J. Chem. Sci. Vol. 126, No. 1, January 2014, pp. 205–212.

Synthesis of new biphenyl-substituted quinoline derivatives, preliminary screening and docking studies

NELLISARA D SHASHIKUMAR[1,*], GANGANAIKA KRISHNAMURTHY[1], HALEHATTI S BHOJYANAIK[2], MAYASANDRA R LOKESH[1] and KAGINALLI S JITHENDRAKUMARA[1]

[1]Department of Chemistry, Sahyadri Science College, Shimoga 577 451, India
[2]Department of PG Studies and Research in Industrial Chemistry, School of Chemical Sciences, Kuvempu University, Shankaraghatta 577 451, Shimoga, India
e-mail: shashikumarnd@gmail.com

MS received 6 April 2013; revised 10 September 2013; accepted 18 September 2013

Abstract. New quinoline derivatives containing biphenyl ring were synthesized and characterized by IR, 1H NMR and mass spectral studies. The synthesized compounds were screened for antimicrobial, anthelmintic activities as well as free radical scavenging property against the DPPH radical. The minimum inhibition concentration values showed promising inhibiting activity and are potent biological agents. The compounds showed minimum binding energy towards β-tubulin. The compounds **11a**, **11c**, **13c** and **13d** have good affinity towards the active pocket and may be considered as a good inhibitor of β-tubulin.

Keywords. Quinoline biphenyl; antioxidant; anthelmintic; docking; β-tubulin.

1. Introduction

Quinoline is a heterocyclic scaffold of paramount importance to living beings. Several quinoline derivatives isolated from natural resources or prepared synthetically are significant with respect to medicinal chemistry and biomedical use. The bark of Cinchona plant (also known as Jesuit's or Cardinal's bark) containing quinine was utilized to treat palpitations,[1,2] fevers and tertians, since more than 200 years. The compounds containing the quinoline motif are most widely used as antimalarials,[3] antibacterials,[4] antifungals,[5] and anticancer agents.[6] Additionally, quinoline derivatives find use in the synthesis of fungicides, virucides, biocides, alkaloids, rubber chemicals and flavouring agents.[7] They are also used as polymers, catalysts, corrosion inhibitors, preservatives and as solvents for resins and terpenes. Furthermore, these compounds find applications in transition metal catalysis for uniform polymerization and luminescence chemistry.[8,9] Owing to this, the synthesis of substituted quinolines has been a subject of great focus in organic chemistry.

*For correspondence

2. Experimental

All the reagents and solvents were used as received from commercial suppliers, unless otherwise stated. All chemicals used for the synthesis were of analytical grade or laboratory grade and purchased from HiMedia Laboratories Pvt. Ltd., Sigma Chemical Co., USA, E Merck, Germany, Sarabhai Merck Company, India, and specialty chemicals were procured as samples from commercial suppliers in India. All equipments were inspected visually for cleanliness and integrity before use. Mass spectra of the synthesized compounds were recorded on Agilent 6320 Ion Trap mass spectrometer. IR spectra were recorded on a Shimadzu IR-470 spectrometer. ^{1}H NMR spectra were recorded on a Bruker DRX-300 Avance spectrometer (300 MHz). Melting point was determined using a Buchi melting point B-540 model and are uncorrected.

2.1 *Synthesis of biphenyl derivatives **4a–b***

The compounds **4a** and **4b** were synthesized by the literature methods.[10–14]

2.2 *Synthesis of quinoline derivatives **6**, **7a**, **7b***

The product 2-chloro-3-formylquinoline **6** synthesized by the reported methods and the compound **6** was

converted to **7a** by hydrolysing the –Cl group by refluxing with aqueous acetic acid. The compound **7b** was obtained by treating the compound **6** with Na_2S/DMF.[15,16]

2.3 *General procedure for the synthesis of **11a**, **11c**, **13a** and **13c***

