peak at *m/z* 300 in the mass spectrum confirmed the structure of the compound.

The conjugated ketenes have been reported to participate as 4π as well as 2π component in [4+2] cycloaddition reactions.[6] Hence, in order to compare the dienic properties of the thiazolic diazadienes with conjugated ketenes, we have examined the reactions of thiazolic diazadiene **1b** with various conjugated ketenes viz vinyl, isopopenyl and dienyl ketenes, generated in situ, from their corresponding acid chlorides in the presence of triethylamine. To our delight, the reactions were found to be very neat resulting in novel bicylic thiazolic pyrimidinones **3** (75–90%) (Table 1).

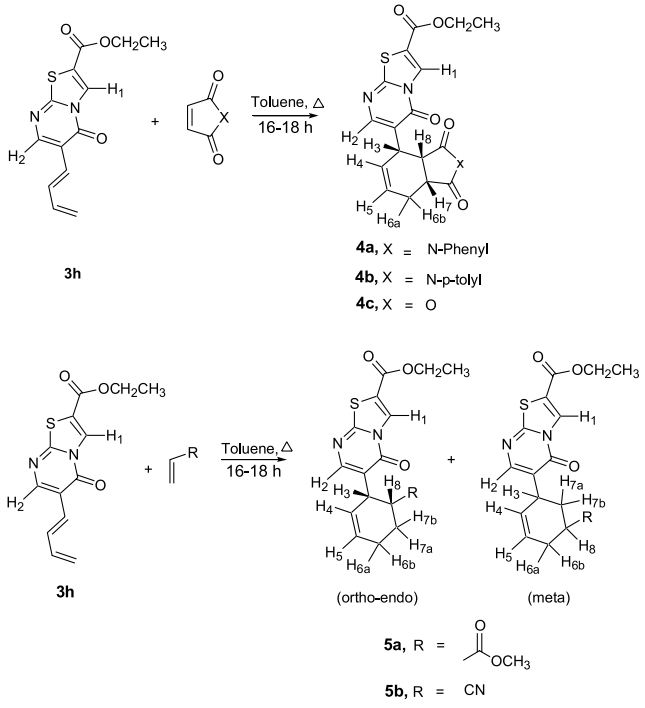
The isolated products **3f–h** were characterized on the basis of the spectral and analytical evidences. The compound

Table 1. Yields and melting points of compounds (**2a–e**)

Compound no.	Ketene used	R=-phenyl	
		Yield (%)	Melting point (°C)
2a	Phenyl	36	158–160
2b	Phenoxy	25	135–136
2c	Chloro	34	185–187
2d	Bromo	28	177–179
2e	Cyano	31	166–167
—	Vinyl	—	—
—	Isopropenyl	—	—
—	Butadienyl	—	—

5-oxo-6-vinyl-5*H*-thiazolo[3,2-*a*]pyrimidine-2-carboxylic acid ethyl ester (**3f**), for example, analyzed for $C_{11}H_{10}N_2O_3S$, showed a molecular ion peak at *m*/*z* 250 in the mass spectrum and the IR spectrum (KBr) showed a strong absorption peak at 1670 cm^{-1} due to α,β-unsaturated carbonyl group and another peak at 1730 cm^{-1} corresponding to the carbonyl of an ester group. The ^1H spectrum exhibited a characteristic triplet at δ 1.43 and a quartet at δ 4.43 for $-OCH_2CH_3$ group. A doublet of doublets (dd) at δ 5.44 ($J=10.0$, 1.4 Hz) corresponding vinylic proton (H_3), one dd at δ 6.25 ($J=16.0$, 1.4 Hz) for vinylic proton (H_4) and one dd at δ 6.64 ($J=16.0$, 10.0 Hz) for vinylic proton (H_5) also support the structure of the product. The ^{13}C spectrum showed characteristic peaks at δ 14.2 and 62.8 corresponding to $-CH_3$ and $-CH_2$ carbons of the $-OCH_2CH_3$ group. Other peaks at 116.4, 118.1, 120.7, 127.1, 128.5, 151.2, 156.9, 159.8 and 160.8 were also in agreement with the assigned structure of the compound.

In recent years, various functionalized pyrimidinones, substituted either at C-5 or C-6 position, have emerged as broad spectrum drugs in the field of chemotherapy and selective antitumour, antiviral, antitubercular and antifungal activities are documented in the literature.[7] It was felt that 5-dienyl pyrimidinones **3h** can be utilized as functional synthons in Diels–Alder cycloadditions reactions for a variety of such substituted fused pyrimidinones.[8] Therefore, we carried out the Diels–Alder cycloaddition reactions of the resulted bicyclic pyrimidinone **3h** with various symmetrical as well as unsymmetrical dienophiles (Scheme 3).



Scheme 3.

