European Journal of Medicinal Chemistry 89 (2015) 138–146

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

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

Original article

Rational design, synthesis and anti-proliferative evaluation of novel 1,4-benzoxazine-[1,2,3]triazole hybrids

Rajitha Bollu [a], Jyothsna Devi Palem [a], Rajashaker Bantu [a], Vijayacharan Guguloth [a], Lingaiah Nagarapu [a, *], Sowjanya Polepalli [b], Nishant Jain [b]

[a] Organic Chemistry Division II (CPC), CSIR-Indian Institute of Chemical Technology, Tarnaka, Hyderabad 500007, India
[b] Centre for Chemical Biology, CSIR-Indian Institute of Chemical Technology, Tarnaka, Hyderabad 500007, India

ARTICLE INFO

Article history:
Received 11 June 2014
Received in revised form
14 October 2014
Accepted 16 October 2014
Available online 18 October 2014

Keywords:
1,2,3-Triazoles
1,4-Benzoxazine
Anti-proliferative
Apoptosis
Cell lines

ABSTRACT

A series of novel 1,2,3-triazole-1,4-benzoxazine hybrids **5a**–**n** were efficiently synthesized employing click chemistry approach and evaluated for anti-proliferative activity against four cancer cell lines such as HeLa (cervical), MIAPACA (pancreatic), MDA-MB-231 (breast) and IMR32 (neuroblastoma). Compounds **5n** and **5g** exhibited promising anti-proliferative activity with GI_{50} values ranging from **1.2** to **2.5** μM and **0.1**–**1.1** μM respectively against all cell lines, like HeLa, MDA-MB-231, MIAPACA and IMR32, while compound **5l** showed significant activity against MDA-MB-231 and IMR32 with GI_{50} values ranging from **1.1** and **1.4** μM. This is the first report on the synthesis and *in vitro* anti-proliferative evaluation of 1,2,3-triazole-1,4-benzoxazine hybrids.

1. Introduction

The 2*H*-1,4-benzoxazin-3-(4*H*)-one scaffold has been extensively studied as an important heterocyclic system for building natural and designed synthetic compounds [1]. The 2*H*-1,4-benzoxazin-3-(4*H*)-ones and 3,4-dihydro-2*H*-1,4-benzoxazines are frequently utilized as suitable scaffolds for the design of biologically active compounds, having various properties such as antibacterial [2], bacterial histidine protein kinases [3], for treating infections caused by *Mycobacterium* [4], for treating cardiovascular disease, myocardial necrosis or arrhythmia [5], peroxisome proliferator activated receptor (PPAR) agonist, diabetes, hyperlipidaemia[6], neuroprotectants [7], inhibitors of nitric oxide synthase, inflammatory, autoimmune, cardiovascular disorders [8,9], inhibitors of the coagulation serine proteases [10], anxiety and depression [11].

In general, 1,2,3-triazoles have received attention not only in organic chemistry but also in medicinal chemistry due to their easy synthesis by click chemistry bearing attractive features as well as numerous biological activities [12–16]. In particular, by combining 1,2,3-triazoles with other pharmacophores *via* click chemistry, a number of compounds with potent antitumour activity were synthesized. For example, a series of 1,2,3-triazole bearing podophyllotoxins proved more potent than etoposide in selected human cancer cell lines [17], a library of 1,2,3-triazole analogues of combretastatin A-4 displayed potent cytotoxic activity against several cancer cell lines with IC_{50} values in nano-molar range [18], a family of bifunctional hybrids of 1,2,3-triazole-tethered β-lactam-chalcones exhibited moderate to good cytotoxic activity [19] and *N*-((1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl)arylamide was identified as a novel and proprietary antitumour molecule with IC_{50} of 46 μM against MCF-7 cancer cell line [20].