The compounds **7a**/**7b** (20 mmol), were mixed with 20 mmol of bromomethylbiphenyl-2′-carboxylic acid methyl ester **4a** and 20 mmol of K_2CO_3 in 20 mL DMF was stirred for 2–3 h at room temperature. After the reaction, it was poured into crushed ice. The separated solid was filtered and washed with 100 mL water. The obtained precipitate (10 mmol) and 10 mmol of corresponding amines were dissolved in 20 mL of methanol and refluxed for 4–5 h. Progress of the reaction was monitored by TLC (methanol : MDC in 2 : 8 ratio). After completion of the reaction, it was poured into ice-cold water (50 mL) and the solid separated was filtered and used without purification for the next step. The obtained solid was dissolved in methanol (25 mL) and mixed with a solution of 25 mmol KOH in 20 mL of water. The reaction mixture was refluxed for 2 h. Then, the methanol was distilled off. To the reaction mixture, 30 mL of distilled water was added and acidified to pH 3–4 using 0.1N HCl solution. Filtered the solid, washed with 10 mL of water and dried in an oven under reduced pressure for 5 h at 50°C.

2.4 *General procedure for synthesis of **11b**, **11d**, **13b** and **13d***

A solution of the compound **7a**/**7b** (20 mmol) is stirred with bromomethylbiphenyl-2′-(N-triphenylmethyl)tetrazole 4b (20 mmol) and K_2CO_3 (20 mmol) in 20 mL of DMF at room temperature for 2–3 h. The reaction mixture was poured into crushed ice, filtered and washed to get intermediate. The obtained precipitate (10 mmol) was dissolved in 20 mL of methanol and 10 mmol of corresponding amines was added. The resulting mixture was refluxed for 4–5 h. The reaction was monitored by TLC (methanol : MDC in 2 : 8 ratio). After completion of the reaction, it was poured into ice-cold water (50 mL) and filtered. The product was used without purification for the next step. The obtained product was dissolved in 20 mL of methanol and refluxed with 25 mmol of aqueous KOH, the completion of reaction checked by TLC (methanol : MDC in 1 : 10 ratio). After completion of the reaction, 1N HCl (5 mL) was added and refluxed for 2 h. The solid obtained after the complete removal of solvent by distillation was stirred with 10 mL of distilled water for 30 min. The solid so obtained was filtered and separated, washed with 10 mL of distilled water and dried in an oven under reduced pressure for 5 h at 50°C.

2.4a *4′-[2-Oxo-3-([1,2,4]triazol-4-yliminomethyl)-2H-quinolin-1-ylmethyl]-biphenyl-2-carboxylic acid*: IR: 3413, 1763, 1701 and 1616 cm^{-1} for –OH, C=O and C=N, respectively. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 7.3–8.7 (m, 16H, Ar-H and -HC=N-), 4.25 (s, 2H, -CH2-Ar), 11.8 (s, 1H, -COOH). ^{13}C NMR 400 MHz, DMSO-d_6: δ 169.4 (-COOH), 164.5 (C=O), 163.7 (C=N), 148.0 (triazole C=N), 120–140 (Ar), 47.7 (-CH_2-N).

2.4b *4′-{2-Oxo-3-[(4-[1,2,4]triazol-1-ylmethyl-phenylimino)-methyl]-2H-quinolin-1-ylmethyl}-biphenyl-2-carboxylic acid*: IR: 3403, 1758.3, 1698 and 1618 cm^{-1} for –OH, C=O and C=N, respectively. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 7.3–8.7 (m, 20H, Ar-H and -HC=N-), 4.25 (s, 2H, -CH_2-Ar), 4.9 (s, 2H, -CH_2-triazole), 11.9 (s, 1H, -COOH). ^{13}C NMR 400 MHz, DMSO-d_6: δ 164.1 (C=O), 163.5 (tetrazole C), 163.7 (C=N), 148.0 (triazole C=N), 120–140 (Ar), 47.7 (-CH_2-N).

2.4c *1-[2′-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-3-([1,2,4]triazol-4-yliminomethyl-1H-quinolin-2-one*: IR: 3465, 1710, 1698 and 1618 cm^{-1} for NH and C=N, respectively. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 6.9–8.5 (m, 16H, Ar-H and -HC=N-), 4.22 (s, 2H, -CH_2-Ar), 5.6 (b, 1H, -NH). ^{13}C NMR 400 MHz, DMSO-d_6: δ 169.4 (-COOH), 164.1 (C=O), 153.5 (C=N), 143.6 & 151.3 (triazole C=N), 120–146 (Ar), 55.7 & 47.7 (-CH_2-).