The reactions of **3h** with symmetrical dienophiles such as *N*-phenylmaleimide, *N*-*p*-tolylmaleimide and maleic anhydride, carried out in refluxing toluene for 16–18 h, were found to be highly diastereoselective resulting in exclusive formation of *endo* adducts **4**. The structures of these *endo* adducts were assigned on the basis of their spectral data and elemental analysis. The compound **4a**, for example, analyzed for $C_{23}H_{17}N_3O_5S$, showed a molecular ion peak at *m*/*z* 447 in the mass spectrum and two strong peaks at 1708 and 1666 cm^{-1} due to an ester carbonyl and α,β-unsaturated carbonyl groups, respectively, in the IR spectrum. The ^1H spectrum exhibited an unresolved ddd at δ 2.40 ($J=7.5$, 15.3 Hz) for H_{6a}, an unresolved ddd at δ 2.99 ($J=4.5$, 15.3 Hz) for H_{6b}, a ddd at δ 3.44 ($J=1.8$, 7.2, 9.3 Hz) for H_7, a dd at δ 3.79 ($J=6.9$, 9.1 Hz) for H_8 and an unresolved dd at δ 3.97 ($J=6.6$ Hz) for H_3 in addition to the multiplets in range 6.21–6.23 for protons H_4 and H_5. Also apparent two sharp singlets at δ 7.99 and 8.58 corresponding to protons H_1 and H_2, respectively. The presence of an unresolved dd at δ 3.97 ($J=6.6$ Hz) for H_3 proton clearly depicts the *syn* stereo-chemical relationship with H_8 proton, thus establishing the *endo* nature of the adduct. The ^{13}C spectrum showed peaks at δ 14.1 ($-CH_3$), 24.3 [C (H-6)], 33.4 [C (H-7)], 39.8 [C (H-8)], 42.0 [C (H-3)], 62.7 ($-OCH_2$), 120.7, 126.2, 126.7, 128.0, 128.2, 128.4, 128.9, 129.4, 131.6, 151.7, 158.3, 159.7, 161.1, 176.2 and 178.3, which were in agreement with the structure assigned above.

The reactions of **3h** with unsymmetrical dienophiles such as methylacrylate and acrylonitrile, in refluxing toluene carried out for 16–18 h, led to the formation of the products, which were found to be a mixture of regioisomers (*ortho*/*meta*: 70:30), their relative ratio being estimated on the basis of the spectral data of the compounds isolated. The major isomer was found to be *ortho–endo* adduct as shown by the presence of a doublet of doublet at δ 4.13 for proton H_3 having coupling constants 3.2 and 9.2 Hz, peaks characteristic for *ortho* addition, in the proton spectrum of **5a**. This also confirmed its *syn* stereochemistry with regards to the neighbouring proton H_8. The *ortho–endo* adduct was further corroborated with the help of ^{13}C and DEPT NMR analysis, the details being mentioned in the experimental section. The *exo*/*endo* nature of the *meta* regio-isomer was not ascertained due to complexity of the spectra.

In conclusion, a generalized and relevant study regarding the reactivity of thiazolic diazadienes **1a** and **1b**, with monosubstituted as well as conjugated ketenes has been investigated leading to the synthesis of various novel bicyclic thiazolic pyrimidinone derivatives **2** and **3**. The manuscript assumes further significance as the 5-dienyl-pyrimidinone **3h**, thus obtained, has been used as a precursor in the synthesis of various substituted bicyclic pyrimidinones **4** and **5** by carrying out reactions with

Table 2. Yields and melting points of compounds (**3a–h**)

Compound no.	Ketene used	R=–OC_2H_5	
		Yield (%)	Melting point (°C)
3a	Phenyl	85	183–184
3b	Chloro	82	193–194
3c	Bromo	72	143–145
3d	Cyano	73	132–133
3e	Phenoxy	88	140–141
3f	Vinyl	75	135–136
3g	Isopropenyl	80	155–156
3h	Butadienyl	90	150–151

symmetrical as well as unsymmetrical dienophiles. The biological and medicinal importance of these pyrimidinones is well established in the literature[11] (Table 2).

3. Experimental

Melting points were determined by open capillary method using Veego Precision Digital Melting Point apparatus (MP-D) and are uncorrected. IR spectra were recorded on a Shimadzu D-8001 spectrophotometer. ^{1}H NMR spectra were recorded in deuterochloroform with Bruker AC-E 200 (200 MHz) and AC-E 300 (300 MHz) spectrometers using TMS as internal standard. Chemical shift values are expressed as ppm downfield from TMS and *J* values are in Hz. Splitting patterns are indicated as s: singlet, d: doublet, t: triplet, m: multiplet and q: quartet. ^{13}C NMR spectra were also recorded on a Bruker AC-200E (50.4 MHz) or AC-E 300 (75.0 MHz) spectrometers in a deuterochloroform using TMS as internal standard. Mass spectra were recorded on Shimadzu GCMS-QP-2000 mass spectrometer. Elemental analyses were performed on Heraus CHN-O-Rapid Elemental Analyzer. Column chromatography was performed on a silica gel (60–120) mesh or Harrison Research Chromatotron using 2 mm plates (silica gel PF_{254}). Dichloromethane dried over di-phosphorous pentoxide and after distillation stored over molecular sieves (4 Å).

3.1. Starting materials

DMF–DMA[9], N′-[5-(benzoyl)thiazol-2-yl]-*N*,*N*-dimethylformamide (**1a**),[5] *N*′-bis [(dimethylamino)methylene]-thiourea, *N*′-[5-(ethoxycarbonyl)thiazol-2-yl]-*N*,*N*-dimethylformamide (**1b**), were prepared according to the reported procedures. Crotonyl-, 3,3-dimethylacryl-, bromoacetyl-, cyanoacetyl-, phenoxyacetyl-, phenylacetyl-, chlorides and sorbyl chloride[10] were prepared from the corresponding acid and thionyl chloride. Chloroacetyl chloride and thionyl chloride were distilled before use.

