Scientific paper

Synthesis of Novel Hybrid Heterocycles as Potential Nematicidal Agents

Srinivas Avula*,[1] and Kalyan Rao Enugala[2]

[1] *Department of Chemistry, Vaagdevi Degree & PG College Kishanpura, Warangal, Telangana, India 506001*

[2] *Department of Physical Sciences, Kakatiya Institute of Technological Sciences, Warangal, Telangana-506009*

* *Corresponding author: E-mail: avula.sathwikreddy@gmail.com*

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Abstract

A series of novel 5-((3a*R*,5*S*,6*S*,6a*R*)-6-((1*H*-pyrazol-3-yl)methoxy)-2,2-dithyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)-3-(4-fluorophenyl)-6-phenyl-3,3a,5,6-tetrahydrothiazolo[4,5-*c*]isoxazoles **10a**–**g** were synthesized by the reaction of chalcone derivatives of (*E*)-2-((3a*R*,5*S*,6*S*,6a*R*)-6-((1*H*-pyrazol-3-yl)methoxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)-5-(4-fluorobenzylidene)-3-phenylthiazolidin-4-ones **9a**–**g** with hydroxylamine hydrochloride. The chemical structures of newly synthesized compounds were elucidated by IR, NMR, MS and elemental analysis. The compounds **10a**–**g** were evaluated for their nematicidal activity against *Dietylenchus myceliophagus* and *Caenorhabditis elegans*, compounds **10b** and **10f** showed appreciable nematicidal activity.

Keywords: Glucose, hybrid heterocycles, Knoevenagel condensation, cyclisation, nematicidal activity.

1. Introduction

Pyrazole derivatives are particularly fascinating compounds that have been shown to have varied biological activities including anticancer,[1] anti-inflammatory,[2] antiviral,[3] antibacterial agents,[4] antimalarial,[5] anti-leishmania,[6] A549 lung cancer cell activities.[7] Formycin and oxy-formycin are commercially available antibiotic systems based on pyrazole unit.[8]

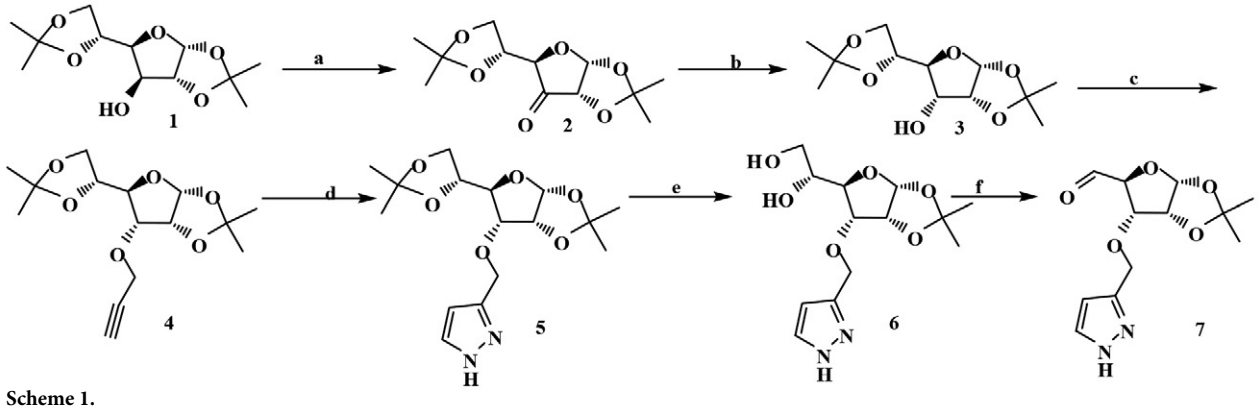
Thiazoles are a well-known group of heterocyclic compounds with a wide range of biological functions, and their success stems from their long history.[9] Thiazole is also a key component of all current pencillins, which have transformed the treatment of bacterial illnesses.[10] Furthermore, the chemistry of thiazolidine ring complexes is of great interest because they include the core structure of many synthetic medicines with biological spectrum activity.[11] Thiazolidinone nuclei are frequently associated with a number of natural products, especially the structure of thiamin, their links with heart and blood glucose advantages such as troglitazone,[12] and their linkage with various metabolites in fungi and primitive marine organisms.[13] Numerous thiazolidinone compounds have demonstrated considerable bioactivity such as antidiarrheal,[14] anticonvulsants,[15] antibacterial,[16] antidiabetic,[17] antihistamine,[18] anticancer,[19] and anti HIV,[20] Ca^{2+}-channel blocker,[21] PAF antagonist,[22] cardio protective,[23] anti-ischemic,[24] COX inhibitory,[25] antiplatelet activating factor,[26] non-peptide thrombin receptor antagonist,[27] and tumor necrosis factor-α antagonist,[28] and nematicidal activities. Isoxazoles derivatives are bioactive molecules with various activities, including antifungal,[29] Aβ precursor protein,[30] protein thyrosine phosphatase 1B inhibitors,[31] antiviral,[32] antihelmintic,[33] anti-inflammatory,[34] anticonvulsant,[35] insecticidal,[36] antitubercular,[37] immunomodulatory,[38] and hypolipidemic.[39]

Nematodes are tiny worms, some of them are plant parasites, and can play an important role in predisposing host systems for invasion by secondary pathogens.[40] Plants attacked by nematodes exhibit slow growth and development, indicating loss of harvest quality and quantity. Namaticides application is intended for human and animal environmental and health issues. For example, effective namaticide such as dibromochloropropane (DBCD) and ethylene dibromide (EDB) have withdrawn from the market due to harmful effects on humans and the environment. Methyl bromide, which is popular in the most effective and most widespread soils, including nematodes, is already banned.

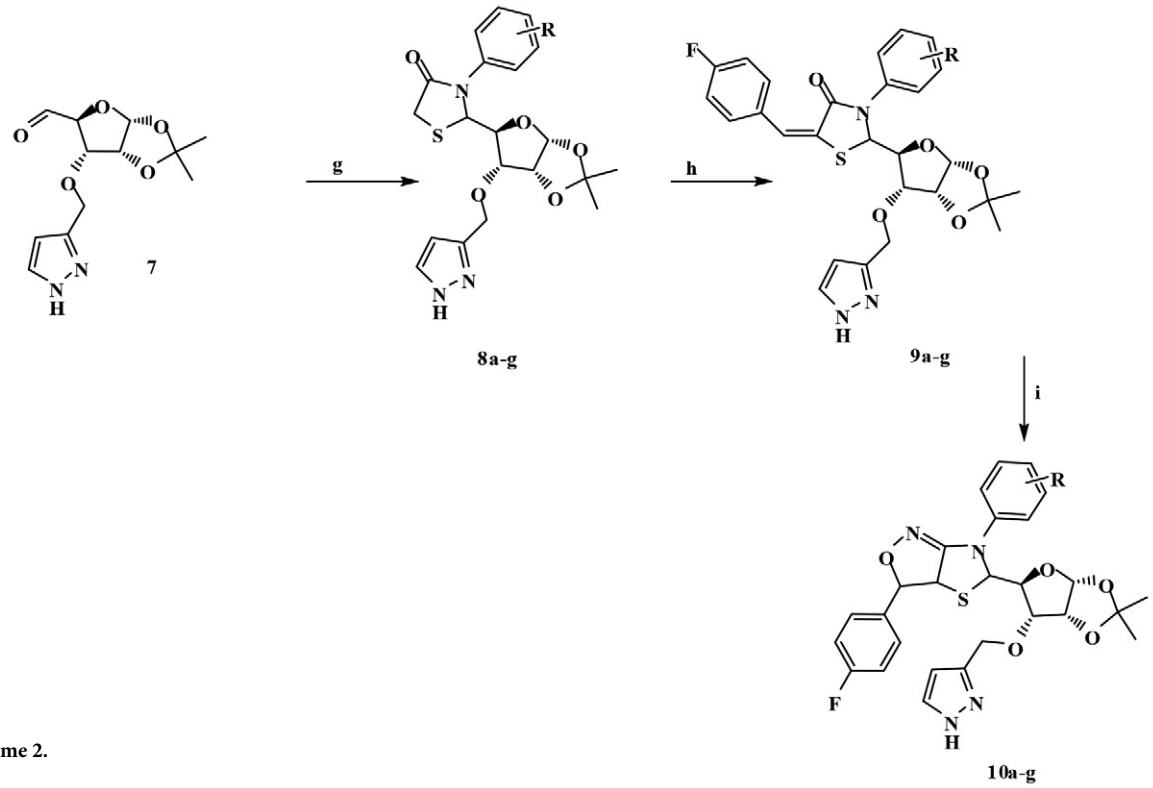
The use of organophosphates and carbamates is projected to increase the withdrawal of methyl bromide, pos-

ing significant environmental challenges. In fact, the highly toxic aldicarb used to control insects and nematodes has been found in ground water.[41] As a result, alternate nematode management strategies and less harmful nematicidal agents must be developed.[42] Examining naturally occurring connections in plants is one method for searching for such nematicidal chemicals. Several such compounds, including alkaloids, phenols, sesquiterpenes, diterpenes, polyacetylenes, and thienyl derivatives, have nematic action.[43] For instance, α-terthienyl is a potent nematicidal chemical.[44] Other linkages to nematic activity are mostly isolated from plants that *Asteraceae* family.[44] Vegetables and equivalents did not evolve into commercial nematodes. Therefore, commercial synthesis must be established.