As shown in Fig. 1, compound (I) and (II) is a potential antibacterial agent and also acts as an inhibitor of bacterial histidine protein kinase [2,4]. The compound (III) possesses D2 receptor antagonistic activity and is a potential antipsychotic agent [21]. 1,4-Benzoxazinone (IV) inhibits the coagulation serine proteases factor Xa, thrombin and factor VIIa [10], and 1,4-benzoxazinone (VI) is a potential agent for treating anxiety and depression [11]. Myocardial necrosis or arrhythmia and 1,4-benzoxazine derivative (V) possesses peroxisome proliferator activated receptor (PPAR) agonist activity and could be used in treating diabetes, hyperlipidaemia and other diabetic complications [6].

As shown in Fig. 2, compound (a) is an aromatase inhibitor which could reduce the growth stimulatory effect of oestrogen-dependent breast cancer [22], compound (b) effectively inhibited

* Corresponding author.
E-mail addresses: lnagarapuiict@yahoo.com, nagarapu@iict.res.in (L. Nagarapu).

http://dx.doi.org/10.1016/j.ejmech.2014.10.051
0223-5234/

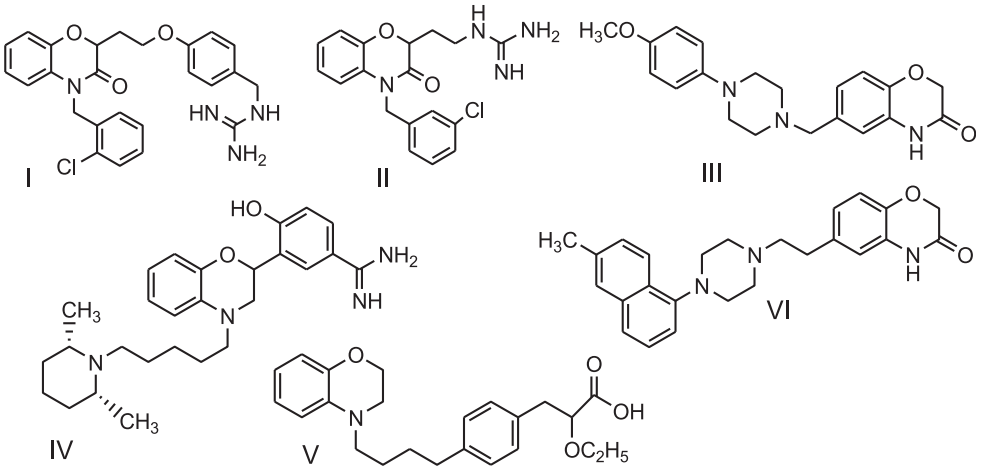


Fig. 1. Representative examples of biologically active 1,4-benzoxazine derivatives.

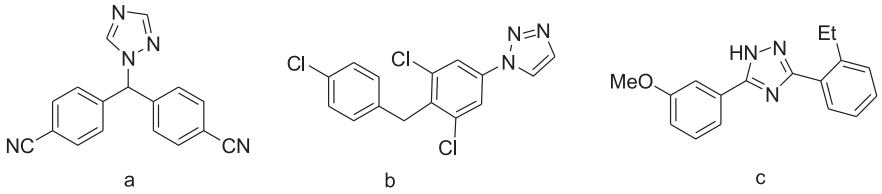


Fig. 2. Triazole based under clinical trial cancer therapy agents.

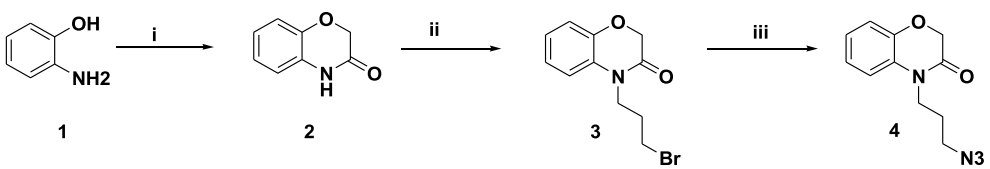
epithelia proliferation [23], while contragestazol (c) exhibited outstanding effect on the suppression of Oophoroma cells [24]. All these compounds are under clinical trials for cancer therapy.