3.2. General procedure for preparation of *N*′-[5-(benzoyl)thiazol-2-yl]-*N*,*N*-dimethylformamide (1a), *N*′-[5-(ethoxycarbonyl)thiazol-2-yl]-*N*,*N*-di-methylformamide (1b)

A solution of phenacyl bromide (5 mmol)/ethylbromoacetate (5 mmol) and *N*′-bis [(dimethylamino) methylene] thiourea (5 mmol) in dichloromethane (15 mL) was stirred under nitrogen at room temperature for 15 min and then triethylamine (10 mmol) was added. The reaction mixture was then stirred for a further 10 h. After removal of the solvent, the residue was chromatographed with dichloromethane–ethylacetate (4/1) as eluent. Solid material was thus, obtained by recrystallisation from diethyl ether.

3.2.1. *N*′-[(5-Benzoyl)thiazol-2-yl]-*N*,*N*-dimethylformamide (1a). Pale yellow solid, yield: 73%; mp 106–108 °C. Anal. Calcd for $C_{13}H_{13}N_3OS$: C, 60.21; H, 5.05; N, 16.20. Found: C, 59.98; H, 4.97; N, 16.01%. IR (KBr) ν_{max}: 2920, 1620, 1401 cm^{-1}. δ_H (200 MHz, $CDCl_3$): 3.10 [s, 3H, $N(CH_3)_2$], 3.12 [s, 3H, $N(CH_3)_2$], 7.40–7.76 (m, 5H, Ar), 7.81 (s, 1H, H_1), 8.25 (s, 1H, H_2). δ_C (75 MHz, $CDCl_3$): 35.3 and 41.4 [2C, $N(CH_3)_2$], 126.8 (SCCO), 130.3, 131.7, 133.2, 137.2, 149.2 (C-4), 156.5 (NCH), 178.2 (SCN) and 185.6 (CO). *m*/*z*: 259 (M^+).

3.2.2. *N*′-[(5-Ethoxycarbonyl)thiazol-2-yl]-*N*,*N*-di-methylformamide (1b). Pale white crystalline solid, yield: 86%; mp 116–118 °C. Anal. Calcd for $C_9H_{13}N_3O_2S$: C, 47.56; H, 5.77; N, 18.49. Found: C, 47.88; H, 5.62; N, 18.35%. IR (KBr) ν_{max}: 3080, 1712, 1618, 1401 cm^{-1}. δ_H (200 MHz, $CDCl_3$): 1.29 (t, 3H, J=8.0 Hz, –O–C–CH_3), 3.01 [s, 3H, $N(CH_3)_2$], 3.04 [s, 3H, $N(CH_3)_2$], 4.23 (q, 2H, J=8.0 Hz, –OCH_2), 7.89 (s, 1H, H_1), 8.27 (s, 1H, H_2). δ_C (75 MHz, $CDCl_3$): 14.1 (–CH_3), 35.4 and 41.6 [2C, $N(CH_3)_2$], 62.8 (–OCH_2), 127.2 (SCCO), 149.6 (C-4), 158.5 (NCH), 172.1 (SCN) and 179.2 (CO). *m*/*z*: 227 (M^+).

3.3. General procedure for the reaction of thiazolic 1,3-diazadienes 1 with conjugated and monosubstituted ketenes

General procedure. To a well-stirred solution of diazadiene **1** (10 mmol) and triethylamine (40 mmol) in dry methylene chloride (30 mL) was added drop wise a solution of crotonyl chloride/3,3-dimethylacryl chloride/sorbyl chloride/chloroacetyl chloride/bromoacetyl chloride/cyanoacetyl chloride/phenyl acetyl chloride/phenoxyacetyl chloride (20 mmol) in dry methylene chloride (30 mL) over a period of 1 h at room temperature (0 °C). After completion of the reaction (TLC), the reaction mixture was first washed with saturated sodium bicarbonate solution (2×25 mL) and water (2×50 mL) and the organic layer dried over anhydrous sodium sulfate. Removal of solvent under reduced pressure yielded the crude product, which was purified by silica gel column chromatography using a mixture of ethylacetate and hexane (1:10, v/v).

3.3.1. 2-Benzoyl-6-phenyl-thiazolo[3,2-*a*]pyrimidin-5-one (2a). Colourless solid, yield: 36%; mp 158–160 °C. Anal. Calcd for $C_{19}H_{12}N_2O_2S$: C, 68.66; H, 3.64; N, 8.43. Found: C, 68.52; H, 3.56; N, 8.32. IR (KBr) ν_{max}: 1685, 1587, 1225 cm^{-1}. δ_H (200 MHz, $CDCl_3$): 7.42–7.93 (m, 10H, ArH), 8.24 (s, 1H, H_1), 8.53 (s, 1H, H_2). δ_C (75 MHz, $CDCl_3$): 119.4, 128.0, 128.2, 128.4, 128.6, 129.0, 129.2, 130.1, 132.7, 133.9, 135.7, 152.0, 157.7, 161.5 and 186.4. *m*/*z*: 332 (M^+).

