Med Chem Res
DOI 10.1007/s00044-016-1538-6

MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis, antimicrobial and nematicidal evaluation of a new class of triazolo[4,3-*c*]quinazolinylthiazolidinones

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Received: 3 December 2014 / Accepted: 15 February 2016

Abstract In an attempt to find a new class of antimicrobial and nematicidal agents, a series of 2-aryl/heteryl-3-(5-phenyl[1,2,4]triazolo[4,3-*c*]quinazolin-3-yl)-1,3-thiazolidin-4-ones **5a-k** was prepared by one-pot three-component reaction, involving 5-phenyl[1,2,4]triazolo[4,3-*c*]quinazolin-3-amine **4**, aryl/heteroaryl aldehydes and thioglycolic acid, and characterized by physicochemical as well as spectral means. All the newly synthesized compounds **5a–k** were tested in vitro for their antimicrobial activity against three representative Gram-positive (*Bacillus subtilis*, *Staphylococcus aureus*, *Micrococcus luteus*), Gram-negative (*Proteus vulgaris*, *Salmonella typhimurium*, *Escherichia coli*) bacteria and four fungal strains (*Candida albicans*, *Aspergillus fumigatus*, *Trichophyton rubrum*, *Trichophyton mentagrophytes*). These compounds **5a–k**, were also evaluated for their nematicidal activity against two nematodes (*Ditylenchus myceliophagus*, *Caenorhabditis elegans*). Except phenyl substituted, all the ten aryl/heteroaryl substituted compounds **5b–k** showed significant antimicrobial and nematicidal properties against tested microorganisms. Particularly, compounds **5b**, **5c**, **5g**, **5h**, **5j** and **5k** containing electron-withdrawing substituents like chlorophenyl, nitrophenyl, furyl and 1,3-benzodioxole exhibited promising activity comparable to employed standards Ampicillin, Amphotericin B and Levamisole, and emerged as potent antimicrobial and nematicidal agents.

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Keywords Triazolo[4,3-*c*]quinazolinylthiazolidinones · Synthesis · Antimicrobial activity · Nematicidal activity

Introduction

Developing new, selective, potent and less toxic antimicrobial agents to combat against life threatening invasive microbial infections and their ever growing multi-drug resistant is a major concern to chemists. Quinazoline being a core skeleton in many natural and synthetic heterocycles possesses a wide range of biological and pharmacological properties particularly, antimicrobial (Kumar *et al.,* 2011), anticancer (Kamal *et al.,* 2011), COX-2 inhibitory (Kumar *et al.,* 2003) and antitumor (Abdel Gawad *et al.,* 2010). Thiazolidinone is also a core structure in various pharmaceuticals with a wide range of biological activities like anticancer (Havrylyuk *et al.,* 2010), anti-HIV (Rawal *et al.,* 2008) and antibacterial (Naceur *et al.,* 2012). On the other hand, the thiazolidinone moiety in heterocycles plays an important role in exerting nematicidal action (Srinivas *et al.,* 2008). Azole heterocycles are able to bind easily with the enzymes and receptors in organisms through weak interactions such as coordination bonds, hydrogen bonds, ion–dipole, cation–π, π–π stacking and hydrophobic effect as well as van der Waals force etc (Zhou and Wang, 2012). Many triazoles display prominent biological activities like antimicrobial (Hacer *et al.,* 2010), anti-inflammatory (Birsen *et al.,* 2012), anticancer (Pramod *et al.,* 2013) and antiviral (Wu *et al.,* 2013). The prevalence of azoles in several natural products, and as drug candidates such as Itraconazole, Voriconazole, Posaconazole and Fluconazole inspired more research towards azole antimicrobial drugs. Moreover, synthesis of triazoles fused/linked with another heterocyclic ring has focused attention due to their diverse

Published online: 29 February 2016

biological activities (Gang *et al.,* 2005; Antipenko *et al.,* 2009).

Nematodes are tiny worms and some of them are plant parasites. These plant parasitic nematodes play an important role in predisposition of the host plant to the invasion by secondary pathogens (Jayasinghe *et al.,* 2003). Plants attacked by nematodes show retarded growth and development, as well as loss in the quality and quantity of the harvest. Due to environmental problems, the use of nematicides such as dibromochloropropane (DBCP) and ethylenedibromide (EDB) was slated and withdrawn from the market. The highly toxic Aldicarb used to control insects and nematodes has been detected in ground water (Xaki *et al.,* 1982). Hence, the use of commercial nematicides is still limited due to their high degree of toxicity. Hence there is a need to develop alternative nematode control methods or less toxic nematicides (Noling and Becker, 1994).

Inspired by the biological profile of quinazoline, triazole and thiazolidinone, and in continuation of our research on the synthesis of biologically active heterocycles (Sanjeeva Reddy *et al.,* 2010, 2011a, b, 2012, 2013), it was thought worthwhile to synthesize a new class of heterocycles confining quinazoline, triazole and thiazolidinone pharmacophores in a single molecular frame work, with expected potentiality against bacteria, fungi and nematodes. In this context, we report herein the synthesis of 2-aryl/heteryl-3-(5-phenyl[1,2,4]triazolo [4,3-*c*]quinazolin-3-yl)-1,3-thiazolidin-4-ones **5a-k,** with varied electronic environment due to aryl moiety on 2nd position of thiazolidinone. In a bid to come up with effective chemotherapeutic agents, compounds **5a-k** were evaluated for their in vitro antimicrobial and nematicidal activities.

Results and discussion

Chemistry

The synthesis of 2-aryl/heteryl-3-(5-phenyl[1,2,4]triazolo[4,3-*c*]quinazolin-3-yl)-1,3-thiazolidin-4-ones **5a-k**, was commenced from the commercially available anthranilamide **1**, which on oxidative cyclocondensation with benzaldehyde resulted 2-phenylquinazolin-4(3*H*)-one **2** (Bakavoli *et al.,* 2009). The compound **2** on reflux, for 2 h, with thionylchloride in presence of *N*,*N*-dimethyl formamide (DMF) afforded 4-chloro-2-phenyl quinazoline **3** in 81 % yield. The intermediate **3** on treating with thiosemicarbazide in ethanol afforded 5-phenyl [1,2,4]triazolo[4,3-*c*]quinazolin-3-amine **4** in 68 % yield. The compound **4** so obtained was subjected to one-pot three-component reaction with various aryl/heteroaryl aldehydes, thioglycolic acid (TGA) and $ZnCl_2$ in dry toluene to obtain the desired thiazolidinones **5a-k** (Scheme 1) in good yield (64–72 %).

