Synthesis and *In Vitro* Study of Hybrid Heterocyclic's as Potential Nematicidal Agents

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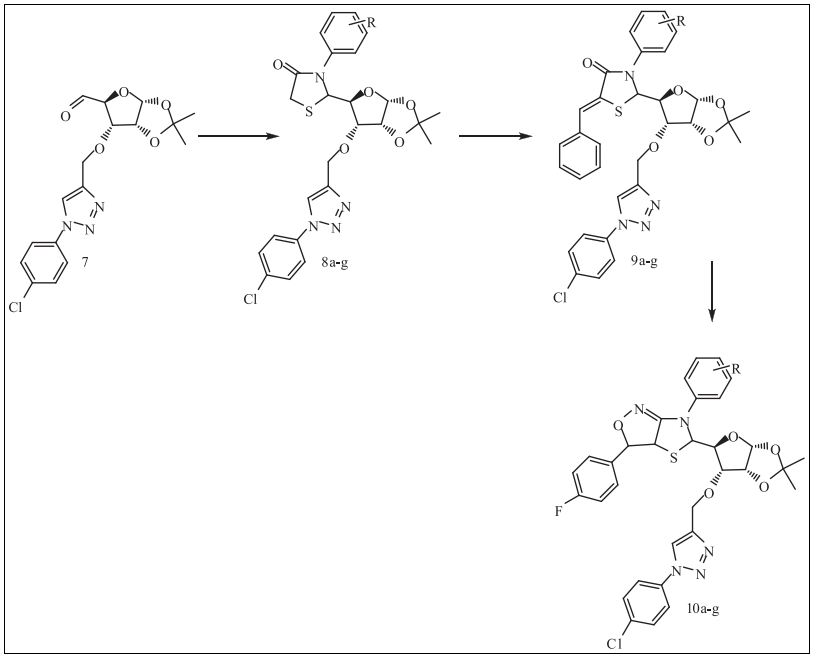


A series of novel 5-((3aR,5S,6S,6aR)-6-((1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)-3-(4-fluorophenyl)-6-phenyl-3,3a,5,6-tetrahydroisoxazolo [3,4-d]thiazoles **10a–g** were synthesized by the reaction of chalcone derivatives of 2-((3aR,5S,6S,6aR)-6-((1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)-3-phenylthiazolidin-4-one **9** with hydroxylamine hydrochloride. The chemical structures of newly synthesized compounds were elucidated by IR, NMR, MS, and elemental analysis. The compounds 10 a–g were evaluated for their nematicidal activity against Dietylenchus myceliophagus and *Caenorhabditis elegans*; compound **10e** and **10f** showed appreciable nematicidal activity. Further, the compounds **10a – g** were screened for their antifungal activity against *Candida albicans* (ATCC 10231), Aspergillus fumigates (HIC 6094), Trichophyton rubrum (IFO 9185), and Trichopyton mentagrophytes (IFO 40996). The compounds **10b** and **10f** displayed notable antifungal activity against all the microorganisms employed. The activity of these compounds is almost equal to the standard. It is also interesting to note that the compounds **10b** and **10f** and **10g** showed activity towards C. albicans at the concentration of 3.75 μM, which is less than the concentration of the standard Amphotericin B.

INTRODUCTION

1,2,3-Triazoles are one of the most important classes of heterocyclic organic compounds, which are reported to be present in a plethora of biological activities for diverse therapeutic areas [1]. The 1,2,3-triazole motif is associated with diverse pharmacological activities such as antibacterial, antifungal, hypoglycemic, antihypertensive, and analgesic properties. Polysubstituted five-membered aza heterocyclics rank the most potent glycosidase inhibitors [2]. Further, this nucleus in combination with or in linking with various other classes of compounds such as amino acids, steroids, aromatic compounds, and carbohydrates became prominent in having various pharmacological properties [3]. 1,2,3-Triazole modified carbohydrates have became easily available after the discovery of the Cu(I) catalyzed azide-alkynes 1,3-dipolar cycloaddition reaction [4] and quickly became a

prominent class of non-natural sugars. The chemistry and biology of triazole modified sugars are dominated by Triazole glycosides [5]. Therefore, the synthesis and investigation of biological activity of 1,2,3-triazole glycosides are important objectives, which also received considerable attention by medicinal chemists.

Thiazoles are familiar group of heterocyclic compounds possessing a wide variety of biological activities, and their utility as medicine is very much established [6]. Thiazole nucleus is also an integral part of all the available penicillins which have revolutionized the therapy of bacterial diseases [7]. Further, the chemistry of thiazolidenone ring system is one considerable interest as it is a core structure in various synthetic pharmaceuticals displaying a broad spectrum of biological activities [8]. The thiazolidenone nucleus also appears frequently in the structure of various natural products notably thiamine, compounds possessing cardiac and glycemic benefits such as troglitazone [9], and many metabolic products of fungi and primitive marine animals, including 2-(aminoalyl)-thiazole-4-carboxylic acids [10]. Numerous thiazolidenone derivatives have shown significant bio activities such as antidiarrhoeal [11], anticonvulsant [12], antimicrobial [13], antidiabetic [14], antihistaminic [15], anticancer [16], anti HIV [17], Ca^{+2} channel blocker [18], PAF antagonist [19], cardioprotective [20], antiischemic [21], COX inhibitory [22], antiplatelet activating factor [23], non-peptide thrombin receptor antagonist [24], tumor necrosis factor-α antagonist [25], and nematicidal activities. Moreover, isoxazole derivatives are an important class of bio active molecules, which exhibit significant activities such as anti fungal [26], Aβ precursor protein [27], protein thyrosine phosphatase 1B inhibitors [28], antiviral [29], antihelmintics [30], anti inflammatory [31], anticonvulsant [32], insecticidal [33], antitubercular [34], immunomodulatory [35], and hypolipermics [36].