3.3.2. 2-Benzoyl-6-phenoxy-thiazolo[3,2-*a*]pyrimidin-5-one (2b). Colourless crystalline solid, yield: 25%; mp 135–136 °C. Anal. Calcd for $C_{19}H_{12}N_2O_3S$: C, 65.50; H, 3.47; N, 8.04. Found: C, 65.65; H, 3.41; N, 7.98. IR (KBr) ν_{max}: 1682, 1579, 1230 cm^{-1}. δ_H (200 MHz, $CDCl_3$):

7.37–7.98 (m, 10H, ArH), 8.31 (s, 1H, H_1), 8.62 (s, 1H, H_2). δ_C (75 MHz, $CDCl_3$): 120.1, 127.2, 128.1, 128.3, 128.6, 129.1, 129.3, 129.9, 131.1, 133.1, 133.9, 151.1, 158.2, 163.0 and 187.0. *m/z*: 348 (M^+).

3.3.3. 2-Benzoyl-6-chloro-thiazolo[3,2-*a*]pyrimidin-5-one (2c). Colourless solid, yield: 34%; mp 185–187 °C. Anal. Calcd for $C_{13}H_7ClN_2O_2S$: C, 53.71; H, 2.43; N, 9.64. Found: C, 53.82; H, 2.38; N, 9.55. IR (KBr) ν_{max}: 1682, 1546, 1323, cm^{-1}. δ_H (200 MHz, $CDCl_3$): 7.27–7.94 (m, 5H, ArH), 8.23 (s, 1H, H_1), 8.63 (s, 1H, H_b). δ_C (75 MHz, $CDCl_3$): 116.2, 124.5, 125.7, 129.0, 132.4, 134.3, 136.7, 150.8, 154.2, 162.2 and 185.8. *m/z*:290 (M^+).

3.3.4. 2-Benzoyl-6-bromo-thiazolo[3,2-*a*]pyrimidin-5-one (2d). Colourless solid, yield: 28%; mp 177–179 °C. Anal. Calcd for $C_{13}H_7BrN_2O_2S$: C, 46.58; H, 2.11; N, 8.36. Found: C, 46.42; H, 2.16; N, 8.32. IR (KBr) ν_{max}: 1676, 1539, 743 cm^{-1}. δ_H (200 MHz, $CDCl_3$): 6.92–7.01 (m, 5H, ArH), 8.12 (s, 1H, H_1), 8.58 (s, 1H, H_2). δ_C (75 MHz, $CDCl_3$): 117.2, 125.4, 126.6, 129.1, 131.7, 134.5, 135.9, 152.0, 153.4, 160.6 and 185.2. *m/z*: 335 (M^+).

3.3.5. 2-Benzoyl-6-cyano-thiazolo[3,2-*a*]pyrimidin-5-one (2e). Light yellow solid, yield: 31%; mp 166–167 °C. Anal. Calcd for $C_{14}H_7N_3O_2S$: C, 59.78; H, 2.51; N, 14.94. Found: C, 59.82; H, 2.44; N, 14.87. IR (KBr) ν_{max}: 2218, 1688, 817 cm^{-1}. δ_H (200 MHz, $CDCl_3$): 7.34–7.99 (m, 5H, ArH), 8.06 (s, 1H, H_1), 8.45 (s, 1H, H_2). δ_C (75 MHz, $CDCl_3$): 115.7, 118.6, 127.2, 127.8, 130.2, 131.9, 135.4, 136.0, 155.6, 163.1, 164.2 and 186.1 *m/z*: 281 (M^+).

3.3.6. 6-Phenyl-5-oxo-5*H*-thiazolo[3,2-*a*]pyrimidine-2-carboxylic acid ethyl ester (3a). Pale white solid, yield: 85%; mp 183–184 °C. Anal. Calcd for $C_{15}H_{12}N_2O_3S$: C, 59.99; H, 4.03; N, 9.33. Found: C, 59.87; H, 3.97; N, 9.27%. IR (KBr) ν_{max}: 1726, 1652, 1597, 743 cm^{-1}. δ_H (200 MHz, $CDCl_3$): 1.41 (t, 3H, $J=8.0$ Hz, –O–C–CH_3), 4.40 (q, 2H, $J=8.0$ Hz, –OCH_2), 6.99–7.37 (m, 5H, ArH) 7.98 (s, 1H, H_1), 8.57 (s, 1H, H_2). δ_C (75 MHz, $CDCl_3$): 14.1 (–CH_3), 62.9 (–OCH_2), 116.7, 121.8, 123.5, 126.7, 129.8, 137.3, 143.6, 154.4, 157.0, 158.1 and 160.0. *m/z*: 300 (M^+).

3.3.7. 6-Chloro-5-oxo-5*H*-thiazolo[3,2-*a*]pyrimidine-2-carboxylic acid ethyl ester (3b). Colourless solid, yield: 82%; mp 193–194 °C. Anal. Calcd for $C_9H_7ClN_2O_3S$: C, 41.79; H, 2.73; N, 10.83. Found: C, 41.82; H, 2.61; N, 10.74%. IR (KBr) ν_{max}: 1728, 1682, 1546, 1323, 923, 744 cm^{-1}. δ_H (200 MHz, $CDCl_3$): 1.43 (t, 3H, $J=8.0$ Hz, –O–C–CH_3), 4.46 (q, 2H, $J=8.0$ Hz, –OCH_2), 8.23 (s, 1H, H_1), 8.63 (s, 1H, H_2). δ_C (75 MHz, $CDCl_3$): 14.1 (–CH_3), 63.1 (–OCH_2), 115.6, 122.2, 126.8, 151.3, 154.9, 159.5 and 161.2. *m/z*: 258 (M^+).

