Amine and thiazole substituted γ-butyrolactones from naturally occurring limonene

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Abstract: Substituted γ -butyrolactones are important structural motifs in several natural products and pharmaceuticals. In this paper, we report the synthesis of novel γ -butyrolactone amine and thiazole derivatives from naturally occurring limonene. Regioselective bromination followed by nucleophilic substitution with different amines and thiourea gave desired products in moderate yield.

Key words: regioselectivity, bromination, amination, thiazole, y-butyrolactone.

Résumé : Les γ -butyrolactones substituées sont d'importants motifs structuraux dans plusieurs produits naturels et pharmaceutiques. Dans ce travail, on a synthétisé de nouveaux dérivés amine et thiazole de la γ -butyrolactone à partir du limonène qu'on peut obtenir de sources naturelles. La bromation régiosélective, suivie d'une substitution nucléophile avec diverses amines et thiourées permet d'obtenir les produits désirés avec des rendements modérés.

Mots-clés : régiosélectivité, bromation, amination, thiazole, y-butyrolactone.

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Introduction

The amine derivatives of γ -butyrolactone are important motifs found in several biologically active natural products and pharmaceuticals. These structural units are very common in antiallergic,¹ antineoplastic,² and antifungal³ compounds, in antimalarial alkaloids⁴ and gastroprotective drugs,⁵ and in new inhibitors of phosphodiesterase and HIV-1 protease.⁶ Moreover, these amino derivatives have been used as building blocks of other important molecules.⁷

In recent years, significant attention has been focused on the synthesis of amine derivatives of γ -butyrolactone. Different research groups have started with an a-halo-y-butyrolactone derivative and a C-protected amino acid in the presence of base,⁸ oxazolone with α -haloketones in the presence of potassium bicarbonate and a phase transfer reagent,9 aza-Michael-type addition using NsONHCO₂Et,¹⁰ and amino hydroxylation of diesters.¹¹ Roos and Effenberger first prepared amino alcohols and then proceeded with stepwise amino protection, ozonolysis, and oxidation.¹² All the research groups have either synthesized N-protected derivatives or used starting materials that contain nitrogen functionality. Also, they have prepared amine derivatives substituted in the lactone ring. In our case, a new type of butyrolactone derivative (3) having a side chain with a carbonyl group has been synthesized from naturally occurring limonene (1).

Thiazole and its derivatives are very useful compounds in various fields of chemistry including medicine and agriculture. For example, the thiazolium ring present in vitamin B_1 serves as an electron sink, and its coenzyme form is important for the decarboxylation of α -keto acids.¹³ This heterocy-

clic system has found broad application in drug development for the treatment of several diseases.¹⁴ To the best of our knowledge, γ -butyrolactones with different substituted amine and thiazole moieties are very rare entries in organic synthesis. In the last few years we have been engaged in the development of limonene to γ -butyrolactone chemistry. Herein we report the regioselective bromination of the side chain of **3** followed by nucleophilic substitution with different amines and thiourea. Amide and sulfonamide derivatives of thiazolobutyrolactone have also been synthesized.

Results and discussion

Limonene (1) was isolated from citrus peel essential oil (extracted with a Clevenger apparatus) using column chromatography. Limonene was identified by gas chromatography – mass spectrometry and with the reference sample procured from Sigma-Aldrich (Germany). α -Terpineol (2) was prepared by selective oxymercuration-demercuration of the external double bond in limonene (Scheme 1). α -Terpineol was subjected to oxidative cleavage using different oxidizing agents such as CrO₃,¹⁵ KMnO₄,¹⁶ and RuCl₃.¹⁷ RuCl₃–NaIO₄ was found to be the best oxidizing agent, giving the highest yield of **3**.

We were interested in introducing amine and sulfur atoms in the side chain of 3 to enhance its activity. But when 3 was treated with primary amine, ring opening was taking place. So we decided to first introduce a halogen atom in the side chain and then carry out the substitution with different amines.