Nematodes are tiny worms, some of them are plant parasites, and can play an important role in the predisposition of the host plant to the invasion by secondary pathogens [37]. Plants attacked by nematodes show retarded growth and development, as well as loss in the quality and quantity of the harvest. The nematicide use is slated for reduction due to environmental problems, and human and animal health concern. For example, effective nematicides such as dibromochloropropane (DBCD) and ethylene dibromide (EDB) have been withdrawn from the market due to their deleterious effects on human and the environment. Methyl bromide, the most effective and widely used fumigant for soil borne pests including nematodes, has already been banned.

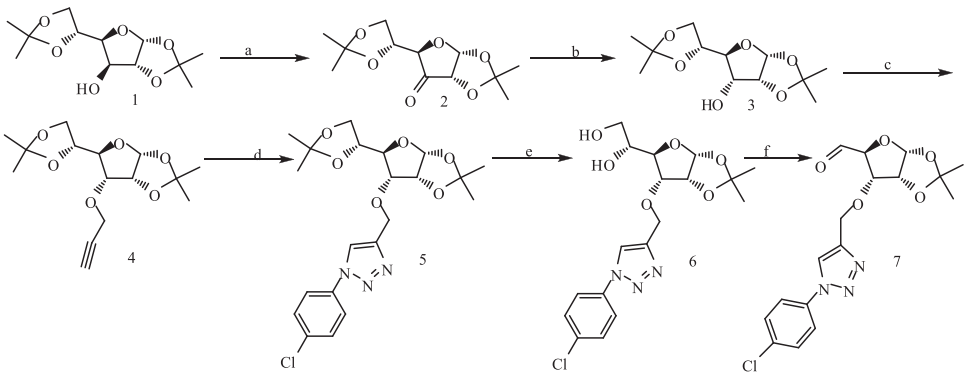
The use of nonfumigant nematicides, based on organophosphates and carbamates, is expected to increase the withdrawal of methyl bromide, which will bring about new environmental concerns. In fact, the highly toxic Aldicarb used to control insects and nematodes has been detected in ground water [38]. Therefore, alternative nematode control methods or less toxic nematicides need to be developed [39]. One way of searching for such nematicidal compounds is to screen naturally occurring compounds in plants. Several such compounds, e.g. alkaloids, phenols, sesquiterpenes, diterpenes, polyacetylenes, and thienyl derivatives, have nematicidal activity [40]. For example, *α*-terthienyl is a highly effective nematicidal compound [41]. Other compounds with nematicidal activity have been isolated from plants, mainly from the family *Asteraceae* [40]. However, compounds of plant origin and their analogs have not been developed into commercial nematicides; hence, there is a need to develop commercial synthesis.

Following the successful introduction of antimicrobial and nematicidal agents, inspired by the biological profile of triazoles, thiazolidinones, isoxazoles, and their increasing importance in pharmaceutical and biological fields and in continuation of our work on biological active molecules [42–55] and in order to enhance the biological activity of triazoles, thiazolidinones and isoxazoles moieties, it was thought to interest to accommodate triazole, thiazolidinones, and isoxazoles moieties in single molecular framework. In this article, we wish to report the synthesis of a new class of hybrid heterocyclics **10a–g** in good yields and their evaluated in *vitro* antifungal and nematicidal activity.

RESULTS AND DISCUSSION

The key intermediate, **8**, required for the synthesis of title compound was prepared according to the procedure outlined in the Scheme 1. Di acetone D-glucose **(1)** prepared from D (+)-glucose by treating with acetone in the presence of catalytic amount of sulfuric acid according to the literature procedure [56], reduction of **2** prepared by Swern oxidation of **1**, with $NaBH_4$ in aq. ethanol at 0°C for 1 h gave **3** (77%), which on subsequent propargylation in DMF in the presence of NaH for 1 h afforded propargyl ether **4** (80%). Now, the propargyl ether converted into triazole 5 (82%) by using 1,3-dipolar cycloaddition with p-chloro phenyl azide was 4carried out at ambient temperature in the presence of $CuSO_4$ and sodium ascorbate in a mixture of 1:1 t-BuOH–H_2O as reported by Sharpless. Acid hydrolysis of 5,6 acetonide 5 in 60% AcOH furnished the diol 6 (85%), which on oxidative cleavage with $NaIO_4$ gave the aldehyde 7. Subsequently, one-pot synthesis of triazole linked thiazolidenone glycosides was carried out by the condensation reaction between **7**, primary aromatic amine and a thio glycolic acid in the presence of $ZnCl_2$ under microwave irradiation/conventional

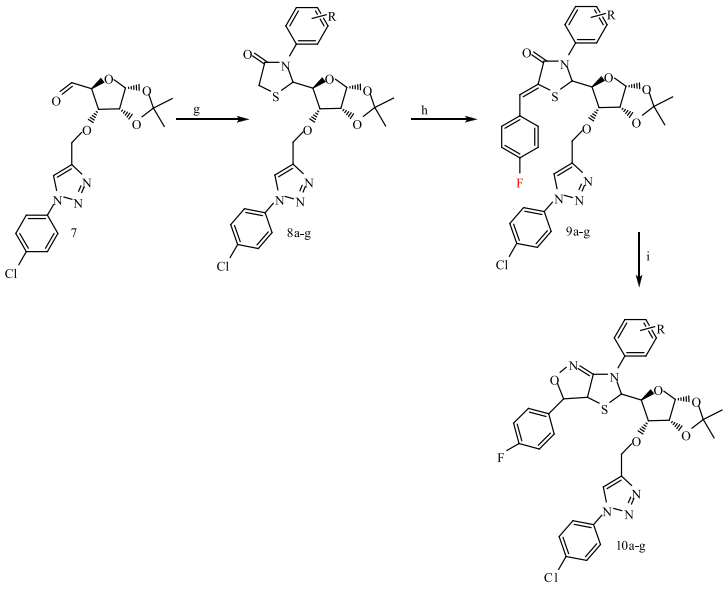
Scheme 1. Synthesis of compound **7**.