3.3.8. 6-Bromo-5-oxo-5*H*-thiazolo[3,2-*a*]pyrimidine-2-carboxylic acid ethyl ester (3c). Pale yellow solid, yield: 72%; mp 143–145 °C. Anal. Calcd for $C_9H_7BrN_2O_3S$: C, 35.66; H, 2.33; N, 9.24. Found: C, 35.49; H, 2.26; N, 9.09%. IR (KBr) ν_{max}: 1730, 1666, 742 cm^{-1}. δ_H (200 MHz, $CDCl_3$): 1.42 (t, 3H, $J=8.0$ Hz, –O–C–CH_3), 4.45 (q, 2H, $J=8.0$ Hz, –OCH_2), 8.19 (s, 1H, H_1), 8.54 (s, 1H, H_2). δ_C (75 MHz, $CDCl_3$): 14.2 (–CH_3), 62.8 (–OCH_2), 115.6, 123.2, 126.9, 152.4, 155.9, 159.7 and 163.1. *m/z*: 303 (M^+).

3.3.9. 6-Cyano-5-oxo-5*H*-thiazolo[3,2-*a*]pyrimidine-2-carboxylic acid ethyl ester (3d). Colourless solid, yield: 73%; mp 132–133 °C. Anal. Calcd for $C_{10}H_7N_3O_3S$: C, 48.19; H, 2.83; N, 16.86. Found: C, 48.28; H, 2.79; N, 16.79%. IR (KBr) ν_{max}: 1742, 1327, 732 cm^{-1}. δ_H (200 MHz, $CDCl_3$): 1.39 (t, 3H, $J=8.0$ Hz, –O–C–CH_3), 4.38 (q, 2H, $J=8.0$ Hz, –OCH_2), 8.21 (s, 1H, H_1), 8.49 MHz (s, 1H, H_2). δ_C (75 MHz, $CDCl_3$): 14.1 (–CH_3), 63.6 (–OCH_2), 115.7, 118.8, 124.3, 125.5, 151.7, 154.9, 160.2 and 163.5. *m/z*: 249 (M^+).

3.3.10. 6-Phenoxy-5-oxo-5*H*-thiazolo[3,2-*a*]pyrimidine-2-carboxylic acid ethyl ester (3e). Colourless solid, yield: 88%; mp 140–141 °C. Anal. Calcd for $C_{15}H_{12}N_2O_4S$: C, 56.95; H, 3.82; N, 8.86. Found: C, 56.86; H, 3.74; N, 8.71%. IR (KBr) ν_{max}: 1728, 1666, 1512, 1334, 1078, 783 cm^{-1}. δ_H (200 MHz, $CDCl_3$): 1.43 (t, 3H, $J=8.0$ Hz, –O–C–CH_3), 4.49 (q, 2H, $J=8.0$ Hz, –OCH_2), 7.33–7.78 (m, 5H, ArH), 8.28 (s, 1H, H_1), 8.75 (s, 1H, H_2). δ_C (75 MHz, $CDCl_3$): 14.2 (–CH_3), 63.0 (–OCH_2), 119.4, 120.8, 127.5, 128.2, 128.4, 128.5, 133.0, 152.1, 157.4, 160.0, and 161.1. *m/z*: 316 (M^+).

3.3.11. 5-Oxo-6-vinyl-5*H*-thiazolo[3,2-*a*]pyrimidine-2-carboxylic acid ethyl ester (3f). Colourless solid, yield: 75%; mp 135–136 °C. Anal. Calcd for $C_{11}H_{10}N_2O_3S$: C, 52.79; H, 4.03; N, 11.19. Found: C, 52.71; H, 3.99; N, 11.11%. IR (KBr) ν_{max}: 1730, 1670, 1504, 1247 cm^{-1}. δ_H (200 MHz, $CDCl_3$): 1.43 (t, 3H, $J=8.0$ Hz, –O–C–CH_3), 4.43 (q, 2H, $J=8.0$ Hz, –OCH_2), 5.44 (dd, 1H, $J=10.0$, 1.4 Hz, H_3), 6.25 (dd, 1H, $J=16.0$, 1.4 Hz, H_4), 6.64 (dd, 1H, $J=16.0$, 10.0 Hz, H_5), 8.07 (s, 1H, H_1), 8.62 (s, 1H, H_2). δ_C (75 MHz, $CDCl_3$): 14.2 (–CH_3), 62.8 (–OCH_2), 116.4, 118.1, 120.7, 127.1, 128.5, 151.2, 156.9, 159.8 and 160.8 *m/z*: 250 (M^+).