The α -halogenation of carbonyl compounds is the step for introducing a heteroatom, generating a stabilized carbon radical

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Scheme 1. Synthesis of γ -butyrolactone (3) from limonene.



or carbanion and providing conjugation to carbonyl groups. Aldehydes and ketones can be halogenated at the α -position with bromine, chlorine, and iodine. Various α -bromination methods for carbonyl compounds have been reported, including the basic method using Br₂, *N*-bromosuccinimide, dioxane/dibromide, and a hexamethylenetetramine–bromine complex under microwave irradiation.¹⁵

For unsymmetrical ketones the preferred order of halogenation is typically CH > CH₂ > CH₃, but mixtures are frequently encountered.¹⁸ In basic conditions the reaction goes through an enolate mechanism where the C-4' group is attacked preferably over the C-2' group to stabilize the enolate (Scheme 1). With acid catalysts, the reaction goes through enol formation, and for enol stabilization an internal carbon (C-2') is brominated rather than the terminal C-4' (Scheme 1). The quantity of brominating reagent is an important factor in controlling consecutive bromination at the same position.¹⁸ The purpose of the catalyst is to provide a small amount of enol or enolate. The reaction can also be carried out without addition of catalyst, as traces of catalyst are always present and these are enough to catalyze enol formation.

We have developed a milder, selective, and controlled bromination of **3** at the C-2' position. In this procedure, 1 mol/L Br₂ in dichloromethane (DCM) was added dropwise to **3** in a 1:1 ratio at room temperature. In situ formation of **4** was monitored and identified by thin layer chromatography (TLC) and liquid chromatography – mass spectrometry (LC-MS). Bis-brominated product was observed with increasing molar concentrations of bromine in DCM. The molar ratio (1:1) is an important factor for selective monobromination at the C-2' position. Isolation of **4** is very difficult owing to the unstable C–Br bond under moist and basic conditions. After the addition of bromine the reaction mixture was immediately dried on a rotary evaporator to remove unreacted bromine and HBr produced under the reaction conditions.

Bromo-substituted γ -butyrolactone (4) was used for amination reactions without further purification. Compounds **5a–5g** were prepared (Table 1) through selective bromination and nucleophilic substitution by different amines in a consecutive manner at the C-2' position of **4**. Aminations of **4** using primary aliphatic amines like cyclohexylamine, benzylamine, and ethylenediamine occurred very rapidly with the γ -butyrolactone ring, and ring-substituted products (A and B) were observed simultaneously as major by-products along with the expected minor product C (Scheme 2). The mixture of products was observed by TLC and LC-MS.

For steric reasons, *tert*-butylamine (entry 3) and isopropylamine (entry 9) remained unreacted even on addition of higher equivalents of amine for a longer time. Primary aromatic amines such as aniline and *p*-toluidine (entries 1 and 2) participated in selective bromine substitution and produced **5a** and **5b** in 58% and 61% yield, respectively. Primary aromatic amines are less reactive than primary aliphatic amines and the expected products were formed in greater quantity (entry 1, 58%; entry 2, 61%) than the ringopened product. It is clear from the results that the bromine substitution rate is much faster than the rate of ring cleavage of the γ -butyrolactone **4**.

Secondary amines were found to be more suitable and selective for aminations of 4. No ring cleavage product was observed. The reactions were carried out with acyclic as well as cyclic (five- and six-member) amines. Compound 5c was obtained in good yield (84%) by the reaction of diethylamine (entry 4) with 4.

Using morpholine and piperidine (entries 5 and 6), the yields obtained for **5d** and **5e** were 69% and 63%, respectively. For piperazine (entry 7) there was the possibility of substitution by both nitrogen atoms, but as one equivalent of **4** and one equivalent of piperazine were used, only monosubstituted product was obtained. The yield obtained with pyrrolidine (entry 8) was less than that obtained with six-member cyclic amines.

Intermediate 4 was further used for the synthesis of another heterocyclic molecule containing both sulfur and nitrogen atoms by Hantzsch thiazole synthesis (Scheme 3). In this reaction, 4 was refluxed with thiourea to give the thiazolecontaining butyrolactone derivative 6 in 68% yield.