heating (Scheme 2). In classical method, the reactions were performed in dry toluene at reflux for a long time (2–4 h), often leading to degradation processes and consequent low yields of isolated products, whereas with the application of microwave-assisted technology, the reaction is completed in only 5–10 min, and the compounds, isolated by conventional workup, are obtained in satisfactory yields, often higher than those achieved by traditional methods [42]. Compound 8 was then reacted with *p*-fluorobenzaldehyde in the presence of anhydrous NaOAc in glacial AcOH at reflux temperature gave chalcone derivatives of triazole linked thiazolidenone glycosides **9**. Compound **9** on cyclocondensation with hydroxyl amine hydrochloride in the presence of anhydrous NaOAc in glacial AcOH at reflux temperature gave Compound **10**. The structures of synthesized compounds were confirmed by IR, NMR, MS, and elemental analysis. Further, the compounds were subject to nematicidal and antibacterial testing.

Antifungal activity. The newly prepared compounds **10a–g** were screened for their antifungal activity against four fungal organisms *viz Candida albicans* (ATCC 10231), *Aspergillus fumigates* (HIC 6094), *Trichophyton rubrum* (IFO 9185), and *Trichophyton mentagrophytes*

Scheme 2. Synthesis of compound **10a–g**. [Color figure can be viewed at wileyonlinelibrary.com]



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.

Reagents and conditions： a) $COCl_2$, CH_2Cl_2, Et_3N, - 78 °C-rt, 1.5h, 83% ; b) $NaBH_4$, EtOH, H_2O, (19:1), 0 °C -rt , 78%; c) Propargyl bromide, NaH, DMF, 0 °C –rt; d) P-Chloro phenyl azide, Sodium ascorbate, $CuSO_4.5H_2O$, t -BuOH/H_2O, 0 °C -rt , 75% ; e) 60%, AcOH, rt , 69% ; f) $NaIO_4$, CH_2Cl_2 , 0 °C –rt, 75% ; g) Ar-NH_2 ,$SHCH_2COOH$, $ZnCl_2$, Toluene , 80 °C , 85% ; h) 4-F- C_6H_4-CHO, AcOH /NaOAc, reflux, 82-88%; i) $NH_2OH.HCl$, AcOH /NaOAc reflux, 78- 84%.

(IFO 40996) by the broth dilution method, recommended by the National Committee for Clinical Laboratory Standards (NCCLS) [57]. The antifungal activity of each compound was compared with the standard drug Amphotericin B. Minimum inhibitory concentration (MIC, μM) was measured and compound with controls; the MIC values of the compounds screened are presented in Table 1.

The antifungal screening data showed moderate activity of the test compounds, among the screened **10b**, **10f**, **and 10g** in which isoxazole moiety bearing p-fluoro phenyl and p-chloro phenyl nucleus, 3-hydroxy, and 4-hydroxy phenyl nucleus on nitrogen in thiazole moiety, respectively, showed high activity against all the microorganisms employed. The activity of these three compounds is almost equal to standard. It is also interesting to note that the compounds **10b, 10f,** and **10g** showed activity towards *C. albicans* at the concentration of 3.75 μM, which is less than the concentration of the standard Amphotericin B. The remaining compounds in which isoxazole moiety bearing p-chloro phenyl and phenyl nucleus, 4-NO_2, 2-methyl, and 4-methyl nucleus in thiazole moiety showed moderate to good antifungal activity (Table 1**)**.

Nematicidal activity. The compounds synthesized 10a–g in this study were also screened for their nematicidal activity against *Dietylenchus myceliophagus* and *Caenorhabditis elegans* by aqueous *in vitro* screening technique [58] at various concentrations. The nematicidal activity of each test compound was compared with the standard drug *Levamisole.* The results have been expressed in terms of LD_{50}, i.e. median lethal dose at which 50% nematodes became immobile (dead). The screened data reveal that, compounds **10e** and **10f** in which isoxazole moiety bearing p-fluoro phenyl and 4-methyl and 3-hydroxy phenyl nucleus on nitrogen in thiazole moiety are the most effective against *D. myceliophagus* and *C. elegans* with LD_{50} 190 and 220 × 10^{-6} respectively; the other test compounds showed moderate activity. The LD_{50} values of the test compounds screened are presented in Table 1.

EXPERIMENTAL

Commercial grade reagents were used as supplied. Solvents except analytical reagent grade were dried and purified according to literature when necessary. Reaction progress and purity of the compounds were checked by thin-layer chromatography (TLC) on pre-coated silica gel F254 plates from Merck and compounds visualized either by exposure to UV light or dipping in 1% aqueous potassium permanganate solution. Silica gel chromatographic columns (60–120 mesh) were used for separations. Optical rotations were measured on a Perkin-Elmer 141 polarimeter by using a 2-mL cell with a path length of 1 dm with $CHCl_3$ or $CDCl_3$ as solvent. All melting points are uncorrected and measured using Fisher–Johns apparatus. IR spectra were recorded as KBr disks on a Perkin-Elmer FT IR spectrometer. The ^{1}HNMR and ^{13}C NMR spectra were recorded on a Varian Gemini spectrometer (300 MHz for ^{1}H and 75 MHz for^{13}C). Chemical shifts are reported as δ ppm against TMS as internal reference and coupling constants *(J)* are reported in Hz units. Mass spectra were recorded on a VG micro mass 7070H spectrometer. Elemental analyses (C, H, N) determined by a Perkin-Elmer 240 CHN elemental analyzer were within ±0.4% of theoretical.