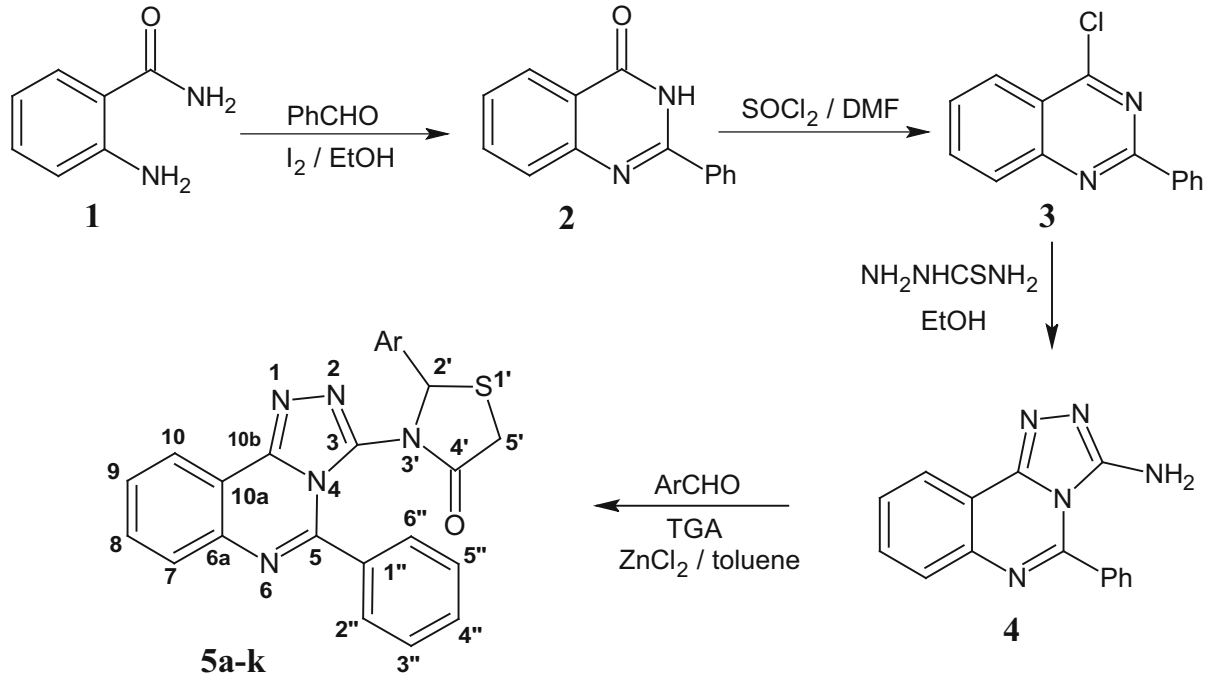
All the newly synthesized compounds were well characterized by elemental analyses IR, ^{1}H-NMR, ^{13}C-NMR and Electron Ionization (EI) mass spectral data. In IR spectra of compounds **5a–k**, disappearance of characteristic absorption bands of NH_2 (3423, 3363 cm^{-1}), and appearance of a characteristic absorption band for C–S–C at about 760 cm^{-1} indicates the ring closure, involving $–NH_2$ group of the compound **4**. Similarly, absence of ^{1}H-NMR signal of $–NH_2$ protons at about δ 5.38, and presence of proton signals at about δ 3.75 and δ 5.86 corresponding to $–CH_2–CO$ and –N–CH–S respectively of the thiazolidinone ring, also support the ring closure involving $–NH_2$. Further evidence was obtained from ^{13}C NMR spectra. For all the compounds **5a–k**, signals corresponding to carbon atoms appeared at about 35.8, 70.0 and 171.6 ppm of thiazolidinone; 149.8 and 158.6 ppm of triazole; 116.4, 128.1, 129.6, 131.4, 132.4, 138.6 and 163.8 ppm of quinazoline. In addition, the *m/z* values obtained from $M^+/(M + 2)^+$ peaks fully supported the structures assigned to compounds **5a-k**.

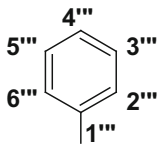
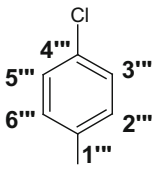
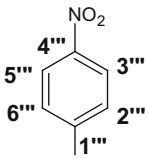
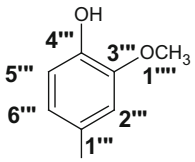
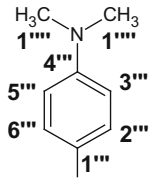
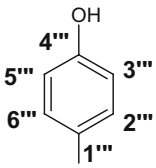
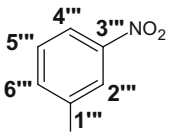
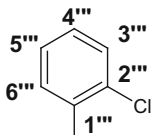
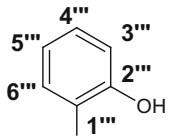
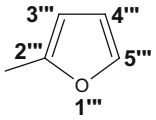
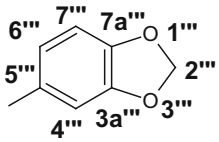
Biological evaluation

Antibacterial activity

In-vitro antibacterial activity of the newly synthesized compounds **5a–k** was studied against three representative Gram-positive bacteria, *Bacillus subtilis* (ATCC 6633), *Staphylococcus aureus* (ATCC 6538p) and *Micrococcus luteus* (IFC 12708), and Gram-negative bacteria, *Proteus vulgaris* (ATCC 3851), *Salmonella typhimurium* (ATCC 14028) and *Escherichia coli* (ATCC 25922), by standard serial dilution method (Cappucino and Sherman, 1999), using a stock solution of 100 μg/mL concentration. Ampicillin was used as standard drug and minimum inhibitory concentrations (MIC; inhibition of 100 % growth) were determined (Table 1).

As evident from the Table 1, most of the newly synthesized compounds, with various substituents at 2nd position of thiazolidinone ring, showed potential antibacterial activity against the bacterial strains employed. Out of 11 screened compounds, **5j** bearing 2-furyl substituent and **5k** bearing 5-(1,3-benzodioxole) substituent, displayed excellent activity almost equal/more than the standard drug Ampicillin against all the tested strains. Further, many of the chloro group or nitro group containing compounds **5b**, **5c**, **5g** and **5h** exhibited better activity than that containing hydroxy, methoxy and methyl groups. Other compounds showed moderate to least activity.