As the thiazole derivative **6** contains a free amino group in its skeleton, it can be further substituted to introduce other functional groups that can lead to enhanced biological activity. Therefore, we substituted the amino group of **6** with different amides and sulfonamides (Scheme 4). Acetyl and benzyl amide derivatives (**6a** and **6b**) were prepared by refluxing **6** with one equivalent of acetyl or benzoyl chloride, respectively, in the presence of a catalytic amount of pyridine. Product **6** was refluxed with the acid chlorides of acetic acid, benzoic acid, and *p*-toluenesulfonic acid in the presence of pyridine to yield **6a** (72%), **6b** (68%), and **6c** (75%), as shown in Scheme 4.

Conclusion

In summary, methods to introduce a diverse set of amino groups onto γ -butyrolactone have been developed. The key intermediate for all of these transformations is γ -butyrolactone bromide derivative **4**, obtained from γ -butyrolactone derivative **3** in a selective bromination reaction. To this intermediate were introduced a variety of substituted amines to produce amino-functionalized γ -butyrolactones.

Experimental section

General

All reactions were conducted using oven-dried glassware.

Entry	Intermediate	Amine	Time (min) / temp. (°C)	Product ^a		Overall yield ^b
1	4	NH ₂	20/55	O HN HN	5a	58%
2	4	H ₃ C	20/60		5b	61%
3	4	H ₂ N	30/60	No reaction		_
4	4	$HN(C_2H_5)_2$	15/55	0 (C ₂ H ₅) ₂ N	5c	84%
5	4	^H N O	20/50		5d	69%
6	4	HZ	20/50	of of o	5e	63%
7	4		30/50		5f	62%
8	4	HZ N	20/50		5g	53%
9	4	NH K	30/60	No reaction		

Table 1. Selective aminations of γ -butyrolactone bromo derivative 4.

^{*a*}All products were characterized by IR, ¹H NMR, ¹³C NMR, and HRMS (ESI) spectral data. ^{*b*}Isolated yields were calculated from 4.

Commercial-grade reagents were used without further purification. Solvents were dried and distilled following usual protocols. Column chromatography was carried out using silica gel (60–120 mesh). TLC was performed on aluminumbacked plates coated with silica gel 60 with F_{254} indicator.

The ¹H NMR and ¹³C NMR spectra were recorded with a 300 MHz spectrometer using CDCl₃. ¹H NMR chemical shifts are expressed in parts per million (δ) relative to CHCl₃ ($\delta = 7.26$); ¹³C NMR chemical shifts are expressed in parts per million (δ) relative to the CDCl₃ resonance ($\delta = 77.0$).

High-resolution mass spectra (HRMS) were obtained using positive electrospray ionization (m/z values are given). Infrared spectra were recorded as thin films on sodium chloride plates. Optical rotation was measured with a HORIBA SEPA-300 polarimeter.

Synthesis of dihydro-5,5-dimethyl-4-(3-oxobutyl)furan-2 (3*H*)-one (3)

To 20 mL of water, NaIO₄ (56.39 g, 0.263 mmol) followed by acetonitrile (10 mL) and carbon tetrachloride (10 mL) was

added and stirred for 5 min. RuCl₃·3H₂O (1.299 mmol) was added and stirred for 10 min. To the reaction mixture, 2 (10 g, 0.064 mmol) was added dropwise at 0 °C. It was stirred at 0 °C for 20 min and then at room temperature for 5–6 h until the reaction was complete. The reaction mixture was partitioned with water and ethyl acetate in a separatory funnel and the water layer was washed with ethyl acetate $(3 \times 30 \text{ mL})$. The combined ethyl acetate layer was dried over sodium sulfate. The solvent was evaporated under vacuum to give 3, which was purified by column chromatography over silica gel using hexane - ethyl acetate (41:9), providing **3** as an oily liquid (8 g, 68%). $[\alpha]_D^{27}$ -43.2° (c = 0.01, MeOH). R_f 0.65 (1:1 hexane – ethyl acetate). IR (CHCl₃) υ_{max} (cm⁻¹): 1781, 1722, 1549, 1251, 1004, 977. ¹H NMR (300 MHz, CDCl₃, δ): 2.48–2.40 (m, 1H), 2.37– 2.35 (m, 2H), 2.20-2.15 (m, 1H), 2.10-2.07 (m, 1H), 2.05 (s, 3H), 1.65–1.60 (m, 1H), 1.45–1.35 (m, 1H), 1.30 (s, 3H), 1.13 (s, 3H). ¹³C NMR (75 MHz, CDCl₃, δ): 207.2 (1C), 174.9 (1C), 86.4 (1C), 44.8 (1C), 41.8 (1C), 34.1 (1C), 29.7 (1C), 27.1 (1C), 22.9 (1C), 21.6 (1C). HRMS (ESI) data (m/z): $[M + H]^+$ calcd. for $C_{10}H_{17}O_3$, 185.2402; found, 185.2402.