Carbohydrates, on the other hand, are a form of molecules with a wide range of stereochemistry that plays a significant part in molecular detection as well as other intracellular functions.[45–49] Carbohydrates can be combined with bioactive compounds to form chemical libraries for drug discovery and development.[50–53] To increase the bioavailability of carbohydrate-derived medications, the hydroxyl groups of molecules are frequently coated with hydrophobic groups, which are then divided into the bloodstream to create Pro pharmaceuticals that are more easily absorbed. In this particular case, the phrase hybrid medicine is in its early phases and appears promising. This is because current anticancer use can result in combinations with two or more pharmacophores.[54] These combi-



Scheme 1.



Scheme 2.

R = (a) C_6H_5; (b) 4-Cl-C_6H_5; (c) 4-NO_2-C_6H_5; (d) 2-CH_3-C_6H_5; (e) 4-CH_3-C_6H_5; (f) 3-OH-C_6H_5; (g) 4-OH-C_6H_5.

nations are designed to target multiple lifting areas of the diseased illness. In continuation of our work on the development of new compounds,[55–60] we synthesized some unique hybrid heterocyclics and tested their nematicidal properties.

2. Result and Discussion

Diacetone D-glucose (**1**) is made from D-(+)-glucose by treating with acetone in the presence of a catalytic quantity of sulfuric acid according to the literature procedure;[61] reduction of **2** prepared by Swern oxidation of **1** with $NaBH_4$ in aqueous solution. Ethanol at 0 °C for 1 h yielded **3** (77%), which on further propargylation in DMF in the presence of NaH for 1 h afforded propargyl ether **4** (80%),[62] which was converted into pyrazole **5** (82%) by cycloaddition with diazomethane at –36 °C. Acid hydrolysis of 5,6-acetonide **5** in 60% AcOH produced the diol **6** (85%), which upon oxidative cleavage with $NaIO_4$ yielded the aldehyde **7**. Consequently, one pot syntheses of pyrazole-linked thiazolidinone glycosides **8a–g** were achieved by the condensation reaction of a primary aromatic amine with a thioglycolic acid in the presence of $ZnCl_2$ in dry toluene at reflux for 90 minutes. Compounds **8a**–**g** were then reacted with *para*-fluorobenzaldehyde in the presence of anhydrous NaOAc in glacial AcOH at reflux temperature to produce chalcone derivatives of pyrazole-linked thiazolidinone glycosides **9a**–**g**.

Reagents and conditions: (a) $COCl_2$, CH_2Cl_2, Et_3N, –78 °C → rt, 1.5 h, 73%; (b) $NaBH_4$, EtOH, H_2O, (19:1), 0 °C → rt, 68%; (c) propargyl bromide, NaH, DMF, 0 °C → rt; (d) diazomethane, –36 °C, 85%; (e) 60%, AcOH, rt, 64%; (f) $NaIO_4$, CH_2Cl_2, 0 °C → rt, 72%; (g) Ar-NH_2, $SHCH_2COOH$, $ZnCl_2$, toluene, 110 °C, 75%; (h) 4-F-C_6H_4-CHO, AcOH/NaOAc, reflux, 72–78%; (i) $NH_2OH{\cdot}HCl$, AcOH/NaOAc, reflux, 70–74%.

Cyclocondensation with hydroxyl amine hydrochloride in the presence of anhydrous NaOAc in glacial AcOH at reflux temperature yielded compounds **10a**–**g**. The structures of the produced compounds were validated by IR, NMR, MS, and elemental analysis. Furthermore, the compounds were tested for nematicidal activity.

3. Nematicidal Activity

Using the aqueous *in vitro* screening technique,[63] substances **10a**–**g** were tested for nematicidal activity against *Caenorhabditis elegans* and *Ditylenchus myceliophagus* at different doses. The findings (Table 1) are presented in terms of LD_{50}, or the median fatal dose at which 50% of the nematodes stopped moving. With LD_{50} values of 200, 220, and 230, 215 ppm, respectively, compound **10b** and compound **10f** are the most effective against *D. myceliophagus* and *C. elegans,* according to the screening data.

Table 1. Nematicidal activity of compounds **10a**–**g**

Compound number	*D. myceliophagus*	*C. elegans*
10a	500	520
10b	200	220
10c	680	620
10d	510	540
10e	740	720
10f	230	215
10g	450	490
Oxamyl	150	180

4. Experimental

All the reagents and solvents (of analytical grade) were purchased from Sigma Aldrich. Reactions were monitored and the purity of compounds were checked with thin-layer chromatography (TLC) on pre-coated Merck silica gel, and chemicals were observed by exposing them to UV light or immersing them in a 1% aqueous potassium permanganate solution. Separations were performed using silica gel chromatographic columns (60–120 mesh size). All melting points are uncorrected and measured using Fisher John's apparatus. IR spectra were recorded using KBr disks on a Perkin-Elmer FT IR spectrometer. The ^1H and ^{13}C NMR spectra were obtained using a Varian Gemini spectrometer (300 MHz for ^1H and 75 MHz for ^{13}C). Chemical shifts are presented in δ (ppm) with TMS as the internal reference, while coupling constants (*J*) are reported in Hz. Mass spectra were collected using a VG micro mass 7070H spectrometer. The Perkin-Elmer 240 CHN elemental analyzer produced elemental analyses (C, H, N) that were within ±0.4% of theoretical values.

3-(((3a*R*,5*R*,6*R*,6a*R*)-5-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[3,2-*d*][1,3]dioxol-6-yloxy)methyl)-1*H*-pyrazole (5). A solution of diazomethane (15 mmol), in diethyl ether (30 mL) and alkyne **4** (3.1 g, 10 mmol) were stored for 6 weeks at –30 °C. After evaporation of the excess of diazomethane and the solvent the residue was purified by column chromatography (silica gel 60–120 mesh, petroleum ether, ethyl acetate 2:1) elution of the provided compound **5** in excellent yield (72%) as a colorless solid. IR (KBr): 3300, 2950, 1550,1520 1450, 1250, 1150 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.9 Hz, 1H, =CH), 6.42 (d, *J* = 3.7 Hz, 1H, =CH), 5.41 (dd, *J* = 3.7 Hz, *J* = 4.5 Hz, 1H, CH), 4.70 (s, 2H, CH_2), 4.20 (d, *J* = 3.9 Hz, 2H, CH), 4.05 (m, 1H, CH), 4.0 (m, 1H, CH), 3.98 (m, 2H, CH_2), 1.54 (s, 6H, 2×CH_3), 1.51 (s, 6H, 2×CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) d 162.1, 131.4, 112.5, 110.2, 106.1, 84.1, 83.2, 82.6. MS: *m/z* (M^++Na) 363.16. Anal. Calcd for $C_{16}H_{24}N_2O_6$: C, 56.46; H, 7.11; N, 8.23. Found: C, 56.43; H, 7.09; N, 8.20.

