European Journal of Medicinal Chemistry 45 (2010) 142–148

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Original article

Application of Huisgen (3 + 2) cycloaddition reaction: Synthesis of 1-(2,3-dihydrobenzofuran-2-yl-methyl [1,2,3]-triazoles and their antitubercular evaluations

Rama P. Tripathi [a,*], Amit Kumar Yadav [a], Arya Ajay [a], Surendra Singh Bisht [a], Vinita Chaturvedi [b], Sudhir Kumar Sinha [b]

[a] Division of Medicinal and Process Chemistry, Central Drug Research Institute, Lucknow 226001, UP, India
[b] Division of Drug Target Discovery and Development, Central Drug Research Institute, Lucknow 226001, CSIR, UP, India

ARTICLE INFO

Article history:
Received 29 May 2009
Received in revised form
18 September 2009
Accepted 25 September 2009
Available online 30 September 2009

Keywords:
1,2,3-Triazoles
[3 + 2] cycloaddition
Cuprous iodide
Antitubercular agents

ABSTRACT

1,4-Disubstituted-1,2,3-triazoles (**3–27**) have been synthesized by [3+2] cycloaddition of different 2-(azidomethyl)-dihydronaptho(benzo)furans (**2a, 2b, 2c** and **2d**) with different alkynes. All the compounds were screened for antitubercular activity against *Mycobacterium tuberculosis* $H_{37}Rv$. Compounds **2a**, **7**, **9**, **12** and **14** exhibited antitubercular activities with MIC ranging from 12.5 to 3.12 μg/ml.

1. Introduction

The rediscovery of "old" reactions invented in the middle of the last century has encouraged the researchers to develop new chemistry in terms of atom economy, eco-friendly nature, yields and simplicity. The reaction between an azide (1,3-dipole) and acetylenes (dipolarophiles) belonging to a concerted (one step) [1,2] 3 + 2 cycloaddition reaction was systematically studied in early 1960s by Huigsen as 1,3-dipolar addition reactions [3–6]. The Huisgen (3 + 2) cycloaddition reaction using azides and alkynes is an important method for the atom economic synthesis of 1,2,3-triazoles [7]. The advantages of 100% atom economy and simple purification method of the resulting products have led to explorations of different catalysts and conditions for this reaction in accessing compound libraries. This reaction has a high status in synthetic organic chemistry as various pharmaceuticals, agrochemicals, polymers, biochemicals, and functional materials [8–11] have been prepared via this reaction. In particular, 1,4-disubstituted triazoles have been used as metal binding compounds, ligand linkers, and triazole-based monophosphine ligands [12–16]. Further, compounds with 1,4-disubstituted triazole moieties have displayed a number of chemotherapeutic properties such as antifungal [17], anticancer [18], growth factor β1 type receptor inhibitory [19] and antitubercular activities [20]. However, the major limitations of the original reaction are the requirement of high reaction temperatures and low regioselectivity. To achieve regioselectivity, high yields and energy efficiency different variables of Cu(I) species have been adopted by Meldal and co-workers, Sharpless and co-workers and many other groups [21]. Keeping in mind the antitubercular activities of triazoles [20] and recent reports that benzofuran and dihydrobenzofuran derivatives are natural product leads to develop new antitubercular agents [22,23] we were interested to synthesize a hybrid molecule consisting of benzofuran and triazole moieties.

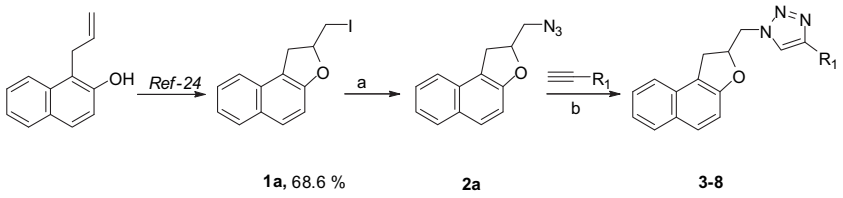
Our method consists of 3 + 2 cycloaddition reaction of 2-(azidomethyl)-benzofurans with different acetylenes in the presence of $CuSO_4 \cdot 5H_2O$ (1 mol%) at moderate temperatures to give respective 1-(2,3)-dihydrobnzofuran-2-yl-methyl [1,2,3]-triazoles in good yields. All the compounds were evaluated for their antitubercular activity against *Mycobacterium tuberculosis* H37Rv.

2. Chemistry

2-(Iodomethyl)-dihydronaphthofuran (**1a**) and 2-(iodomethyl)-dihydrobenzofuran derivatives (**1b–d**) were prepared in good

* Corresponding author. Tel.: +91 522 2612412; fax: +91 522 2623405.
E-mail address: rpt.cdri@gmail.com (R.P. Tripathi).

0223-5234/$ – see front matter © 2009 Elsevier Masson SAS. All rights reserved.
doi:10.1016/j.ejmech.2009.09.036



Scheme 1. Synthesis of 1,4-disubstituted 1,2,3-triazoles (**3**–**8**). Reaction conditions: (a) NaN_3, Cu-powder, 90 °C, DMF; (b) Na-ascorbate (5 mol%), *t*-BuOH:H_2O, 2:1, $CuSO_4 \cdot 5H_2O$ (1 mol%), 90 °C, 4 h.

yields by oxidative cyclization following earlier reported method [24]. The reaction of these iodomethyl-dihydronaphtho (or benzo)-furans **1a**, **1b**, **1c** and **1d** with sodium azide in the presence of Cu-powder (as catalyst) at 90 °C in *N*,*N*-dimethylformamide yielded the respective 2-(azidomethyl)- dihydronapthofuran (**2a**) and 2-(azidomethyl)-dihydrobenzofuran derivatives **2b, 2c,** and **2d** in good yields. The (3 + 2) cycloaddition of the 2-azidomethyldihydronaphtho (or benzo)furans (**2a–d)** with different alkynes *viz.* 1-octyne, 1-heptyne, 3-butyn-1-ol, 1-octyn-3-ol, phenylaceytylene, 3-phenyl-1-propyne, propargyl alcohol (Schemes 1 and 2) in the presence of Na-ascorbate (5 mol%), *t*-BuOH:H_2O (2:1), and $CuSO_4 \cdot 5H_2O$ (1 mol%), at 90 °C afforded the corresponding 1,4-disubstuted-1,2,3-triazole compounds **3**–**27** in good yields (Tables 1 and 2).

3. Biology

The newly synthesized compounds were screened for their antimycobacterial activity against *M. tuberculosis* H37Rv employing agar microdilution method [25]. Isoniazid (INH) and ethambutol were used as standard drugs.

4. Results and discussions

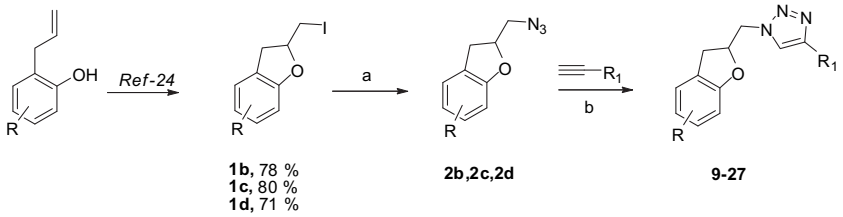
4.1. Chemistry

The structures of compounds **2a**–**d** were in accordance with their spectroscopic data. The IR spectra of the compounds in general exhibited the absorption band at around 2100–2110 cm^{-1} indicating that the azido group was present in the compounds. The ES mass spectra of the compounds showed their respective $[M + H]^+$ peaks. In the ^1H NMR spectrum of the compound **2a** the one methine proton of C-2 appeared as multiplet at around δ 5.17–5.04 ppm, while the methylene protons of C-3 merged with multiplet of one of the methylene proton of azidomethyl group appeared at around δ 3.71–3.49 ppm. The other methylene proton of azidomethyl group was observed as double doublet at δ 3.29 ppm with $J_1 = 15.6$ Hz, $J_2 = 6.7$ Hz. All aromatic protons were observed at their usual chemical shift δ 7.83–7.16 ppm. In the ^{13}C NMR spectrum one methylene carbon of azidomethyl group appeared at δ 55.0 ppm and methylene carbon of dihydronapthofuran ring (C-3) at δ 32.2 ppm while C-2 carbon was observed at δ 82.1 ppm. All the aromatic carbons were observed in a chemical shift range of δ 112.4–157.0 ppm. Almost similar ^1H NMR and ^{13}C NMR spectral patterns were noticed for compounds **2b–d**.