5a; Ar =	5b; Ar =	5c; Ar =	5d; Ar =
			
5e; Ar =	**5f; Ar =**	**5g; Ar =**	**5h; Ar =**
			
5i; Ar =	**5j; Ar =**	**5k; Ar =**	
			

Scheme 1 Schematic route for the synthesis of 2-aryl/heteryl-3-(5-phenyl[1,2,4]triazolo[4,3-*c*]quinazolin-3-yl)-1,3-thiazolidin-4-ones **5a-k**

The structure–activity relationship (SAR) revealed that thiazolidine ring is essential for antimicrobial activity (Bonde and Gaikwad, 2004). From this perspective, studies of the literature data revealed that the negative charge of the oxygen of C=O group and positive charge of nitrogen in NH contribute positively in favor of antibacterial activity. It was hypothesized that difference in charges between two heteroatoms of the same dipolar

Table 1 Antimicrobial and nematicidal activity of the newly synthesized compounds **5a-k**

Compounds	Minimum inhibitory concentration (MIC) in μg/mL										LD_{50} values (ppm)	
	Antibacterial activity						Antifungal activity				Nematicidal activity	
	B. S	*S. A*	*M. L*	*P. V*	*S. T*	*E. C*	*C. A*	*A. F*	*T. R*	*T. M*	*D. M*	*C. E*
5a	50.00	12.50	25.00	50.00	12.50	50.0	50.00	25.00	12.50	25.00	740	610
5b	3.12	1.56	1.56	6.25	1.56	12.50	3.12	6.25	3.12	3.12	210	190
5c	1.56	6.25	3.12	1.56	6.25	12.50	6.25	3.12	3.12	6.25	190	220
5d	6.25	12.50	25.00	6.25	1.56	25.00	25.00	3.12	6.25	3.12	320	200
5e	12.50	6.25	3.12	25.00	12.50	12.50	12.5	6.25	6.25	25.00	360	450
5f	3.12	25.00	1.56	12.50	3.12	25.00	25.00	12.50	25.00	25.00	510	270
5g	6.25	1.56	3.12	3.12	1.56	12.50	6.25	6.25	3.12	6.25	210	220
5h	1.56	3.12	1.56	1.56	1.56	6.25	6.25	3.12	6.25	6.25	200	210
5i	12.5	1.56	25.0	3.12	6.25	12.50	25.00	6.25	12.5	12.50	320	360
5j	1.56	1.56	1.56	3.12	1.56	12.50	6.25	3.12	3.12	3.12	170	180
5k	1.56	1.56	1.56	1.56	3.12	6.25	3.12	1.56	3.12	3.12	160	170
Ampicillin	1.56	1.56	1.56	3.12	3.12	12.50	–	–	–	–	–	–
Amphotericin B	–	–	–	–	–	–	6.25	3.12	3.12	3.12	–	–
Levamisole	–	–	–	–	–	–	–	–	–	–	160	180

B. S, Bacillus subtilis; *S. A, Staphylococcus aureus*; *M. L, Micrococcus luteus*; *P. V, Proteus vulgaris*; *S. T, Salmonella typhimurium*; *E. C, Escherichia coli*; *C. A, Candida albicans*; *A. F, Aspergillus fumigatus*; *T. R, Trichophyton rubrum*; *T. M, Trichophyton mentagrophytes*; *D. M, Ditylenchus myceliophagus*; *C. E, Caenorhabditis elegans*

pharmacophore site ($X^{\delta-}$–$Y^{\delta+}$) may facilitate the inhibition of bacteria. Additionally this is in good agreement with the mode of antibacterial action of the compounds bearing ($X^{\delta-}$–$Y^{\delta+}$) pharmacophore site (Chohan *et al.,* 2010).

Further, the literature study revealed that the activity of thiazolidinone ring increases, when substituted with aryl/heteryl groups at N3 (3rd) and C2 (2nd) positions (Havrylyuk *et al.,* 2010, 2012, 2013; Lesyk *et al.,* 2011). The substitution with heteryl at C2 position increases polarity of the pharmacophore, and the presence of electron-withdrawing substitution on aromatic ring at C2 position of thiazolidinone displaying varied degree of inhibition, against Gram-positive and Gram-negative bacteria, comparable to the employed standard drug.

The presence of nitro/chloro group on phenyl ring at C2 position of thiazolidinone played an important role in activity. It was reported that the nitro/chloro group present on the phenyl ring form complexes with metaloenzymes, particularly those which are responsible in basic physiology such as cytochrome oxidase. These compounds (**5b**, **5c**, **5g** and **5h**) may react with the peptidoglycan layer of the bacterial cell wall and damage it by penetrating in such a manner that the phenyl ring gets entered inside the cell by puncturing it, followed by bacterial cell death (Kant *et al.,* 2008). Sometimes these compounds when present in low concentrations may cause bacteriostatic conditions, which slow down the growth of bacteria.

Antifungal assay

The newly synthesized compounds **5a-k** were also screened for their in vitro antifungal activity against four fungal strains, *Candida albicans* (ATCC 10231), *Aspergillus fumigatus* (HIC 6094), *Trichophyton rubrum* (IFO 9185) and *Trichophyton mentagrophytes* (IFO 40996), by standard serial dilution method (Cappucino and Sherman, 1999), using a stock solution of 100 μg/mL concentration. Amphotericin B was used as standard drug and MIC values were determined in terms of μg/mL (Table 1).

The perusal of antifungal activity data (Table 1) indicated that most of the compounds exhibited good activity. Compounds bearing electron-withdrawing groups such as chloro and nitro (**5b**, **5c**, **5g**, **5h**) were found to be more active than the compounds bearing electron-donating groups. Compounds **5j** and **5k** bearing 2-furyl and 5-(1,3-benzodioxole) substituent respectively displayed high activity comparable to reference drug Amphotericin B. In brief, compounds **5b**, **5c**, **5g**, **5h**, **5j** and **5k** emerged as potential antimicrobial agents.

Nematicidal activity

The new compounds **5a–k** were assayed for their nematicidal activity (McBeth and Bergeson, 1953) against *Ditylenchus myceliophagus* and *Caenorhabditis elegans*. The results were expressed in terms of median lethal dose

(LD_{50}), at which 50 % nematodes became immobile/dead and compared with standard Levamisole (Table 1). The LD_{50} values of compounds screened revealed that, **5j** and **5k**, bearing heteroaryl substituents are beneficial and displayed excellent nematicidal activity with LD_{50} values of 160–180 *ppm*, which are equal to standard Levamisole, and emerged as most potent nematicidal agents. Compounds bearing chloro and nitro groups (**5b**, **5c**, **5g** and **5h**) favored in displaying better nematicidal activity than the compounds with electron-releasing groups (**5d**, **5e**, **5f** and **5i**). Finally, compounds **5b**, **5c**, **5g**, **5h**, **5j** and **5k** emerged as potential nematicidal agents.