2.4d *1-[2′-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-3-[(4-[1,2,4]triazol-1-ylmethyl-phenylimino)-methyl]-1H-quinolin-2-one*: IR: 3445, 1710, 1698 and 1618 cm^{-1} for NH and C=N, respectively. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 7.2–8.6 (m, 20H, Ar-H and -HC=N-), 4.18 (s, 2H, -CH_2-Ar), 4.82 (s, 2H, -CH_2-triazole), 5.75 (b, 1H, -NH). ^{13}C NMR 400 MHz, DMSO-d_6: δ 164.1 (C=O), 163.5 (tetrazole C), 153.5 (C=N), 143.6 & 151.3 (triazole C=N), 120–140 (Ar), 47.7 (-CH_2-N).

2.4e *4′-[3-([1,2,4]Triazol-4-yliminomethyl)-quinolin-2-ylsulphanylmethyl]-biphenyl-2-carboxylic acid*: IR: 3415, 1770, 1705 and 1612 cm^{-1} for –OH, C=O and

C=N, respectively. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 6.9–8.4 (m, 16H, Ar-H and -HC=N-), 4.32 (s, 2H, -CH_2-Ar), 11.2 (s, 1H, -COOH). ^{13}C NMR 400 MHz, DMSO-d_6: δ 169.4 (-COOH), 160.8 (S-C=N ring), 157.0 (C=N), 148.2 (triazole C=N), 121.3–148.7 (Ar), 38.5 (-CH_2-S).

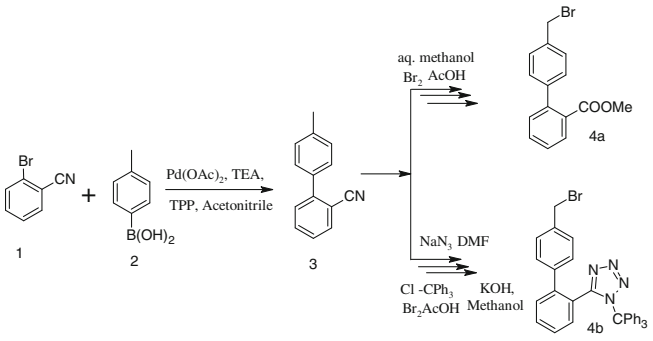
2.4f *4′-{3-[(4-[1,2,4]triazol-1-ylmethyl-phenylimino)-methyl]-quinolin-2-ylsulphanylmethyl}-biphenyl-2-carboxylic acid*: IR: 3403, 1758, 1698 and 1618 cm^{-1} for –OH, C=O and C=N, respectively. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 7.2–8.6 (m, 20H, Ar-H and -HC=N-), 4.42 (s, 2H, -CH_2-Ar), 4.85 (s, 2H, -CH_2-triazole), 11.74 (s, 1H, -COOH), ^{13}C NMR 400 MHz, DMSO-d_6: δ 163.5 (tetrazole C), 160.6 (S-C=N ring), 157.2 (C=N), 148.6 & 151.3 (triazole C=N), 120–148 (Ar), 38.5 (-CH_2-S).

2.4g *{2-[2′-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl-sulphanyl]-quinolin-3-ylmethylene}-[1,2,4]triazol-4-yl-amine*: IR: 3340, 1703 and 1611 cm^{-1} for NH and C=N, respectively. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 7.0–8.5 (m, 16H, Ar-H and -HC=N-), 4.34 (s, 2H, -CH_2-Ar), 5.3 (b, 1H, -NH). ^{13}C NMR 400 MHz, DMSO-d_6: δ 169.1 (-COOH), 160.6 (S-C=N ring), 160.1 (C=N), 143.6 (triazole C=N), 121.3–148.7 (Ar), 55.7 (-CH_2-triazole), 38.5 (-CH_2-S).

2.4h *{2-[2′-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl-sulphanyl]-quinolin-3-ylmethylene}-(4-[1,2,4]triazol-1-ylmethyl-phenyl)-amine*: IR: 1655, 1709 and 3410 cm^{-1} for C=N and NH, respectively. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 7.3–8.5 (m, 20H, Ar-H and -HC=N-), 4.48 (s, 2H, -CH_2-Ar), 4.78 (s, 2H, -CH_2-triazole), 5.67 (b, 1H, -NH). ^{13}C NMR 400 MHz, DMSO-d_6: δ 163.5 (tetrazole C), 160.6 (S-C=N ring), 160.1 (C=N), 143.6 & 151.3 (triazole C=N), 122–148.7 (Ar), 55.7 (-CH_2-triazole), 38.5 (-CH_2-S).