Similarly the structures of compounds **3**–**27** were established on the basis of their spectroscopic data. In IR spectra of the above compounds the absorption peak corresponding to azido group was not observed around 2100 cm^{-1}. In the ^1H NMR spectrum of compound **3** the vinylic proton of C-5 on triazole ring was merged with two aromatic protons and appeared as multiplet at around δ 7.49–7.33 ppm while the one aromatic proton was observed as multiplet at around δ 7.30–7.23 ppm. The three aromatic protons of naphthyl ring were observed as three distinct doublets at δ 7.75 ppm, δ 7.66 ppm, and δ 7.07 ppm with coupling constant of 8.1 Hz, 8.8 Hz, and 8.7 Hz, respectively. The methylene protons of C-3 on dihydronapthofuran ring appeared as multiplet at around δ 4.73–4.51 ppm while two methylene protons were observed as two discrete double doublet at δ 3.63 ppm with $J_1 = 15.7$ Hz, $J_2 = 9.8$ Hz and at δ 3.25 ppm with $J_1 = 15.7$ Hz, $J_2 = 7.12$ Hz. The six protons of hexyl chain appeared as multiplet at around δ 1.24–1.20 ppm and the remaining seven protons of hexyl chain were observed as three distinct triplet at δ 2.63 ppm, $J = 7.3$ Hz (2H); δ 1.55 ppm, $J = 6.9$ Hz (2H); and δ 0.84 ppm, $J = 6.1$ Hz (3H). In ^{13}C NMR spectrum of compound **3,** five methylene carbons of hexyl chain were observed δ 22.9, 26.0, 29.2, 29.7, 31.9 ppm while one methylene carbon in between the triazole and benzofuran moieties appeared at δ 53.9 ppm and methylene carbon the dihydronapthofuran ring (C-3) at δ 32.0 ppm. The vinylic carbon (C-2) was observed at δ 81.7 ppm. All aromatic carbons were observed at their usual chemical shifts.

4.2. Biology

All the newly synthesized compounds including 2-azidomethyldihydronaphtho (benzo)furans and 1-(2,3-dihydro naphtha-(benzo)-furan-2-yl-methyl) [1,2,3]-triazoles were screened against *M. tuberculosis* H37Rv. As evident from Table 3 one of the compounds 2-azidomethyldihydronaphthofurans **2a** proved to be potent antitubercular with MIC 3.12 μg/ml comparable to the standard drug ethambutol. The cycloaddition products 1-(2,3-dihydronaphthofuran-2-yl-methyl)[1,2,3]triazoles of compound **2a** with different alkynes in general were less active than compound **2a**. Among 1-(2,3-dihydronaphthofuran-2-yl-methyl)[1,2,3]triazoles only compound **7** with *n*-pentyl substituent exhibited mild antitubercular activity with



Scheme 2. Synthesis of 1,4-disubstituted 1,2,3-triazoles (**9**–**27**). Reaction conditions: (a) NaN_3, Cu-powder, 90 °C, DMF; (b) Na-ascorbate (5 mol%), *t*-BuOH + H_2O, 2:1, $CuSO_4 \cdot 5H_2O$ (1 mol%), 90 °C, 4 h.

Table 1
Synthesis of 2-(azidomethyl)dihydronapthofuran (**2a**) and 1,4-disubstituted-1,2,3-triazoles (**3**–**8**).

Entry	Compound no.	R_1	Yield (%)
1	**2a**	–	89
2	**3**	$-(CH_2)_5CH_3$	86
3	**4**	$-C_6H_5$	95
4	**5**	$-CH_2OH$	86
5	**6**	$-CH_2C_6H_5$	91
6	**7**	$-(CH_2)_4CH_3$	89
7	**8**	$-CH_2CH_2OH$	64

MIC 12.5 μg/ml, other compounds of the series were inactive as their MIC was >12.5 μg/ml.

Among all the 2-azidomethyldihydrobenzofurans none of them showed significant inhibition of the mycobacterial growth. However, among 1-(2,3-dihydrobenzofuran-2-yl-methyl)[1,2,3]-triazoles, compounds **9** and **12** with 4-*n*-pentyl and *n*-hexyl substituent, respectively, in the triazole moiety and compound **14** with 4-hydroxymethyl substituent exhibited mild in vitro antitubercular activity with MIC 12.5 μg/ml against *M. tuberculosis* H37Rv strain. Other compounds of the series were inactive as their MIC values were >12.5 μg/ml. No definite SAR could be established in this series of compounds. One of the possible reasons for the inactivity of few of the compounds may be that the compounds are unable to reach the growing mycobacterial cell; however, detailed biological studies are needed to find out definite reasons for their inactivity.

5. Conclusions

In summary, we have synthesized a new class of hybrid molecules 1-(2,3-dihydronaphtho(benzo)furan-2-yl-methyl) 4-alkyl/aryl-1,2,3-triazoles employing an old chemistry of 3 + 2 cycloaddition of azides and acetylenes in good to very good yields. One of the intermediates 2-azidomethyldihydronaphthofuran exhibited potent antitubercular activity comparable to standard drug ethambutol. The hybrid molecules did show only mild antitubercular activities. The synthetic methodology and the compounds developed may open a new door towards the synthesis of interesting biologically active compounds.

Table 2
Synthesis of 2-(azidomethyl)-dihydrobenzofuran derivatives (**2b**–**2d**) and 1,4-disubstituted-1,2,3-triazoles (**9**–**27**).

Entry	Compound no.	R	R_1	Yield (%)
1	**2b**	-4-CHO	–	64
2	**2c**	-2,5-Di-Me	–	75
3	**2d**	-4-CN	–	74
4	**9**	-4-CHO	$-(CH_2)_4CH_3$	94
5	**10**	-4-CHO	$-CH_2OH$	73
6	**11**	-4-CHO	$-C_6H_5$	92
7	**12**	-4-CHO	$-(CH_2)_5CH_3$	90
8	**13**	-4-CHO	$-CH_2C_6H_5$	95
9	**14**	-2,5-Di-Me	$-CH_2OH$	86
10	**15**	-2,5-Di-Me	$-CH_2C_6H_5$	95
11	**16**	-2,5-Di-Me	$-(CH_2)_5CH_3$	90
12	**17**	-2,5-Di-Me	$-C_6H_5$	91
13	**18**	-2,5-Di-Me	$-(CH_2)_4CH_3$	86
14	**19**	-2,5-Di-Me	$-CH(OH)-(CH_2)_4CH_3$	74
15	**20**	-2,5-Di-Me	$-CH_2CH_2OH$	87
16	**21**	-4-CN	$-C_6H_5$	94
17	**22**	-4-CN	$-CH_2C_6H_5$	59
18	**23**	-4-CN	$-(CH_2)_5CH_3$	87
19	**24**	-4-CN	$-(CH_2)_4CH_3$	78
20	**25**	-4-CN	$-CH_2CH_2OH$	75
21	**26**	-4-CN	$-CH_2OH$	77
22	**27**	-4-CN	$-CH(OH)-(CH_2)_4CH_3$	85

Table 3
In vitro antitubercular activity of 2-(azidomethyl)dihydronapthofuran, 2-(azidomethyl) dihydrobenzofuran derivatives (**2a**–**2d**) and 1,4-disubstituted-1,2,3-triazoles (**3**–**27**).

Compd no.	cLog P[a]	MIC (μg/mL) *M. tuberculosis* H37Rv
2a	2.96	3.12
2b	1.47	>12.5
2c	2.41	>12.5
2d	2.38	>12.5
3	5.63	>12.5
4	4.74	>12.5
5	2.48	>12.5
6	4.83	>12.5
7	5.17	12.5
8	2.82	>12.5
9	3.25	12.5
10	4.12	>12.5
11	3.34	>12.5
12	1.93	6.25
13	4.28	>12.5
14	1.33	12.5
15	4.19	>12.5
16	4.62	>12.5
17	4.25	>12.5
18	2.27	>12.5
19	3.37	>12.5
20	3.46	>12.5
21	4.26	>12.5
22	3.80	>12.5
23	1.45	>12.5
24	1.11	>12.5
25	4.36	>12.5
26	0.30	>25.0
27	2.62	>25.0
Isoniazid	0.668	0.75
Ethambutol	0.1188	3.25

[a] cLogP was determined by OSIRIS Property Explorer Programme available at http://www.organic-chemistry.org/prog/peo.

6. Experimental

6.1. Chemistry

Commercially available reagent grade chemicals were used as received. All reactions were followed by TLC on E. Merck Kieselgel 60 F_{254}, with detection by UV light, spraying a 20% $KMnO_4$ aq. solution. Column chromatography was performed on silica gel (60–120 mesh E. Merck). IR spectra were recorded as thin films (KBr) or neat $CHCl_3$ solution with a Perkin Elmer Spectrum RX-1 (4000–450 cm^{-1}) spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on a Brucker DRX-200 MHz and 50 MHz, respectively, in $CDCl_3$ and DMSO. Chemical shift values are reported in ppm relative to TMS (tetramethylsilane) as internal reference, unless otherwise stated; bs (broad singlet), s (singlet), d (doublet), t (triplet), m (multiplet); *J* in hertz. ESI mass spectra were performed using Quattro II (Micromass). Melting points were determined by open capillary method and uncorrected. Elemental analyses were performed on a Perkin–Elmer 2400 II elemental analyzer.