(*R*)-1-((3a*R*,5*R*,6*R*,6a*R*)-6-((1*H*-pyrazol-3-yl)methoxy)-2,2-dimethyltetrahydrofuro[3,2-*d*][1,3]dioxol-5-yl) ethane-1,2-diol (6). A mixture of **5** (3g,8.82 mmol) in 60% aq. AcOH (25 mL) was stirred at room temperature for 12 h. Reaction mixture was neutralized with anhy. $NaHCO_3$ (15 g) and extracted with EtOAc (3 × 40 mL). The combined organic layers were dried (Na_2SO_4), evaporated and residue purified by column chromatography (60–120 mesh silica gel, 41% ethyl acetate in petroleum ether) to afford **6** (2.6 g, 82%) as a pale yellow solid; mp 148–151 °C. IR (KBr): 3350, 2950, 1465, 1510,1380, 1120 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38 (d, *J* = 4.7 Hz, 1H, Ar-H), 6.27 (d, *J* = 4.1 Hz, 1H, ArH), 5.40 (d, *J* = 5.1 Hz, 1H, CH), 4.67 (s, 2H, CH_2), 4.41 (s, 1H, OH), 4.20 (t, 1H, CH), 4.11 (m, 1H, CH), 4.04 (m, 1H, CH), 3.70 (m, 2H, CH_2), 3.48 (m, 1H, CH), 3.09 (s, 1H, OH), 1.54 (s, 6H, 2×CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) d 162.1, 131.4, 112.5, 106.1, 106.0, 83.3, 83.2, 72.6, 64.6, 63.5, 26.3. MS: *m/z* (M^++Na) 32 4.10. Calculated for $C_{13}H_{20}N_2O_6$; C, 51.99; H, 6.71; N, 9.33. Found: C, 51.96; H, 6.69; N, 9.30.

General procedure for the synthesis of compounds 8a–g. $NaIO_4$ (0.130 g, 0.61 mmol) was added at 0 °C to a solution of diol **6** (0.200 g, 0.66 mmol) in CH_2Cl_2 (5 mL), and the mixture was stirred for 6 hours at room temperature. Extracted the product with CH_2Cl_2 (2 × 10 mL). After drying (Na_2SO_4) and evaporating, a quantitative yield of aldehyde **7** (0.150 g) was obtained as a yellow liquid that was utilized in the subsequent procedure.

$ZnCl_2$ (0.100 g, 0.751 mmol) was added to a stirred mixture of **7** (0.150 g, 0.559 mmol), aromatic amine (0.395 mmol), and anhydrous thioglycolic acid (0.160 g, 0.211 mmol) in dry toluene (5 mL) after 2 minutes of refluxing the mixture on an oil bath for 60 minutes. Ethyl acetate was used to extract the residue after the filtrate had cooled and been concentrated to dryness under lower pressure. Brine and a 5% sodium bicarbonate solution were used to wash the ethyl acetate layer. At lower pressure, the organic layer was dried over Na_2SO_4 and evaporated until it was completely dry. Using hexane-ethyl acetate as an eluent, column chromatography on silica gel (60–120 mesh) was used to purify the resulting crude product.

2-((3a*R*,5*S*,6*S*,6a*R*)-6-((1*H*-pyrazol-3-yl)methoxy)-2,2- dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)-3-phenylthiazolidin-4-one (8a). IR (KBr): 3050, 2870, 1710, 1490, 1385, 1156, 790 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45(d, *J* = 5.1 Hz, 1H, Ar-H), 7.32 (t, 3H, Ar-H), 7.23 (t, 1H, Ar-H), 7.12 (m, 2H, Ar-H), 6.23 (d, *J* = 5.1 Hz, 1H, ArH), 5.52 (d, *J* = 4.2 Hz, 1H, CH), 5.03 (m, 1H, CH), 4.84 (m, 1H, CH), 4.74 (d, *J* = 4.5 Hz, 1H, CH), 4.47 (s, 2H, CH_2), 4.20 (t, 1H, CH), 3.78 (q, 2H, CH_2), 1.54 (s, 6H, 2×CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) d 173.3, 162.1, 136.7, 131.4, 129.9, 127.3, 124.9, 112.5 (d, *J* = 8.8 Hz), 106.1, 83.2, 80.7, 73.8, 64.6, 32.0, 26.3; MS: *m/z* (M^++Na) 440.10. Calculated for $C_{20}H_{23}N_3O_5S$: C, 57.54; H, 5.55; N, 10.07. Found: C, 57.51; H, 5.52; N, 10.04.

2-((3a*R*,5*S*,6*S*,6a*R*)-6-((1*H*-pyrazol-3-yl)methoxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)-3-(4-chlorophenyl)thiazolidin-4-one (8b). IR (KBr): 2900, 1690, 1485, 1376, 1056, 790 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.44 (d, *J* = 5.1 Hz, 1H, Ar-H), 7.34 (d, *J* = 5.1 Hz, 2H, Ar-H), 7.06 (d, *J* = 6.1 Hz, 2H, Ar-H), 6.23 (d, *J* = 5.9 Hz, 1H, Ar-H), 5.52 (d, *J* = 5.6 Hz, 1H, CH), 5.02 (m, 1H, CH), 4.84 (m, 1H, CH), 4.74 (d, *J* = 5.3 Hz, 1H, CH), 4.57 (s, 2H, CH_2), 4.20 (t, 1H, CH), 3.77 (q, 2H, CH_2), 1.54 (s, 6H, 2×CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) d 173.3, 162.1, 136.3, 131.4, 131.1, 129.9, 125.1, 112.5 (d, *J* = 9.6Hz), 106.1, 83.2, 81.3, 80.1, 73.8, 64.6, 32.0, 26.3; MS: *m/z* (M^++Na) 474.10. Calculated for $C_{20}H_{22}ClN_3O_5S$: C, 53.15; H, 4.91; N, 9.30. Found: C, 53.11; H, 4.89; N, 9.28.

2-((3a*R*,5*S*,6*S*,6a*R*)-6-((1*H*-pyrazol-3-yl)methoxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)-3-(4-nitrophenyl)thiazolidin-4-one (8c). IR (KBr): 2920, 1660, 1585, 1376, 1340, 1140 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.08 (d, *J* = 5.1 Hz, 2H, Ar-H), 7.33 (d, *J* = 5.6 Hz, 2H, Ar-H), 7.27 (d, *J* = 5.7 Hz, 1H, Ar-H), 6.14 (d, *J* = 5.6 Hz, 1H, Ar-H), 5.60 (d, *J* = 4.9 Hz, 1H, CH), 4.84 (d, *J* = 4.5 Hz, 1H, CH), 4.74 (s, 1H, CH), 4.52 (s, 2H, CH_2), 4.42 (m, 1H, CH), 4.20 (t, 1H, CH), 3.67 (q, 2H, CH_2), 1.54 (s, 6H, 2×CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.3, 162.1, 146.4, 145.1, 131.4, 126.4, 120.9, 112.5 (d, *J* = 9.9 Hz), 106.0, 83.2, 83.1, 80.7, 73.8, 64.6, 32.0, 26.3; MS: *m/z* (M^++Na) 485.09. Calculated for $C_{20}H_{22}N_4O_7S$: C, 51.94; H, 4.79; N, 12.11. Found: C, 51.92; H, 4.77; N, 12.09.

2-((3a*R*,5*S*,6*S*,6a*R*)-6-((1*H*-pyrazol-3-yl)methoxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)-3-*ortho*-tolylthiazolidin-4-one (8d). IR (KBr): 3050, 1710, 1500, 1420, 1150, 1080 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.22–7.20 (m, 3H, Ar-H), 7.07 (m, 1H, Ar-H), 6.18 (d, *J* = 5.8 Hz, 1H, Ar-H), 5.58 (d, *J* = 6.1 Hz, 1H, CH), 4.84 (m, 1H, CH), 4.75 (m, 1H, CH), 4.68 (s, 2H, CH_2), 4.20 (t, 1H, CH), 3.64 (q, 2H, CH_2), 2.19 (s, 3H, CH_3), 1.54 (s, 6H, 2×CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.7, 162.1, 136.0, 134.9, 131.4, 128.5, 127.0, 126.2, 112.5 (d, *J* = 8.6 Hz), 106.0, 81.2, 80.7, 74.3, 64.6, 32.0, 26.3, 17.4; MS: *m/z* (M^++Na) 452.0. Calculated for $C_{21}H_{25}N_3O_5S$: C, 58.45; H, 5.84; N, 9.74. Found: C, 58.43; H, 5.82; N, 9.72.