(Z)-2-((3aR,5S,6S,6aR)-6-((1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)-5-(4-fluorobenzylidene)-3-phenylthiazolidin-4-one (9a). A mixture of compound **8a** (0.01 mol), *p*-fluoro benzaldehyde (0.02 mol), and sodium acetate (0.01 mol) in anhydrous glacial acetic acid (20 mL) was refluxed for 3 h. The reaction mixture was concentrated and then poured into ice cold water; the

Table 1

Antibacterial and nematicidal activity of 10 a–g.

	Antifungal activity Minimum inhibitory concentration (MIC, μg/mL)				Nematicidal activity	
					D. myceliophagus	*C. elegans*
Compound	*C. albicans*	*A. fumigatus*	*Trichophyton rubrum*	*Trichophyton mentagrophytes*	*LD 50 values*	
10a	30.0	60.0	30.0	60.0	790	760
10b	3.75	3.75	3.75	3.75	850	770
10c	15.0	30.0	30.0	7.50	560	360
10d	7.50	30.0	—	15.0	600	550
10e	15.0	15.0	7.50	7.50	190	240
10f	3.75	3.75	3.75	3.75	270	220
10g	3.75	3.75	3.75	3.75	950	870
Amphotericin B	7.50	3.75	3.75	3.75	—	—
Levamisole	—	—	—	—	160	180

solid thus separated, was filtered, washed with water, and crystallized from glacial acetic acid. To afford pure **9a** (83% yield) as yellow solid 225–228°C; IR (KBr) ν 3438, 3228, 2982, 2972, 2940, 2831, 1712, 1610, 1532, 1516, 1418, 1218, 683 cm^{-1} ^{1}HNMR (300 MHz, DMSO-d_6): δ 8.04 (s,1H,Ar—H), 7.80 (s, 1H, CH═C), 7.51 (d, J = 9.2 Hz, 2H, Ar—H), 7.42 (d, J = 8.9 Hz, 2H,Ar—H), 7.32–7.12 (5H, m, Ar –H), 6.91–6.87 (m, 5H, Ar—H + CH-S), 5.74 (d, J = 3.6 Hz,1H, C_1H), 4.60 (t, J = 3.9 Hz,1H, C_2H), 4.50 (s, 2H, OCH_2), 3.96–3.93 (m, 1H,C_4H), 3.30 (dd, J = 9.1,4.2 Hz, 1H, C_3H), 1.53 (s, 3H,CH_3), 1.31 (m, 3H,CH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 171.6, 144.2, 141.2, 138.6, 134.8, 134.2, 128.9, 128.2, 127.4,124.6, 122.2, 119.6, 119.2, 104.8, 81.2, 78.5, 74.4, 66.9, 52.0,26.5; MS: m/z (M^+ + Na) 617.10. *Anal.* Calcd for $C_{32}H_{29}ClN_4O_5S$: C, 62.28; H, 4.74; N, 9.08. Found: C, 61.53; H, 4.65; N, 9.03.The other compounds **9b–g** were also prepared by the similar procedure.

(Z)-3-(4-chlorophenyl)-2-((3aR,5S,6S,6aR)-6-((1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)-5-(4-fluorobenzylidene)thiazolidin-4-one (9b). The compound was obtained as dark yellow solid: mp 232–235°C; IR (KBr) ν 3432, 3226, 2981, 2969, 2822, 1714, 1610, 1535, 1510, 1409, 1216, 686 cm^{-1}; ^{1}HNMR (300 MHz, DMSO-d_6): δ 8.06 (s,1H, Ar—H), 7.82 (s, 1H, CH═C), 7.52 (d, J = 9.2 Hz, 4H, Ar—H), 7.43 (d, J = 8.9 Hz, 4H,Ar—H), 6.91–6.87 (m, 5H, Ar—H + CH-S), 5.72 (d, J = 3.6 Hz,1H, C_1H), 4.60 (t, J = 3.9 Hz,1H, C_2H), 4.51 (s, 2H, OCH_2), 3.96–3.91 (m, 1H,C_4H,), 3.31 (dd, J = 9.1,4.2 Hz, 1H, C_3H), 1.55 (s, 3H,CH_3), 1.32 (m, 3H,CH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 170.6, 138.4, 134.8, 133.2,130.8, 129.4,128.6, 124.6, 122.2, 119.4, 111.2, 104.9, 81.5, 74.5, 66.3, 52.6, 34.6, 26.5; MS: m/z (M^+ + H) 669.10. *Anal.* Calcd for $C_{32}H_{27}Cl_2FN_4O_5S$: C, 57.40; H, 4.06; N, 8.37. Found: C, 57.21; H, 4.01; N, 8.03.