6.1.1. General experimental procedure for preparation of 2-(azidomethyl)-1,2-dihydronaphtho[2,1-b] furan and 2-(azidomethyl)-1,2-dihybenzo[2,1-b] furan derivatives (*2a*–*d*)

To a magnetically stirred solution of the 2-(idomethyl)-1,2-dihydronaphtho[2,1-b] furan (**1a**) or 2-(idomethyl)-1,2-dihybenzo[2,1-b] furan derivatives (**1b**–**d**) (1 equivalent) in DMF, NaN_3 (1.2 equivalent) and Cu-powder (catalyst, 10 mol%) was cautiously added and reaction mixture was stirred for 6–8 h at 90 °C. Reaction progress was monitored by TLC. The reaction mixture was diluted with water and

extracted by ethylacetate; organic layer was washed by water (3 × 200 mL), dried (anhyd. Na_2SO_4) and evaporated under reduced pressure to get crude mass. The latter was chromatographed over silica gel (60–120 mesh) using a gradient of hexane–ethylacetate as eluent to give desired products.

*6.1.1.1. 2-(Azidomethyl)-1,2-dihydronaphtho[2,1-b]furan (**2a**).* Reddish liquid, yield (89%); IR (Neat) cm^{-1}: 2102 (N_3), 1244 (C–O–C); ESIMS: 226 $(M+H)^+$; ^1H NMR (200 MHz, $CDCl_3 + CCl_4$): δ 7.83 (d, $J = 8.1$ Hz, 1H, Ar–H), 7.71 (d, $J = 8.8$ Hz, 1H, Ar–H), 7.43–7.56 (m, 2H, Ar–H), 7.26–7.36 (m, 1H, Ar–H), 7.16 (d, $J = 8.7$, 1H, Ar–H), 5.04–5.17 (m, 1H, CH of dihydrofuran ring), 3.71–3.49 (m, 3H, 1H, H-3a of dihydrofuran ring, CH_2 of azidomethyl), 3.29 (dd, $J_1 = 6.7$ Hz, $J_2 = 6.7$ Hz, 1H, H-3b of dihydrofuran ring); ^{13}C NMR (50 MHz, $CDCl_3 + CCl_4$): δ 157.0, 131.1, 129.9, 129.8, 129.2, 127.2, 123.5, 123.0, 117.7, 112.4, 82.1, 55.0, 32.2. Anal. Calcd for $C_{13}H_{11}N_3O$: C, 69.32; H, 4.92; N, 18.66%. Found: C, 69.34; H, 4.90; N, 18.65%.

*6.1.1.2. 2-(Azidomethyl)-2,3-dihydrobenzofuran-5-carbaldehyde (**2b**).* Yellowish liquid, yield (64%); IR (Neat) cm^{-1}: 2104 (N_3), 1685 (C═O), 1247 (C–O–C); ESIMS: 204 $(M+H)^+$; ^1H NMR (200 MHz, $CDCl_3 + CCl_4$): δ 9.76 (s, 1H, CHO), 7.60–7.66 (m, 2H, Ar–H), 6.87 (d, $J = 8.1$ Hz, 1H, Ar–H), 5.02–5.04 (m, 1H, CH of dihydrofuran ring), 3.27–3.58 (m, 3H, 1H, H-3a of dihydrofuran ring, CH_2 azido), 3.11 (dd, $J_1 = 6.6$ Hz, $J_2 = 6.6$ Hz, 1H, H-3b of dihydrofuran ring); ^{13}C NMR (50 MHz, $CDCl_3 + CCl_4$): δ 189.8, 164.6, 133.4, 131.4, 127.7, 126.1, 110.1, 82.9, 54.6, 32.2. Anal. Calcd for $C_{10}H_9N_3O_2$: C, 59.11; H, 4.46; N, 20.68%. Found: C, 59.13; H, 4.45; N, 20.67%.

*6.1.1.3. 2-(Azidomethyl)-4,7-dimethyl-2,3-dihydrobenzofuran (**2c**).* Reddish liquid, yield (75%); IR (Neat) cm^{-1}: 2104 (N_3); ESIMS: 218 $(M+CH_3)$; ^1H NMR (200 MHz, $CDCl_3 + CCl_4$): δ 6.88 (d, $J = 7.6$ Hz, 1H, Ar–H), 6.61 (d, $J = 7.6$ Hz, 1H, Ar–H), 5.02–4.94 (m, 1H, m, 1H, CH of dihydrofuran ring), 3.46–3.43 (m, 2H, CH_2 azidomethyl), 3.31 (dd, $J_1 = 15.6$ Hz, $J_2 = 6.6$ Hz, 1H, H-3a), 3.02 (dd, $J_1 = 15.6$ Hz, $J_2 = 6.5$ Hz, 1H, H-3b), 2.22 (s, 3H, Ar–CH_3), 2.16 (s, 3H, Ar–CH_3); ^{13}C NMR (50 MHz, $CDCl_3 + CCl_4$): δ 157.7, 139.8, 135.1, 132.1 (C-8), 129.9 (C-7), 125.4 (C-9), 81.6 (C-2), 54.8 (C-6), 33.8 (C-3), 19.0 (C-12), 15.3 (C-11). Anal. Calcd for $C_{11}H_{13}N_3O$: C, 65.01; H, 6.45; N, 20.68%. Found: C, 65.30; H, 6.40; N, 20.60%.

*6.1.1.4. 2-(Azidomethyl)-2,3-dihydrobenzofuran-5-carbonitrile (**2d**).* Yellowish liquid, yield (74%); IR (Neat) cm^{-1}: 3020 (C–H), 2220 (CN), 2107 (N_3); ESIMS: 224 $(M+Na)^+$; ^1H NMR (200 MHz, $CDCl_3 + CCl_4$): δ 7.42–7.39 (m, 2H, Ar–H), 6.83 (d, $J = 6.0$ Hz, 1H, Ar–H), 5.08–4.96 (m, 1H, 1H, CH of dihydrofuran ring), 3.61–3.26 (m, 3H, CH_2 of azidomethyl, H-3a), 3.11 (dd, $J_1 = 16.1$ Hz, $J_2 = 6.8$ Hz, 1H, H-3b); ^{13}C NMR (50 MHz, $CDCl_3 + CCl_4$): δ 162.9, 133.9, 129.1, 128.0, 119.1, 110.8, 104.9, 82.7, 54.5, 32.3. Anal. Calcd for $C_{10}H_8N_4O$: C, 59.99; H, 4.03; N, 27.99%. Found: C, 59.96; H, 4.20; N, 27.91%.

*6.1.2. General experimental procedure for preparation of 1,2,3-triazole (**3**–**27**)*

The mixture of 2-(azidomethyl)-1,2-dihydronaphtho[2,1-b] furan (1 mmol) or 2-(azidomethyl)-1,2-dihydrobenzo[2,1-b] furan derivatives (1 mmol) and alkyne (1.2 mmol) were suspended in a 2:1 mixture of *tert*-butyl alcohol and water. Sodium ascorbate (5 mol% freshly prepared solution in water) was added followed by addition of $CuSO_4 \cdot 5H_2O$ (1 mol%, freshly prepared solution in of water). The heterogeneous mixture was stirred vigorously for 6 h, the reaction mixture was diluted with ice cold water and precipitate thus obtained was collected by filtration and washed with ice cold water and dried under vacuum to give a crude mass which was purified by a short column of silica gel (60–120) using hexane:EtOAc as eluent to give desired products (**3**–**27**).

*6.1.2.1. 1-((1,2-Dihydronaphtho[2,1-b]furan-2-yl) methyl)-4-hexyl-1H-1,2,3-triazole (**3**).* White solid, mp 108–110 °C, yield (86%); IR (KBr) cm^{-1}: 2923 (C–H stretching), 1633 (C═C–), 1255 (C–O–C stretching); ESIMS: 336 $(M+H)^+$; ^1H NMR (200 MHz, $CDCl_3 + CCl_4$): δ 7.75 (d, $J = 8.1$ Hz, 1H, Ar–H), 7.66 (d, $J = 8.8$ Hz, 1H, Ar–H), 7.37–7.49 (m, 3H, Ar–H, triazole ring proton), 7.23–7.30 (m, 1H, Ar–H), 7.07 (d, $J = 8.7$ Hz, 1H, Ar–H), 5.23–5.30 (m, 1H, CH of dihydrofuran ring), 4.51–4.73 (m, 2H, CH_2), 3.63 (dd, $J_1 = 15.7$ Hz, $J_2 = 9.6$ Hz, 1H, H-3a), 3.25 (dd, $J_1 = 15.7$ Hz, $J_2 = 9.6$ Hz, 1H, H-3b), 2.63 (t, $J = 7.3$ Hz, 2H, CH_2 of hexyl chain), 1.57 (m, 2H, CH_2), 1.24 (bs, 6H, $3CH_2$) 0.84 (bs, 3H, CH_3), ^{13}C NMR (50 MHz, $CDCl_3 + CCl_4$): δ 156.5, 148.7, 131.0, 129.8, 129.0, 127.3, 123.6, 123.0, 121.9, 117.7, 112.0, 81.7, 53.9, 32.0, 31.9, 29.7, 29.2, 26.0, 22.9, 14.6. Anal. Calcd for $C_{21}H_{25}N_3O$: C, 75.19; H, 7.51; N, 12.53%. Found: C, 75.23; H, 7.48; N, 12.50%.

