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

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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 Mycobacetrium 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.

Keywords: Triazoles, Huisgen [3 + 2] cycloaddition, copper catalyst, antitubercular agents.

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1. Introduction

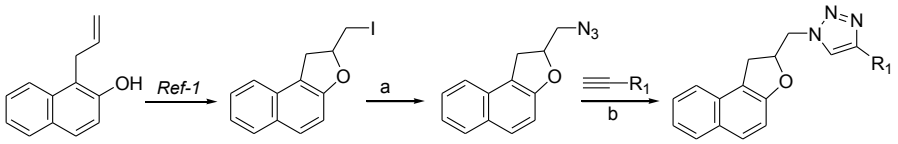
The rediscovery of "old" reactions invented in the middle of the last century has encouraged the researchers to develop new chemistry in terms of atom economy, eco-friendly nature, yields and simplicity. One of such a reaction is the reaction between an azide (1,3-dipole) and acetylenes (dipolarophiles) belonging to a concerted (one step) [1] 3+2 cycloaddition reaction systematically studied in early sixties by Huigsen as 1,3-dipolar addition reactions [2]. The Huisgen (3+2) cycloaddition reaction using azides and alkynes is an important method for the atom economic synthesis of 1,2,3-triazoles [3]. 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 [4] 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 [5]. Further, compounds with 1,4-disubstituted triazole moiety have displayed a number of chemotherapeutic properties such as antifungal [6], anticancer [7], growth factor β1 type receptor inhibitory [8] and Antitubercular activities [9]. 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 [10]. Keeping in mind the Antitubercular activities of triazoles [9] and recent reports that benzofuran and dihydrobezofuran derivatives are natural product leads to develop new antituberculaar agents [11,12] we were interested to synthesise a hybrid molecule consisting of benzofuran and triazole moieties.

Our method consists in 3+2 cycloaddition reaction of of 2-(azidomethyl)-benzofurans with different acetylenes in presence of $CuSO_4.5H_2O$ (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 M. tuberculosis H37Rv.

2. Chemistry

2-(Iodomethyl)-dihydronapthofuran (**1a**) and 2-(iodomethyl)-dihydrobenzofuran derivatives (**1b-1d**) were prepared in good yields by oxidative cyclization following earlier reported method [13]. The reaction of these iodomethyl dihydronaphto (or benzo) furans **1a**, **1b**, **1c** and **1d** with sodium azide in presence of Cu- powder (as catalyst) at 90 °C in N,N-dimethyformamide yielded the respective 2-(azidomethyl)-dihydronapthofuran (**2a**) and 2-(azidomethyl)- dihydrobenzofuran derivatives **2b, 2c,** and **2d** in good yields. (3+2) cycloaddition of the 2-azidomethyl dihydronaphtho (or benzo) furans (**2a-2d)** with different alkynes *viz.* 1-octyne, 1-heptyne, 3-butyn-1-ol, 1-octyn-3-ol, phenylaceytylene, 3-phenyl-1-propyne, propargyl alcohol in presence of Na-ascorbate (5 mol %), t-BuOH : H_2O (2:1), and $CuSO_4.5H_2O$ (1 mol %), at 90 °C afforded the corresponding 1, 4-disubstuted-1, 2, 3-triazole compounds **3-27** in good yields (scheme 1 and scheme 2).



1a, 68.6 % **2a** **3-8**

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, $CuSO_4.5H_2O$ (1 mol%), 90 °C, 4h

3. Biology

The newly synthesized compounds were screened for their antibacterial activity against M. tuberculosis H37Rv employing agar microdilution method [14] respectively. INH and ethambutol were used as standard drugs.