Considering the above facts, it is of our interest to integrate both 1,4-benzoxazine and triazole pharmacophore units in one molecular platform to generate a newer scaffold for biological evaluation [25–30]. These 1,2,3-triazoles were efficiently prepared through Cu(I) catalysed click chemistry. In continuation to our ongoing research activities [31–38], to discover and develop tumour growth inhibitors and apoptotic inducers as potential new anti cancer-agents, we herein report an efficient method for the synthesis of novel 1,4-benzoxazine-1,2,3-triazole hybrids **5a**–**n** in excellent yields. The synthesized hybrids **5a**–**n** were evaluated for their *in vitro* anti-proliferative activity against four human cancer cell lines such as HeLa (cervical), MIAPACA (pancreatic), MDA-MB-231 (breast) and IMR32 (neuroblastoma) using an SRB cell proliferation assay to estimate the viability or growth. Significantly, the compounds **5n** and **5g** showed promising anti-proliferative activity with GI_{50} values ranging from **1.2** to **2.5** μM and **0.1**–**1.1** μM respectively against all cell lines, like HeLa, MDA-MB-231, MIAPACA and IMR32 human cancer cell lines.

2. Results and discussion

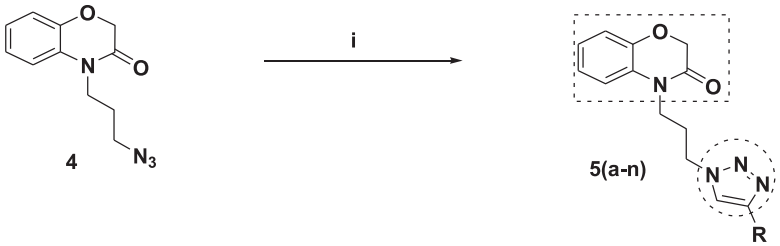
2.1. Chemistry

The synthesis of the desired 4-(3-azidopropyl)-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-ones was performed in three steps starting from amino phenol using 1,3-dibromo propane and sodium azide as intermediates. The first synthetic step involved the subsequent acylation of aminophenol with TEBA, $NaHCO_3$ and chloroacetyl chloride in chloroform, about 12 h and "*in situ*" cyclization delivered benzoxazinone **2** [39]. In the presence of K_2CO_3 and catalytic amount of TBAI, a secondary amine **2** was alkylated with 1,3-dibromo propane in DMF solution about 1 h to give the corresponding tertiary amine **3** under room temperature conditions, in good yields. Organic azide **4** were generated *in situ* by reacting alkyl bromide **3** with NaN_3 at 120 °C in DMF solution for 12 h, and subsequently, copper salt, sodium ascorbate, and alkynes (procured from commercial sources) were added without isolating the intermediate organic azides (Scheme 1). Finally, using a one-pot protocol, 1,4-benzoxazin-1,2,3-triazole hybrids **5a**–**n** were



Reagent & conditions: i) TEBA, $NaHCO_3$, Chloroacetyl chloride, $CHCl_3$,12 h, reflux, 55°C ii) 1,3-dibromo propane, TBAI, K_2CO_3, DMF, RT, 1 h, iii) NaN_3, TBAB, DMF, 12 h, reflux, 120°C

Scheme 1. Synthesis of 1,4-benzoxazine azide **4**.



Reagents & conditions: i) $CuSO_4.5H_2O$, Sodium ascorbate, THF:H_2O (1:1), rt, 24 h

Scheme 2. Synthesis of 1,4-benzoxazine-1,2,3-triazole hybrides **5(a–n).**

obtained in excellent yields from organic azide 4-(3-azidopropyl)-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one (**4**) (Scheme 2) (Table 1).