3. Results and discussion

Biphenyl derivatives (**4a**, **b**) were synthesized by Suzuki coupling reaction[10–13] of 2-cyano-1-bromobenzene (**1**) with 4-methylphenyl boronic acid (**2**) in presence of palladium acetate-triphenylphosphine, in basic condition (TEA) and acetonitrile as solvent to give product **3** (scheme 1). The product 4′-methylbiphenyl-2-carbonitrile **3**, was hydrolysed in acidic condition to produce the 4′-methylbiphenyl-2-carboxylic acid, followed by bromination gives the product **4a**. Also, the product **3** was



Scheme 1. Synthetic scheme of biphenyl derivatives.

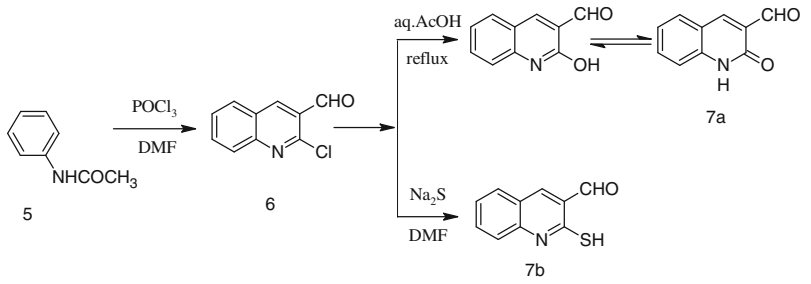
reacted with sodium azide in DMF to give the tetrazole derivative, which on protecting the tetrazole –NH with triphenylmethyl chloride and followed by bromination yields the product **4b**.

2-Chloro-3-formylquinoline (**6**) has been synthesized by Vilsmeier–Haack reaction using acetanilide, POCl3/DMF (scheme 2).[14–16] Functional group transformation of formyl group can be used to get new derivatives. The product **6** was converted to **7a** by acid hydrolysis of the –Cl group. On treating **6** with Na_2S/DMF, substitutes the –Cl group with –SH group giving the product **7b** (scheme 2).

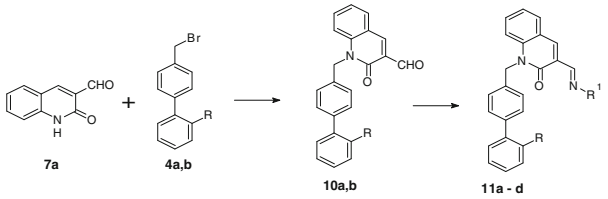
The product **7a** was converted into new Schiff base derivatives (**11a–d**) by condensation with biphenyl derivatives (**4a, b**) in K_2CO_3/DMF, followed by different amines in ethanol and then deprotection of carboxylic acid by base-catalysed hydrolysis in aqueous alcohol (scheme 3). Similarly, the product **7b** was converted to products **13a–d**, except the deprotection of tetrazole is done by acid-catalysed hydrolysis (scheme 4).

Structures of the obtained products were confirmed by elemental analysis, IR, ^{1}H NMR and mass spectral data. The IR spectrum of the compounds **11a–d** recorded as KBr pellet, showed two peaks between 1700 and 1640 cm^{-1} for –C=N– (outside the ring) and the absence of ring –C=N– stretching frequency conforms N-alkylation. Compounds **13a–d** showed two peaks between 1700 and 1600 cm^{-1} for –C=N– of inside ring and outside the ring. Also, the absence of aldehyde group frequency in the range of 1700 cm^{-1} gave an account of the formation of Schiff base.