4: Results and Discussions

4.1. Chemistry

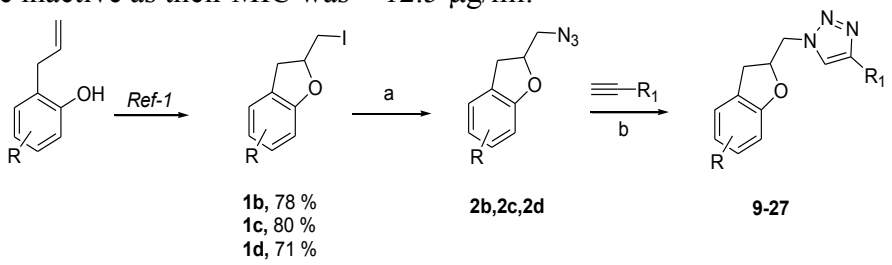
The structures of compounds **2a-2d** were in accordance with their spectroscopic data. The IR spectrum of the compounds in general exhibited the absorption band at around 2100-2110 cm^{-1} indicating that the azido group present in compounds. The ES mass spectra (ESMS) of the compounds showed their respective $[M + H]^+$ peaks. In the ^1H NMR spectrum of the compound **2a** the one methine proton of C-2 appear 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 observed at δ 82.1 ppm. All aromatic carbons were appeared from δ 112.4 to 157.0 ppm. Almost similar ^1H-NMR and ^{13}C-NMR patterns were observed for compounds **2b-2d**.

Similarly the structures of compounds **3-27** were established on the basis their spectroscopic data. In IR spectrum of compounds the peak corresponding to azido functionality at around 2100-2110 cm^{-1} was disappeared. In the ^1H-NMR spectrum of compound **3** the vinylic proton of C-5 on triazole ring merged with two aromatic protons and appeared as multiplet at around δ 7.49-7.33 ppm while the one aromatic proton observed as multiplet at around δ 7.30-7.23 ppm. The three aromatic protons of naphthyl ring were display three distinct doublet at δ 7.75 ppm, δ 7.66 ppm, and δ 7.07 ppm with coupling constant 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 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 were 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 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 of azidomethyl group appeared at δ 53.9 ppm and methylene carbon of dihydronapthofuran ring (C-3) at δ 32.0 ppm. The vinylic carbon (C-2) observed at δ 81.7 ppm. All aromatic carbons were observed at their usual.

4.2 Biology

All the newly synthesized compounds including 2-azidomethyl dihydronaphtho (benzo) furans and 1-(2,3-dihydro naphtha(benzo)-furan-2yl-methyl) [1.2,3]–triazoles were screened against M. tuberculosis H37Rv. As evident from table 3 one of the compounds 2-azidomethyl dihydronaphthofurans **2a** proved to potent Antitubercular with MIC 3.12 μg/ml comparable to the standard drug ethambutol. The cycloaddition products 1-(2,3-dihydro naphthofuran-2yl-methyl) [1.2,3]–triazoles of compound **2a** with different alkynes in general were less active than compound **2a**. Among 1-(2,3-dihydro naphthofuran-2yl-methyl) [1.2,3]–triazoles only compound **7** with n-pentyl substitutent

exhibited mild Antitubercular activity with MIC 12.5 μg/ml, other compounds of the series were inactive as their MIC was > 12.5 μg/ml.



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, $CuSO_4.5H_2O$ (1 mol%), 90 °C, 4h

S. No.	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

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

Among all the 2-azidomethyl dihydrobenzofurans none of them showed significant inhibition of the mycobacterial growth. However, among 1-(2,3-dihydrobenzo-furan-2-yl-methyl) [1.2,3]–triazoles, compounds **9** and **12** with 4-n-pentyl substituent in the triazole moiety and compound **14** with 4-benzyl substitutent exhibited mild in vitro Antitubercular activity with MIC 12.5 μg/ml activity 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 mycobacerial cell; however, detailed biological studies are needed to find out definite reasons for their inactivity.

5. Conclusion

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 cyloddition of azides and acetylenes in good to very good yields. One

of the intermediates 2-azido methyl dihydronaphthofurand 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.