Representative procedure for the synthesis of dihydro-5,5dimethyl-4-(2-(phenyl amino)-3-oxobutyl)furan-2(3H)-one (5a)

To compound 3 (200 mg, 1.08 mmol) dissolved in 1 mL dichloromethane, 0.1 mL of 1 mol/L Br₂ in dichloromethane was added dropwise and stirred at room temperature for 5 min. The completion of the reaction was monitored by TLC and LC-MS. The reaction mixture was dried in a rotary evaporator to remove extra bromine and HBr present in the reaction mixture. To the resulting brominated product, aniline (1.08 mmol) and 1-2 drops of triethylamine were added and stirred at 55-60 °C in a water bath. After the completion of the reaction, the reaction mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with a minimum amount of NaHCO₃ solution and then with water. It was dried over sodium sulfate and concentrated in a rotary evaporator. Purification was performed by silica gel column chromatography using hexane : ethyl acetate (95:5 to 80:20) to give **5a** as an oily liquid (173 mg, 58%); $[\alpha]_{D}^{27}$ +61.7° (c = 0.01, MeOH). R_f 0.90 (1:1 hexane – ethyl acetate). IR (CHCl₃) v_{max} (cm⁻¹): 3622, 3018, 2975, 1758, 1712, 1513, 1476, 1420, 1229, 1046, 723. ¹H NMR (300 MHz, CDCl₃, δ): 7.20–6.53 (m, 5H), 3.98 (br s, NH), 2.62–2.54 (dd, J =8.05, 7.08 Hz, 1H), 2.50-2.43 (m, 1H), 2.32-2.28 (m, 1H), 2.23-2.19 (m, 1H), 2.16 (s, 3H), 1.80-1.78 (m, 1H), 1.54-1.49 (m, 1H), 1.45 (s, 3H), 1.26 (s, 3H). ¹³C NMR (75 MHz, CDCl₃, δ): 207.2 (1C), 175.0 (1C), 146.2 (1C), 129.6 (2C), 118.7 (1C), 113.2 (1C), 86.7-85.9 (1C), 62.4-61.8 (1C), 45.2 (1C), 42.6-41.8 (1C), 34.8-35.1 (1C), 31.4-31.2 (1C), 30.0–29.7 (1C), 27.4–26.3 (1C), 23.3–21.9 (1C). HRMS (ESI) data (m/z): $[M + H]^+$ calcd. for $C_{16}H_{22}NO_3$, 276.3508; found, 276.1692.

Dihydro-5,5-dimethyl-4-(2-(*p*-tolylamino)-3-oxobutyl) furan-2(3*H*)-one (5b)

The compound was purified by column chromatography over silica gel using hexane – ethyl acetate (41:9), providing **5b** as an oily liquid (191 mg, 61%). R_f 0.53 (1:1 hexane – ethyl acetate). IR (CHCl₃) υ_{max} (cm⁻¹): 3622, 3018, 2975,

1759, 1722, 1513, 1476, 1420, 1229, 1046, 723. ¹H NMR (300 MHz, CDCl₃, δ): 6.98 (d, J = 7.87, 2H), 6.49 (d, J = 7.87, 2H), 3.91 (br s, NH), 2.74–2.53 (m, 1H), 2.49–2.42 (m, 1H), 2.40–2.31 (m, 2H), 2.22 (s, 3H), 2.18–2.12 (m, 3H), 1.69–1.84 (m, 1H), 1.44–1.36 (m, 4H), 1.26–1.24 (s, 3H). ¹³C NMR (75 MHz, CDCl₃, δ): 209.9 (1C), 175.2 (1C), 144.1–143.9 (1C), 129.9–129.2 (3C), 113.2–113.1 (2C), 86.6–86.3 (1C), 62.6–62.0 (1C), 45.0 (1C), 42.6–41.6 (1C), 35.0–34.7 (1C), 31.2–31.0 (1C), 27.2–27.0 (1C), 21.9–21.7 (1C), 20.2 (1C). HRMS (ESI) data (*m*/*z*): [M + H]⁺ calcd. for C₁₇H₂₄NO₃, 290.3774; found, 290.3773.