*6.1.2.2. 1-[(1,2-Dihydronaphtho[2,1-b]furan-2-yl)methyl]-4-phenyl-1H-1,2,3-triazole (**4**).* White solid, mp 166 °C, yield (95%); IR (KBr) cm^{-1}: 2922 (C–H stretching), 1629 (C═C), 1252 (C–O–C); ESIMS: 328 $(M+H)^+$; ^1H NMR (200 MHz, $CDCl_3$ + DMSO-d_6): δ 8.51 (s, 1H, triazole ring proton), 7.83–7.77 (m, 2H, Ar–H), 7.71 (d, $J = 8.8$ Hz, 1H, Ar–H), 7.61 (d, $J = 8.1$ Hz, 1H, Ar–H), 7.24–7.49 (m, 6H, ArH), 7.13 (d, $J = 8.7$ Hz, 1H, ArH), 5.41–5.48 (m, 1H, CH of dihydrofuran ring), 4.76–4.80 (m, 2H, –NCH_2), 3.72 (dd, $J_1 = 15.9$, $J_2 = 9.7$ Hz, 1H, H-3a), 3.39 (dd, $J_1 = 15.8$ Hz, $J_2 = 6.8$ Hz, 1H, H-3b); ^{13}C NMR (50 MHz, $CDCl_3$ + DMSO-d_6): δ 161.5, 152.0, 136.2, 135.9, 134.5, 134.2, 134.0, 133.2, 132.2, 130.7, 128.5, 128.2, 127.4, 123.2, 117.3, 86.6, 58.9, 36.7, 34.6. Anal. Calcd for $C_{21}H_{17}N_3O$: C, 77.04; H, 5.23; N, 12.84%. Found: C, 77.10; H, 5.20; N, 12.88%.

*6.1.2.3. (1-[(1,2-Dihydronaphtho[2,1-b] furan-2-yl) methyl]-1H-1,2,3-triazol-4-yl) methanol (**5**).* Yellowish solid, mp 114 °C, yield (86%), IR (KBr) cm^{-1}: 3356 (OH); ESIMS: 282 $(M+H)^+$; ^1H NMR (200 MHz, $CDCl_3 + CCl_4$): δ 7.76 (s, 1H, triazol ring proton), 7.72 (d, $J = 8.1$ Hz, 1H, Ar–H), 7.61 (d, $J = 8.8$ Hz, 1H, Ar–H), 7.49 (d, $J = 8.0$ Hz, 1H, Ar–H), 7.33–7.41 (m, 1H, Ar–H), 7.18–7.26 (m, 1H, Ar–H), 7.03 (d, $J = 8.7$ Hz, 1H, Ar–H), 5.20–5.34 (m, 1H, CH of dihydrofuran ring), 4.52–4.72 (m, 4H, –OCH_2, –NCH_2), 3.61 (dd, $J_1 = 15.7$ Hz, $J_2 = 9.6$, 1H, H-3a), 3.25 (dd, $J_1 = 15.7$ Hz, $J_2 = 7.1$, 1H, H-3b), ^{13}C NMR (50 MHz, $CDCl_3 + CCl_4$): δ 161.4, 135.8, 134.5, 134.4, 133.8, 132.0, 128.3, 127.9, 122.7, 117.1, 86.5, 61.0, 58.6, 36.7. Anal. Calcd for $C_{16}H_{15}N_3O_2$: C, 68.31; H, 5.37; N, 14.94%. Found: C, 68.28; H, 5.39; N, 14.98%.

*6.1.2.4. 4-Benzyl-1-[(1,2-dihydronaphtho[2,1-b]furan-2-yl)methyl]-1H-1,2,3- triazole (**6**).* White solid, mp 118 °C, yield (91%); IR (KBr) cm^{-1}: 2919 (C–H), 1631 (C═C), 1253 (C–O–C); ESIMS: 342 $(M+H)^+$; ^1H NMR (200 MHz, $CDCl_3$ + DMSO-d_6): δ 7.74 (d, $J = 8.1$ Hz, 1H, Ar–H), 7.62 (d, $J = 8.8$ Hz, 1H, Ar–H), 7.28–7.50 (m, 3H, triazol ring proton + 2×Ar–H), 6.97–7.24 (m, 7H, Ar–H), 5.27–5.30 (m, 1H, CH of dihydrofuran ring), 4.59–4.63 (m, 2H, –NCH_2), 3.93 (s, 2H, CH_2), 3.61 (dd, $J_1 = 15.8$ Hz, $J_2 = 9.9$ Hz, 1H, H-3a), 3.25 (dd, $J_1 = 15.8$ Hz, $J_2 = 6.9$, 1H, H-3b); ^{13}C NMR (50 MHz, $CDCl_3 + CCl_4$): δ 161.4, 151.9, 144.4, 135.8, 134.5, 134.4, 133.8, 133.7, 133.6, 132.0, 131.8, 131.4, 131.1, 128.3, 128.1, 128.0, 122.8, 117.0, 86.4, 58.7, 37.1, 36.6, 34.8. Anal. Calcd for $C_{22}H_{19}N_3O$: C, 77.40; H, 5.61; N, 12.31%. Found: C, 77.35; H, 5.90; N, 12.34%.

*6.1.2.5. 1-((1,2-Dihydronaphtho[2,1-b]furan-2-yl) methyl)-4-pentyl-1H-1,2,3-triazole (**7**).* Brown solid, mp 100 °C, yield (89%); IR (KBr) cm^{-1}: 2926 (C–H), 1632 (C═C), 1252 (C–O–C); ESIMS: 322 $(M+H)^+$; ^1H NMR (200 MHz, $CDCl_3 + CCl_4$): δ 7.74 (d, $J = 8.0$ Hz, 1H, Ar–H), 7.65 (d, $J = 8.8$ Hz, 1H, Ar–H), 7.35–7.48 (m, 3H, 2 Ar–H, triazole ring proton), 7.20–7.29 (m, 1H, Ar–H), 7.06 (d, $J = 8.7$ Hz, 1H, Ar–H), 5.18–5.32 (m, 1H, CH of dihydrofuran ring), 4.49–4.72 (m,

2H, –NCH_2), 3.61 (J_1 = 15.7 Hz, J_2 = 9.7 Hz, 1H, H-3a), 3.23 (dd, J_1 = 15.7 Hz, J_2 = 7.1 , 1H, H-3b), 2.63 (t, J = 7.3 Hz, 2H, pentyl chain CH_2), 1.65 (m, 2H, CH_2), 1.26 (bs, 4H, 2×CH_2) 0.84 (t, J = 6.5 Hz, 3H, CH_3), ^{13}C NMR (50 MHz, $CDCl_3 + CCl_4$): δ 156.5, 148.6, 131.0, 129.8, 129.1, 126.9, 123.6, 123.0, 120.6, 117.7, 112.0, 81.7, 53.9, 31.9, 31.7, 29.4, 26.0, 24.0, 22.8, 14.4. Anal. Calcd for $C_{20}H_{23}N_3O$: C, 74.74; H, 7.21; N, 13.07%. Found: C, 74.72; H, 7.22; N, 13.30%.

*6.1.2.6. 2-(1-((1,2-Dihydronaphtho[2,1-b] furan-2-yl) methyl)-1H-1,2,3-triazol-4-yl) ethanol (**8**).* Brown solid, mp 111 °C, yield (64%); IR (KBr) cm^{-1}: 3020 (C–H), 1216 (C–O–C); ESIMS: 296 $(M + H)^+$; ^{1}H NMR (200 MHz, $CDCl_3 + CCl_4$): δ 6.71–6.86 (m, 3H, Ar–H), 6.52-6.61 (m, 2H, triazole ring proton + Ar–H), 6.33–6.41 (m, 1H, Ar–H), 6.16 (d, J = 8.76 Hz, 1H, Ar–H), 4.35–4.40 (m, 1H, CH of dihydrofuran ring), 3.59–3.81 (m, 2H, NCH_2), 3.27 (bs, 3H, CH_2, OH), 2.74 (dd, J_1 = 15.7 Hz, J_2 = 9.7 Hz, 1H,H-3a), 2.36 (dd, J_1 = 15.7 Hz, J_2 = 6.8, 1H, H-3b), 1.96 (bs, 2H, CH_2); ^{13}C NMR (50 MHz, $CDCl_3 + CCl_4$): δ 156.4, 130.9, 129.9, 129.8, 129.0, 126.9, 123.6, 122.9, 117.6, 112.4, 81.4, 61.3, 54.2, 32.0, 29.0. Anal. Calcd for $C_{17}H_{17}N_3O_2$: C, 69.14; H, 5.80; N, 14.23%. Found: C, 69.17; H, 5.85; N, 14.20%.