S. No.	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 2 Synthesis of 2-(azidomethyl)-dihydrobenzofuran derivatives (**2b-2d**) and 1, 4-disubstituted-1, 2, 3-triazoles (**9-27**)

Compd no.	cLog P*	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	NA
4	4.74	NA
5	2.48	NA
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
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

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**)

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

NA = Not active

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 or in KBr soln 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 derivative (2a, and 2b-2d)

To a magnetically stirred solution of the 2-(azidomethyl)-1,2-dihydronaphtho[2,1-b] furan (**2a**) or 2-(azidomethyl)-1,2-dihybenzo[2,1-b] furan derivatives (**2b-2d**) (1 mmol) in DMF, NaN_3 (1.2 mmol) 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 ethyl acetate; organic layer was washed by water (3 x 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- EtOAc as eluent to give desired products.

6.1.1.1. 2-(azidomethyl)-1,2-dihydronaphtho[2,1-b] furan (2a).

IR (Neat) cm^{-1}: 2102, 1244; 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.

6.1.1.2. 2-(azidomethyl)-2,3-dihydrobenzofuran-5-carbaldehyde (2b).

IR (Neat) cm^{-1}: 2104, 1685, 1247; 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 azidomethyl), 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.

6.1.1.3 . 2-(azidomethyl)-4,7-dimethyl-2,3-dihydrobenzofuran (2c).

IR (Neat) cm^{-1}: 2104; 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, 129.9, 125.4, 81.6, 54.8, 33.8, 19.0, 15.3.

6.1.1.4. 2-(azidomethyl)-2,3-dihydrobenzofuran-5-carbonitrile(2d).

IR (Neat) cm^{-1}: 3020, 2361, 2107; 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 azidometyl, 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.

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 $CuSO_4.5H_2O$ (1 mol %, freshly prepared solution in of water). The heterogeneous mixture was stirred vigorously for 6 h, the reaction mixture diluted with ice cold water and precipitate thus obtained was collected by filtration and washed with ice cold water and dried under vaccum 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).

IR (KBr) cm^{-1}: 2923, 1633, 1255; 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, CH_2x3) 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.

6.1.2.2. 1-[(1,2-dihydronaphtho[2,1-b] furan-2-yl) methyl]- 4-phenyl-1H-1,2,3- triazole (4).

IR (KBr) cm^{-1}: 2922, 1629, 1252; ESIMS: 328 $(M+H)^+$; ^{1}H 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.

6.1.2.3. (1-[(1,2-dihydronaphtho[2,1-b] furan-2-yl) methyl]- 1H-1,2,3-triazol-4-yl) methanol (5).

IR (KBr) cm^{-1}: 3356, 2361; ESIMS: 282 $(M+H)^+$; ^{1}H 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), 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.

6.1.2.4. 4-benzyl-1-[(1,2-dihydronaphtho[2,1-b]furan-2-yl)methyl]- 1H-1,2,3- triazole (6).

IR (KBr) cm^{-1}: 2919, 1631, 1253; ESIMS: 342 $(M+H)^+$; ^{1}H 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 + 2xAr-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), 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.

6.1.2.5. 1-(1,2-dihydronaphtho[2,1-b] furan-2-yl) methyl)-4-pentyl-1H-1,2,3-triazole (7).

IR (KBr) cm^{-1}: 2926, 1632, 1252; ESIMS: 322 $(M+H)^+$; ^{1}H 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, 2xAr-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), 3.61 (J_1 = 15.7 Hz,

J_2= 9.7,, 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, 2xCH_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.

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).

IR (KBr) cm^{-1}: 3020, 1216; 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, CH_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.

6.1.2.7. 2-((4-pentyl-1H-1,2,3-triazol-1-yl)methyl)-2,3-dihydrobenzofuran-5-carbaldehyde (9).

IR (KBr) cm^{-1}: 2928, 1685, 1218; 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, 2xAr-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), 1.57 (bs, 2H), 1.25 (bs, 4H), 0.87 (t, J = 6.5 Hz, 3H); ^{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.