The proton NMR spectra of the compounds recorded in $CDCl_3$/DMSO-d_6 showed a singlet peak at 12–10 ppm due to the carboxylic acid proton, a broad peak between 4 and 6 ppm confirms the presence of tetrazole –NH. The biphenyl-substituted two methylic protons appear in the range of 3–4 ppm as a singlet. The mass spectra of the compounds showed molecular ion peak M^+ at [M+1] m/z values corresponding to the



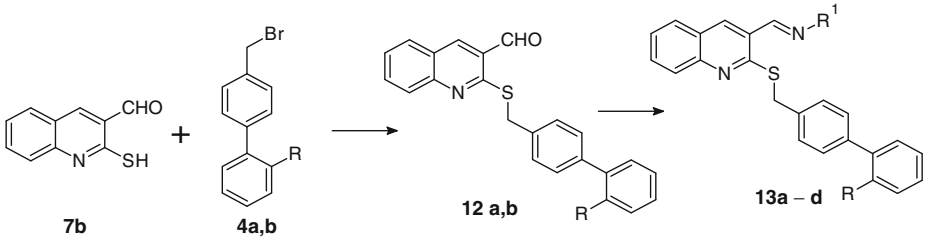
Scheme 2. Synthesis of quinoline derivatives.



where **4** or **10 a** = -COOH, **b** =

	R	R^1
11a	-COOH	
11b		
11c	-COOH	
11d		

Scheme 3. Synthesis of N-biphenyl quinoline derivatives.



where **4** or **10 a** = -COOH, **b** =

	R	R^1
11a	-COOH	
11b		
11c	-COOH	
11d		

Scheme 4. Synthesis of S-biphenyl quinoline derivatives.

Table 1. Physical properties, analytical data and mass spectral data of compounds **11a–d** and **13a–d**.

Sl. No.	Compound	% yield*	M.P. (in °C)	Elemental analysis C	H	N	M/z value
1	**11a**	67.8	171–173	69.39 (69.48)	4.28 (4.26)	15.56 (15.58)	450.5
2	**11b**	72.3	152–154	73.49 (73.46)	4.63 (4.67)	12.90 (12.98)	540.6
3	**11c**	65.2	120–122	65.87 (65.95)	3.95 (4.04)	26.68 (26.62)	474.5
4	**11d**	42.3	154–156	70.25 (70.32)	4.53 (4.47)	22.31 (22.37)	564.6
5	**13a**	53.6	119–122	67.12 (67.08)	4.10 (4.11)	14.98 (15.04)	466.5
6	**13b**	81.2	95–97	71.32 (71.33)	4.61 (4.53)	12.56 (12.60)	556.6
7	**13c**	50.2	101(dec.)	63.86 (63.79)	4.02 (3.91)	25.59 (25.75)	490.5
8	**13d**	63.7	182–184	68.41 (68.37)	4.39 (4.35)	21.73 (21.75)	580.6

*Percentage yield, are on the basis of the final product

molecular weight. Table 1 contains the data of elemental analysis, m/z values, melting point and percentage yields of the synthesized compounds.

3.1 *Antimicrobial activity*

Antibacterial activity carried out by well diffusion method using nutrient agar medium, DMSO as control and chloramphenicol is used as a standard bactericide. Antifungal activity was carried out by well diffusion method using potato dextrose agar (PDA) medium, DMSO as control and fluconazole is used as a standard fungicide.[17–19] Biological properties of the synthesized compounds are screened for bacterial and fungal strains (tables 2 and 3). Most of the synthesized compounds showed inhibition property against the strains used. Among the test samples, **11b** and **13a** showed more activity when compared to the standards used. After comparing the zone of inhibition, the selected compounds were checked for their MIC (minimum inhibition concentration) values. The MIC values of less than 30 μg/mL are shown in table 3. It is observed that, most of the samples showed promising activity. The compounds **11d** and **13d** with two traizole rings have been considered as good inhibitors.

3.2 *Antioxidant activity*

Antioxidant activity of the synthesized derivatives was evaluated using the DPPH free radical scavenging assay by standard methods.[20,21] Data given in table 4 represents the DPPH free radical scavenging activity of the prepared compounds **11a–d** and **13a–d**. All the compounds showed scavenging activity of more than 50%. Thus, the compounds are good antioxidant agents, which are capable of reacting with a free radical.

Table 2. Antimicrobial activity – zone of inhibition.

Sl. No	Comp.	Zone of inhibition (mm) Antibacterial *S. aureus*	*B. subtilis*	*S. typhi*	*E. coli*	Antifungal *S. coccus*	*C. albicans*	*A. niger*
1	**11a**	2	6	9	5	7	7	11
2	**11b**	8	7	6	12	11	8	10
3	**11c**	5	6	6	7	5	7	6
4	**11d**	5	9	6	11	10	9	9
5	**13a**	9	10	7	6	11	10	11
6	**13b**	6	8	9	5	7	5	7
7	**13c**	–	2	8	4	6	7	6
8	**13d**	–	3	9	11	12	6	5
9	Std1.*	08	07	10	10	09	–	–
10	Std2.#	–	–	–	–	–	08	09
11	DMSO	0	0	0	0	0	0	0

*Chloramphenicol, #Fluconazole

Table 3. Antimicrobial activity – minimum inhibition concentration.