*6.1.2.7. 2-((4-Pentyl-1H-1,2,3-triazol-1-yl)methyl)-2,3-dihydrobenzofuran-5-carbaldehyde (**9**).* Greenish solid, mp 115 °C, yield (91%); IR (KBr) cm^{-1}: 2928 (C–H), 1685 (C═O), 1218 (C–O–C); ESIMS: 300 $(M + H)^+$; ^{1}H NMR (200 MHz, $CDCl_3 + CCl_4$): δ 9.76 (s, 1H, CHO), 7.65–7.62 (m, 3H, 2×Ar–H, triazole ring proton), 6.87 (d, J = 8.6 Hz, 1H, Ar–H), 5.26 (bs, 1H, CH of dihydrofuran ring), 4.73–4.66 (m, 2H), 3.46 (dd, J_1 = 15.9 Hz, J_2 = 9.1 Hz, 1H, H-3a), 3.12 (dd, J_1 = 16.0 Hz, J_2 = 6.0 Hz, 1H, H-3b), 2.62 (bs, 2H, CH_2), 1.57 (bs, 2H, CH_2), 1.25 (bs, 4H, 2CH_2), 0.87 (t, J = 6.5 Hz, 3H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3 + CCl_4$): δ 190.2, 164.2, 133.1, 131.5, 127.5, 126.6, 110.1, 82.3, 32.0, 31.7, 29.2, 25.9, 22.7, 14.4. Anal. Calcd for $C_{17}H_{21}N_3O_2$: C, 68.20; H, 7.07; N, 14.04%. Found: C, 68.18; H, 7.15; N, 14.00%.

*6.1.2.8. 2-[(4-(Hydroxymethyl)-1H-1,2,3-triazol-1-yl)methyl]-2,3-dihydrobenzofuran-5-carbaldehyde (**10**).* White solid, mp 165 °C, yield (73%); IR (KBr) cm^{-1}: 3448 (O–H), 1677 (C═O), 1603 (C═C); ESIMS: 260 $(M + H)^+$; ^{1}H NMR (200 MHz, $CDCl_3 + CD_3OD$): δ 9.77 (s, 1H, CHO), 7.80 (s, 1H, triazole ring proton), 7.71–7.67 (m, 2H, 2×Ar–H), 6.92 (d, J = 8.54 Hz, 1H, Ar–H), 5.33–5.30 (bs, 1H, CH of dihydrofuran ring), 4.81–4.59 (m, 4H, –OCH_2, –NCH_2), 3.53 (dd, J_1 = 16.2 Hz, J_2 = 9.4 Hz, 1H, H-3a), 3.17 (dd, J_1 = 16.1 Hz, J_2 = 7.1 Hz, 1H, H-3b); ^{13}C NMR (50 MHz, $CDCl_3 + CD_3OD$): δ 195.3, 168.5, 137.5, 135.2, 131.6, 130.6, 129.9, 127.8, 114.3 86.3, 59.8, 57.9, 35.9. Anal. Calcd for $C_{13}H_{13}N_3O_3$: C, 60.22; H, 5.05; N, 16.21%. Found: C, 60.25; H, 5.60; N, 16.15%.

*6.1.2.9. 2-[(4-Phenyl-1H-1,2,3-triazol-1-yl)methyl]-2,3-dihydrobenzofuran-5-carbaldehyde (**11**).* White solid, mp 174 °C, yield (92%); IR (KBr) cm^{-1}: 1684 (C═O), 1606 (C═C), 1252 (C–O–C); ESIMS: 306 $(M + H)^+$; ^{1}H NMR (200 MHz, DMSO-d_6): δ 9.78 (s, 1H, CHO), 8.59 (s, 1H, Ar–H), 7.83–7.68 (m, 4H, Ar–Hx4), 7.46–7.31 (m, 3H, Ar–Hx2, triazole ring proton), 6.98 (d, J = 8.1 Hz, 1H, Ar–H), 5.42 (bs, 1H, CH dihydrofuran ring), 4.86–4.67 (m, 2H, –NCH_2), 3.54–3.37(m, 1H, H-3a), 3.19–3.07 (dd, 1H, J_1 = 6.5 Hz, J_2 = 16.4 Hz); ^{13}C NMR (50 MHz, $CDCl_3$ + DMSO-d_6): δ 196.4, 169.4, 152, 138.0, 136.2, 136.0, 134.4, 133.5, 133.4, 131.6, 130.7, 127.7, 115.0, 58.5, 36.8. Anal. Calcd for $C_{18}H_{15}N_3O_2$: C, 70.81; H, 4.95; N, 13.76%. Found: C, 70.77; H, 4.99; N, 13.73%.

*6.1.2.10. 2-[(4-Hexyl-1H-1,2,3-triazol-1-yl)methyl]-2,3-dihydrobenzofuran-5-carbaldehyde (**12**).* White solid, mp 108 °C, yield (90%); IR (KBr) cm^{-1}: 2926 (C–H), 1683 (C═O), 1606 (C═C); ESIMS: 314 $(M + H)^+$; ^{1}H NMR (200 MHz, $CDCl_3 + CCl_4$): δ 9.77 (s, 1H, CHO), 7.63 (s, 2H, Ar–H), 7.36 (s, 1H, triazole ring proton), 6.87 (d, J = 8.1 Hz, 1H), 5.24–5.26 (m, 1H, CH of dihydrofuran ring), 4.72–4.64 (m, 2H, –NCH_2), 3.38 (dd, J_1 = 9.2 Hz, J_2 = 15.8 Hz, 1H, H-3a), 3.12 (dd, J_1 = 6.5 Hz, J_2 = 15.8 Hz, 1H, H-3b), 2.62 (t, 2H, CH_2), 1.56 (m, 2H, CH_2), 1.24 (m, 6H, 3CH_2), 0.84 (t, 3H, –CH_3); ^{13}C NMR (50 MHz, $CDCl_3 + CCl_4$): δ 190.3, 164.2, 133.1, 131.5, 127.5, 126.6, 110.1, 82.4, 53.7, 31.9, 29.6, 29.2, 25.9, 22.9, 14.5. Anal. Calcd for $C_{18}H_{23}N_3O_2$: C, 68.98; H, 7.40; N, 13.41%. Found: C, 68.93; H, 7.35; N, 13.35%.

*6.1.2.11. 2-[(4-Benzyl-1H-1,2,3-triazol-1-yl) methyl]-2,3-dihydrobenzofuran-5-carbaldehyde (**13**).* White solid, mp 136 °C, yield (95%); IR (KBr) cm^{-1}: 1684 (C═O), 1608 (C═C), 1249 (C–O–C); ESIMS: 320 $(M + H)^+$; ^{1}H NMR (200 MHz, $CDCl_3 + CCl_4$): δ 9.79 (s, 1H, CHO), 7.65–7.62 (m, 2H, Ar–H, triazole ring proton), 7.29–7.10 (m, 6H, Ar–H), 6.84 (d, J = 8.7 Hz, 1H, Ar–H), 5.27–5.24 (m, 1H, CH dihydrofuran ring), 4.64–4.58 (m, 2H, –NCH_2), 4.01 (s, 2H, CH_2Ph), 3.46 (dd, J_1 = 16.2, J_1 = 9.6 Hz, 1H, H-3a), 3.12 (dd, J_1 = 16.2, J_1 = 6.8 Hz,, 1H, H-3b); ^{13}C NMR (50 MHz, $CDCl_3 + CCl_4$): δ 190.7, 164.2, 148.2, 139.2, 133.1, 131.4, 129.0, 127.4, 126.9, 126.7, 123.1, 110.2, 82.3, 53.8, 32.5, 31.8. Anal. Calcd for $C_{19}H_{17}N_3O_2$: C, 71.46; H, 5.37; N, 13.16%. Found: C, 71.39; H, 5.40; N, 13.13%.