2-((3a*R*,5*S*,6*S*,6a*R*)-6-((1*H*-pyrazol-3-yl)methoxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)-3-*para*-tolylthiazolidin-4-one (8e). IR (KBr): 3000, 2900, 1720, 1520, 1470, 1380, 1120 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45 (d, *J* = 6.1 Hz, 1H, Ar-H), 7.19 (d, *J* = 6.3 Hz, 2H, Ar-H), 7.07 (d, *J* = 6.4 Hz, 2H, Ar-H), 6.24 (d, *J* = 6.7 Hz, 1H, Ar-H), 5.52 (d, *J* = 6.1 Hz, 1H, CH), 5.03 (d, *J* = 6.1 Hz, 1H, CH), 4.84 (m, 1H, CH), 4.74 (d, *J* = 5.9 Hz, 1H, CH), 4.57 (s, 2H, CH_2), 4.20 (t, 1H, CH), 3.78 (q, 2H, CH_2), 2.34 (s, 3H, CH_3), 1.54 (s, H, 2×CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.3, 162.1, 136.4, 135.4, 131.4, 131.1, 121.0, 112.4 (d, *J* = 8.4 Hz), 106.1, 83.2, 81.3, 80.7, 73.8,

64.6, 32.0, 26.3, 21.3; MS: *m/z* (M^++Na) 454.3. Calculated for $C_{21}H_{25}N_3O_5S$: C, 58.45; H, 5.84; N, 9.74. Found: C, 58.43; H, 5.82; N, 9.71.

2-((3a*R*,5*S*,6*S*,6a*R*)-6-((1*H*-pyrazol-3-yl)methoxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)-3-(3-hydroxyphenyl)thiazolidin-4-one (8f). IR (KBr): 3350, 1725, 1700, 1550, 1379, 1450, 1290 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36 (d, *J* = 5.2 Hz, 1H, Ar-H), 7.21 (t, 1H, Ar-H), 6.89 (m, 1H, Ar-H), 6.85 (m, 1H, Ar-H), 6.71 (m, 1H, Ar-H), 5.96 (d, *J* = 5.4 Hz, 1H, Ar-H), 5.54 (d, *J* = 4.9 Hz, 1H, CH), 4.84 (m, 1H, CH), 4.74 (d, *J* = 4.8 Hz, 1H, CH), 4.63 (m, 1H, CH), 4.61 (s, 2H, CH_2), 4.20 (t, 1H, CH), 3.64 (q, 2H, CH_2), 1.54 (s, 6H, 2×CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.3, 162.1, 159.8, 137.8, 132.4, 131.4, 116.9, 115.8, 112.5 (d, *J* = 9.2 Hz), 111.0, 106.1, 83.2, 81.3, 80.7, 73.8, 64.6, 32.0, 26.3; MS: *m/z* (M^++Na) 456.10. Calculated for $C_{20}H_{23}N_3O_6S$: C, 55.42; H, 5.35; N, 9.69. Found: C, 55.40; H, 5.33; N, 9.67.

2-((3a*R*,5*S*,6*S*,6a*R*)-6-((1*H*-pyrazol-3-yl)methoxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)-3-(4-hydroxyphenyl)thiazolidin-4-one (8g). IR (KBr): 3400, 1710, 1520, 1380, 1295, 1150 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34 (d, *J* = 4.9 Hz, 1H, Ar-H), 6.97–6.93 (m, 4H, Ar-H), 5.96 (d, *J* = 4.6 Hz, 1H, Ar-H), 5.53 (d, *J* = 4.2 Hz, 1H, CH), 4.84 (m, 1H, CH), 4.74 (d, *J* = 4.2 Hz, 1H, CH), 4.58 (s, 2H, CH_2), 4.47 (q, 1H, CH), 4.20 (t, 1H, CH), 3.66 (q, 2H, CH_2), 1.54 (s, 6H, 2×CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.3, 162.2, 157.6, 131.4, 129.0, 127.0 (d, *J* = 9.0 Hz), 117.6, 112,5, 106.1, 83.2, 81.3, 80.7, 73.8, 64.6, 32.0, 26.3; MS: *m/z* (M^++Na) 454.06. Calculated for $C_{20}H_{23}N_3O_6S$: C, 55.42; H, 5.35; N, 9.69. Found: C, 55.40; H, 5.33; N, 9.67.

General procedure for the synthesis of compounds 9a–g. Compound **8a** (0.01 mol), sodium acetate (0.01 mol), and *para*-fluorobenzaldehyde (0.02 mol) were combined in anhydrous glacial acetic acid (20 mL) and refluxed for 3 hours. After concentrating the reaction mixture and pouring it into ice-cold water, the separated solid was filtered, rinsed with water, and allowed to crystallize from glacial acetic acid. Pure **9a** (83%) can be obtained as a yellow solid with mp 215–218 °C.

(*E*)-2-((3a*R*,5*S*,6*S*,6a*R*)-6-((1*H*-pyrazol-3-yl)methoxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)-5-(4-fluorobenzylidene)-3-phenylthiazolidin-4-one (9a). IR (KBr): 3000, 1720, 1585, 1520, 1380, 1179, 1010 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.51–7.47 (m, 4H, Ar-H), 7.35 (t, 2H, Ar-H), 7.17–7.10 (m, 4H, Ar-H), 6.17 (s, 1H, =CH), 6.16 (d, *J* = 5.2 Hz, 1H, Ar-H), 5.53 (d, *J* = 5.9 Hz, 1H, CH), 4.84 (dd, *J* = 5.3 Hz, *J* = 5.6 Hz, 1H, CH), 4.74 (d, *J* = 5.8 Hz, 1H, CH), 4.64 (s, 2H, CH_2), 4.45 (d, *J* = 5.2 Hz, 1H, CH), 4.20 (t, 1H, CH), 1.54 (s, 6H, 2×CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.4, 163.7, 162.1, 136.2, 135.0, 132.5, 131.6, 131.4, 129.6, 126.2, 124.3, 122.4, 115.0, 112.5, 106.1, 83.2, 81.3, 79.8, 72.8, 64.6, 26.3; MS: *m/z* (M^++Na) 546.10. Calculated for $C_{27}H_{26}FN_3O_5S$: C, 61.94; H, 5.01, N, 8.03. Found: C, 61.92; H, 5.00; N, 8.01.

(*E*)-2-((3a*R*,5*S*,6*S*,6a*R*)-6-((1*H*-pyrazol-3-yl)methoxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)-3-(4-chlorophenyl)-5-(4-fluorobenzylidene)thiazolidin-4-one (9b). IR (KBr): 2900, 1695, 1580, 1546, 1469, 1380, 1160, 792 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.48 (s, 1H, Ar-H), 7.46 (m, 2H, Ar-H), 7.38 (s, 4H, Ar-H), 7.14 (t, 2H, Ar-H), 6.76 (s, 1H, =CH), 6.21 (d, *J* = 6.5 Hz, 1H, Ar-H), 5.54 (d, *J* = 6.8 Hz, 1H, CH), 4.94 (dd, *J* = 5.4 Hz, 5.9 Hz, 1H, CH), 4.74 (d, *J* = 6.1 Hz, 1H, CH), 4.66 (s, 2H, CH_2), 4.45 (dd, *J* = 5.2 Hz, 5.1 Hz, 1H, CH), 4.20 (t, 1H, CH), 1.54 (s, 6H, 2×CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.4, 163.7, 162.1, 135.8, 135.0, 132.5, 131.6, 129.7, 129.0, 124.6, 122.4, 115.0, 112.5, 106.1, 83.2, 81.3, 79.8, 72.8, 64.6, 26.3; MS: *m/z* (M^++Na) 580.4. Calculated for $C_{27}H_{25}ClFN_3O_5S$: C, 58.11; H, 4.52; N, 7.53. Found: C, 58.09; H, 4.50; N, 7.51.

(*E*)-2-((3a*R*,5*S*,6*S*,6a*R*)-6-((1*H*-pyrazol-3-yl)methoxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)-5-(4-fluorobenzylidene)-3-(4-nitrophenyl)thiazolidin-4-one (9c). IR (KBr): 2950, 1694, 1570, 1542, 1360, 1380, 1274 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.26 (d, *J* = 5.1 Hz, 2H, Ar-H), 7.73 (d, *J* = 5.5 Hz, 2H, Ar-H), 7.51 (m, 2H, Ar-H), 7.20 (d, *J* = 5.7 Hz, 1H, Ar-H), 7.15 (t, 1H, Ar-H), 6.78(s, 1H, =CH), 6.15 (d, *J* = 5.8 Hz, 1H, Ar-H), 5.54 (d, *J* = 5.9 Hz, 1H, CH), 4.84 (dd, *J* = 6.1 Hz, 6.5 Hz, 1H, CH), 4.74 (d, *J* = 6.4 Hz, 1H, CH), 4.64 (s, 2H, CH_2), 4.48 (m, 1H, CH), 4.20 (t, 1H, CH), 1.54 (s, 6H, 2×CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 163.7, 162.4, 163.7, 145.7, 144.3, 135.0, 132.4, 131.6, 126.8, 122.4, 120.5, 115.0, 112.5, 106.1, 83.2, 81.3, 79.8, 72.8, 64.6, 26.3; MS: *m/z* (M^++H) 569.1. Calculated for: $C_{27}H_{25}FN_4O_7S$: C, 57.04; H, 4.43; N, 9.85. Found: C, 57.01; H, 4.41; N, 9.82.