3.3.12. 5-Oxo-6-isopropenyl-5*H*-thiazolo[3,2-*a*]pyrimidine-2-carboxylic acid ethyl ester (3g). Colourless crystalline solid, yield: 80%; mp 155–156 °C. Anal. Calcd for $C_{12}H_{12}N_2O_3S$: C, 54.53; H, 4.58; N, 10.60. Found: C, 54.49; H, 4.50; N, 10.56%. IR (KBr) ν_{max}: 1726, 1666, 1591, 1353 cm^{-1}. δ_H (200 MHz, $CDCl_3$): 1.37 (t, 3H, $J=$ 8.0 Hz, –O–C–CH_3), 2.16 (s, 3H, –CH_3), 4.39 (q, 2H, $J=$ .0 Hz, –OCH_2), 5.28 (s, 1H, H_3), 5.79 (s, 1H, H_4), 8.04 (s, 1H, H_1), 8.59 (s, 1H, H_2). δ_C (75 MHz, $CDCl_3$): 14.1 (–CH_3), 19.8 (olefinic-CH_3), 62.7 (–OCH_2), 117.1, 118.4, 121.2, 128.0, 128.7, 150.9, 157.1, 159.7 and 161.2. *m/z*: 264 (M^+).

3.3.13. 5-Oxo-6-dienyl-5*H*-thiazolo[3,2-*a*]pyrimidine-2-carboxylic acid ethyl ester (3h). Yellow crystalline solid, yield: 90%; mp 150–151 °C. Anal. Calcd for $C_{13}H_{12}N_2O_3S$: C, 56.51; H, 4.38; N, 10.14. Found: C, 56.39; H, 4.34; N, 10.01%. IR (KBr) ν_{max}: 1726, 1668, 1548, 1093, 902 cm^{-1}. δ_H (200 MHz, $CDCl_3$): 1.40 (t, 3H, $J=8.0$ Hz, –O–C–CH_3), 4.42 (q, 2H, $J=8.0$ Hz, –OCH_2), 5.19 (dd, 1H, $J=10.0$, 2.0 Hz, H_3), 5.36 (dd, 1H, $J=16.0$, 2.0 Hz, H_4), 6.41–6.50 (m, 2H, H_5, H_6), 7.30 (m, 1H, H_7) 8.05 (s, 1H, H_1), 8.60 (s, 1H, H_2). δ_C (75 MHz, $CDCl_3$): 14.1 (–CH_3), 62.8 (–OCH_2), 116.4, 118.8, 120.8, 124.4, 127.2, 133.2, 137.5, 150.9, 156.8, 159.8 and 160.8. *m/z*: 276 (M^+).

3.4. General procedure for Diels–Alder cycloaddition between 3c and dienophiles

Bicyclic pyrimidinone **3c** (5.0 mmol) and dienophiles [*N*-phenylmaleimide (5.0 mmol), *N*-tolylmaleimide (5.0 mmol), maleic anhydride (5.0 mmol), methylacrylate (5.2 mmol) and acrylonitrile (5.2 mmol)] were refluxed in dry toluene for 16–18 h. The solvent was removed under reduced pressure and the crude product thus obtained was purified by recrystallisation from a mixture (1:5, v/v) of ethylacetate and hexane.

3.4.1. 6-(1,3-Dioxo-2-phenyl-2,3,3a,4,7,7a-hexahydro-1*H*-isoindol-4-yl)-5-oxo-5*H*-thiazolo[3,2-*a*]pyrimidine-2-carboxylic acid ethyl ester (4a). Light yellow solid, yield: 82%; mp 207–208 °C. Anal. Calcd for $C_{23}H_{19}N_3O_5S$: C, 61.46; H, 4.26; N, 9.35. Found: C, 61.86; H, 4.61; N, 9.32%. IR (KBr) ν_{max}: 1708, 1666, 1510, 1386 cm^{-1}. δ_H (300 MHz, $CDCl_3$): 1.42 (t, 3H, $J=7.2$ Hz, –O–C–CH_3), 2.40 (unresolved ddd, $J=7.5$, 15.3 Hz, 1H, H_{6a}), 2.99 (unresolved ddd, $J=4.5$, 15.3 Hz, 1H, H_{6b}), 3.44 (ddd, $J=1.8$, 7.2, 9.3 Hz, 1H, H_7), 3.79 (dd, $J=6.9$, 9.1 Hz, 1H, H_8), 3.97 (unresolved dd, $J=6.6$ Hz, 1H. H_3), 4.42 (q, $J=7.2$ Hz, 2H, –OCH_2), 6.21–6.23 (m, 2H, H_4 and H_5), 7.15–7.43 (m, 5H, ArH), 7.99 (s, 1H, H_1), 8.58 (s, 1H, H_2). δ_C (75 MHz, $CDCl_3$): 14.1 (–CH_3), 24.3 [C (H-6)], 33.4 [–C (H-7)], 39.8 [–C (H-8)], 42.0 [–C (H-3)], 62.7 (–OCH_2), 120.7, 126.2, 126.7, 128.0, 128.2, 128.4, 128.9, 129.4, 131.6, 151.7, 158.3, 159.7, 161.1, 176.2 and 178.3. *m/z*: 449 (M^+).