The synthesized 1,4-benzoxazin-1,2,3-triazole hybrids **5a–n** were confirmed on the basis of their spectral data. In ^{1}H NMR spectra, the characteristic singlet signal appeared for triazole **5a–n** in the range of δ 7.37–7.99 ppm. The structures for all these compounds were further confirmed by HRMS analysis. For instance, **5a** displayed a molecular ion peak at *m/z* 335.14975 $[M+H]^+$ suggesting the molecular formula of $C_{19}H_{18}N_4O_2$. Additionally, the IR spectra for the target compounds **5a–n** exhibited characteristic absorption bands at 1662–1680 cm^{-1} and 1501, 1466, 1400 cm^{-1} which corresponded to C=O and N–N, N=N, respectively.

2.2. Effects of the compounds on the viability of human cancer cells

The *in vitro* anti-proliferative activity of the designed compounds **5a–n** were evaluated against a panel of four different human cancer cell lines, HeLa (cervical), MIAPACA (pancreatic), MDA-MB-231 (breast) and IMR32 (neuroblastoma) summarized in Table 2. The compounds were picked for an advanced assay against these four human cancer cell lines at five different concentrations (0.01, 0.1, 1, 10, 100 μM). GI_{50} (growth inhibitory activity) was calculated and these values corresponded to the concentration of the compound causing 50% decrease in the net cell growth as compared to the standard drugs, Doxorubicin and Paclitaxel. Results were calculated for each of these parameters if the level of activity was reached; however, if the effect was not achieved, the value was expressed as greater or less than the maximum or minimum concentration tested.

Based on Table 2, the synthesized compounds **5a–n** showed significant to moderate cancer cell growth inhibition with GI_{50} values ranging from **0.1** to **>100** μM. The effect of various substituents on the 1,4-benzoxazine moiety was examined. The structure-activity relationship (SAR) study revealed that the orientation of substituent on 1,2,3-triazole ring is not only crucial but also required 1,4-benzoxazine along with a propyl linker for inducing the anti-proliferative activity against these cancer cell lines. In particular, the compounds **5g**, **5l**, **5m** and **5n** showed promising anti-proliferative activity with GI_{50} values ranging from **0.1** to **1.1**, **1.1** to **23.2**, **0.1** to **12.5** and **1.2–2.5** μM respectively, against the four human cancer cell lines. Among them, compounds **5g** and **5n** showed potent anti-proliferative activity against all the four human cancer cell lines. The substituents on 1,4-benzoxazine containing triazin ring [phenathracyl (**5e**), pyridyl (**5i**) and butyl (**5k**)] were associated with a significant increase in the growth inhibitory effect against MIAPACA, MDA-MB-231 and IMR32 human cancer cell lines. In comparison, the saturated alkyl chain on triazin ring of the compounds **5g** and **5n** were more active than the remaining compounds, in particular on HeLa, MIAPACA, MDA-MB-231 and IMR32 cancer cell lines. Finally, we observed that the saturated alkane chain, aromatic hydrocarbon, and pyridyl groups on triazin containing 1,4-benzoxazine moiety, played an important role in the anti-proliferative activity (Fig 3).

3. Conclusion

Taken together, we synthesized a series of novel 1,2,3-triazole-1,4-benzoxazine hybrids **5a–n** in good yields and performed anti-proliferative activity against four different human cancer cell lines, namely HeLa, MIAPACA, MDA-MB-231 and IMR32 (cervical, pancreatic, breast and neuroblastoma, respectively). Among the tested cancer cell lines, Compound **5n** and **5g** exhibited promising anti-proliferative activity with GI_{50} values ranging from **1.2** to **2.5** μM and **0.1–1.1** μM respectively against all cell lines, like HeLa, MDA-MB-231, MIAPACA and IMR32, while compound **5l** showed significant activity against MDA-MB-231 and IMR32 with GI_{50} values ranging from **1.1** and **1.4** μM. We succeeded in the orientation of substituent change on ring along with 1,4-benzoxazine and propyl linker which played a critical role in exhibiting promising anti-proliferative activities. This study provides valuable information for further design and developing more newer and potent anti-proliferative agents.