(Z)-2-((3aR,5S,6S,6aR)-6-((1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)-5-(4-fluorobenzylidene)-3-(4-nitrophenyl)thiazolidin-4-one (9c). The compound was obtained as brown solid: mp 216–218°C; IR (KBr) ν 3432, 3226, 2982, 2971, 2830, 1710, 1608, 1536, 1512, 1414,1374, 1216, 865, 632 cm^{-1}; ^{1}HNMR (300 MHz, DMSO-d_6): δ 8.26 (d, J = 8.7 Hz, 2H), 8.04 (s,1H,Ar—H), 7.84 (s, 1H, CH═C), 7.51 (d, J = 9.2 Hz, 2H, Ar—H), 7.42 (d, J = 8.5 Hz, 2H,Ar—H), 6.91–6.87 (m, 5H, Ar—H + CH-S), 6.82 (d, J = 9.8 Hz, 2H, Ar—H), 5.71 (d, J = 3.6 Hz,1H, C_1H), 4.62 (t, J = 3.9 Hz,1H, C_2H), 4.53 (s, 2H, OCH_2), 3.96–3.91 (m, 1H,C_4H), 3.76 (s, 2H, CH_2), 3.28 (dd, J = 9.1,4.2 Hz, 1H, C_3H), 1.52 (s, 3H,CH_3), 1.34 (m, 3H,CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.6, 147.5, 144.4, 143.2,138.4, 134.8,130.6, 131.2,128.6, 124.6, 122.4, 119.8, 111.8, 104.9, 81.5, 78.2, 74.8, 66.9, 52.4, 26.8; MS: m/z (M^+ + Na) 692.10. *Anal.* Calcd for $C_{31}H_{29}ClFN_5O_7S$: C, 55.56; H, 4.36; N, 10.30. Found: C, 55.26; H, 4.29; N, 10.10.

(Z)-2-((3aR,5S,6S,6aR)-6-((1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)-5-(4-fluorobenzylidene)-3-o-tolylthiazolidin-4-one (9d). This compound was obtained as brown solid. mp 201–203°C;IR (KBr) ν 3432, 3236, 2982, 2972, 2830, 1710, 1705,1610, 1548, 1514, 1418, 1260, 865 cm^{-1}; ^{1}HNMR (300 MHz, DMSO-*d6*): δ 8.23 (d, J = 8.7 Hz, 2H, Ar—H), 8.04 (s,1H,Ar—H), 7.84 (s, 1H, CH═C), 7.54 (d, J = 9.2 Hz, 2H, Ar—H), 7.45–6.82 (m, 4H, Ar—H), 6.91–6.87 (m, 5H, Ar—H + CH-S), 5.74 (d, J = 3.6 Hz,1H, C_1H), 4.62 (t, J = 3.9 Hz,1H, C_2H), 4.54 (s, 2H, OCH_2), 3.96–3.91 (m, 1H,C_4H), 3.26 (dd, J = 9.1,4.2 Hz, 1H, C_3H), 2.1 (s, 3H,CH_3) 1.53 (s, 3H,CH_3), 1.36 (m, 3H,CH_3); ^{13}C NMR (75 MHz, DMSO-*d6*): δ 170.6, 144.6, 138.7, 134.8,134.3, 130.6, 129.4, 128.6, 125.8,125.6,122.6, 119.8, 111.6, 104.8, 81.7, 78.6, 74.7, 66.5, 52.4, 26.6,16.5; MS: m/z (M^+ + H) 636.10. *Anal.* Calcd for $C_{32}H_{30}ClFN_4O_5S$: C, 61.06; H, 4.66; N, 8.63. Found: C, 60.86; H, 4.59; N, 8.61.

(Z)-2-((3aR,5S,6S,6aR)-6-((1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)-5-(4-fluorobenzylidene)-3-p-tolylthiazolidin-4-one (9e). This compound was obtained as brown solid. mp 231–235°C; IR (KBr) ν 3428, 3230, 2986, 2976, 2832, 1708, 1698,1608, 1538, 1514, 1416, 1261, 859 cm^{-1}; ^{1}HNMR (300 MHz, $CDCl_3$): δ 8.22 (d, J = 8.7 Hz, 2H, Ar—H), 8.06 (s,1H,Ar—H), 7.84 (s, 1H, CH═C), 7.54 (d, J = 9.2 Hz, 2H, Ar—H), 7.39 (d, J = 8.33 Hz, 2H, Ar—H), 7.15 (d, J = 8.3 Hz, 2H, Ar—H), 6.91–6.87 (m, 5H, Ar—H + CH—S), 5.76 (d, J = 3.6 Hz,1H, C_1H), 4.66 (t, J = 3.9 Hz,1H, C_2H), 4.54 (s, 2H, OCH_2), 3.96–3.91 (m, 1H,C_4H), 3.26 (dd, J = 9.1,4.2 Hz, 1H, C_3H), 2.3 (s, 3H,CH_3) 1.53 (s, 3H, CH_3), 1.36 (m, 3H,CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.6, 143.2, 137.4, 133.6,132.3, 131.2, 128.4, 127.9, 124.8,122.9, 119.2, 111.2, 103.8, 81.2, 78.1, 74.1, 65.9, 51.4, 26.1,16.1; MS: m/z (M^+ + H) 649.10. *Anal.* Calcd for $C_{33}H_{30}ClFN_4O_5S$: C, 61.06; H, 4.66; N, 8.63. Found: C, 60.82; H, 4.45; N, 8.43.

(Z)-2-((3aR,5S,6S,6aR)-6-((1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)-5-(4-fluorobenzylidene)-3-(3-hydroxyphenyl)thiazolidin-4-one (9f). This compound was obtained as gray solid. mp 218–221°C; IR (KBr) ν 3533, 3424, 3230, 2982, 2970, 2831, 1710, 1614, 1537,1514, 1416, 1260, 864 cm^{-1}; ^{1}HNMR (300 MHz, DMSO – d_6): δ 8.24 (d, J = 8.7 Hz, 2H, Ar—H), 8.03 (s,1H,Ar—H), 7.80 (s, 1H, CH═C), 7.56 (d, J = 9.2 Hz, 2H, Ar—H), 7.14–6.70 (m, 4H,Ar—H), 6.91–6.87 (m, 5H, Ar—H + CH—S), 5.76 (d, J = 3.6 Hz,1H, C_1H), 5.40 (s, 1H, OH), 4.66 (t, J = 3.9 Hz,1H, C_2H), 4.54 (s, 2H,

OCH_2), 3.93–3.96 (m, 1H,C_4H), 3.26 (dd, J = 9.1,4.2 Hz, 1H, C_3H), 1.53 (s, 3H,CH_3), 1.38 (m, 3H,CH_3); ^{13}C NMR (75 MHz, DMSO – d_6): δ 171.6, 158.3, 144.2, 143.2, 138.2, 134.6, 134.4, 130.6, 128.6,124.6, 122.2, 120.1, 119.4, 114.6, 111.8, 107.6,106.8, 81.8, 78.6, 74.8, 64.9, 54.9, 41.1; MS: m/z (M^+ + Na) 673.20. *Anal.* Calcd for $C_{32}H_{28}ClFN_4O_6S$: C, 59.03; H, 4.33; N, 8.60. Found: C, 58.82; H, 4.15; N, 8.49.