6.1.2.8. 2-[(4-(hydroxymethyl)-1H-1,2,3-triazol-1-yl) methyl]-2,3-dihydrobenzofuran-5-carbaldehyde (10).

IR (KBr) cm^{-1}: 3448, 2362, 1677, 1603; 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, 2xAr-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), 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.

6.1.2.9. 2-[(4-phenyl-1H-1,2,3-triazol-1-yl) methyl]-2,3-dihydrobenzofuran-5-carbaldehyde (11).

IR (KBr) cm^{-1}: 1684, 1606, 1252; 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.

6.1.2.10. 2-[(4-hexyl-1H-1,2,3-triazol-1-yl) methyl]-2,3-dihydrobenzofuran-5-carbaldehyde (12).

IR (KBr) cm^{-1}: 2926, 1683, 1606; ESIMS: 314 $(M+H)^+$; ^1H 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), 1.56 (m, 2H), 1.24 (m, 6H), 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.

6.1.2.11. 2-[(4-benzyl-1H-1,2,3-triazol-1-yl) methyl]-2,3-dihydrobenzofuran-5-carbaldehyde (13).

IR (KBr) cm^{-1}: 1684, 1608, 1249; ESIMS: 320 $(M+H)^+$; ^1H 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 = 6.8Hz,, 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.

6.1.2.12. 1-[(4,7-dimethyl-2,3-dihydrobenzofuran-2-yl) methyl]-1H-1,2,3-triazol-4-yl methanol (14).

IR (Neat) cm^{-1}: 3367, 2924, 1590, 1455; ESIMS: 260 $(M+H)^+$; ^1H 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), 3.30 (dd, J_1 = 15.5, J_2= 8.6 Hz, 1H), 2.88 (dd, J_1 = 15.0, J_2 = 7.0 Hz, 1H), 2.15 (s, 3H), 2.14 (s, 3H); ^{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.

6.1.2.13. 4-benzyl-1-[(4,7-dimethyl-2,3-dihydrobenzofuran-2-yl) methyl]-1H-1,2,3-triazole (15).

IR (Neat) cm^{-1}: 3020, 1725, 1216, 756; ESIMS: 320 $(M+H)^+$; ^1H 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.

6.1.2.14. 1-[(4,7-dimethyl-2,3-dihydrobenzofuran-2-yl) methyl]-4-hexyl-1H-1,2,3-triazole (16).

IR (Neat) cm^{-1}: 2927, 1592, 1259 ; ESIMS: 314 $(M+H)^+$, ^1H 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**),** 2.20 (s, 3H, Ar-CH_3), 2.15 (s, 3H, Ar-CH_3), 1.63-1.56 (m, 2H), 1.29-1.25 (m, 6H), 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.

6.1.2.15. 1-[(4,7-dimethyl-2,3-dihydrobenzofuran-2-yl) methyl]-4-phenyl-1H-1,2,3-triazole (17).

IR (KBr) cm^{-1}: 3020, 1216, 763; ESIMS: 306 $(M+H)^+$; ^1H 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.

6.1.2.16. 1-[(4,7-dimethyl-2,3-dihydrobenzofuran-2-yl) methyl]-4-pentyl-1H-1,2,3-triazole (18).

IR (Neat) cm^{-1}: 2930, 2360, 1216; ESIMS: 300 $(M+H)^+$; ^1H 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), 1.68-1.54 (m, 2H), 1.37-1.19 (m , 4H), 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.

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).

IR (KBr) cm^{-1} 3381, 3018, 2929, 1593, 1216; ESIMS: 330 $(M+H)^+$; ^1H 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), 3.32-3.20 (m, 1H, H-3a), 2.94-2.83 (m, 1H, H-3b), 2.22-2.15 (m, 6H), 1.83 (bs, 2H), 1.30 (bs, 6H), 0.90 (bs, 3H); ^{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.