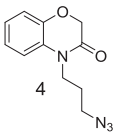
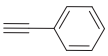
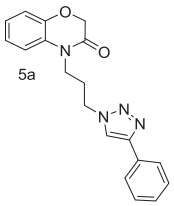
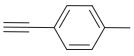
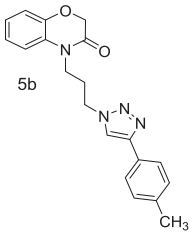
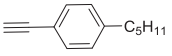
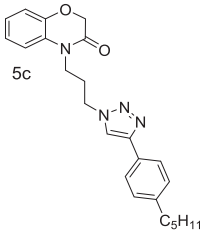
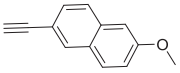
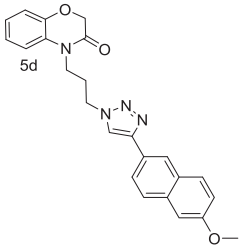
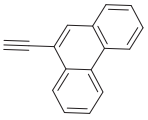
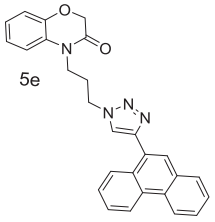
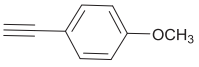
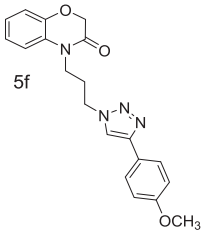
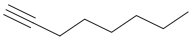
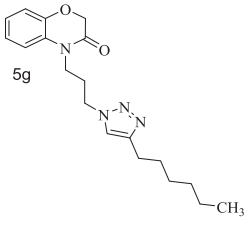
4. Experimental protocols

4.1. Biological study

4.1.1. Materials and methods cell cultures, maintenance and anti proliferative evaluation

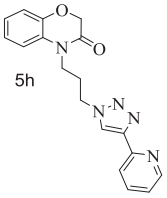
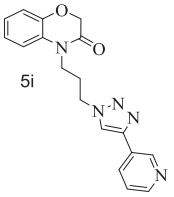
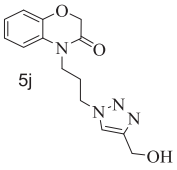
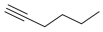
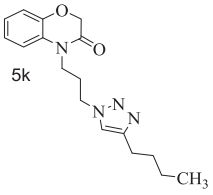
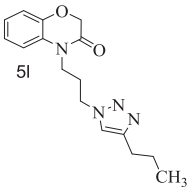
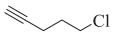
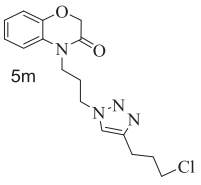
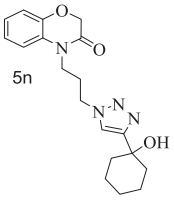
The cell lines, HeLa, MIAPACA, MDA MB 231 and IMR32 (cervical, pancreatic, breast and neuroblastoma) used in this study were procured from American Type Culture Collection (ATCC), USA. The synthesized test compounds were evaluated for their *in vitro* anti-proliferative activity in these four different human cancer cell lines. A protocol of 48 h continuous drug exposure was used and an SRB cell proliferation assay was used to estimate cell viability or growth. All the cell lines were grown in Dulbecco's modified Eagle's medium (containing 10% FBS in a humidified atmosphere of 5% CO_2 at 37 °C). Cells were trypsinized when sub-confluent from T25 flasks/60 mm dishes and seeded in 96-well plates in 100 μL aliquots at plating densities depending on the doubling time of individual cell lines. The microtiter plates were incubated at 37 °C, 5% CO_2, 95% air, and 100% relative humidity for 24 h prior to the addition of experimental drugs and were incubated for 48 h with different doses (0.01, 0.1, 1, 10, 100 μM) of the prepared derivatives. After incubation at 37 °C for 48 h, the cell monolayers were fixed by the addition of 10% (wt/vol) cold trichloroacetic acid and incubated at 4 °C for 1 h and were then stained with 0.057% SRB dissolved in 1% acetic acid for 30 min at room temperature. Unbound SRB was washed with 1% acetic acid. The protein–bound dye was dissolved in 10 mM Tris base solution for OD determination at 510 nm using a microplate reader (Enspire, Perkin Elmer, USA). Using the seven absorbance

Table 1
1,4-benzoxazine-1,2,3-triazole hybrides **5**(**a**–**n**).