Dihydro-5,5-dimethyl-4-(2-(diethylamino)-3-oxobutyl) furan-2(3*H*)-one (5c)

The compound was purified by column chromatography over silica gel using hexane – ethyl acetate (17:3), providing **5c** as an oily liquid (231 mg, 84%). R_f 0.50 (1:1 hexane – ethyl acetate). IR (CHCl₃) υ_{max} (cm⁻¹): 3616, 3019, 2975, 2400, 1756, 1720, 1514, 1417, 1203, 1046, 928. ¹H NMR (300 MHz, CDCl₃, δ): 2.77–2.61 (m, 2H), 2.57–2.51 (m, 2H), 2.46–2.39 (m, 2H), 2.30–2.28 (m, 1H), 2.28 (s, 3H), 1.82–1.77 (m, 1H), 1.72–1.60 (m, 1H), 1.51 (s, 3H), 1.33 (s, 3H), 1.27–1.13 (m, 6H). ¹³C NMR (75 MHz, CDCl₃, δ): 201.2 (1C), 174.9 (1C), 86.9–86.4 (1C), 60.6 (1C), 52.6–51.0 (2C), 45.4–42.1 (1C), 35.1–34.3 (1C), 33.7 (1C), 32.7 (1C), 27.7–27.1 (1C), 23.5–22.1 (1C), 14.4 (2C). HRMS (ESI) data (*m/z*): [M + H]⁺ calcd. for C₁₄H₂₆NO₃, 256.3611; found, 256.3689.

Dihydro-5,5-dimethyl-4-(2-morpholino-3-oxobutyl)furan-2 (3*H*)-one (5d)

The compound was purified by column chromatography over silica gel using hexane – ethyl acetate (8:17), providing **5d** as an oily liquid (200 mg, 69%). $[\alpha]_D^{27}$ –46.4° (c = 0.01, MeOH). R_f 0.19 (1:1 hexane – ethyl acetate). IR (CHCl₃) υ_{max} (cm⁻¹): 3616, 3019, 2975, 2400, 1758, 1720, 1514, 1423, 1217, 1046, 1031, 928. ¹H NMR (300 MHz, CDCl₃, δ): 3.70–3.69 (4H), 3.13–2.97 (1H), 2.63–2.59 (3H), 2.52–2.51 (3H), 2.33–2.29 (1H), 2.25–2.21 (s, 3H), 2.18–2.17 (1H), 1.90–1.70 (1H), 1.46 (s, 3H), 1.26 (s 3H). ¹³C NMR (75 MHz, CDCl₃, δ): 210.5 (1C), 175.2 (1C), 85.6 (1C), 71.3 (1C), 66.3–66.1 (2C), 49.0–48.8 (2C), 42.1–41.8 (1C), 33.8 (1C), 28.6 (1C), 27.5 (1C), 26.4 (1C), 20.9 (1C). HRMS (ESI) data (m/z): [M + H]⁺ calcd. for C₁₄H₂₄NO₃, 270.3447; found, 270.3448.

Dihydro-5,5-dimethyl-4-(2-(piperidin-1-yl-3-oxobutyl) furan-2(3*H*)-one (5e)