*6.1.2.12. 1-[(4,7-Dimethyl-2,3-dihydrobenzofuran-2-yl)methyl]-1H-1,2,3-triazol-4-yl methanol (**14**).* Yellowish liquid, yield (86%); IR (Neat) cm^{-1}: 3367 (O–H), 2924 (C–H), 1590 (C═C); ESIMS: 260 $(M + H)^+$; ^{1}H NMR (200 MHz, $CDCl_3 + CCl_4$): δ 7.74 (s, 1H, OH), 7.34 (s, 1H, triazole ring proton), 6.80 (d, J = 7.6 Hz, 1H, Ar–H), 6.54 (d, J = 7.6 Hz, 1H, Ar–H), 5.07 (bs, 1H, CH dihydrofuran ring), 4.68–4.60 (m, 4H, OCH_2, NCH_2), 3.30 (dd, J_1 = 15.5, J_2 = 8.6 Hz, 1H, H-3a), 2.88 (dd, J_1 = 15.0, J_2 = 7.0 Hz, 1H, H-3b), 2.15 (s, 3H, Ar–CH_3), 2.14 (s, 3H, Ar–CH_3); ^{13}C NMR (50 MHz, $CDCl_3 + CCl_4$): δ 157.2, 139.8, 135.3, 132.2, 129.9, 125.1, 123.8, 122.3, 80.7, 54.4, 33.7, 32.5, 19.0, 14.9. Anal. Calcd for $C_{14}H_{17}N_3O_2$: C, 64.85; H, 6.61; N, 16.20%. Found: C, 64.80; H, 6.67; N, 16.18%.

*6.1.2.13. 4-Benzyl-1-[(4,7-dimethyl-2,3-dihydrobenzofuran-2-yl)-methyl]-1H-1,2,3-triazole (**15**).* Yellowish liquid, yield (95%); IR (Neat) cm^{-1}: 3020 (C–H), 1216 (C–O–C); ESIMS: 320 $(M + H)^+$; ^{1}H NMR (200 MHz, $CDCl_3 + CCl_4$): δ 7.34–7.12 (m, 7H, Ar–H, triazole ring proton), 6.83 (d, J = 7.6 Hz, 1H, Ar–H), 6.57 (d, J = 7.6 Hz, 1H, Ar–H), 5.11–5.04 (m, 1H, CH dihydrofuranring), 4.67–4.41 (m, 2H, –NCH_2), 4.04 (s, 2H, –CH_2Ph), 3.30 (dd, J_1 = 15.8 Hz, J_2 = 9.3 Hz, 1H), 2.93 (dd, J_1 = 15.8 Hz, J_2 = 9.2 Hz, 1H), 2.15 (s, 3H, Ar–CH_3), 2.07 (s, 3H, Ar–CH_3); ^{13}C NMR (50 MHz, $CDCl_3 + CCl_4$): δ 156.8, 148.1, 139.3, 132.3, 129.8, 129.1, 129.0, 128.9, 126.8, 123.9, 123.3, 119.6, 116.9, 80.6, 54.1, 32.6, 32.2, 19.0, 15.2. Anal. Calcd for $C_{20}H_{21}N_3O$: C, 75.21; H, 6.63; N, 13.16%. Found: C, 75.15; H, 6.69; N, 13.10%.

*6.1.2.14. 1-[(4,7-Dimethyl-2,3-dihydrobenzofuran-2-yl)methyl]-4-hexyl-1H-1,2,3-triazole (**16**).* Orange liquid, yield (90%); IR (Neat) cm^{-1}: 2927 (C–H), 1592 (C═C), 1259 (C–O–C); ESIMS: 314 $(M + H)^+$, ^{1}H NMR (200 MHz, $CDCl_3 + CCl_4$): δ 7.34 (s, 1H, triazole ring proton), 6.80 (d, J = 7.6 Hz, 1H, Ar–H), 6.53 (d, J = 7.62 Hz, 1H, Ar–H), 5.11–5.04 (m, 1H, CH dihydrofuran ring), 4.67–4.51 (m, 2H, –NCH_2), 3.29 (dd, J_1 = 15.7 Hz, J_2 = 9.2 Hz, 1H, H-3a), 2.92 (dd, J_1 = 15.4 Hz, J_2 = 6.7 Hz, 1H, H-3b), 2.69 (t, J = 7.4 Hz, 2H, CH_2), 2.20 (s, 3H, Ar–CH_3), 2.15 (s, 3H, Ar–CH_3), 1.63–1.56 (m, 2H, CH_2), 1.29–1.25 (m, 6H, 3CH_2), 0.91 (t, J = 6.4 Hz, 3H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3 + CCl_4$): δ 157.3, 148.6, 139.8, 135.3, 132.2, 129.8, 123.9, 121.8, 80.9, 54.0, 32.0, 29.7, 29.2, 25.9, 24.7, 22.9, 19.0, 15.3, 14.5. Anal. Calcd for $C_{19}H_{27}N_3O$: C, 72.81; H, 8.68; N, 13.41%. Found: C, 72.75; H, 8.72; N, 13.39%.

*6.1.2.15. 1-[(4,7-Dimethyl-2,3-dihydrobenzofuran-2-yl)methyl]-4-phenyl-1H-1,2,3-triazole (**17**).* White solid, mp 122–124 °C, yield (91%); IR (KBr) cm^{-1}: 3020 (C–H), 1216 (C–O–C); ESIMS: 306

$(M+H)^+$; ^{1}H NMR (200 MHz, $CDCl_3+CCl_4$): δ 7.88–7.76 (m, 3H, Ar–H), 7.43–7.24 (m, 3H, Ar–H, triazole ring proton), 6.85 (d, $J=7.6$ Hz, 1H, Ar–H), 6.58 (d, $J=7.6$ Hz, 1H, Ar–H), 5.17–5.09 (m, 1H, CH dihydrofuran ring), 4.76–4.51 (m, 2H, –NCH_2), 3.33 (dd, $J_1=15.7$ Hz, $J_2=8.7$ Hz, 1H, H-3a), 2.96 (dd, $J_1=15.7$ Hz, $J_2=6.8$ Hz, 1H, H-3b), 2.22 (s, 3H, Ar–CH_3), 2.16 (s, 3H, Ar–CH_3); ^{13}C NMR (50 MHz, $CDCl_3+CCl_4$): δ 157.3, 148.3, 139.9, 135.5, 132.4, 131.0, 130.9, 130.0, 129.2, 128.5, 128.4, 126.1,125.2, 122.4, 80.9, 54.3, 33.7, 19.0, 15.4. Anal. Calcd for $C_{19}H_{19}N_3O$: C, 74.73; H, 6.27; N, 13.76%. Found: C, 74.70; H, 6.30; N, 13.72%.

*6.1.2.16. 1-[(4,7-Dimethyl-2,3-dihydrobenzofuran-2-yl)methyl]-4-pentyl-1H-1,2,3-triazole (**18**).* Yellowish liquid, yield (86%); IR (Neat) cm^{-1}: 2930 (C–H), 1216 (C–O–C); ESIMS: 300 $(M+H)^+$; ^{1}H NMR (200 MHz, $CDCl_3+CCl_4$): δ 7.34 (s, 1H, triazole ring proton), 6.80 (d, $J=7.6$ Hz, 1H, Ar–H), 6.54 (d, $J=7.6$ Hz, 1H, Ar–H), 5.12–5.04 (m, 1H, CH dihydrofuran ring), 4.68–4.45 (m, 2H, –NCH_2), 3.30–3.18 (m, 1H, H-3a), 3.00–2.81 (m, 1H, H-3b), 2.69 (t, $J=7.3$ Hz, 2H), 2.21–2.15 (m, 6H, 2Ar–CH_3), 1.68–1.54 (m, 2H, CH_2), 1.37–1.19 (m, 4H, $2CH_2$), 0.92 (t, 3H, $J=6.5$ Hz, CH_3); ^{13}C NMR (50 MHz, $CDCl_3+CCl_4$): δ 157.3, 139.8, 135.3, 132.2, 129.8, 125.1, 123.9, 116.8, 80.9, 54.0, 32.3, 31.7, 29.4, 25.9, 24.7, 19.0, 15.3, 14.4. Anal. Calcd for $C_{18}H_{25}N_3O$: C, 72.21; H, 8.42; N, 14.03%. Found: C, 72.10; H, 8.48; N, 14.21%.

*6.1.2.17. 1-(1-((4,7-Dimethyl-2,3-dihydrobenzofuran-2-yl)methyl)-1H-1,2,3-triazol-4-yl)hexan-1-ol (**19**).* White semi solid, yield (74%); IR (KBr) cm^{-1} 3381(O–H), 3018 (C–H), 1593(C=C), 1216 (C–O–C); ESIMS: 330 $(M+H)^+$; ^{1}H NMR (200 MHz, $CDCl_3+CCl_4$): δ 7.35 (s, 1H, triazole ring proton), 6.83 (d, $J=7.6$ Hz, 1H, Ar–H), 6.56 (d, $J=7.5$ Hz, 1H, Ar–H), 5.11 (bs, 1H, CH dihydrofuran ring), 4.70 (m, 3H, -NCH_2, CHOH), 3.32–3.20 (m, 1H, H-3a), 2.94–2.83 (m, 1H, H-3b), 2.22–2.15 (m, 6H, 2Ar–CH_3), 1.83 (bs, 2H, CH_2), 1.30 (bs, 6H, $3CH_2$), 0.90 (bs, 3H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3+CCl_4$):157.2, 139.8, 135.4, 132.4, 129.9, 123.9, 122.3, 80.6, 80.1, 37.8, 33.7, 32.4, 32.0, 22.9, 19.0, 15.3, 14.4. Anal. Calcd for $C_{19}H_{27}N_3O_2$: C, 69.27; H, 8.26; N, 12.76%. Found: C, 69.34; H, 8.35; N, 12.90%.