(*E*)-2-((3a*R*,5*S*,6*S*,6a*R*)-6-((1*H*-pyrazol-3-yl)methoxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)-5-(4-fluorobenzylidene)-3-*ortho*-tolylthiazolidin-4-one (9d). IR (KBr): 3000, 1530, 1710, 1490, 1380, 1250, 1140 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.43 (m, 2H, Ar-H), 7.36 (d, *J* = 5.1 Hz, 1H, Ar-H), 7.27 (dd, *J* = 5.1 Hz, 5.7 Hz, 1H, Ar-H), 7.22 (m, 2H, Ar-H), 7.10 (m, 2H, Ar-H), 7.07 (m, 1H, Ar-H), 6.72 (s, 1H, =CH), 6.21 (d, *J* = 4.8 Hz, 1H, Ar-H), 5.56 (d, *J* = 4.8 Hz, 1H, CH), 4.84 (t, 1H, CH), 4.74 (d, *J* = 5.2 Hz, 1H, CH), 4.67 (s, 2H, CH_2), 4.25 (m, 1H, CH), 4.20 (m, 1H, CH), 2.22 (s, 3H, CH_3), 1.54 (s, 6H, 2×CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.2, 164.5, 162.7, 162.5, 135.5, 135.0, 134.7, 132.5, 131.6, 130.8, 128.3, 126.3, 125.7, 122.4, 115.0, 112.5, 106.1, 83.2, 81.3, 79.8, 73.1, 64.6, 26.3, 17.4. MS: *m/z* (M^++Na) 558.03. Calculated for $C_{28}H_{28}FN_3O_5S$: C, 62.56; H, 5.25; N, 7.82. Found: C, 62.54; H, 5.23; N, 7.80.

(*E*)-2-((3a*R*,5*S*,6*S*,6a*R*)-6-((1*H*-pyrazol-3-yl)methoxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)-5-(4-fluorobenzylidene)-3-*para*-tolylthiazolidin-4-one (9e). IR (KBr): 2950, 1710, 1590, 1565, 1485, 1385, 1250, 1160 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.53 (d, *J* = 6.2 Hz, 1H, Ar-H), 7.42–7.40 (m, 2H, Ar-H), 7.34 (d, *J* = 5.9 Hz, 2H, Ar-H), 7.21 (d, *J* = 5.6 Hz, 2H, Ar-H), 7.14 (t, 2H, Ar-H), 6.78 (s, 1H, =CH), 6.31 (d, *J* = 5.9 Hz, 1H, Ar-H), 4.84 (m, 1H, CH), 4.74 (d, *J* = 5.9 Hz, 1H, CH), 4.64 (m, 1H, CH), 4.65 (s, 2H, CH_2), 4.20 (t, 1H, CH), 2.34 (s, 3H, CH_3), 1.54 (s, 6H, 2×CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.4, 163.7, 162.1, 135.0, 134.7, 132.5, 131.6, 130.9, 122.4, 121.0, 115.0, 112.5, 106.1, 83.2, 81.3, 79.8, 72.8, 64.6, 26.3, 21.3. MS: *m/z* (M^++H) 538.12. Calculated for $C_{28}H_{28}FN_3O_5S$: C, 62.56; H, 5.25; N, 7.82. Found: C, 62.54; H, 5.23; N, 7.80.

(*E*)-2-((3a*R*,5*S*,6*S*,6a*R*)-6-((1*H*-pyrazol-3-yl)methoxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)-5-(4-fluorobenzylidene)-3-(3-hydroxyphenyl)thiazolidin-4-one (9f). IR (KBr): 3500, 1725, 1580, 1200, 1465, 1380, 1264 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.52–7.50 (m, 2H, Ar-H), 7.40 (d, *J* = 6.5 Hz, 1H, Ar-H), 7.18 (t, 1H, Ar-H), 7.14 (t, 2H, Ar-H), 7.07 (s, 1H, Ar-H), 6.92 (d, *J* = 6.4 Hz, 1H, Ar-H), 6.81 (s, 1H, =CH), 6.59 (d, *J* = 6.8 Hz, 1H, Ar-H), 6.25 (d, *J* = 6.2 Hz, 1H, Ar-H), 5.52 (d, *J* = 6.9 Hz, 1H, CH), 4.84 (dd, *J* = 5.4, 5.1 Hz), 4.74 (d, *J* = 4.7 Hz, 1H, CH), 4.56 (s, 2H, CH_2), 4.43 (m, 1H, CH), 4.20 (t, 1H, CH), 3.86 (s, 1H, OH), 1.54 (s, 6H, 2×CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.4, 163.7, 162.1, 158.8, 137.4, 135.0, 132.5, 132.3, 131.6, 122.4, 117.3, 115.8, 115.0, 112.5, 110.0, 106.1, 83.2, 81.2, 79.8, 72.8, 64.6, 26.3. MS: *m/z* (M^++Na) 560.01. Calculated for $C_{27}H_{26}FN_3O_6S$: C, 60.10; H, 4.86; N, 7.79. Found: C, 60.08; H, 4.84; N, 7.76.

(*E*)-2-((3a*R*,5*S*,6*S*,6a*R*)-6-((1*H*-pyrazol-3-yl)methoxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)-5-(4-fluorobenzylidene)-3-(4-hydroxyphenyl)thiazolidin-4-one (9g). IR (KBr): 3550, 1730, 1560, 1520, 1380, 1290, 1250, 1160 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.48–7.46 (m, 2H, Ar-H), 7.29 (d, *J* = 6.7 Hz, 2H, Ar-H), 7.14 (t, 2H, Ar-H), 6.84 (d, *J* = 7.5 Hz, 2H, Ar-H), 6.76 (s, 1H, =CH), 6.22 (d, *J* = 6.9 Hz, 1H, Ar-H), 5.54 (d, *J* = 5.9 Hz, 1H, CH), 4.84 (dd, *J* = 4.9, 4.7 Hz, 1H, CH), 4.74 (d, *J* = 4.9 Hz, 1H, CH), 4.66 (s, 2H, CH_2), 4.46 (m, 1H, CH), 4.20 (t, 1H, CH), 3.68 (s, 1H, OH), 1.54 (s, 6H, 2×CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.4, 163.7, 162.1, 157.7, 135.0, 132.5, 131.6, 128.4, 126.5, 122.4, 117.6, 115.0, 112.5, 106.1, 83.2, 81.3, 79.8, 72.8, 64.6, 26.3. MS: *m/z* (M^++H) 540.05. Calculated for $C_{27}H_{26}FN_3O_6S$: C, 60.10: H, 4.86; N, 7.79. Found: C, 60.08; H, 4.84; N, 7.76.

General procedure for the synthesis of compounds 10a–g. Compound **9a** (0.01 mol), sodium acetate (0.01 mol), and hydroxylamine hydrochloride (0.02 mol) were combined in 20 mL of anhydrous glacial acetic acid and refluxed for 8 hours. To obtain pure **10a** (87% yield) as a brown solid, the reaction mixture was concentrated and then put into ice-cold water. The resulting solid was then separated, filtered, and rinsed with ice water before crystallizing from ethanol: mp 245–248 °C.

5-((3a*R*,5*S*,6*S*,6a*R*)-6-((1*H*-pyrazol-3-yl)methoxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)-3-(4-fluorophenyl)-6-phenyl-3,3a,5,6-tetrahydrothiazolo[4,5-*c*]isoxazole (10a). IR (KBr): 3250, 1576, 1560, 1520, 1490, 1382, 1260, 1160, 980 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.44 (d, *J* = 4.8 Hz, 1H, Ar-H), 7.20–7.19 (m, 4H, Ar-H), 6.99 (t, 2H, Ar-H), 6.77 (t, 1H, Ar-H), 6.59 (dd, *J* = 5.4 Hz, 5.2 Hz, 2H, Ar-H), 6.45 (d, *J* = 5.3 Hz, 1H, CH), 6.28 (d, *J* = 5.9 Hz, 1H, Ar-H), 5.55 (d, *J* = 6.9 Hz, 1H, CH), 5.05 (d, *J* = 4.6 Hz, 1H, CH), 4.67 (s, 2H, CH_2), 4.36 (m, H, CH), 4.22 (m, 1H, CH), 4.20 (m, 1H, CH), 4.15 (d, *J* = 4.9 Hz, 1H, CH), 1.54 (s, 6H, 2×CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.3, 162. 1,138.5, 131.6, 129.9, 126.0, 115.2 (d, *J* = 8.2 Hz), 112.5, 106.1, 83.2, 82.5, 81.6, 81.3, 75.6, 67.7, 64.6, 26.3. MS: *m/z* (M^++Na) 559.05. Calculated for $C_{27}H_{27}FN_4O_5S$: C, 60.21; H, 5.05; N, 10.40. Found: C, 60.21; H, 5.05; N, 10.40.