The compound was purified by column chromatography over silica gel using hexane – ethyl acetate (8:17), providing **5e** as an oily liquid (182 mg, 63%). $[\alpha]_D^{27}$ –55.3° (c = 0.01, MeOH). R_f 0.50 (hexane – ethyl acetate, 1:1). IR (CHCl₃) υ_{max} (cm⁻¹): 3620, 3089, 2975, 2400, 1759, 1730, 1519, 1423, 1227, 1046, 928. ¹H NMR (300 MHz, CDCl₃, δ): 2.75–2.46 (m, 4H), 2.32 (s, 3H), 2.25–2.09 (m, 4H), 1.75–1.71 (m, 1H), 1.55–1.36 (m, 10H), 1.20 (s, 3H). ¹³C NMR (75 MHz, CDCl₃, δ): 208.7–207.6 (1C), 175.5–174.9 (1C), 86.9–86.4 (1C), 71.4 (1C), 52.5–51.2 (2C), 43.7–42.1 (1C), 55.2–34.3 (1C), 32.7 (1C), 29.9–29.2 (1C), 27.7–27.3 (1C), 26.1–25.6 (2C), 25.1–24.9 (1C), 22.8–22.2 (1C). HRMS





Scheme 3. Synthesis of amine and thiazole derivatives from 3.



Scheme 4. Synthesis of amide and sulfonamide derivatives of 6.



(ESI) data (m/z): [M + H]⁺ calcd. for C₁₅H₂₅NO₃, 268.3719; found, 268.3718.

Dihydro-5,5-dimethyl-4-(2-(piperazin-1-yl-3-oxobutyl) furan-2(3*H*)-one (5f)

The compound was purified by column chromatography over silica gel using hexane – ethyl acetate (8:17), providing **5f** as an oily liquid (180 mg, 62%). $[\alpha]_D^{27}$ –65.9° (c = 0.01, MeOH). R_f 0.44 (9:1 hexane – ethyl acetate). IR (CHCl₃) υ_{max} (cm⁻¹): 3620, 3288, 3089, 2975, 2400, 1759, 1730, 1519, 1423, 1227, 1046, 928. ¹H NMR (300 MHz, CDCl₃, δ): 2.95–2.92 (m, 1H), 2.53–2.43 (m, 5H), 2.22–2.03 (m, 9H), 1.77–1.60 (m, 1H), 1.55–1.44 (m, 1H), 1.37 (s, 3H), 1.17 (s, 3H). ¹³C NMR (75 MHz, CDCl₃, δ): 208.4 (1C), 175.6 (1C), 87.2–86.9 (1C), 72.0–71.2 (1C), 62.0 (2C), 50.4–49.9 (2C), 43.4–43.2 (1C), 35.2–35.0 (1C), 30.3–29.0 (1C), 27.7–27.4 (1C), 25.4–24.8 (1C), 22.3–22.2 (1C). HRMS (ESI) data (*m/z*): [M + H]⁺ calcd. for C₁₄H₂₆NO₃, 269.3600; found, 269.3597.

Dihydro-5,5-dimethyl-4-(2-(pyrrolidine-1-yl-3-oxobutyl) furan-2(3*H*)-one (5g)

The compound was purified by column chromatography over silica gel using hexane – ethyl acetate (8:17), providing **5g** as an oily liquid (145 mg, 53%). $[\alpha]_D^{27}$ –38.3° (c = 0.01, MeOH). R_f 0.11 (hexane – ethyl acetate, 1:1). IR (CHCl₃) υ_{max} (cm⁻¹): 3619, 3018, 2975, 2400, 1758, 1720, 1520, 1218, 1046, 928. ¹H NMR (300 MHz, CDCl₃, δ): 2.89–2.83 (m, 1H), 2.66–2.58 (m, 3H), 2.51–2.35 (m, 3H), 2.30–2.26 (m, 1H), 2.18 (s, 3H), 2.02–1.98 (m, 2H), 1.85–1.78 (m, 3H), 1.65 (m, 1H), 1.45 (s, 3H), 1.26 (s, 3H). ¹³C NMR (75 MHz, CDCl₃, δ): 208.6 (1C), 174.1–173.5 (1C), 85.4–85.2 (1C), 71.2 (1C), 49.9–48.8 (2C), 41.8–41.4 (1C), 40.7–40.3 (1C), 34.2–33.5 (1C), 26.3–25.9 (1C), 25.8–25.2 (2C), 22.7–22.4 (1C), 21.2–20.8 (1C). HRMS (ESI) data (m/z): [M + H]⁺ calcd. for C₁₄H₂₄NO₃, 254.3453; found, 254.3531.