Conclusions

In conclusion, a new series of 1,3-thiazoldin-4-ones linked to the annealed triazolo-quinazoline **5a-k** has been prepared in good yields, through an easy, convenient and economic one-pot three-component synthetic method. All the newly synthesized compounds were well characterized by IR, NMR, MS spectra and elemental analyses. The in vitro antibacterial and antifungal evaluation showed that most of the synthesized thiazolidinone analogs could effectively inhibit the growth of the tested bacteria and fungi. Particularly, compounds **5b**, **5c**, **5g**, **5h**, **5j** and **5k** containing electron-withdrawing chloro, nitro groups and heteroaryl substituents like furyl and 1,3-benzodioxole exhibited prominent antimicrobial activity comparable to standards Ampicillin and Amphotericin B. Further, nematicidal screening revealed that compounds with furyl **5j** and 1,3-benzodioxole **5k** were equipotent to standard Levamisole.

In brief, presence of heteroaryl substituents and electron-withdrawing groups are beneficial to improve the antimicrobial and nematicidal properties than their analogs.

Experimental

Chemistry

Sigma–Aldrich chemicals were used as such without further purification. Progress of reactions and purity of compounds were checked by thin-layer chromatography (TLC) on pre-coated silica gel F-254 plates from Merck and compounds visualized by exposure to UV light. Column chromatography was performed on silica gel 60–120 mesh. Melting points were determined with a Fisher–Johns apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer Fourier transform-infrared (FT-IR) spectrometer, using KBr pellet. ^{1}H and ^{13}C NMR spectra (in DMSO-d_6) were recorded on a Varian Gemini spectrometer, operating at 300, 75 MHz, respectively. The chemical shifts are reported as parts per million (δ ppm) down field using TMS as the internal standard and coupling constants (J) are reported in Hz units. Mass spectra were obtained on a VG micromass 7070H spectrometer. Elemental analyses were performed on a Perkin-Elmer 240 CHN elemental analyzer.

*Synthesis of 4-chloro-2-phenylquinazoline (**3**)* Compound **2** (5 mmol) was added in portions to a stirred thionyl chloride (30 mL), followed by DMF (5 mL) and the mixture was refluxed for 90 min at 80 °C. The reaction mixture was cooled and the excess thionylchloride was removed under reduced pressure. The residue thus obtained was dissolved in dichloromethane (60 mL) and washed with a saturated solution of sodium carbonate, brine and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the solid obtained was recrystallized from ethanol to give pure compound **3** as pale brown solid; yield 81 %; mp 123–125 °C; IR (KBr, cm^{-1}): 3053 (Ar–H), 1616 (C=N), 1603 (C=C), 689 (C–Cl); ^{1}H-NMR (300 MHz, DMSO-d_6): δ 7.61–7.73 (m, 4H, ArH, H-7, H-8, H-9, H-10), 7.89–7.93 (m, 2H, ArH, H-2′′, H-6′′), 8.17–8.22(m, 3H, ArH, H-3′′, H-4′′, H-5′′),; MS *m*/*z*: 240 (M^+), 242 ($M^+ + 2$). *Anal.* Calcd for $C_{14}H_9ClN_2$: C, 69.86; H, 3.77; N, 11.64. Found: C, 69.86; H, 3.68; N, 11.66.

*Synthesis of 5-phenyl[1,2,4]triazolo[4,3-c]quinazolin-3-amine (**4**)* A mixture of compound **3** (2.82 g, 0.01 mol) and thiosemicarbazide (0.01 mol) in ethanol (20 mL) was refluxed for 8 h. The reaction mixture was cooled to room temperature, the solid separated, was filtered off, dried and purified by column chromatography (silica gel 60–120 mesh) using EtOAc: *n*-hexane (3:2) as eluent, to afford the pure compound **4** as brown solid; yield 68 %; mp 181–183 °C; IR (KBr, cm^{-1}): 3423, 3363 (NH_2), 3038 (Ar–H), 1622 (C=N), 1601 (C=C); ^{1}H-NMR (300 MHz, DMSO-d_6): δ 5.38 (bs, 2H, NH_2, H-3′), 7.48–7.58 (m, 4H, ArH, H-7, H-8, H-9, H-10), 7.72–7.80 (m, 2H, ArH, H-2′′, H-6′′), 7.99–8.15(m, 3H, ArH, H-3′′, H-4′′, H-5′′); MS *m*/*z*: 261 (M^+). *Anal.* Calcd for $C_{15}H_{11}N_5$:C, 68.95; H, 4.24; N, 26.80. Found: C, 68.95; H, 4.22; N, 26.77.

*General procedure for the synthesis of 2-aryl/heteryl-3-(5-phenyl[1,2,4]triazolo[4,3-c]quinazolin-3-yl)-1,3-thiazolidin-4-ones (**5a-k**)* To a stirred mixture of compound **4** (0.01 mol), aryl/heteroaryl aldehyde (0.01 mol) and TGA (0.02 mol) in dry toluene (20 mL), was added $ZnCl_2$ (0.01 mol) and refluxed for about 5 h. After cooling, the reaction mixture was filtered, concentrated under reduced pressure, and the residue was taken-up in ethyl acetate. The ethyl acetate layer was washed with 5 % sodium bicarbonate solution and finally with brine. The organic layer

was dried over Na_2SO_4 and evaporated to dryness at reduced pressure. The crude product thus obtained was purified by column chromatography on silica gel (60–120 mesh) with hexane-ethylacetate as eluent to get the pure compounds **5a-k**.