Entry	Azide	Alkyne	Product	Yield (%)[a]
a				69
b	4			83
c	4			64
d	4			79
e	4			79
f	4			89
g	4			73

(*continued on next page*)

Table 1 (*continued*)

Entry	Azide	Alkyne	Product	Yield (%)[a]
h	4			70
i	4			68
j	4			80
k	4			74
l	4			77
m	4			74
n	4			62

[a] Isolated Yield.

measurements [time zero, (Tz), control growth, (C), and test growth in the presence of drug at the five concentration levels (Ti)], the percentage growth was calculated at each of the drug concentrations levels. Percentage growth inhibition was calculated as:

$[(Ti-Tz)/(C-Tz)] \times 100$ for concentrations for which $Ti >/= Tz$

$[(Ti-Tz)/Tz] \times 100$ for concentrations for which $Ti < Tz$.

The dose response parameter, growth inhibition of 50% (GI_{50}) was calculated from $[(Ti-Tz)/(C-Tz)] \times 100 = 50$, which is the drug concentration resulting in a 50% reduction in the net protein increase (as measured by SRB staining) in control cells during the drug incubation. Values were calculated for this parameter if the level of activity is reached; however, if the effect is not reached or is exceeded, the value for that parameter was expressed as greater or less than the maximum or minimum concentration tested.

Table 2
(GI_{50})[a] values of the tested compounds against four human cancer cell lines.

S. no.	Compounds	HeLa	MIAPACA	MDA-MB-231	IMR32
1	**5a**	9.0 ± 0.7	94.0 ± 0.5	4.9 ± 0.6	**0.37 ± 0.02**
2	**5b**	14.3 ± 0.84	>100	**1.12 ± 0.2**	4.4 ± 0.09
3	**5c**	>100	>100	5.0 ± 0.7	43.5 ± 0.8
4	**5d**	>100	>100	5.0 ± 0.6	**1.3 ± 0.05**
5	**5e**	>100	8.4 ± 0.3	>100	0.13 ± 0.03
6	**5f**	4.9 ± 0.2	15.7 ± 0.7	41.5 ± 0.1	49.9 ± 0.7
7	**5g**	**0.10 ± 0.3**	**0.15 ± 0.09**	**1.1 ± 0.08**	**0.71 ± 0.07**
8	**5h**	10.0 ± 0.9	5.8 ± 0.07	4.8 ± 0.5	2.0 ± 0.08
9	**5i**	>100	8.2 ± 0.5	3.0 ± 0.7	0.86 ± 0.05
10	**5j**	7.3 ± 0.5	**1.01 ± 0.6**	5.7 ± 0.2	5.5 ± 0.3
11	**5k**	**1.02 ± 0.5**	2.5 ± 0.1	3.6 ± 0.3	5.7 ± 0.7
12	**5l**	23.2 ± 0.6	2.6 ± 0.3	**1.1 ± 0.04**	**1.4 ± 0.06**
13	**5m**	**0.10 ± 0.3**	12.5 ± 0.5	6.4 ± 0.5	**0.2 ± 0.06**
14	**5n**	**2.0 ± 0.5**	**2.5 ± 0.5**	**1.2 ± 0.1**	**1.2 ± 0.06**
Doxorubicin[b]		**0.073 ± 0.001**	**0.097 ± 0.002**	**0.085 ± 0.001**	**0.023 ± 0.002**
Paclitaxel[b]		**0.025 ± 0.001**	**0.056 ± 0.002**	**0.091 ± 0.005**	**0.075 ± 0.003**

The significance of bold is indication nearer value to standard drug.
[a] GI_{50}: 50% Growth inhibition, concentration of drug (in μM) resulting in a 50% reduction in net protein increase compared with control cells.
[b] Positive controls.