Sl. No	Comp.	MIC of the compounds (μg/mL)						
		Antibacterial				Antifungal		
		S. aureus	*B. subtilis*	*S. typhi*	*E. coli*	*S. coccus*	*C. albicans*	*A. niger*
1	**11a**	–	21	30	30	27	22	12
2	**11b**	20	17	–	09	17	21	14
3	**11d**	–	12	–	14	19	13	19
4	**13a**	15	10	–	25	15	17	16
5	**13b**	–	13	–	–	29	21	25
6	**13d**	–	25	29	12	14	30	27

Table 4. Antioxidant activity by DPPH radical scavenging method.

Sl. No.	Compounds	% scavenging activity at different concentrations (μg/mL)				
		25	50	100	250	500
1	**11a**	12.25	24.25	56.87	71.83	81.76
2	**11b**	07.81	18.62	30.54	41.53	65.23
3	**11c**	10.52	21.85	54.23	61.28	78.75
4	**11d**	39.63	53.35	80.48	91.56	97.51
5	**13a**	12.86	21.56	32.79	42.13	56.52
6	**13b**	10.23	22.83	33.56	51.23	62.81
7	**13c**	06.32	12.52	21.83	34.54	49.42
8	**13d**	25.15	40.32	60.58	93.64	98.25
9	BHT*	12.35	25.72	58.51	86.25	94.32

*Butylated hydroxytoluene

Among them, **11d** and **13d** were more active when compared to the standard BHT. The graphical representation of antioxidant activity is given in figure 1.

3.3 *Anthelmintic activity*

Results of anthelmintic activity of synthesized compounds are given in table 5. Graphical representation of anthelmintic activity is given as supplementary material (figure 2). It is clear that all the newly synthesized compounds exhibit more activity than the standard, against the earthworms used. Concentration of test samples and the standard used was 10 mg/mL in DMF. The impact of most of the compounds was more than that of standard. Activity may occur due to the presence of more potential quinoline, triazole and tetrazole rings in the compounds. Procedure for anthelmintic activity is supplied as Supplementary information.

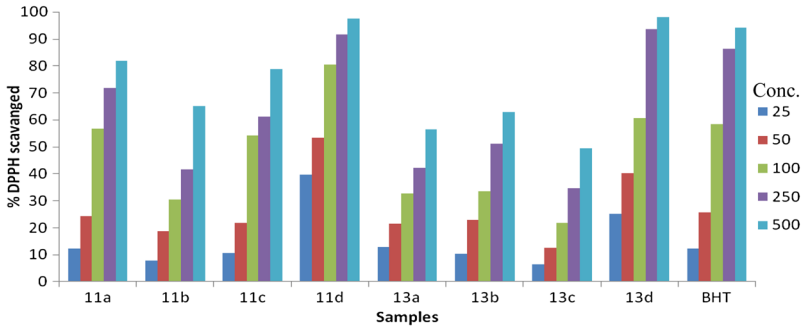


Figure 1. DPPH free radical scavenging activity.

Table 5. Anthelmintic activity.

	Compounds	Time (min)		
		Pin pinch	Paralysis	Death
1	**11a**	12.07	15.00	28.50
2	**11b**	24.00	28.45	42.00
3	**11c**	13.45	21.00	28.00
4	**11d**	17.34	25.49	29.50
5	**13a**	21.50	27.00	36.00
6	**13b**	12.34	22.00	40.50
7	**13c**	14.00	22.54	25.00
8	**13d**	11.50	16.00	24.00
9	Albendazole (standard)	18	25.00	28.20
10	DMF	18.39	32.47	46.08

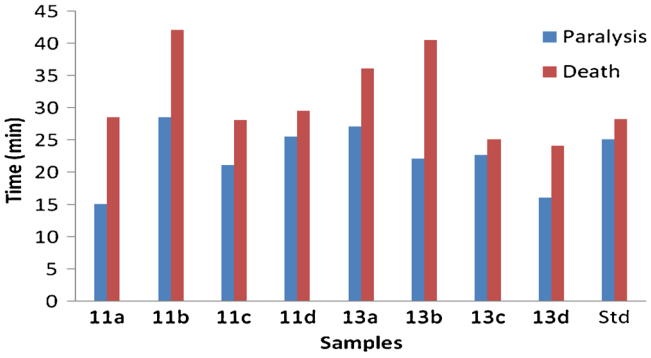


Figure 2. Anthelmintic activity.