(Z)-2-((3aR,5S,6S,6aR)-6-((1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)-5-(4-fluorobenzylidene)-3-(4-hydroxyphenyl)thiazolidin-4-one (9g). This compound was as dark yellow solid. mp 283–285°C;IR (KBr) ν 3539, 3421, 3230, 2985, 2978, 2831, 1710, 1612, 1543,1516, 1412, 1252, 861 cm^{-1}; ^{1}HNMR (300 MHz, $CDCl_3$): δ 8.22 (d, J = 8.7 Hz, 2H, Ar—H), 8.06 (s,1H,Ar—H), 7.83 (s, 1H, CH═C), 7.54 (d, J = 9.2 Hz, 2H, Ar—H), 7.10–6.70 (m, 4H,Ar—H), 6.91–6.89 (m, 5H, Ar—H + CH—S), 5.76 (d, J = 3.6 Hz,1H, C_1H), 5.28 (s, 1H, OH), 4.65 (t, J = 3.9 Hz,1H, C_2H), 4.52(s, 2H, OCH_2), 3.91–3.94 (m, 1H,C_4H), 3.34 (dd, J = 9.1,4.2 Hz, 1H, C_3H), 1.52 (s, 3H,CH_3), 1.36 (m, 3H,CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.2, 157.8, 143.8, 143.2, 133.9, 133.4, 130.2, 127.6, 121.9, 120.5, 1198.8, 114.2, 111.2, 106.8, 81.4, 78.2, 73.8, 62.9, 54.2, 40.9, 34.9; MS: m/z (M^+ + H) 651.20. *Anal.* Calcd for $C_{32}H_{28}ClFN_4O_6S$: C, 59.03; H, 4.32; N, 8.59. Found: C, 58.72; H, 4.29; N, 8.42.

5-((3aR,5S,6S,6aR)-6-((1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)-3-(4-fluorophenyl)-6-phenyl-3,3a,5,6-tetrahydroisoxazolo[3,4-d]thiazole (10a). A mixture of compound 9a (0.01 mol), hydroxyl amine hydrochloride (0.02 mol) and sodium acetate (0.01 mol) in anhydrous glacial acetic acid (20 mL), was refluxed for 8 h.The reaction mixture was concentrated and then poured into ice cold water, the solid thus separated, was filtered, washed with ice water, and crystallized from ethanol to afford pure **10a** (87% yield) as brown solid: mp 255–258°C; IR (KBr) ν 3478, 3238, 2982, 2972, 2940, 2831, 1712, 1600, 1570, 1516, 1418, 1218, 683 cm^{-1} ^{1}HNMR (300 MHz, DMSO-d_6): δ 8.04 (s,1H,Ar—H), 7.51 (d, J = 9.2 Hz, 2H, Ar—H), 7.45 (s, 1H, CH—N), 7.40 (d, J = 8.9 Hz, 2H,Ar—H), 7.32–7.12 (5H, m, Ar –H), 6.91–6.87 (m, 4H, Ar—H), 5.78 (d, J = 3.6 Hz,1H, C_1H), 5.70 (d, J = 2.2 Hz, 1H, CH—O), 4.69 (d, J = 2.2 Hz,1H, CH—S), 4.60 (t, J = 3.9 Hz,1H, C_2H), 4.50 (s, 2H, OCH_2), 3.96–3.93 (m, 1H,C_4H), 3.30 (dd, J = 9.1,4.2 Hz, 1H, C_3H), 1.53 (s, 3H,CH_3), 1.31 (m, 3H, CH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 171.6,164.0,161.8, 144.2, 141.2, 136.2, 138.6, 134.8, 134.2, 128.9, 128.2, 127.4,124.6, 122.2, 119.6, 119.2,115.7, 104.8, 81.2, 78.5,71.8, 74.4, 66.9, 52.0,40.1, 26.5; MS: m/z (M^+ + Na) 672.10. *Anal.* Calcd for $C_{32}H_{29}ClFN_5O_5S$: C, 59.12; H, 4.50; N, 10.77. Found: C, 58.83; H, 4.35; N, 10.43.The other compounds **10b–g** were also prepared by the similar procedure.