5-((3a*R*,5*S*,6*S*,6a*R*)-6-((1*H*-pyrazol-3-yl)methoxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)-6-(4-chlorophenyl)-3-(4-fluorophenyl)-3,3a,5,6-tetrahydrothiazolo[4,5-*c*]isoxazole (10b). IR (KBr): 3200, 1540, 1420, 1382, 1350, 1264, 1162, 982, 790 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45 (d, *J* = 6.4 Hz, 1H, Ar-H), 7.27 (d, *J* = 5.2 Hz, 2H, Ar-H), 7.20 (d, *J* = 5.6 Hz, 2H, Ar-H), 7.02 (t, 2H, Ar-H), 6.58 (d, *J* = 5.4 Hz, 2H, Ar-H), 6.37 (d, *J* = 5.1 Hz, 1H, Ar-H), 6.27 (d, *J* = 5.8 Hz, 1H, CH), 5.01 (d, *J* = 5.9 Hz, 1H, CH), 4.65 (s, 2H, CH_2), 4.59 (d, *J* = 5.0 Hz, 1H, CH), 4.22–4.20 (m, 3H, CH), 4.15 (s, 1H, CH), 1.54 (s, 6H, 2×CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.3, 162.1, 136.7, 131.6, 130.4, 129.8, 127.1, 115.2 (d, *J* = 9.6 Hz), 112.5, 106.1, 83.2, 82.5, 81.6, 81.3, 75.6, 67.7, 64.6, 26.3. MS: *m/z* (M^++H) 573.04. Calculated for $C_{27}H_{26}ClFN_4O_5S$: C, 56.59; H, 4.57; N, 9.78. Found: C, 56.56; H, 4.55; N, 9.76.

5-((3a*R*,5*S*,6*S*,6a*R*)-6-((1*H*-pyrazol-3-yl)methoxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)-3-(4-fluorophenyl)-6-(4-nitrophenyl)-3,3a,5,6-tetrahydrothiazolo[4,5-*c*]isoxazoles (10c). IR (KBr): 2900, 1585, 1560, 1540, 1490, 1384, 1355, 1120, 976 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.09 (d, *J* = 5.8 Hz, 2H, Ar-H), 7.41 (d, *J* = 5.1 Hz, 1H, Ar-H), 7.20 (m, 2H, Ar-H), 6.99 (t, H, Ar-H), 6.86 (d, *J* = 5.8 Hz, 2H, Ar-H), 6.38 (d, *J* = 5.6 Hz, 1H, CH), 6.28 (d, *J* = 5.9 Hz, 1H, Ar-H), 5.53 (d, *J* = 6.5 Hz, 1H, CH), 5.05 (d, *J* = 6.7 Hz, 1H, CH), 4.89 (m, 1H, CH), 4.76 (s, 2H, CH_2), 4.22–4.20 (m, 2H, CH_2), 4.15 (s, 1H, CH), 1.54 (s, 6H, 2×CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.3, 162.1, 148.2, 144.5, 131.6, 129.9, 126.7, 124.9, 115.8 (d, *J* = 8.6 Hz), 112.5, 106.1, 83.2, 82.5, 81.6, 81.5, 75.6,

67.7, 64.6, 26.3. MS: *m/z* (M^++Na) 606.04. Calculated for $C_{27}H_{26}FN_5O_7S$: C, 55.57; H, 4.49; N,12.00. Found: C, 55.55; H, 4.46; N, 11.98.

5-((3a*R*,5*S*,6*S*,6a*R*)-6-((1*H*-pyrazol-3-yl)methoxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)-3-(4-fluorophenyl)-6-*ortho*-tolyl-3,3a,5,6-tetrahydrothiazolo[4,5-*c*]isoxazole (10d). IR (KBr): 2989, 1590, 1570, 1530, 1450, 1384, 1250, 1165, 994 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34 (d, *J* = 6.2 Hz, 1H, Ar-H), 7.19 (m, 2H, Ar-H), 7.07 (m, 2H, Ar-H), 6.99 (t, 2H, Ar-H), 6.76 (t, 1H, Ar-H), 6.50 (d, *J* = 6.4 Hz, 1H, Ar-H), 6.35 (d, *J* = 5.4 Hz, 1H, CH), 6.23 (d, *J* = 5.3 Hz, 1H, Ar-H), 5.50 (d, *J* = 4.7 Hz, 1H, CH), 5.0 (d, *J* = 4.3 Hz, 1H, CH), 4.69 (s, 2H, CH_2), 4.46 (m, 1H, CH), 4.22 (d, *J* = 4.9 Hz, 1H, CH), 4.20 (m, 1H, CH), 4.15 (d, *J* = 4.3 Hz, 1H, CH), 2.26 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.3, 162.1, 138.1, 135.7, 131.6, 129.9, 129.4, 127.9, 126.9, 125.7, 115.5 (d, *J* = 9.6 Hz), 112.5, 106.1, 82.5, 82.1, 81.6, 81.3, 75.9, 67.7, 64.6, 26.3, 17.4. MS: *m/z* (M^++Na) 578.03. Calculated for $C_{29}H_{29}FN_4O_5S$: C, 60.86; H, 5.29; N, 10.14. Found: C, 60.83; H, 5.27; N, 10.12.

5-((3a*R*,5*S*,6*S*,6a*R*)-6-((1*H*-pyrazol-3-yl)methoxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)-3-(4-fluorophenyl)-6-*para*-tolyl-3,3a,5,6-tetrahydrothiazolo[4,5-*c*]isoxazole (10e). IR (KBr): 1490, 1280, 1569, 2970, 1593, 1384, 1160, 1595, 986 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.44 (d, *J* = 6.3 Hz, 1H, CH), 7.20 (m, 2H, Ar-H), 7.06 (d, *J* = 5.3 Hz, 2H, Ar-H), 6.99 (m, 2H, Ar-H), 6.54 (d, *J* = 5.2 Hz, 2H, Ar-H), 6.45 (d, *J* = 5.4 Hz, 1H, Ar-H), 6.28 (d, *J* = 4.3 Hz, 1H, Ar-H), 5.55 (d, *J* = 4.8 Hz, 1H, CH), 5.04 (d, *J* = 4.2 Hz, 1H, CH), 4.67 (s, 2H, CH_2), 4.36 (m, 1H, CH), 4.22 (d, *J* = 4.4 Hz, 1H, CH), 4.20 (m, 1H, CH), 4.15 (d, *J* = 4.6 Hz, 1H, CH), 2.33 (s, 1H, CH), 1.54 (s, 6H, 2×CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.3, 162.1, 138.2, 135.7, 131.6, 131.4, 131.1, 125.7, 115.8 (d, *J* = 9.1 Hz), 112.5, 106.1, 83.2, 82.5, 81.6, 75.6, 67.7, 64.6, 26.3, 21.3. MS: *m/z* (M^++Na) 575.06. Calculated for $C_{28}H_{29}FN_4O_5S$: C, 60.86; H, 5.29; N, 10.14. Found: C, 60.84; H, 5.27; N, 10.11.