Table 6. Docking scores.

Sl. No.	Compounds	Docking Score E_{total} (kJ mol^{-1})
1	**11a**	−241.95
2	**11c**	−251.30
3	**13c**	−286.69
4	**13d**	−289.96
5	Albenzazole	−199.31

3.4 *Docking studies*

In correlation to *in vitro* anthelmintic activity, it is thought worthwhile to carry out *in silico* studies to support the *in vitro* activity. Automated docking was used to assess the orientation of inhibitors bound in the active pockets of β-tubulin(PDB ID: 1OJ0). Molecular docking of selected ligands molecules with β-tubulin revealed that all the compounds have exhibited better docking score when compared to the standard albendazole. Procedure for docking is supplied as Supplementary information.

Among the newly synthesized molecules **11a**, **11c**, **13c** and **13d** have showed a good *in vitro* activity and docking score with β-tubulin protein. The compounds **11a**, **11c**, **13c** and **13d** have showed maximum binding affinity with the −241.95, −251.30, −286.69 and −289.96 kJ mol^{-1}, respectively. These docking scores are considered as good inhibitor of β-tubulin when compared to the standard drug albenzazole which is −199.31 kJ mol^{-1}, the values obtained in docking studies are tabulated in table 6.

Results showed that the synthesized compounds have less energy compared to the standard drugs, which suggest that synthesized compounds have excellent affinity towards the target protein.

4. Conclusion

The new compounds **11a–d** and **13a–d** were prepared by simple transformation and coupling reactions. The obtained products were characterized by elemental analysis, IR, NMR and mass spectral data. The synthesized compounds were screened for antimicrobial activity at the MIC level and *in vitro* antioxidant activity as well as anthelmintic activity. The compounds **11d** and **13d** showed more activity, which can be attributed to the triazole and tetrazole rings. All the compounds are potent towards the activities carried out. Docking study of the synthesized compounds was done with β-tubulin protein. All the compounds showed good docking scores.

Supplementary information

The supplementary information can be seen at www.ias.ac.in/chemsci.

Acknowledgements

Authors are thankful to the Department of Industrial Chemistry, Kuvempu University, Shimoga, Management and staff of Alkem Laboratories Ltd., R&D center, Bangalore, Karnataka, India, Sri. Venkateshwara

Industries and Mandli Industrial Estate, Shimoga for providing necessary facilities.