*2-Phenyl-3-(5-phenyl[1,2,4]triazolo[4,3-c]quinazolin-3-yl)-1,3-thiazolidin-4-one (**5a**)* This compound was prepared and purified by the above mentioned general procedure. It was obtained as an orange solid; yield 72 %; mp 160–162 °C; IR (KBr, cm^{-1}) : 3061 (Ar–H), 1709 (C=O), 1627 (C=N), 1602 (C=C), 757 (C–S–C); ^{1}H-NMR (300 MHz, DMSO-d_6): δ 3.72 (s, 2H, CH_2–CO, H-5′, H-5′), 5.82 (s, 1H, N–CH–S, H-2′), 6.42–6.60 (m, 2H, ArH, H-2‴, H-6‴), 6.75–7.10 (m, 3H, ArH, H-3‴, H-4‴, H-5‴), 7.44–7.56 (m, 3H, ArH, H-3″, H-4″, H-5″), 7.76–7.83 (m, 3H, ArH, H-2″, H-6″, H-9), 8.10–8.25 (m, 3H, ArH, H-7, H-8, H-10); ^{13}C NMR (75 MHz, DMSO-d_6): δ 35.6 (CH_2, C-5′), 69.6 (CH, C-2′), 116.3 (C, C-10a), 127.4 (CH, C-4‴, CH, C-10), 128.3 (CH, C-2″, CH, C-6″), 129.5 (CH, C-9, CH, C-3‴, CH, C-5‴), 131.1 (CH, C-4″), 131.9 (CH, C-2‴, CH, C-6‴), 132.4 (CH, C-7, CH, C-3″, CH, C-5″), 133.8 (CH, C-8, C, C-1″), 138.4 (C, C-1‴), 147.1 (C, C-3), 149.6 (C, C-6a), 158.8 (C, C-10b), 163.7 (C, C-5), 172.0 (C, C-4′); MS *m/z*: 423 (M^+). *Anal.* Calcd for $C_{24}H_{17}N_5OS$:C, 68.07; H, 4.05; N, 16.54. Found: C, 68.01; H, 3.99; N, 16.53.

*2-(4-Chlorophenyl)-3-(5-phenyl[1,2,4]triazolo[4,3-c]quinazolin-3-yl)-1,3-thiazolidin-4-one (**5b**)* This compound was prepared and purified by the above mentioned general procedure. It was obtained as a white solid; yield 70 %; mp 158–160 °C; IR (KBr, cm^{-1}) : 3058 (Ar–H), 1610 (C=N), 1603 (C=C), 1034 (Ar–Cl), 769 (C–S–C) ^{1}H-NMR (300 MHz, DMSO-d_6): δ 3.74 (s, 2H, CH_2-CO, H-5′, H-5′), 5.83 (s, 1H, N–CH–S, H-2′), 6.70 (d, $J = 8.2$ Hz, 2H, ArH, H-2‴, H-6‴), 7.32 (d, $J = 8.2$ Hz, 2H, ArH, H-3‴, H-5‴), 7.46–7.55 (m, 3H, ArH, H-3″, H-4″, H-5″), 7.76–7.83 (m, 3H, ArH, H-2″, H-6″, H-9), 8.16–8.24(m, 3H, ArH, H-7, H-8, H-10); ^{13}C NMR (75 MHz, DMSO-d_6): δ 35.8 (CH_2, C-5′), 69.8 (CH, C-2′), 116.4 (C, C-10a), 128.1 (C, C-10, CH, C-2″, CH, C-6″), 129.3 (CH, C-4″, CH, C-3‴, CH, C-5‴), 130.9 (CH, C-9, CH, C-2‴, CH, C-6‴), 131.8 (CH, C-3″, CH, C-5″), 132.2 (CH, C-7, C, C-1″), 133.8 (CH, C-8), 136.2 (C, C-4‴), 138.6 (C, C-1‴), 148.1 (C, C-3), 149.6 (C, C-6a), 158.7 (C, C-10b), 163.6 (C, C-5), 172.2 (C, C-4′); MS m/z: 457 (M^+), 459 ($M^+ + 2$). *Anal.* Calcd for $C_{24}H_{16}ClN_5OS$:C, 62.95; H, 3.52; N, 15.29. Found: C, 62.94; H, 3.49; N, 15.25.

*2-(4-Nitrophenyl)-3-(5-phenyl[1,2,4]triazolo[4,3-c]quinazolin-3-yl)-1,3-thiazolidin-4-one (**5c**)* This compound was prepared and purified by the above mentioned general procedure. It was obtained as a red solid; yield 65 %; mp 142–144 °C; IR (KBr, cm^{-1}): 3058 (Ar–H), 1610 (C=N), 1603 (C=C), 1349 (NO_2), 757 (C–S–C); ^{1}H-NMR (300 MHz, DMSO-d_6): δ 3.74 (s, 2H, CH_2–CO, H-5′, H-5′), 5.84 (s, 1H, N–CH–S, H-2′), 7.10–7.20 (m, 3H, ArH, H-4″, H-2‴, H-6‴), 7.50–7.60 (m, 4H, ArH, H-2″, H-6″, H-3″, H-5″), 7.78–7.86 (m, 3H, ArH, H-3‴, H-4‴, H-9), 8.15–8.22 (m, 3H, ArH, H-7, H-8, H-10); ^{13}C NMR (75 MHz, DMSO-d_6): δ 35.4(CH_2, C-5′), 70.1 (CH, C-2′), 116.3 (C, C-10a), 122.6 (CH, C-3‴, CH, C-5‴), 128.0 (CH, C-10), 129.4 (CH, C-2‴, CH, C-6‴, CH, C-4″), 130.4 (CH, C-9, CH, C-2‴, CH, C-6‴), 131.4 (CH, C-3″, CH, C-5″), 132.2 (CH, C-7, C, C-1″), 133.8 (CH, C-8), 145.0 (C, C-1‴), 147.2 (C, C-4‴), 148.4 (C, C-3), 149.4 (C, C-6a), 158.6 (C, C-10b), 163.4 (C, C-5), 172.4 (C, C-4′); MS *m/z*: 468 (M^+); *Anal.* Calcd for $C_{24}H_{16}N_6O_3S$:C, 61.53; H, 3.44; N, 17.94. Found: C, 61.51; H, 3.42; N, 17.93.