*6.1.2.18. 2-(1-((4,7-Dimethyl-2,3-dihydrobenzofuran-2-yl)methyl)-1H-1,2,3-triazol-4-yl)ethanol (**20**).* White solid, mp 110 °C, yield (87%); IR (KBr) cm^{-1}: 3409 (O–H), 3018 (C–H),1591 (C=C), 1216(C–O–C); ESIMS: 274 $(M+H)^+$; ^{1}H NMR (200 MHz, $CDCl_3+CCl_4$): δ 7.48 (s, 1H, triazole ring proton), 6.76 (d, $J=7.5$ Hz, 1H, Ar–H), 6.50 (d, $J=7.5$ Hz, 1H, Ar–H), 5.03–5.00 (m, 1H, CH dihydrofuran ring), 4.61–4.41 (m, 2H, –NCH_2), 3.81 (bs, 1H, OH), 3.24–3.11 (m, 1H, H-3a), 2.89–2.75 (m, 3H, H-3b, CH_2), 2.14–2.03 (m, 8H, -CH_2, Ar–$CH_3\times2$); ^{13}C NMR (50 MHz, $CDCl_3+CCl_4$): δ 157.3, 139.8, 135.4, 132.4, 129.8, 125.1, 123.9, 122.3, 61.8, 54.3, 32.4, 29.1, 18.9, 15.3. Anal. Calcd for $C_{15}H_{19}N_3O_2$: C, 65.91; H, 7.01; N, 15.37%. Found: C, 65.85; H, 7.10; N, 15.30%.

*6.1.2.19. 2-((4-Phenyl-1H-1,2,3-triazol-1-yl)methyl)-2,3-dihydrobenzofuran-5-carbonitrile (**21**).* White solid, mp 182 °C, yield (94%); IR (KBr) cm^{-1}: 2925 (C–H), 2223(CN), 1609 (C=C), 1246 (C–O–C); ESIMS: 303 $(M+H)^+$; ^{1}H NMR (200 MHz, $CDCl_3+CCl_4$): δ 7.82 (s, 1H, Ar–H), 7.67 (d, $J=6.8$ Hz, 2H, Ar–H), 7.33–7.18 (m, 5H, Ar–H, triazole ring proton), 6.76 (d, $J=8.8$ Hz, 1H, Ar–H), 5.25–5.18 (m, 1H, CH dihydrofuran ring), 4.70–4.58 (m, 2H, –NCH_2), 3.39 (dd, $J_1=16.4$ Hz, $J_2=9.4$ Hz, 1H, H-3a), 3.08 (dd, $J_1=16.4$ Hz, $J_2=7.2$, 1H, H-3b); ^{13}C NMR (50 MHz, $CDCl_3+CCl_4$): δ 134.0, 129.3, 129.1, 128.5, 127.7, 126.0, 121.2, 119.1, 110.8, 105.0, 63.0, 53.5, 32.1. Anal. Calcd for $C_{18}H_{14}N_4O$: C, 71.51; H, 4.67; N, 18.53%. Found: C, 71.40; H, 4.73; N, 18.45%.

*6.1.2.20. 2-((4-Benzyl-1H-1,2,3-triazol-1-yl)methyl)-2,3-dihydrobenzofuran-5-carbonitrile (**22**).* White solid, mp 142 °C, yield (59%); IR (KBr) cm^{-1}: 3019 (C–H), 2226 (CN), 1607 (C=O), 1217 (C–O–C); ESIMS: 317 $(M+H)^+$; ^{1}H NMR (200 MHz, $CDCl_3+CCl_4$): δ 7.37 (s, 1H), 7.33 (s, 1H), 7.28–7.06 (m, 6H, Ar–H), 6.74 (d, $J=8.18$ Hz, 1H, Ar–H), 5.28–5.16 (m, 1H, CH dihydrofuran ring), 4.68–4.49 (m, 2H, –NCH_2), 3.98 (s, 2H, –CH_2Ph), 3.42 (dd, $J_1=16.4$ Hz, $J_2=9.6$ Hz, 1H, H-3a), 3.12 (dd, $J_1=16.4$ Hz, $J_2=6.8$ Hz, 1H, H-3b); ^{13}C NMR (50 MHz, $CDCl_3+CCl_4$): δ 162.3, 139.1, 133.9, 129.3, 128.9, 128.8, 127.5, 126.9, 118.8, 110.5, 105.4, 81.9, 53.5, 32.5, 30.1. Anal. Calcd for $C_{19}H_{16}N_4O$: C, 72.13; H, 5.10; N, 17.71%. Found: C, 72.10; H, 5.20; N, 17.65%.

*6.1.2.21. 2-((4-Hexyl-1H-1,2,3-triazol-1-yl)methyl)-2,3-dihydrobenzofuran-5-carbonitrile (**23**).* White solid, mp 148 °C, yield (87%); IR (KBr) cm^{-1}: 2221 (CN), 1612 (C=C), 1253 (C–O); ESIMS: 311 $(M+H)^+$; ^{1}H NMR (300 MHz, $CDCl_3+CCl_4$): δ 7.44–7.28 (m, 3H, Ar–H, triazole ring proton), 6.84 (d, $J=8.28$ Hz, 1H, Ar–H), 5.28–5.23 (m, 1H, CH dihydrofuran ring), 4.78–4.58 (m, 2H, –NCH_2), 3.39 (dd, $J_1=16.0$ Hz, $J_2=6.3$ Hz, 1H, H-3a), 3.13 (dd, $J_1=16.0$ Hz, $J_2=4.5$ Hz, 1H, H-3a), 2.65 (bs, 2H, CH_2), 1.60 (bs, 2H,CH_2), 1.28 (bs, 6H, $3CH_2$), 0.90 (t, $J=5.94$ Hz, 3H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3+CCl_4$): δ 162.5, 134.0, 129.4, 127.7, 119.1, 110.2, 105.2, 82.2, 53.5, 32.1, 31.9, 29.6, 29.1, 22.9, 14.4. Anal. Calcd for $C_{18}H_{22}N_4O$: C, 69.65; H, 7.14; N, 18.05%. Found: C, 69.50; H, 7.17; N, 18.25%.

*6.1.2.22. 2-((4-Pentyl-1H-1,2,3-triazol-1-yl)methyl)-2,3-dihydrobenzofuran-5-carbonitrile (**24**).* White solid, mp 134 °C, yield (78%); IR (KBr) cm^{-1}: 2221 (CN), 1611 (C=C), 1253 (C–O–C); ESIMS: 297 $(M+H)^+$; ^{1}H NMR (300 MHz, $CDCl_3+CCl_4$): δ 7.43–7.38 (m, 3H, Ar–H, triazole ring proton), 6.83 (d, $J=8.3$ Hz, 1H, Ar–H), 5.26–5.25 (m, 1H, dihydrofuran ring proton), 4.71–4.57 (m, 1H, –NCH_2), 3.44 (dd, , $J_1=15.9$ Hz, $J_2=9.3$ HZ, 1H, H-3a), 3.14 (dd, , $J_1=15.9$ Hz, $J_2=4.5$ Hz, 1H, H-3b), 2.64 (bs, 2H, CH_2), 1.60 (bs, 2H, CH_2), 1.30–1.26 (m, 6H, $3CH_2$), 0.91 (t, $J=6.6$ Hz, 3H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3+CCl_4$): δ 162.4, 133.9, 129.3, 129.1, 127.7, 118.8, 110.6, 105.4, 82.6, 53.4, 32.3, 32.1, 31.7, 29.4, 22.7, 14.4. Anal. Calcd for $C_{17}H_{20}N_4O$: C, 68.89; H, 6.80; N, 18.90%. Found: C, 68.85; H, 6.86; N, 18.87%.

*6.1.2.23. 2-((4-(2-Hydroxyethyl)-1H-1,2,3-triazol-1-yl)methyl)-2,3-dihydrobenzofuran-5-carbonitrile (**25**).* White solid, mp 132 °C, yield (75%); IR (KBr) cm^{-1}: 3410 (O–H), 2221 (N_3), 1251 (C–O–C); ESIMS: 271 $(M+H)^+$; ^{1}H NMR (300 MHz, $CDCl_3+CCl_4$): δ 7.56 (s, 1H), 7.47–7.35 (m, 3H, Ar–H, triazole ring proton), 6.87 (d, $J=8.3$ Hz, 1H, Ar–H), 5.33–5.24 (m, 1H, CH dihydrofuran ring), 4.74–4.58 (m, 2H, –NCH_2), 3.94 (bs, 2H, –OCH_2), 3.47 (dd, $J_1=16.2$ Hz, $J_2=9.4$ Hz, 1H, H-3a), 3.14 (dd, $J_1=16.2$ Hz, $J_2=7.0$ Hz, 1H, H-3b), 2.91 (t, $J=6.33$ Hz, 2H, CH_2); ^{13}C NMR (50 MHz, $CDCl_3+CCl_4$): δ 167.5, 138.7, 134.1, 132.9, 124.1, 115.6, 109.3, 87.1, 66.0, 58.2, 37.0, 34.3. Anal. Calcd for $C_{14}H_{14}N_4O_2$: C, 62.21; H, 5.22; N, 20.73%. Found: C, 62.13; H, 5.25; N, 11.82%.