3.4.2. 6-(1,3-Dioxo-2-p-tolyl-2,3,3a,4,7,7a-hexahydro-1*H*-isoindol-4-yl)-5-oxo-5*H*-thiazolo[3,2-*a*]pyrimidine-2-carboxylic acid ethyl ester (4b). Pale white solid, yield: 81%; mp 213–215 °C. Anal. Calcd for $C_{24}H_{21}N_3O_5S$: C, 62.19; H, 4.57; N, 9.07. Found: C, 62.49; H, 4.22; N, 8.99%. IR (KBr) ν_{max}: 1712, 1669, 1512 cm^{-1}. δ_H (300 MHz, $CDCl_3$): 1.41 (t, 3H, $J=7.2$ Hz, –O–C–CH_3), 2.39 (s, 3H, –CH_3) 2.42 (unresolved ddd, $J=7.5$, 15.2 Hz, 1H, H_{6a}), 3.01 (unresolved ddd, $J=4.2$, 15.2 Hz, 1H, H_{6b}), 3.43 (ddd, $J=1.8$, 7.5, 9.5 Hz, 1H, H_7), 3.81 (dd, $J=6.6$, 9.2 Hz, 1H, H_8), 3.96 (unresolved dd, $J=6.8$ Hz, 1H. H_3), 4.41 (q, $J=7.2$ Hz, 2H, –OCH_2), 6.20–6.23 (m, 2H, H_4 and H_5), 6.98–7.01 (d, $J=8.0$ Hz, 2H, ArH), 7.02–7.04 (d, $J=8.0$ Hz, 2H, ArH), 7.98 (s, 1H, H_1), 8.59 (s, 1H, H_2). δ_C (75 MHz, $CDCl_3$): 14.1 (–O–C–CH_3), 20.9 (–CH_3) 24.3 [–C (H-6)], 33.3 [–C(H-7)], 39.9 [–C(H-8)], 42.1 [–C(H-3)], 62.8 (–OCH_2), 120.6, 125.8, 126.4, 127.8, 128.4, 129.1, 130.2, 131.4, 135.2, 152.6, 158.2, 159.6, 161.2, 176.3 and 178.2. *m/z*: 463 (M^+).

3.4.3. 6-(1,3-Dioxo-1,3,3a,4,7,7a-hexahydro-isobenzofuran-4-yl)-5-oxo-5*H*-thiazolo[3,2-*a*]pyrimidine-2-carboxylc acid ethyl ester (4c). Colorless solid, yield: 72%; mp 219–221 °C. Anal. Calcd for $C_{17}H_{14}N_2O_6S$: C, 54.54; H, 3.77; N, 7.48. Found: C, 54.68; H, 3.67; N, 7.34%. IR (KBr) ν_{max}: 1710, 1665, 1514 cm^{-1}. δ_H (300 MHz, $CDCl_3$): 1.42 (t, 3H, $J=7.2$ Hz, –O–C–CH_3), 2.40 (unresolved ddd, $J=7.4$, 15.1 Hz, 1H, H_{6a}), 2.99 (unresolved ddd, $J=4.3$, 15.2 Hz, 1H, H_{6b}), 3.44 (ddd, $J=1.7$, 7.2, 9.5 Hz, 1H, H_7), 3.82 (dd, $J=6.5$, 9.5 Hz, 1H, H_8), 3.97 (unresolved dd, $J=6.6$ Hz, 1H. H_3), 4.41 (q, $J=7.2$ Hz, 2H, –OCH_2), 6.19–6.23 (m, 2H, H_4 and H_5), 7.99 (s, 1H, H_1), 8.61 (s, 1H, H_2). δ_C (75 MHz, $CDCl_3$): 14.1 (–O–C–CH_3), 24.4 [–C (H-6)], 34.1 [–C (H-7)], 39.5 [–C (H-8)], 42.2 [–C (H-3)], 62.7 (–OCH_2), 122.6, 125.8, 127.8, 128.4, 130.2, 135.2, 158.2, 158.9, 160.4, 175.3 and 177.2. *m/z*: 374 (M^+).