*2-(4-Hydroxy-3-methoxyphenyl)-3-(5-phenyl[1,2,4]triazolo[4,3-c]quinazolin-3-yl)-1,3-thiazolidin-4-one (**5d**)* This compound was prepared and purified by the above mentioned general procedure. It was obtained as a white solid; yield 68 %; mp 163–164 °C; IR (KBr, cm^{-1}): 3360–3280 (–OH), 3056 (Ar–H), 1612 (C=N), 1605 (C=C), 1033 (C–O–C), 757 (C–S–C); ^{1}H-NMR (300 MHz, DMSO-d_6): δ 3.64 (s, 3H, –OCH_3, H-1‴′), 3.74 (s, 2H, CH_2–CO, H-5′, H-5′), 4.87 (s, 1H, –OH, H-4‴), 5.84 (s, 1H, N–CH–S, H-2′), 6.84–7.16 (m, 3H, ArH, H-2‴, H-5‴, H-6‴), 7.42–7.63 (m, 3H, ArH, H-3″, H-4″, H-5″), 7.76–7.83 (m, 3H, ArH, H-2″, H-6″, H-9), 8.13–8.21 (m, 3H, ArH, H-7, H-8, H-10); ^{13}C NMR (75 MHz, DMSO-d_6): δ 35.9 (CH_2, C-5′), 54.4 (OCH_3, C-1‴′), 68.8 (CH, C-2′), 115.1 (CH, C-2‴), 116.2 (C, C-10a), 117.6 (CH, C-5‴), 124.1 (CH, C-6‴), 128.1 (CH, C-10, CH, C-2″, CH, C-6″), 129.5 (CH, C-4″), 131.0 (CH, C-9), 131.8 (CH, C-3″, CH, C-5″), 132.6 (CH, C-7, C, C-1″), 134.0 (CH, C-8), 136.2 (C, C-1‴), 147.8 (C, C-4‴), 148.5 (C, C-3), 149.8 (C, C-6a), 154.2, (C, C-3‴), 158.8 (C, C-10b), 163.5 (C, C-5), 171.9 (C, C-4′); MS *m/z*: 469 (M^+); *Anal.* Calcd for $C_{25}H_{19}N_5O_3S$:C, 63.95; H, 4.08; N, 14.92. Found: C, 63.91; H, 4.05; N, 14.90.

*2-(4-(Dimethylamino)phenyl)-3-(5-phenyl[1,2,4]triazolo[4,3-c]quinazolin-3-yl)-1,3-thiazolidin-4-one (**5e**)* This compound was prepared and purified by the above mentioned general procedure. It was obtained as a white solid; yield 69 %; mp 159–161 °C; IR (KBr, cm^{-1}): 3059 (Ar–H), 1610 (C=N), 1606 (C=C), 757 (C–S–C); ^{1}H-NMR (300 MHz, DMSO-d_6): δ 2.94 (s, 6H, –$N(CH_3)_2$, H-1‴′), 3.74 (s, 2H, CH_2–CO, H-5′, H-5′), 5.84 (s, 1H, N–CH–S, H-2′), 6.88 (d, $J = 8.4$ Hz, 2H, ArH, H-2‴, H-6‴), 7.28 (d, $J = 8.4$ Hz, 2H, ArH, H-3‴, H-5‴), 7.52–7.63 (m, 3H, ArH, H-3″, H-4″, H-5″), 7.76–7.83 (m, 3H, ArH, H-2″,

H-6″, H-9), 8.13–8.21 (m, 3H, ArH, H-7, H-8, H-10); ^{13}C NMR (75 MHz, DMSO-d_6): δ 35.5 (CH_2, C-5′), 44.6 (N–CH_3, C-1‴′, N–CH_3, C-1‴′), 69.6 (CH, C-2′), 116.4 (C, C-10a, CH, C-3‴, CH, C-5‴), 128.1 (C, C-10, CH, C-2″, CH, C-6″), 128.8 (C, C-1‴), 129.9 (CH, C-4″, CH, C-2‴, CH, C-6‴), 130.8 (C, C-9), 131.9 (CH, C-3″, CH, C-5″), 132.4 (CH, C-7, C, C-1″), 133.6 (CH, C-8), 146.4(C, C-4‴), 148.6 (C, C-3), 149.6 (C, C-6a), 158.8 (C, C-10b), 163.4 (C, C-5), 171.8 (C, C-4′); MS *m/z*: 466 (M^+); *Anal.* Calcd for $C_{26}H_{22}N_6OS$:C, 66.93; H, 4.75; N, 18.01. Found: C, 66.91; H, 4.73; N, 17.97.

*2-(4-Hydroxyphenyl)-3-(5-phenyl[1,2,4]triazolo[4,3-c]quinazolin-3-yl)-1,3-thiazolidin-4-one (**5f**)* This compound was prepared and purified by the above mentioned general procedure. It was obtained as an orange solid; yield 64 %; mp 171–173 °C; IR (KBr, cm^{-1}): 3380–3310 (–OH), 3059 (Ar–H), 1610 (C=N), 1606 (C=C), 757 (C–S–C); ^{1}H-NMR (300 MHz, DMSO-d_6): δ 3.74 (s, 2H, CH_2–CO, H-5′, H-5′), 5.24 (s, 1H, –OH, H-4″), 5.84 (s, 1H, N–CH–S, H-2′), 6.92 (d, $J = 8.6$ Hz, 2H, ArH, H-3‴, H-5‴), 7.24 (d, $J = 8.6$ Hz, 2H, ArH, H-2‴, H-6‴), 7.52–7.63 (m, 3H, ArH, H-3″, H-4″, H-5″), 7.76–7.83 (m, 3H, ArH, H-2″, H-6″, H-9), 8.13–8.21 (m, 3H, ArH, H-7, H-8, H-10); ^{13}C NMR (75 MHz, DMSO-d_6): δ 35.4 (CH_2, C-5′), 69.5 (CH, C-2′), 116.6 (C, C-10a), 118.1(CH, C-3‴, CH, C-5‴), 128.1 (CH, C-10, CH, C-2″, CH, C-6″), 129.6 (CH, C-4″), 131.0 (CH, C-9, CH, C-2‴, CH, C-6‴), 131.8 (CH, C-3″, CH, C-5″), 132.7 (CH, C-7, C, C-1″), 133.4 (CH, C-8), 134.2 (C, C-1‴), 148.6 (C, C-3), 149.8 (C, C-6a), 156.9 (C, C-4‴), 158.7(C, C-10b), 163.9 (C, C-5), 171.9 (C, C-4′); MS *m/z*: 439 (M^+); *Anal.* Calcd for $C_{24}H_{17}N_5O_2S$:C, 65.59; H, 3.90; N, 15.94. Found: C, 65.55; H, 3.88; N, 15.91.