4.2. General information

All the solvents and reagents were purchased from commercial suppliers and were used without further purification. Melting points were measured with a Fischer-Johns melting point apparatus and were uncorrected. Nuclear Magnetic Resonance spectra were recorded on 300 (Bruker) and 500 MHz (Varian) spectrometers in appropriate solvents using TMS as internal standard or the solvent signals as secondary standards and the chemical shifts are represented in δ scales. Multiplicities of NMR signals are designated as s (singlet), d (doublet), t (triplet), br (broad), m (multiplet, for unresolved lines), etc. ^{13}C NMR spectra were recorded on 75 MHz spectrometer. IR spectra were recorded on Perkin–Elmer model 683 or 1310 spectrometers with sodium chloride optics or KBr pellets with neat. ESI-MS were recorded on Thermo Finnigan LCQ ion trap mass spectrometer equipped with electron spray ionization. High-resolution mass spectra were obtained by using ESI-QTOF mass spectrometer. All the experiments were monitored by analytical thin layer chromatography (TLC) performed on silica gel G F_{254} pre-coated plates. After elution, the plate was visualized for the spots on TLC plates which was achieved either by exposure to UV (254 nm) light, iodine vapour and/or by dipping the plates in phosphomolybdic acid-ceric (IV) sulphate-sulphuric acid solution (PMA solution) and heating the plates at 110 °C. Solvents were removed under vacuum and heated in a water bath at 40 °C. Silica gel (60–120 mesh) was used for column chromatography. Columns were packed as the slurry of silica gel in hexane and equilibrated with the appropriate solvent/solvent mixture prior to use. The compounds were loaded neat or as a concentrated solution using the appropriate solvent system. Appropriate names (if possible) for all the new compounds were given with the help of Chem BioOffice v12.0; 2012.

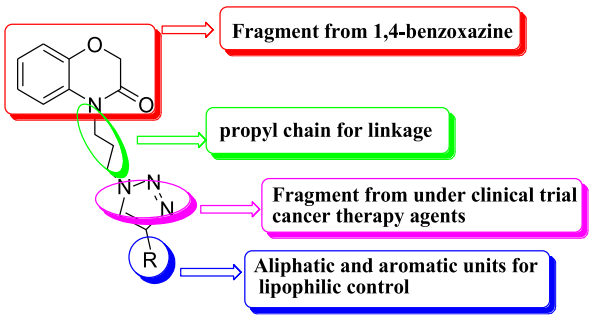


Fig. 3. Design strategy for new 1,4-benzoxazin-1,2,3-triazole hybrids.

4.3. Synthesis of 2H-benzo[b][1,4]oxazin-3(4H)-one (**2**)

To a mixture of 2-aminophenol (49.98 mmol), TEBA (50 mmol) and $NaHCO_3$ (200 mmol) in $CHC1_3$ (30 mL) was added a solution of 2-chloroacetyl chloride (72.21 mmol) in $CHC1_3$ (5 mL) for 1 h. Dropwise at 0 °C. The reaction mixture was stirred for another 1 h at the same temperature and then heated to 55 °C for 10 h with stirring. The resulting mixture was concentrated under vacuum and then 50 mL of water was added. The precipitate was collected, recrystallized from ethanol to give 2*H*-benzo[*b*][l,4]oxazin-3(4*H*)-one as a white solid (48% yield). ^1H NMR (500 MHz, $CDCl_3$): δ 4.55 (s, 2H, CH_2), 6.97–6.86 (m, 4H, Ar–H), 9.53 (br s, 1H, NH).