*6.1.2.24. 2-((4-(Hydroxymethyl)-1H-1,2,3-triazol-1-yl)methyl)-2,3-dihydrobenzofuran-5-carbonitrile (**26**).* White solid, mp 152 °C, yield (77%); IR (KBr) cm^{-1}: 3426 (O–H), 1251 (C–O–C); ESIMS: 257 $(M+H)^+$; ^{1}H NMR (300 MHz, $CDCl_3+CCl_4$): δ 7.71 (s, 1H, Ar–H), 7.42–7.35 (m, 2H, Ar–H, triazole ring proton), 6.83 (d, $J=8.6$ Hz, 1H, Ar–H), 5.30–5.22 (m, 1H, CH dihydrofuran ring), 4.73–4.56 (m, 4H, –NCH_2, –OCH_2), 3.44-3.35 (m, 2H, H-3a, OH), 3.11 (dd, $J_1=16.2$ Hz, $J_2=7.0$ Hz, 1H, H-3b); ^{13}C NMR (50 MHz, $CDCl_3+CCl_4$): δ 162.5, 133.9, 129.3, 128.9, 127.8, 119.3, 110.8, 104.5, 82.1, 56.3, 53.4, 32.1. Anal. Calcd for $C_{13}H_{12}N_4O_2$: C, 60.93; H, 4.72; N, 21.86%. Found: C, 60.89; H, 4.80; N, 21.84%.

*6.1.2.25. 2-((4-(1-Hydroxyhexyl)-1H-1,2,3-triazol-1-yl)methyl)-2,3-dihydrobenzofuran-5-carbonitrile (**27**).* White solid, mp 112 °C, yield (85%); IR (KBr) cm^{-1}: 3387 (O–H), 2928 (C–H), 2224 (CN), 1610 (C=C), 1248 (C–O–C); ESIMS: 327 $(M+H)^+$; ^{1}H NMR

(300 MHz, $CDCl_3 + CCl_4$): δ 7.57 (s, 1H, Ar–H), 7.45 (d, $J = 8.4$ Hz, 1H, Ar–H), 7.39 (s, 1H triazole ring proton), 6.85 (d, $J = 8.31$ Hz, 1H, Ar–H), 5.32–5.23 (m, 1H, CH dihydrofuran ring), 4.83–4.58 (m, 3H,–NCH_2, –CH(OH)–), 3.46 (dd, $J_1 = 16.3$ Hz, $J_2 = 9.5$ Hz, 1H, H-3a), 3.14 (dd, $J_1 = 16.3$ Hz, $J_2 = 6.9$ Hz, 1H, H-3b), 2.71 (bs, 1H, OH), 1.79–175 (m, 2H,CH_2), 1.30–1.26 (m, 6H, $3CH_2$), 0.91 (t, $J = 6.0$ Hz, 3H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3 + CCl_4$): δ 162.4, 134.1, 129.4, 127.6, 119.1, 110.8, 105.2, 82.0, 67.3, 53.7, 37.7, 32.2, 32.1, 22.9, 14.4. Anal. Calcd for $C_{18}H_{22}N_4O_2$: C, 66.24; H, 6.79; N, 17.17%. Found: C, 66.20; H, 6.82; N, 17.20%.

7. Biological activity

7.1. Activity against M. tuberculosis H37Rv strain

Drug susceptibility and determination of MIC of the test compounds/drugs against H37Rv were performed by agar micro-dilution method where two-fold dilutions of each test compound were added into 7H10 agar supplemented with OADC and organism. A culture of *M. tuberculosis* H37Rv growing on L–J medium was harvested in 0.85% saline with 0.05% Tween-80. A suspension of 1 mg/mL concentration of extracts/compounds was prepared in DMSO. This suspension was added to (in tubes) 7H10 Middle Brook's medium (containing 1.7 mL medium and 0.2 mL OADC supplement) at different concentrations of compound keeping the volume constant, i.e. 0.1 mL. Medium was allowed to cool by keeping the tubes in slanting position. These tubes were then incubated at 37 °C for 24 h followed by streaking of H37Rv (5×10^4 bacilli per tube). These tubes were then incubated at 37 °C. Growth of bacilli was seen after 30 days of incubation. Tubes having the compounds were compared with control tubes where medium alone was incubated with H37Rv. The concentration at which complete inhibition of colonies occurred was taken as active concentration of test compound.

Acknowledgements

Authors are thankful to UGC and CSIR New Delhi for the award of JRF and SRF, respectively. We sincerely thank SAIF CDRI for providing spectroscopic data and microanalyses of the compounds. Financial assistance from DRDO and DBT New Delhi is also gratefully acknowledged.

Appendix A. Supplementary data

General procedure and scan spectral data of compounds are available online at www.sciencedirect.com. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ejmech.2009.09.036.

References

[1] R.B. Woodward, R. Hoffmann, Angew. Chem. Int. Ed. Engl. 81 (1969) 797–869.
[2] R.B. Woodward, R. Hoffmann, Angew. Chem. Int. Ed. Engl. 8 (1969) 781–853.
[3] R. Huisgen, Angew Chem Int Ed Engl 75 (1963) 604–637.
[4] R. Huisgen, Angew. Chem. Int. Ed. Engl. 2 (1963) 565–598.
[5] R. Huisgen, Angew. Chem. Int. Ed. Engl. 75 (1963) 741–754.
[6] R. Huisgen, Angew. Chem. Int. Ed. Engl. 2 (1963) 633–645.
[7] R. Huisgen, 1,3-Dipolar Cycloaddition Chemistry. in: A. Padwa (Ed.). Wiley, New York, 1984.
[8] E.H. Ryu, Y. Zhao, Org. Lett. 7 (2005) 1035.
[9] G.K. Such, J.F. Quinn, A. Quinn, E. Tjipto, F. Caruso, J. Am. Chem. Soc. 128 (2006) 9318–9319.
[10] S. Löber, P. Rodriguez-Loaiza, P. Gmeiner, Org. Lett. 5 (2003) 1753–1755.
[11] J.F. Lutz, Angew. Chem. Int. Ed. Engl. 46 (2007) 1018–1025.
[12] D. Liu, W. Gao, Q. Dai, X. Zhang, Org. Lett. 7 (2005) 4907–4910.
[13] R.J. Detz, S.A. Heras, R.D. Gelder, P.W.N.M. van Leeuwen, H. Hiemstra, J.N.H. Reek, et al., Org. Lett. 8 (2006) 3227–3230.
[14] V. Aucagne, D.A. Leigh, Org. Lett. 8 (2006) 4505–4507.
[15] Y. Li, J.C. Huffman, A.H. Flood, Chem. Commun. (2007) 2692–2694.
[16] S. Chuprakov, N. Chernyak, A.S. Dudnik, V. Gevorgyan, Org. Lett. 9 (2007) 2333–2336.
[17] N.G. Aher, V.S. Pore, N.N. Mishra, A. Kumar, P.K. Shukla, A. Sharma, et al., Bioorg. Med. Chem. Lett. 19 (2009) 759–763.
[18] A. Kamal, N. Shankaraiah, V. Devaiah, K.L. Reddy, A. Juvekar, S. Sen, et al., Bioorg. Med. Chem. Lett. 18 (2008) 1468–1473.
[19] D.K. Kim, J. Kim, H.J. Park, Bioorg. Med. Chem. Lett. 14 (2004) 2401–2405.
[20] B.K. Singh, A.K. Yadav, B. Kumar, A.N. Gaikwad, S.K. Sinha, V. Chaturvedi, et al., Carbohydr. Res. 343 (2008) 1153–1162.
[21] A. Dondoni, Chem. Asian J. 2 (2007) 700–708 and references cited therein.
[22] S. Prado, H. Ledeit, S. Michel, M.I. Koch, J.C. Darbord, S.T. Cole, et al., Bioorg. Med. Chem. 14 (2006) 5423–5428.
[23] R.C. Brent, Nat. Prod. Rep. 20 (2003) 535–557.
[24] A.K. Yadav, B.K. Singh, N. Singh, R.P. Tripathi, Tetrahedron Lett. 48 (2007) 6628–6632.
[25] H. Saito, H. Tomioka, K. Sato, M. Emori, T. Yamane, K. Yamashita, Antimicrob. Agents Chemother. 35 (1991) 542.