6-(4-chlorophenyl)-5-((3aR,5S,6S,6aR)-6-((1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)-3-(4-fluorophenyl)-3,3a,5,6-tetrahydroisoxazolo[3,4-d]thiazole (10b). The compound was obtained as dark yellow solid mp 242–245°C; IR (KBr) ν 3482, 3233, 2980, 2972, 2942, 2821, 1714, 1600, 1572, 1518, 1416, 1212, 681 cm^{-1} ^{1}HNMR (300 MHz, DMSO-d_6): δ 8.04 (s,1H,Ar—H), 7.53 (d, J = 9.2 Hz, 2H, Ar—H), 7.42 (s, 1H, CH—N), 7.30 (d, J = 8.9 Hz, 2H,Ar—H), 7.22–7.12 (4H, m, Ar –H), 6.91–6.87 (m, 4H, Ar—H), 5.78 (d, J = 3.6 Hz,1H, C_1H), 5.70 (d, J = 2.2 Hz, 1H, CH—O), 4.69 (d, J = 2.2 Hz,1H, CH—S), 4.60 (t, J = 3.9 Hz,1H, C_2H), 4.50 (s, 2H, OCH_2), 3.96–3.93 (m, 1H,C_4H), 3.30 (dd, J = 9.1,4.2 Hz, 1H, C_3H), 1.53 (s, 3H,CH_3), 1.31 (m, 3H,CH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 171.6,164.0,161.8,144.2, 141.2, 136.2, 138.6, 134.8, 134.2,129.6,128.9,128.2, 127.4,126.1,124.6, 122.2, 119.6, 119.2,117.5,115.7, 104.8, 81.2, 78.5,71.8, 74.4, 66.9, 52.0,40.1, 26.5; MS: m/z (M^+ + Na) 672.10. *Anal.* Calcd for $C_{32}H_{28}Cl_2FN_5O_5S$: C, 56.14; H, 4.12; N, 10.23. Found: C, 56.03; H, 4.05; N, 10.13.

5-((3aR,5S,6S,6aR)-6-((1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)-3-(4-fluorophenyl)-6-(4-nitrophenyl)-3,3a,5,6-tetrahydroisoxazolo[3,4-d]thiazole (10c). The compound was obtained as red solid. mp 251–255°C; IR (KBr) ν 3484, 3237, 2985, 2974, 2944, 2825, 1714, 1600, 1572,1535, 1518, 1416, 1215, 681 cm^{-1} ^{1}HNMR (300 MHz, DMSO-d_6): δ 8.04 (s,1H,Ar—H), 7.56 (d, J = 9.2 Hz, 2H, Ar—H), 7.44 (s, 1H, CH—N), 7.30 (d, J = 8.9 Hz, 2H,Ar—H), 7.22–7.12 (4H, m, Ar –H), 6.91–6.87 (m, 4H, Ar—H), 5.78 (d, J = 3.6 Hz,1H, C_1H), 5.72 (d, J = 2.2 Hz, 1H, CH—O), 4.70 (d, J = 2.2 Hz,1H, CH—S), 4.60 (t, J = 3.9 Hz,1H, C_2H), 4.50 (s, 2H, OCH_2), 3.96–3.93 (m, 1H,C_4H), 3.30 (dd, J = 9.1,4.2 Hz, 1H, C_3H), 1.53 (s, 3H,CH_3), 1.31 (m, 3H,CH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 171.4,163.0,161.8,143.2, 140.2, 135.2, 134.6,134.2,129.6,128.6,128.2, 127.6,126.1,124.4, 122.2, 119.5, 119.0,117.2,115.3, 104.5, 81.7, 78.2,71.7, 74.1, 66.9, 52.0,40.1, 26.5; MS: m/z (M^+ + Na) 695.10. *Anal.* Calcd for $C_{32}H_{28}ClFN_6O_7S$: C, 55.29; H, 4.06; N, 12.09. Found: C, 55.03; H, 3.95; N, 11.83.

5-((3aR,5S,6S,6aR)-6-((1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)-3-(4-fluorophenyl)-6-o-tolyl-3,3a,5,6-tetrahydroisoxazolo[3,4-d]thiazole (10d). The compound was obtained as yellow solid. mp 189–193°C;IR (KBr) ν 3428, 3231, 2980, 2970, 2820, 1710, 1705,1600, 1548, 1510, 1418, 1250, 862 cm^{-1}; ^{1}HNMR (300 MHz, DMSO-*d6*): δ 8.23 (d, J = 8.7 Hz, 2H, Ar—H), 8.04 (s,1H,Ar—H), 7.54 (d, J = 9.2 Hz, 2H, Ar—H), 7.45 (s, 1H, CH—N), 7.25–6.82 (m, 4H, Ar—H), 6.91–6.87 (m, 4H, Ar—H),

5.72 (d, J = 2.2 Hz, 1H, CH—O), 5.68 (d, J = 2.2 Hz, 1H, S—CH), 5.64 (d, J = 3.6 Hz,1H, C_1H), 4.62 (t, J = 3.9 Hz,1H, C_2H), 4.54 (s, 2H, OCH_2), 3.96–3.91 (m, 1H,C_4H), 3.26 (dd, J = 9.1,4.2 Hz, 1H, C_3H), 2.1 (s, 3H,CH_3) 1.53 (s, 3H,CH_3), 1.36 (m, 3H,CH_3); ^{13}C NMR (75 MHz, DMSO-*d6*): δ 170.6, 144.6, 138.7, 134.8,134.3, 130.6, 129.4, 128.6, 125.8,125.6,122.6, 119.8, 111.6, 104.8, 81.7, 78.6, 74.7, 66.5, 52.4, 26.6, 21.3; MS: m/z (M^+ + H) 664.10. *Anal.* Calcd for $C_{33}H_{31}ClFN_5O_5S$: C, 59.68; H, 4.70; N, 10.54. Found: C, 59.26; H, 4.59; N, 10.31.