6.1.2.18. 2-(1-((4,7-dimethyl-2,3-dihydrobenzofuran-2-yl)methyl)-1H-1,2,3-triazol-4-yl)ethanol (20).

IR (KBr) cm^{-1}: 3409, 3018,1591,1216; ESIMS: 274 $(M+H)^+$; ^1H 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_3x2); ^{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.

6.1.2.19. 2-((4-phenyl-1H-1,2,3-triazol-1-yl)methyl)-2,3-dihydrobenzofuran-5-carbonitrile (21).

IR (KBr) cm^{-1}: 2925, 2223, 1609, 1246; ESIMS: 303 $(M+H)^+$; ^1H 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.

6.1.2.20. 2-((4-benzyl-1H-1,2,3-triazol-1-yl)methyl)-2,3-dihydrobenzofuran-5-carbonitrile (22).

IR (KBr) cm^{-1}: 3019, 2226, 1607, 1217; ESIMS: 317 $(M+H)^+$; ^1H 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.

6.1.2.21. 2-((4-hexyl-1H-1,2,3-triazol-1-yl)methyl)-2,3-dihydrobenzofuran-5-carbonitrile (23).

IR (KBr) cm^{-1}: 3454, 2221, 1612, 1253; ESIMS: 311 $(M+H)^+$; ^1H 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, CH_2x3), 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.

6.1.2.22. 2-((4-pentyl-1H-1,2,3-triazol-1-yl)methyl)-2,3-dihydrobenzofuran-5-carbonitrile (24).

IR (KBr) cm^{-1}: 3415, 2221, 1611, 1253; ESIMS: 297 $(M+H)^+$; ^1H 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), 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.

6.1.2.23. 2-((4-(2-hydroxyethyl)-1H-1,2,3-triazol-1-yl)methyl)-2,3-dihydroben-zofuran-5-carbonitrile (25).

IR (KBr) cm^{-1}: 3410, 2362, 2221, 1251, 1032; 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), 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.

6.1.2.24. 2-((4-(hydroxymethyl)- 1H-1,2,3-triazol-1-yl)methyl-2,3-dihydrobenzofuran-5-carbonitrile (26).

IR (KBr) cm^{-1}: 3426, 1251, 1007; 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), 3.44-3.35 (m, 2H), 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.

6.1.2.25. 2-((4-(1-hydroxyhexyl)- 1H-1,2,3-triazol-1-yl)methyl-2,3-dihydrobenzofuran-5-carbonitrile (27).

IR (KBr) cm^{-1}: 3387, 2928, 2224, 1610, 1248; 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, -C<u>H</u>(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), 1.30-1.26 (m, 7H), 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.

7. Biological activity

7.1. Activity against M. tuberculosis H37Ra strain

All of the synthesized compounds were evaluated for their efficacy against M. tuberculosis H37Ra at active concentration ranging from 50 mg/mL to MIC using two-fold dilutions in the initial screen. Log phase culture of M. tuberculosis H37Ra is diluted so as to give final OD550 nm of 0.05 in Sauton's medium. In 96-well white plates 190 mL of culture is dispensed in each well. A dimethyl sulfoxide (DMSO) solution of test compounds is dispensed into 96- well plates so as to make final test concentration of 25 mg/mL (5 mg test compound is dispensed into 10 mL of DMSO). Then the plate is

incubated at 37 °C/5% CO2 for 5 days. On 5th day 15 mL Alamar Blue solution is added to each well of the plate. The plate is again incubated overnight at 37 °C/5% CO2 incubator. The fluorescence is read on BMG polar star with excitation frequency at 544 nm and emission frequency at 590 nm. The compounds, which were found to be active (>90% inhibition as compared with control) at this concentration are then tested at 6 serial dilutions starting from 50 to 1.56 mg/mL.

7.2. Activity against M. tuberculosis H37Rv strain

Drug susceptibility and determination of MIC of the test compounds/drugs against M. tuberculosis H37Rv were performed by agar microdilution 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 M. tuberculosis H37Rv (5 x104 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.

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