*2-(3-Nitrophenyl)-3-(5-phenyl[1,2,4]triazolo[4,3-c]quinazolin-3-yl)-1,3-thiazolidin-4-one (**5g**)* This compound was prepared and purified by the above mentioned general procedure. It was obtained as a brown solid; yield 67 %; mp 168–171 °C; IR (KBr, cm^{-1}): 3046 (Ar–H), 1620 (C=N), 1606 (C=C), 1342 (NO_2), 759 (C–S–C); ^{1}H-NMR (300 MHz, DMSO-d_6): δ 3.74 (s, 2H, CH_2-CO, H-5′, H-5′), 5.84 (s, 1H, N–CH–S, H-2′), 7.48–7.62 (m, 7H, ArH, H-3″, H-4″, H-5″, H-1‴, H-5‴), 7.74–7.82 (m, 3H, ArH, H-9, H-2‴, H-4‴,), 8.12–8.21 (m, 3H, ArH, H-7, H-8, H-10); ^{13}C NMR (75 MHz, DMSO-d_6): δ 35.9 (CH_2, C-5′), 67.8 (CH, C-2′), 116.4 (C, C-10a), 120.2 (CH, C-4‴), 126.2 (CH, C-2‴), 128.2 (CH, C-10, CH, C-2″, CH, C-6″), 129.6 (CH, C-4″), 130.1 (CH, C-9), 131.0 (CH, C-5‴), 131.8 (CH, C-3″, CH, C-5″), 132.6 (CH, C-7, CH, C-1″), 133.4 (CH, C-8), 134.6 (CH, C-6‴), 138.6 (C, C-1‴), 141.1 (CH, C-5‴), 148.4 (C, C-3, C, C-3‴), 149.8 (C, C-6a), 158.6 (C, C-10b), 163.6 (C, C-5), 172.0 (C, C-4′); MS *m/z*: 468 (M^+); *Anal.* Calcd for $C_{24}H_{16}N_6O_3S$:C, 61.53; H, 3.44; N, 17.94. Found: C, 61.53; H, 3.39; N, 17.91.

*2-(2-Chlorophenyl)-3-(5-phenyl[1,2,4]triazolo[4,3-c]quinazolin-3-yl)-1,3-thiazolidin-4-one (**5h**)* This compound was prepared and purified by the above mentioned general procedure. It was obtained as a white solid; yield 65 %; mp 170–172 °C; IR (KBr, cm^{-1}): 3059 (Ar–H), 1610 (C=N), 1606 (C=C), 757 (C–S–C); ^{1}H-NMR (300 MHz, DMSO-d_6): δ 3.76 (s, 2H, CH_2–CO, H-5′, H-5′), 5.88 (s, 1H, N–CH–S, H-2′), 7.04–7.16 (m, 4H, ArH, H-3‴, H-4‴, H-5‴, H-6‴), 7.55–7.61 (m, 3H, ArH, H-3″, H-4″, H-5″), 7.74–7.86 (m, 3H, ArH, H-2″, H-6″, H-9), 8.12–8.19 (m, 3H, ArH, H-7, H-8, H-10); ^{13}C NMR (75 MHz, DMSO-d_6): δ 35.6 (CH_2, C-5′), 62.8 (CH, C-2′), 110.5 (C, C-1‴), 116.6 (C, C-10a), 124.2 (CH, C-5‴), 127.8 (CH, C-2″, CH, C-6″), 128.4 (CH, C-10, CH, C-4‴), 129.4 (CH, C-4″, CH, C-3‴), 130.2 (CH, C-6‴), 131.0 (CH, C-9), 131.8 (CH, C-3″, CH, C-5″), 132.4 (CH, C-7, C, C-1″), 134.1 (CH, C-8), 139.0 (C, C-2‴), 148.3 (C, C-3), 149.6 (C, C-6a), 158.9 (C, C-10b), 163.7 (C, C-5), 171.8 (C, C-4′); MS *m/z*: 457 (M^+), 459 ($M^+ + 2$); *Anal.* Calcd for $C_{24}H_{16}ClN_5OS$:C, 62.95; H, 3.52; N, 15.29. Found: C, 62.88; H, 3.49; N, 15.24.

*2-(2-Hydroxyphenyl)-3-(5-phenyl[1,2,4]triazolo[4,3-c]quinazolin-3-yl)-1,3-thiazolidin-4-one (**5i**)* This compound was prepared and purified by the above mentioned general procedure. It was obtained as a white solid; yield 68 %; mp 166–169 °C; IR (KBr, cm^{-1}): 3376–3305 (–OH), 3059 (Ar–H), 1610 (C=N), 1606 (C=C), 757 (C–S–C); ^{1}H-NMR (300 MHz, DMSO-d_6): δ 3.74 (s, 2H, CH_2–CO, H-5′, H-5′), 5.84 (s, 1H, N–CH–S, H-2′), 6.22 (s, 1H, –OH, H-4‴), 6.82–7.12 (m, 4H, ArH, H-3‴, H-4‴, H-5‴, H-6‴), 7.52–7.63 (m, 3H, ArH, H-3″, H-4″, H-5″), 7.76–7.83 (m, 3H, ArH, H-2″, H-6″, H-9), 8.13–8.21 (m, 3H, ArH, H-7, H-8, H-10); ^{13}C NMR (75 MHz, DMSO-d_6): δ 35.4 (CH_2, C-5′), 63.2 (CH, C-2′), 114.2 (C, C-2‴), 116.6 (C, C-10a), 118.4(C, C-1″), 122.4 (CH, C-5‴), 128.2 (CH, C-10, CH, C-2″, CH, C-6″), 129.6 (CH, C-4″, CH, C-4‴), 130.8 (CH, C-9, CH, C-6‴),131.4 (CH, C-3″, CH, C-5″), 132.0 (CH, C-7), 132.9 (C, C-1″), 134.3 (CH, C-8), 148.5 (C, C-3), 149.4 (C, C-6a), 154.2 (CH, C-2‴), 158.6 (C, C-10b), 163.8 (C, C-5), 172.0 (C, C-4′); MS *m/z*: 439 (M^+); *Anal.* Calcd for $C_{24}H_{17}N_5O_2S$:C, 65.59; H, 3.90; N, 15.94. Found: C, 65.56; H, 3.88; N, 15.90.