3.4.4. 6-(6-Methoxycarbonyl-cyclohex-2-enyl)-5-oxo-5*H*-thiazolo[3,2-*a*]pyrimidine-2-carboxylic acid ethyl ester (*ortho*)/6-(5-methoxycarbonyl-cyclohex-2-enyl)-5-oxo-5*H*-thiazolo[3,2-*a*]pyrimidine-2-carboxylic acid ethyl ester (*meta*)(5a). Colourless crystalline solid, yield: 68%; mp 103–104 °C. Anal. Calcd for $C_{17}H_{18}N_2O_5S$: C, 56.34; H, 5.01; N, 7.73. Found: C, 56.61; H, 4.95; N, 7.69%. IR (KBr) ν_{max}: 1724, 1683, 1508 cm^{-1}. δ_H (300 MHz, $CDCl_3$): 1.40 [t, 6H, $J=7.2$ Hz, 2×–O–C–CH_3 (*o* and *m*)], 1.72–1.80 [m, 2H, H_{7a}, H_{7b} (*o*)], 1.91–1.93 [m, 2H, H_{7a}, H_{7b} (*m*)], 2.14–2.20 [m, 2H, H_{6a}, H_{6b} (*o*)], 2.22–2.24 [m, 2H, H_{6a}, H_{6b} (*m*)], 2.89–2.91 [m, 1H, H_8 (*m*)], 3.01 [unresolved dd, $J=5.4$, 7.5 Hz, 1H, H_8 (*o*)], 3.58 [s, 3H, –OCH_3 (*o*)], 3.64 [s, 3H, –OCH_3 (*m*)], 3.95 [ddd, $J=3.1$, 5.4, 10.5 Hz, 1H, H_3 (*m*)], 4.13 [dd, $J=3.2$, 9.2 Hz, 1H, H_3 (*o*)], 4.41 [q, $J=7.2$ Hz, 4H, 2×–CH_2 (*o* and *m*)], 5.61–5.63 [m, 1H, H_4 (*m*)], 5.64–5.66 [m, 1H, H_4 (*o*)], 5.98–6.00 [m, 1H, H_5 (*m*)], 6.01–6.03 [m, 1H, H_5 (*o*)], 7.88 [s, 1H, H_1 (*o*)], 7.91 [s, 1H, H_1 (*m*)], 8.51 [s, 1H, H_2 (*o*)], 8.53 [s, 1H, H_2 (*m*)]. δ_C (75 MHz, $CDCl_3$): 14.2 [–O–C–CH_3 (*o* and *m*)], 21.5 [–C (H-7) (*m*)], 22.5 [–C (H-7) (*o*)], 22.6 [–C (H-6) (*o*)], 24.2 [–C (H-6) (*m*)], 29.1 [–C (H-8) (*o*)], 30.1 [–C (H-8) (*m*)], 34.3 [–C (H-3) (*m*)], 37.2 [–C (H-3)], 52.8 [–OCH_3 (*o*)], 53.4 [–OCH_3 (*m*)], 62.7 [–OCH_2 (*o* and *m*)], 117.4 (*o*), 118.0 (*m*), 120.9 (*o*), 121.0 (*m*), 123.3 (*o*), 123.5 (*m*), 127.3 (*o*), 127.4 (*m*), 129.5 (*o*), 130.2 (*m*), 152.1 (*o*), 152.3 (*m*), 153.6 (*o*), 153.7 (*m*), 159.5 (*o*), 160.1 (*m*), 162.2 (*o*), 162.3 (*m*), 163.6 (*o*) and 163.7 (*m*). *m/z*: 362 (M^+).

3.4.5. 6-(6-Cyano-cyclohex-2-enyl)-5-oxo-5*H*-thiazolo[3,2-*a*]pyrimidine-2-carboxylic acid ethyl ester (*ortho*)/6-(5-cyano-cyclohex-2-enyl)-5-oxo-5*H*-thiazolo[3,2-*a*]pyrimidine-2-carboxylic acid ethyl ester (*meta*)(5b). Light yellow crystalline solid, yield: 75%; mp 107–108 °C. Anal. Calcd for $C_{16}H_{15}N_3O_3S$: C, 58.34; H, 4.59; N, 12.76. Found: C, 58.51; H, 4.41; N, 12.69%. IR (KBr) ν_{max}: 1718, 1676, 1508 cm^{-1}. δ_H (300 MHz, $CDCl_3$): 1.41 [t, 6H, $J=7.2$ Hz, 2×–O–C–CH_3 (*o* and *m*)], 1.71–1.82 [m, 2H, H_{7a}, H_{7b} (*o*)], 1.88–1.92 [m, 2H, H_{7a}, H_{7b} (*m*)], 2.15–2.19 [m, 2H, H_{6a}, H_{6b} (*o*)], 2.21–2.24 [m, 2H, H_{6a}, H_{6b} (*m*)], 2.89–2.91 [m, 1H, H_8 (*m*)], 3.03 [unresolved dd, $J=5.4$, 7.4 Hz, 1H, H_8 (*o*)], 3.89 [ddd, $J=3.2$, 5.4, 10.5 Hz, 1H, H_3 (*m*)], 4.11 [dd, $J=3.2$, 9.6 Hz, 1H, H_3 (*o*)], 4.43 [q, $J=7.2$ Hz, 4H, 2×–CH_2 (*o* and *m*)], 5.59–5.62 [m, 1H, H_4 (*m*)], 5.63–5.68 [m, 1H, H_4 (*o*)], 5.88–5.99 [m, 1H, H_5 (*m*)], 6.03–6.08 [m, 1H, H_5 (*o*)], 7.84 [s, 1H, H_1 (*o*)], 7.89 [s, 1H, H_1 (*m*)], 8.52 [s, 1H, H_2 (*o*)], 8.53 [s, 1H, H_2 (*m*)]. δ_C (75 MHz $CDCl_3$): 14.1 [–O–C–CH_3 (*o* and *m*)], 21.6 [–C (H-7) (*m*)], 22.5 [–C (H-7) (*o*)], 22.7 [–C (H-6) (*o*)], 24.2 [–C (H-6) (*m*)], 28.8 [–C (H-8) (*o*)], 30.2 [–C (H-8) (*m*)], 34.4 [–C (H-3) (*m*)], 37.2 [–C (H-3)], 62.9 [–OCH_2 (*o* and *m*)], 118.7 (*o*), 118.8 (*m*), 121.0 (*o*), 121.2 (*m*), 124.4 (*o*), 124.7 (*m*), 126.7 (*o*), 126.8 (*m*), 129.5 (*o*), 130.1 (*m*), 152.0 (*o*), 152.1 (*m*), 152.9 (*o*), 153.0 (*m*), 157.5 (*o*), 157.6 (*m*), 159.6 (*o*), 159.7 (*m*), 162.1 (*o*) and 162.3 (*m*). *m/z*: 329 (M^+).

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