3-(5-((3a*R*,5*S*,6*S*,6a*R*)-6-((1*H*-pyrazol-3-yl)methoxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)-3-(4-fluorophenyl)-3,3a-dihydroisoxazolo[3,4-*d*]thiazol-6(5*H*)-yl)phenol (10f). IR (KBr): 3550, 1594, 1572, 1476, 1383, 1294, 1267, 1194, 964 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40 (d, *J* = 4.5 Hz, 1H, Ar-H), 7.20 (m, 2H, Ar-H), 7.02–6.99 (m, 2H, Ar-H), 6.36 (d, *J* = 5.2 Hz, 1H, Ar-H), 6.28 (d, *J* = 4.9 Hz, 1H, Ar-H), 6.26 (m, 1H, Ar-H), 6.20 (t, 1H, Ar-H), 6.12 (m, 1H, ArH), 5.50 (d, *J* = 4.9 Hz, 1H, CH), 5.05 (d, *J* = 5.7 Hz, 1H, CH), 4.72 (s, 2H, CH_2), 4.50 (m, 1H, CH), 4.28 (m, 2H, CH), 4.15 (s, 1H, CH), 3.88 (s, 1H, OH), 1.54 (s, 6H, 2×CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.3, 162.1, 160.1, 138.8, 133.7, 131.6, 131.4, 129.8 (d, *J* = 8.2 Hz), 118.1, 116.4, 115.6 (d, *J* = 8.6 Hz), 112.5, 111.4, 106.1, 83.2, 82.5, 81.6, 81.3, 75.6, 67.7, 64.6, 26.3. MS: *m/z* (M^++H) 555.03. Calculated for $C_{27}H_{27}FN_4O_6S$: C, 58.47; H, 4.91; N, 10.10. Found: C, 58.45; H, 4.90; N, 10.08.

4-(5-((3a*R*,5*S*,6*S*,6a*R*)-6-((1*H*-pyrazol-3-yl)methoxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)-3-(4-fluorophenyl)-3,3a-dihydroisoxazolo[3,4-*d*]thiazol-6(5*H*)-yl)phenol (10g). IR (KBr): 3500, 1564, 1550, 1530, 1383, 1294, 1284, 1167, 995 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45 (d, *J* = 5.8 Hz, 1H, Ar-H), 7.20 (m, 2H, Ar-H), 6.99 (t, 2H, Ar-H), 6.67 (d, *J* = 5.3 Hz, 2H, Ar-H), 6.45–6.43 (m, 2H, Ar-H), 6.28 (d, *J* = 4.8 Hz, 1H, Ar-H), 5.55 (d, *J* = 4.8 Hz, 1H, CH), 5.08 (d, *J* = 4.9 Hz, 1H, CH), 4.67 (s, 2H, CH_2), 4.37 (m, 1H, CH), 4.22 (d, *J* = 5.6 Hz, 1H, CH), 4.20 (m, 1H, CH), 4.15 (d, *J* = 5.3 Hz, 1H, CH), 3.63 (s, 1H, OH), 1.54 (s, 6H, 2×CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.3, 162.1, 157.9, 133.0, 131.6, 129.9 (d, *J* = 8.2 Hz), 127.1, 116.7, 115.8 (d, *J* = 8.6 Hz), 112.5, 106.1, 83.2, 82.5, 81.6, 75.6, 67.7, 64.6, 26.3; MS: *m/z* (M^++Na) 577.04. Calculated for $C_{27}H_{27}FN_4O_6S$: C, 58.47; H, 4.91; N, 10.10. Found: C, 58.47; H, 4.91; N, 10.10.

5. Conclusion

A series of novel hybrid heterocycles **10a–g** were synthesized and evaluated for potential nematicidal activity. Compounds **10b** and **10f** exhibited appreciable nematicidal activity at minimum concentrations.

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Conflict of intrest

Author declares no conflict of interest including suggested reviewers.

6. References

1. F. E. Bennani, L. Doudach, Y. Cherrah, Y. Ramli, K. Karrouchi, M. Ansar, M. E. Abbes Faouzi, *Bioorg. Chem.* **2020**, *97*, 103470. **DOI:** 10.1016/j.bioorg.2019.103470
2. R. Surendra Kumar, I. A. Arif, A. Ahmed, A. Idhayadhulla, *Saudi. J. Bio. Sci.* **2015**, *23*, 614–620. **DOI:** 10.1016/j.sjbs.2015.07.005
3. A. R. I. Morsy, S. H. Mahmoud, N. M. Abou Shama, W. Arafa, G. A. Yousef, A. A. Khalil, S. K. Ramadan, *RSC Adv.* **2024**, *14*, 27935–27947. **DOI:** 10.1039/D4RA04728A
4. M. U. Rehman, F. He, X. Shu, J. Guo, Z. Liu, S. Cao, S. Long, *Eur. J. Med. Chem.* **2025**, *282*, 117081. **DOI:** 10.1016/j.ejmech.2024.117081
5. L. Ravindar, S. A. Hasbullah, K. P. Rakesh, N. I. Hassan, *Eur.*