5-((3aR,5S,6S,6aR)-6-((1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)-3-(4-fluorophenyl)-6-p-tolyl-3,3a,5,6-tetrahydroisoxazolo[3,4-d]thiazole (10e). The compound was obtained as brown solid. mp 221–225°C; IR (KBr) ν 3428, 3230, 2986, 2976, 2832, 1708, 1698,1600,1570, 1514, 1416, 1261, 859 cm^{-1}; ^{1}HNMR (300 MHz, DMSO-d_6): δ 8.22 (d, J = 8.7 Hz, 2H, Ar—H), 8.06 (s,1H,Ar—H), 7.54 (d, J = 9.2 Hz, 2H, Ar—H), 7.42 (s, 1H, CH—N) 7.39 (d, J = 8.33 Hz, 2H, Ar—H), 7.15 (d, J = 8.3 Hz, 2H, Ar—H), 6.91–6.87 (m, 4H, Ar—H), 5.76 (d, J = 3.6 Hz,1H, C_1H), 5.70 (d, J = 2.2 Hz, 1H, CH—O), 5.62 (d, J = 2.2 Hz, 1H, S—CH), 4.66 (t, J = 3.9 Hz,1H, C_2H), 4.54 (s, 2H, OCH_2), 3.96–3.91 (m, 1H,C_4H), 3.26 (dd, J = 9.1,4.2 Hz, 1H, C_3H), 2.3 (s, 3H,CH_3) 1.53 (s, 3H,CH_3), 1.36 (m, 3H,CH_3); ^{13}C NMR (75 MHz, DMSO – d_6): δ 172.6, 143.2, 137.4, 133.6,132.3, 131.2, 128.4, 127.9, 124.8,122.9, 119.2, 111.2, 103.8, 81.2, 78.1, 74.1, 65.9, 51.4, 26.1,16.1; MS: m/z (M^+ + Na) 686.10. *Anal.* Calcd for $C_{33}H_{31}ClFN_5O_5S$: C, 59.68; H, 4.70; N, 10.54. Found: C, 59.52; H, 4.55; N, 10.43.

3-(5-((3aR,5S,6S,6aR)-6-((1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)-3-(4-fluorophenyl)-3,3a-dihydrothiazolo[4,5-c]isoxazol-6(5H)-yl)phenol (10f). The compound was obtained as gray solid. mp 228–231°C; IR (KBr) ν 3533, 3424, 3230, 2982, 2970, 2831, 1710, 1600,1514, 1416, 1260, 864 cm^{-1}; ^{1}HNMR (300 MHz, DMSO – d_6): δ 8.22 (d, J = 8.7 Hz, 2H, Ar—H), 8.01 (s,1H,Ar—H), 7.54 (d, J = 9.2 Hz, 2H, Ar—H), 7.42 (s, 1H, CH—N), 7.14–6.90 (m, 4H,Ar—H), 6.88–6.86 (m, 4H, Ar—H), 5.62 (d, J = 2.2 Hz, 1H, S—CH), 5.74 (d, J = 3.6 Hz,1H, C_1H), 5.70 (d, J = 2.2 Hz, 1H, CH—O), 5.39 (s, 1H, OH), 4.64 (t, J = 3.9 Hz,1H, C_2H), 4.52 (s, 2H, OCH_2), 3.95–3.93 (m, 1H,C_4H), 3.24 (dd, J = 9.1,4.2 Hz, 1H, C_3H), 1.51 (s, 3H,CH_3), 1.34 (m, 3H,CH_3); ^{13}C NMR (75 MHz, DMSO – d_6): δ 171.6, 158.3, 145.8,144.2, 143.2, 134.6, 134.4, 130.6, 128.6,122.2, 120.1, 119.4, 114.6, 111.8, 107.6,106,98.2, 81.8, 78.6, 74.8, 64.9, 54.9, 41.1; MS: m/z (M^+ + H) 666.20. *Anal.* Calcd for $C_{32}H_{29}ClFN_5O_6S$: C, 57.70; H, 4.39; N, 10.51. Found: C, 57.32; H, 4.15; N, 10.39.

4-(5-((3aR,5S,6S,6aR)-6-((1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)-3-(4-fluorophenyl)-3,3a-dihydrothiazolo[4,5-c]isoxazol-6(5H)-yl)phenol (10g). This compound was as brown solid. mp 273–275°C;IR (KBr) ν 3539, 3421, 3230, 2985, 2978, 2831, 1710, 1600, 1516, 1412, 1252, 861 cm^{-1}; ^{1}HNMR (300 MHz, DMSO-d_6): δ 8.23 (d, J = 8.7 Hz, 2H, Ar—H), 8.04 (s,1H,Ar—H), 7.54 (d, J = 9.2 Hz, 2H, Ar—H), 7.40 (s, 1H, CH—N), 7.10–6.70 (m, 4H,Ar—H), 6.91–6.89 (m, 4H, Ar—H), 5.76 (d, J = 3.6 Hz,1H, C_1H), 5.70 (d, J = 2.2 Hz, 1H, CH—O), 5.67 (d, J = 2.2 Hz, 1H, S—CH) 5.28 (s, 1H, OH), 4.65 (t, J = 3.9 Hz,1H, C_2H), 4.52(s, 2H, OCH_2), 3.91–3.94 (m, 1H,C_4H), 3.34 (dd, J = 9.1,4.2 Hz, 1H, C_3H), 1.52 (s, 3H, CH_3), 1.36 (m, 3H,CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.2, 157.8, 143.8, 143.2, 133.9, 133.4, 130.2, 127.6, 121.9, 120.5, 1198.8, 114.2, 111.2, 106.8, 81.4, 78.2, 73.8, 62.9, 54.2, 40.9, 34.9; MS: m/z (M^+ + Na) 688.20. *Anal.* Calcd for $C_{32}H_{29}ClFN_5O_6S$: C, 57.70; H, 4.39; N, 10.51. Found: C, 57.42; H, 4.45; N, 10.49.

CONCLUSION

In conclusion, a series of a new class of hybrid heterocyclics **10a–g** have been synthesized. The antifungal activity of these compounds was evaluated against various fungi. Among synthesized compounds **10b, 10f,** and **10g** showed good activity and emerged as potential molecules for further development. The compounds also were also evaluated for their nematicidal activity. **10e** and **10f** showed an appreciable nematicidal activity.

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