References

1. Levy S and Azoulay S 1994 *J. Cardiovas. Electrophysiol.* **5** 635
2. Wenckebach K F 1923 *J. Am. Med. Assoc.* **81** 472
3. (a) Bilker O, Lindo V, Panico M, Etiene A E, Paxton T, Dell A, Rogers M, Sinden R E and Morris H R 1998 *Nature* **392** 289; (b) Roma G, Braccio M D, Grossi G, Mattioli F and Ghia H 2000 *Eur. J. Med. Chem.* **35** 1021; (c) Chen Y L, Fang K C, Sheu J Y, Hsu S L and Tzeng C C 2000 *J. Med. Chem.* **44** 2374; (d) Winstanley P A 2000 *Parasitol. Today* **16** 146
4. (a) Fang K C, Chen Y L, Sheu J Y, Wang T C and Tzeng C C 2000 *J. Med. Chem.* **43** 3809; (b) Chevalier J, Atifi S, Eyraud A, Mahamoud A, Barbe J and Pages J M 2001 *J. Med. Chem.* **44** 4023; (c) Phan L T, Jian T, Chen Z, Qiu Y L, Wang Z, Beach T, Polemeropoulos A and Or Y S 2004 *J. Med. Chem.* **47** 2965; (d) Benkovic S J, Baker S J, Alley M R K, Woo Y H, Zhang Y K, Akama T, Mao W, Baboval J, Rajagopalan P T R, Wall M, Kahng L S, Tavassoli A and Shapiro L 2005 *J. Med. Chem.* **48** 7468
5. (a) Majerz-Maniecka K, Oleksyn B, Musiol R, Podeszwa B and Polanski J In Abstracts of Papers, Joint Meeting on Medicinal Chemistry, Vienna, Austria 2005, *Sci. Pharm.* **73** 194; (b) Vargas L Y, Castelli M V, Kouznetsov V V, Urbina J M, Lopez S N, Sortino M, Enriz R D, Ribas J C and Zacchino S 2003 *Bioorg. Med. Chem.* **11** 1531; (c) Singh M, Singh M P and Ablordeppey S Y 1996 *Drug Dev. Ind. Pharm.* **22** 377
6. (a) Dassonneville L, Lansiaux A, Wattelet A, Wattez N, Mahieu C, Van Miert S, Pieters L and Bailly C 2000 *Eur. J. Pharmacol.* **409** 9; (b) Dassonneville L, Bonjean K, De Pauw-Gillet, Colson M C, Houssier P, Quetin-Leclercq C, Angenot J and Ablordeppey L S Y 2002 *Bioorg. Med. Chem.* **10** 1337; (c) Bailly C 1999 *Biochemistry* **38** 7719; (d) Bailly C, Laine W, Baldeyrou B, De Pauw-Gillet M -C, Colson P, Houssier C, Cimanga K, Miert S V, Vlietinck A J and Pieters L 2000 *AntiCancer Drug Des.* **15** 191
7. (a) Jones G 1996 *Comprehensive heterocyclic chemistry* II (eds) A R Katritzky, C W Rees and E F Scriven (Pergamon: Oxford) **5**, 167; (b) Holla B S, Mahalinga M, Karthikeyan M S, Akberalib P M and Shettyc N S 2006 *Bioorg. Med. Chem.* **14** 2040
8. (a) Smirnov R F, Tikhomirov B I, Marinchenko G V and Yakubchik A I 1973 *Polym. Sci. U.S.S.R.* **15** 832; (b) Całus S, Gondek E, Danel A, Jarosz B, Pokładko M and Kityk A V 2007 *Mater. Lett.* **61** 3292
9. Caeiro G, Lopes J M, Magnoux P, Ayrault P and Ribeiro F R 2007 *J. Catal.* **249** 234
10. Carini D J, Duncia J V, Aldrich P E, Chiu A T, Johnson A L, Pierce M E, Price W A, Santella J B, Wells G J, Wexler R R, Wong P C, Yoo S E and Timmermans PBWM 1991 *J. Med. Chem.* **34** 2525
11. Kohler B, Langer M and Mosandl T 1998 *Ger. Pat. Appl. DE*19632643C1
12. Amatore C, Jutand A and Negri S 1990 *J. Organomet. Chem.* **390** 389
13. Sharp M J and Snieckus V 1985 *Tetrahedron Lett.* **26** 5997
14. Copar A, Antoncic L and Antoncic M T 2006 *Int. Pat. Appl. WO* 2006/103068A1
15. Shashikumar N D, Krishnamurthy G, SundaraRajRao K, Shridhara K, BhojyaNaik H S and Nagarajan K 2010 *Org. Process Res. Dev.* **14** 918
16. Sharath N, BhojyaNaik H S, VinayKumar B and JoyHoskeri 2011 *Brit. J. Pharma. Res.* **1** 46
17. (a) Bhimagouda S P, Krishnamurthy G, Bhojyanaik H S, Prashant R L and Manjunath G 2010 *Eur. J. Med. Chem.* **45** 3329; (b) Shashikumar N D 2013 *J. Chem.* Article ID 240381, **2013** 1
18. Roger J S, Asitha A, Scot C, John L, Mohammed A, Kashem H K, Josephine K, Jennifer A, Kowalski S S, Pullen T, Roma J P, Roth C R, Sarko N S, Wilsyn M P, Winters J P and Wolak C L 2007 *Bioorg. Med. Chem. Lett.* **17** 3660
19. Ozden O G, Taner E, Hakan G and Sulhiye Y 2007 *Bioorg. Med. Chem. Lett.* **17** 2233
20. Rohini D S, Alexandar M J N and Chandrasekar 2011 *RJPBCS* **2** 194
21. Gbolade A A and Adeyemi A A 2008 *Fitoterapia* **79** 223