J.Pharm. Sci. **2023**, *183,* 106365.
DOI: 10.1016/j.ejps.2022.106365
6. H. G. Berhe, Y. S. Birhan, B. Y. Beshay, H. J. H Ariaya Hymete, A. A. Bekhit Berhe, *Bioorg. Med. Chem.* **2024**, *18*, 1–15.
DOI: 10.1186/s13065-023-01111-0
7. S. Lian, H. Su, B. X. Zhao, W. Y. Liu, L. W. Zheng, J. Y. Miao, *Bioorg. Med. Chem.* **2009**, 7085–7092.
DOI: 10.1016/j.bmc.2009.09.004
8. G. Tiwari, A. Khanna, R. Tyagi, V. K. Mishra, C. Narayana, R. Sagar. *Sci. Rep.* **2024**, *14*, 529.
DOI: 10.1038/s41598-023-50202-4
9. A. Scribner, S. Meitz, M. Fisher, M. Wyvratt, P. Leavitt, P. Liberator, A. Gurnett, C. Brown, J. Mathew, D. Thompson, D. Schmatz, T. Biftu, *Bioorg. Med. Chem. Lett,* **2008**, *18*, 5263–5267. **DOI:** 10.1016/j.bmcl.2008.08.063
10. S. Onca, M. Punar, H. Eracosy, *Chemotherapy*, **2004**, *50*, 98–100. **DOI:** 10.1159/000077810
11. C. V. Dave, M. C. Shukla, *Indian J. Chem,* **2000***, 39B,* 210–214.
12. M. N. Ghazzi, E. Perez, T. K. Antonucci, H. Driscoll, S. M. Hunang, B. W. Faja, *Diabetes*, **1997**, *46*, 433–439.
DOI: 10.2337/diab.46.3.433
13. U. Scmidt, R. Utz, A. Liberknecht, H. Griesser, B. Potzolli, J. Bahr, K. Wagner, P. Fischer, *Synthesis,* **1987**, 233–236.
14. M. V. Diurno, O. Mazzoni, A. A. Luzzo, A. Bolognese, *Il Farmaco*, **1992**, *52*, 237–245.
15. N. Ergene, G. Gapan, *Il Farmaco*, **1994**, *49*, 237–244.
16. J. S. Viswajanani, S. Ajay, S. Smita, K. Seema, P. Manisha, B. Pragya, M. Tarun, R. Ashok, K. Jagmohan, M. Anitha, *Arkivoc*, **2005**, 46–59.
17. H. Ueno, T. Oe, I. Snehiro, S. Nakamura, *US Patent*, **1997**, 5594116.
18. T. Previtera, M. G. Vigortia, M. Bisila, F. Orsini, F. Benetolla, G. Bombieri, *Eur. J. Med. Chem.* **1994**, *29*, 317–324.
DOI: 10.1016/0223-5234(94)90102-3
19. M. Y. Ebied, O. A. Fathallah, M. I. El-Zaheer, M. M. Kamel, W. A. Abdon, M. M. Anwer, *Bull. Fac. Pharm*, **1996**, *34*, 125–131.
20. R. K. Rawal, Y. S. Prabhakar, S. B. Katti, E. Declercq, *Bioorg. Med. Chem,* **2005**, *13*, 6771–6776.
DOI: 10.1016/j.bmc.2005.07.063
21. T. Kato, T. Ozaki, K. Tamura, *J. Med. Chem,* **1999**, *42*, 3134–3146. **DOI:** 10.1021/jm9900927
22. Y. Tanabe, G. Suzukamo, Y. Komuro, N. Imanishi, S. Morooka, M. Enomoto, M. Kojima, Y. Sanemistu, M. Mizutani, *Tetrahedron Lett*. **1991**, *32*, 379–382.
DOI: 10.1016/S0040-4039(00)92633-9
23. T. Kato, T. Ozaki, N. Ohi, *Tetrahedron Asymmetry*, **1999**, *10*, 3963–3968. **DOI:** 10.1016/S0957-4166(99)00441-3
24. Y. Adachi, Y. Suzuki, N. Homma, M. Fukazawa, K. Tamura, I. Nishie, O. Kurumaro, *Eur. J. Pharmacol*. **1999**, *367*, 267–274.
DOI: 10.1016/S0014-2999(98)00938-8
25. R. Ottana, E. Mazzon, L. Dugo, F. Monforte, F. Macari, L. Sautebin, D. De Luca, M. G. Vigorita, S. Alcaro, F. Orusto, *Eur. J. Pharmacol.* **2002**, *448*, 71–80.
DOI: 10.1016/S0014-2999(02)01888-5
26. T. Yanabe, H. Yamamoto, M. Murakami, K. Yanagi, Y. Kubota, H. Okumara, Y. Sanemistu, G. Suzukamo, *Chem. Soc. Perkin Trans*. **1995**, *17*, 935. **DOI:** 10.1039/p19950000935
27. Y. Kato, Y. Kita, M. Nisho, Y. Hirasawa, K. Ito, T. Yamanaka, Y. Motoyana, J. Seki, *Eur. J. Pharm.* **1999**, *384*, 197–202.
DOI: 10.1016/S0014-2999(99)00658-5
28. Y. Ali, M. S. Alam, H. Hamid, A. Hussain, A. Dulap, F. Hussain, S. Bano, C. Karbanda, *New J. Chem.* **2016**, *40*, 711–723.
DOI: 10.1039/C5NJ00078E
29. J. T. Desai, C. K. Desai, K. R. Desai, *J. Iran. Chem. Soc*, **2008**, *5*, 67–73. **DOI:** 10.1007/BF03245817
30. A. Burns, R. Jacoby, R. Levy. *Bri. J. Psychiatry*, **1990**, *157*, 72–94. **DOI:** 10.1192/bjp.157.1.86
31. Y. C Sung, H. A. Jin, D. H. Jae, K. K. Seung, Y. B. Ji, S. H. Sang, Y. S. Eun, S. K. Sang, R. K. Kwang, G. C. Hyae, K. C. Joong, *Bull. Kor. Chem. Soc.* **2003**, *24*, 1455–1464.
32. Y. S. Lee, S. M. Park, B. H. Kim, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1126–1128. **DOI:** 10.1016/j.bmcl.2008.12.103
33. J. F. Hansen, S. A. Stronge, *J. Heterocycl. Chem.* **1977**, *14*, 1289.
DOI: 10.1002/jhet.5570140734
34. T. K. Adhikari, A. Vasudeva, M. Girisha, *Indian J. Chem.* **2009***, 48B,* 430–437.
35. F. A. Ragab, N. M. Eid, H. A. Tawab, *Pharmazie*, **1997**, *52*, 926–929.
36. H. Kai, T. Ichiba, M. Tomida, H. Nakai, K. Morita, *J. Pest. Sci.* **2000**, *25*, 267–273. **DOI:** 10.1584/jpestics.25.267
37. V. V. Kachadia, M. R. Patel, S. H. Joshi, *J. Sci. I. R. Iran*, **2004**, *15*, 47–51.
38. M. Mączyński, M. Zimecki, E. Drozd-Szczygieł, S. Ryng, *Cell. Mol. Biol.Lett*, **2005**, *10*, 613–619.
39. N. K. Jacob, G. K. Nampurath, *Indian Drugs*, **2004**, *41*, 76–79.
40. U. L. B. Jayasinghe, B. M. M. Kumarihamy, A. G. D. Bandara, E. A. Vasquez, W. Karus, *Nat. Prod. Res.* **2003**, *17*, 259–262.
DOI: 10.1080/1057563021000060121
41. M. H. Xaki, D. Moran, D. Harries, *Am. J. Pub. Health*, **1982**, 72, 1391–1395. **DOI:** 10.2105/AJPH.72.12.1391
42. W. Noling, J. O. Becker, *J. Nematol.* **1994**, *26*, 573–586.
43. O. Yuji, N. Sengual, P. Eli, R. Uzi, Y. Zohara, S. Yitzhak, *Phytopathology*, **2000**, *90*, 710–715.
DOI: 10.1094/PHYTO.2000.90.7.710
44. J. Kagan, P. A. Kagan, H. E. Bushe, *J. Chem. Ecol*, **1984**, *10*, 1115–1122. **DOI:** 10.1007/BF00987517
45. H. Lis, N. Sharon, *Chem. Rev.* **1998**, *98*, 637–674.
DOI: 10.1021/cr940413g
46. C. R. Bertozzi, L. L. Kiessling, *Chem. Glycobiol. Sci.* **2001**, *291*, 2357–2364. **DOI:** 10.1126/science.1059820
47. K. Singh, R. Tyagi, V. K. Mishra, G. Tiwari, R. Sagar, *Syn. Open,* **2023**, *7*, 322–352.
48. C. Narayana, P. Kumari, R. Sagar, *Org. Lett.* **2018**, *20*, 4240–4244. **DOI:** 10.1021/acs.orglett.8b01656
49. S. G. Sampath Kumar, C. T. Campbell, C. Weier, K. Yarema, *J. Drug Future*. **2006**, *31*, 1099–1116.
DOI: 10.1358/dof.2006.031.12.1049173
50. P. Pouillart, I. Cerutti, G. Ronco, P. Villa, C. Chany, *Int. J. Cancer,* **1991***, 49*, 89–95. **DOI:** 10.1002/ijc.2910490117
51. P. Kumari, C. Narayana, S. Dubey, A. Gupta, R. Sagar, *Org. Biomol. Chem.* **2018**, *16*, 2049–2059.

52. P. Kumari, C. Narayana, G. Tiwari, R. Sagar: Glycohybrid molecules in medicinal chemsitry: present status and future prospective In Carbohydrates in drug discovery and development, Ed. V. K. Tiwari, *Elsevier*, **2020**, pp 451–479. **DOI:** 10.1016/B978-0-12-816675-8.00011-7
53. X. Cao, *Acta Pharm. Sin. B,* **2022**, *12*, 3783–3821. **DOI:** 10.1016/j.apsb.2022.05.020
54. A. Varki, *Glycobiology*, **1993**, *3*, 97–130. **DOI:** 10.1093/glycob/3.2.97
55. A. Srinivas, *Russ. J. Org. Chem.* **2025**, *61*, 527–534. **DOI:** 10.1134/S1070428024604382
56. A. Srinivas, *Russ. J. Org. Chem.* **2024**, *1*, 84–92.
57. A. Srinivas, *Res. J. Chem. Environ.* **2024**, *28,* 61–69. **DOI:** 10.25303/283rjce061069
58. A. Srinivas, *Russ. J. Org. Chem.* **2023**, *11*, 1940–1951. **DOI:** 10.1134/S107042802311012X
59. A. Srinivas, S. Rajitha, P. Suresh, *Russ. J. Gen. Chem.* **2023**, *5*, 1201–1209. **DOI:** 10.1134/S1070363223050213
60. A. Srinivas, S. Shamili. S. Kavitha, I. Farheen, *J. Heterocycl. Chem.* **2023**, *60*, 116–122. **DOI:** 10.1002/jhet.4568
61. P. A. Levene, G. M. Meyer, *J. Biol.Chem*, **1931**, *92*, 257–262. **DOI:** 10.1016/S0021-9258(18)76514-9
62. A. Srinivas, M. Sunitha, P. Karthik, G. Rajesh Kumar, K. Vasumathi Reddy, *J. Heterocycl. Chem.* **2018**, *55,* 1564–1573. **DOI:** 10.1002/jhet.3187
63. C. W. McBeth, G. B. Bergerson, *Phytopathology*, **1953**, *43*, 264.

Povzetek

Z reakcijo halkonskih derivatov *(E)*-2-((3a*R*,5*S*,6*S*,6a*R*)-6-((1*H*-pirazol-3-il)metoksi)-2,2-dimetiltetrahidrofuro[2,3-*d*][1,3]dioksol-5-il)-5-(4-fluorobenziliden)-3-feniltiazolidin-4-onov **9a**–**g** in hidroksilamin hidroklorida smo pripravili serijo 5-((3a*R*,5*S*,6*S*,6a*R*)-6-((1*H*-pirazol-3-il)metoksi)-2,2-ditiltetrahidrofuro[2,3-*d*][1,3]dioksol-5-il)-3-(4-fluorofenil)-6-fenil-3,3a,5,6-tetrahidrotiazolo[4,5-*c*]izoksazolov **10a**–**g**. Strukture novih spojin smo določili s pomočjo IR, NMR, MS in elementne analize. Za spojine **10a**–**g** smo določili tudi nematicidno aktivnost proti *Dietylenchus myceliophagus* in *Caenorhabditis elegans* ter ugotovili, da spojini **10b** and **10f** izkazujeta znatno aktivnost.