4-(2-Amino-4-methyl-thiazol-5-ylmethyl)-5,5-dimethyldihydro-furan-2-one (6)

Thiourea (82.6 mg, 1.08 mmol) was dissolved in 20 mL of distilled water with heating in a round-bottomed flask equipped with a reflux condenser. Compound **4** (200 mg, 1.08 mmol) dissolved in 2 mL of methanol was added dropwise to the thiourea solution and the reaction mixture was refluxed till the reaction was complete. The reaction mixture was cooled and made alkaline with a saturated solution of NaHCO₃ and extracted with ethyl acetate. The ethyl acetate layer was washed twice with distilled water, dried over Na₂SO₄, and concentrated in a rotary evaporator. Purification was performed by recrystallization with hot dichloromethane to give **6**. Crystalline powder (137.4 mg, 68%); mp 152–

154 °C; $[α]_D^{27}$ –44.3° (*c* = 0.01, MeOH). *R_f* 0.18 (ethyl acetate). ¹H NMR (300 MHz, CDCl₃, δ): 2.76–2.70 (m, 1H), 2.65–2.51 (m, 2H), 2.44–2.28 (m, 2H), 2.09 (s, 3H), 1.43 (s, 3H), 1.33 (s, 3H). ¹³C NMR (75 MHz, CDCl₃, δ): 175.0 (1C), 165.0 (1C), 143.3 (1C), 116.6 (1C), 86.1 (1C), 47.2 (1C), 34.7 (1C), 27.4 (1C), 26.2 (1C), 21.8 (1C), 14.6 (1C). HRMS (ESI) data (*m*/*z*): [M + H]⁺ calcd. for C₁₁H₁₇N₂O₂S, 241.1011; found, 241.3394.

N-[5-(2,2-Dimethyl-5-oxo-tetrahydro-furan-3-ylmethyl)-4methyl-thiazol-2-yl]-acetamide (6a)

The compound was purified by recrystallization with hot dichloromethane to give **6a**. Crystalline powder (84.5 mg, 72%), mp 203–204 °C. R_f 0.59 (ethyl acetate). ¹H NMR (300 MHz, CDCl₃, δ): 2.87–2.81 (m, 1H), 2.71–2.59 (m, 2H), 2.38–2.30 (m, 2H), 2.25 (s, 3H), 2.24 (s, 3H), 1.46 (s, 3H), 1.37 (s, 3H). ¹³C NMR (75 MHz, CDCl₃, δ): 175.0 (1C), 168.3 (1C), 156.6 (1C), 141.7 (1C), 122.6 (1C), 86.4 (1C), 47.7 (1C), 35.2 (1C), 27.9 (1C), 26.6 (1C), 23.5 (1C), 22.4 (1C), 15.0 (1C). HRMS (ESI) data (*m*/*z*): [M + H]⁺ calcd. for C₁₄H₂₃N₂O₃S, 283.3666; found, 283.3683.

N-[5-(2,2-Dimethyl-5-oxo-tetrahydro-furan-3-ylmethyl)-4methyl-thiazol-2-yl]-4-methyl-benzenesulfonamide (6c)

The compound was purified by recrystallization with hot dichloromethane to give **6c**. Crystalline powder (123.1 mg, 75%), mp 245–247 °C. R_f 0.51 (ethyl acetate). ¹H NMR (300 MHz, CDCl₃, δ): 7.75 (d, J = 7.5 Hz, 2H), 7.25 (d, J = 7.9 Hz), 2.68–2.63 (m, 1H), 2.60–2.58 (m, 2H), 2.41 (s, 3H), 2.36–2.27 (m, 2H), 2.24 (s, 3H), 1.45 (s, 3H), 1.33 (s, 3H). ¹³C NMR (75 MHz, CDCl₃, δ): 174.3 (1C), 168.5 (1C), 155.6 (1C), 143.2 (1C), 138.6 (1C), 130.3 (1C), 129.5 (2C), 126.7 (2C), 85.8 (1C), 46.4 (1C), 34.8 (1C), 27.7 (1C), 26.6 (1C), 22.2 (1C), 21.7 (1C), 11.9 (1C). HRMS (ESI) data (m/z): [M + H]⁺ calcd. for C₁₉H₂₇N₂O₄S₂, 395.5162; found, 395.5187.

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