*2-(Furan-2-yl)-3-(5-phenyl[1,2,4]triazolo[4,3-c]quinazolin-3-yl)-1,3-thiazolidin-4-one (**5j**)* This compound was prepared and purified by the above mentioned general procedure. It was obtained as a pale brown solid; yield 67 %; mp 170–172 °C; IR (KBr, cm^{-1}): 3061 (Ar–H), 1709 (C=O), 1627 (C=N), 1602 (C=C), 1462 (C=C), 1082 (C–O), 757 (C–S–C); ^{1}H-NMR (300 MHz, DMSO-d_6): δ 3.72 (s, 2H, CH_2–CO, H-5′, H-5′), 5.91 (s, 1H, N–CH–S, H-2′), 6.16 (d,

$J = 7.7$ Hz, 1H, ArH, H-3‴), 6.55–7.14 (m, 2H, ArH, H-4‴, H-5‴), 7.44–7.56 (m, 3H, ArH, H-3″, H-4″, H-5″), 7.80–7.85 (m, 3H, ArH, H-2″, H-6″, H-9), 8.10–8.21(m, 3H, ArH, H-7, H-8, H-10); ^{13}C NMR (75 MHz, DMSO-d_6): δ 34.6 (CH_2, C-5′), 64.3 (CH, C-2′), 103.6 (CH, C-3‴), 110.8 (CH, C-4‴), 116.8 (C, C-10a), 128.0 (CH, C-10, CH, C-2″, CH, C-6″), 129.6 (CH, C-4″), 131.4 (CH, C-9, CH, C-3″, CH, C-5″), 132.7 (CH, C-7, C, C-1″), 133.8 (CH, C-8), 144.2 (CH, C-5‴), 148.9 (C, C-3), 149.8 (C, C-6a), 158.2 (C, C-2‴), 161.7 (C, C-10b), 162.9 (C, C-5), 171.8 (C, C-4′); MS *m/z*: 413 (M^+); *Anal.* Calcd for $C_{22}H_{15}N_5O_2S$:C, 63.91; H, 3.66; N, 16.94. Found: C, 63.88; H, 3.61; N, 16.92.

2-(1,3-Benzodioxol-5-yl)-3-(5-phenyl[1,2,4]triazolo[4,3-c]quinazolin-3-yl)-1,3-thiazolidin-4-one ***(5k)*** This compound was prepared and purified by the above mentioned general procedure. It was obtained as a brown solid; yield 66 %; mp 161–163 °C; IR (KBr, cm^{-1}): 3061 (Ar–H), 1709 (C=O), 1627 (C=N), 1602 (C=C), 1130 (C–O), 757 (C–S–C); ^{1}H-NMR (300 MHz, DMSO-d_6): δ 3.72 (s, 2H, CH_2–CO, H-5′, H-5′), 5.54 (s, 2H, O–CH_2–O, H-2‴, H-2‴), 5.84 (s, 1H, N–CH–S, H-2′), 6.55–6.72 (m, 3H, ArH, H-4‴, H-6‴, H-7‴), 7.44–7.56 (m, 3H, ArH, H-3″, H-4″, H-5″), 7.75–7.84 (m, 3H, ArH, H-2″, H-6″, H-9), 8.18–8.25(m, 3H, ArH, H-7, H-8, H-10); ^{13}C NMR (75 MHz, DMSO-d_6): δ 35.6 (CH_2, C-5′), 69.4 (CH, C-2′), 100.1 (CH_2, C-2‴), 116.3 (C, C-10a, CH, C-4‴), 118.2 (CH, C-7‴), 122.4 (CH, C-6‴), 128.2 (CH, C-10, CH, C-2″, CH, C-6″), 129.5 (CH, C-4″), 131.2 (CH, C-9), 131.9 (CH, C-3″, CH, C-5″), 132.4 (CH, C-7, C, C-1″), 133.9 (CH, C-8), 136.2 (C, C-5‴), 146.4(C, C-7a‴), 148.6 (C, C-3a‴), 147.2 (C, C-3), 149.8 (C, C-6a), 158.7 (C, C-10b), 163.9 (C, C-5), 172.2 (C, C-4′); MS *m/z*: 467 (M^+); *Anal.* Calcd for $C_{25}H_{17}N_5O_3S$:C, 64.23; H, 3.67; N, 14.98. Found: C, 64.21; H, 3.63; N, 14.94.

Antimicrobial assay

Antibacterial

All the newly synthesized compounds **5a**–**k** were tested in vitro for their antibacterial activity against three Gram-positive bacteria, *Bacillus subtilis* (ATCC 6633), *Staphylococcus aureus* (ATCC 6538p) and *Micrococcus luteus* (IFC 12708), and three Gram-negative bacteria, *Proteus vulgaris* (ATCC 3851), *Salmonella typhimurium* (ATCC 14028) and *Escherichia coli* (ATCC 25922), by standard serial dilution method using a stock solution of 100 μg/mL concentration. Double strength broth was used as culture media and DMSO was used as a solvent control. The stock solutions of the test compounds were serially diluted in test tubes containing 1 mL of serial medium to get the concentration of 50.00–1.56 μg/mL and than incubated with 100 μL of suspension of selected microorganism in sterile saline. The inoculated test tubes were incubated at 37 °C for 24 h. Amphicillin was used as a standard drug and was also tested under identical conditions for comparison with the newly synthesized compounds.

Antifungal activity

The in vitro antifungal activity was evaluated against *Candida albicans* (ATCC 10231), *Aspergillus fumigatus* (HIC 6094), *Trichophyton rubrum* (IFO 9185) and *Trichophyton mentagrophytes* (IFO 40996) by standard serial dilution method using a stock solution of 100 μg/mL concentration. Sabouraud dextrose broth was employed as culture media and DMSO as a solvent control. The stock solutions of the test compounds were serially diluted in test tubes containing 1 mL of the sterile medium to get the concentration of 50.00–1.56 μg/mL and then inoculated with 100 μL of suspension of the respective organisms in sterile saline. The inoculated test tubes were incubated at 28 °C for 48 h. Antifungal activity was determined by measuring MIC. Amphotericin B was also assessed under identical conditions for comparison with the newly synthesized compounds.

Nematicidal assay

All the compounds **5a**–**k** were assayed for their nematicidal activity by aqueous in vitro screening technique (McBeth and Bergeson, 1953) at various concentrations. For the nematicidal assay the *Ditylenchus myceliophagus* was extracted from the cultivated mushrooms (*Agaricus bisporus*) infected with the nematode. The *Caenorhabditis elegans* was grown on 10 cm 8P plates on a *E. coli* NA22 bacteria diet, which grow in a very thick layer and constitute an abundant food source for large quantities on nematode. The nematode water suspension was collected in petridishes. Suspension of adult worms from five-day old culture was diluted with approximately 100–250 nematodes/mL of water, 100 μL of the nematode suspension was introduced into a solution of each test compound at various concentrations in a well of 24-well plates and incubated at 25 °C. The percentage of immobile (dead) nematodes was recorded after 2 days. The results have been expressed in terms of LD_{50} i.e. median lethal dose at which 50 % nematodes become immobile and compared with the standard Levamisole.

Acknowledgments The authors are grateful to the UGC, New Delhi, India, for providing financial assistance in the form of UGC-BSR, One-Time Research Grant and to the Director, Indian Institute of Chemical Technology (IICT), Hyderabad, India for providing spectral data.

Compliance with ethical standards

Conflict of interest The authors have declared no conflict of interest.

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