4.4. Synthesis of 4-(3-bromopropyl)-2H-benzo[b][1,4]oxazin-3(4H)-one (**3**)

To a stirred solution of compound **2** (20 mmol) in DMF (15 mL), ice cold solution of 1,3-dibromopropane (20 mmol) in 100 mL of DMF with vigorous stirring and tetra-*n*-butyl ammonium iodide (2 mol%), K_2CO_3 (60 mmol) was added at room temperature. The reaction mixture was stirred for 1 h and then poured into 800 mL of brine. Thus, suitably substituted 4*H*-benzo[1,4]oxazin-3-one (**2**) was deprotonated with K_2CO_3 and alkylated with 1,3-dibromopropane. The aqueous phase was extracted with ethyl acetate, and the combined organic extracts were dried on Na_2SO_4. After filtration, the solvent was removed under reduced pressure and the crude product was purified by silica gel chromatography using an eluent of 35% ethyl acetate in hexane. Yield: 62%; ^1H NMR (500 MHz, $CDCl_3$): δ 2.23–2.28 (m, 2H, CH_2), 3.48 (t, $J = 6.3$ Hz, 2H, CH_2–Br), 4.10 (t, $J = 7.4$ Hz, 2H, CH_2), 4.60 (s, 2H, CH_2), 7.00–7.03 (m, 2H, Ar–H), 7.05–7.08 (m, 2H, Ar–H).

4.5. Synthesis of 4-(3-azidopropyl)-2H-benzo[b][1,4]oxazin-3(4H)-one (**4**)

A mixture of sodium azide (10 mmol), alkyl bromide **3** (50 mmol), tetrabutylammonium bromide (5–10 mol%), DMF (30 mL) were refluxed with efficient stirring for 12 h at 120 °C. The product was cooled to room temperature and extracted with ethyl acetate and cold water, dried over sodium sulphate and evaporated under vacuum. The residue obtained was purified over silica gel

column chromatography to afford compound **4** in 75% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.78–1.97 (m, 4H, $2CH_2$), 4.02 (t, J = 6.3 Hz, 2H, CH_2), 4.57–4.58 (m, 2H, CH_2), 6.99–7.04 (m, 4H, Ar–H).

4.6. General procedure for the synthesis of 1,4-benzoxazine-1,24-triazoles ***5a–n***

To a solution of alkyne (43 mmol) with azide (43 mmol) in THF/H_2O (1:1), was added $CuSO_4.5H_2O$ (8.6 mmol), sodium ascorbate (17.2 mmol) at room temperature. The reaction mixture was stirred at room temperature for 24 h, then H_2O was added and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered, concentrated under reduced pressure. The desired product was purified by column chromatography using an eluent of 50% ethyl acetate in hexane.

4.6.1. 4-(3-(4-phenyl-1-H-1,2,3-triazol-1-yl)propyl)-2H-benzo[b][1,4]oxazin-3(4H)-one (***5a***)

Light blue solid (69% yield): m.p: 118–121 °C; IR (KBr, ν): 3427, 3132, 2957, 1680, 1605, 1501, 1466, 1400, 1278, 1223, 1129, 1049, 975, 773, 749 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.37–2.42 (m, 2H, CH_2), 4.07 (t, J = 6.9 Hz, 2H, CH_2), 4.48 (t, J = 6.7 Hz, 2H, CH_2), 4.62 (s, 2H, CH_2), 6.91–6.93 (m, 1H, Ar–H), 6.99–7.04 (m, 3H, Ar–H), 7.33–7.36 (m, 1H, Ar–H), 7.41–7.45 (m, 2H, Ar–H), 7.82–7.85 (m, 2H, Ar–H), 7.92 (s, 1H, N–N–CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 27.76, 38.21, 47.82, 67.51, 114.59, 117.34, 120.29, 120.45, 123.06, 124.23, 125.69, 128.16, 128.28, 128.83, 130.46, 130.88, 132.45, 145.30, 164.73; MS (ESI): m/z 335[M+H]$^+$; HRMS: Calcd for $C_{19}H_{18}N_4O_2$: 335.15025, Found: 335.14975.

4.6.2. 4-(3-(4-p-tolyl-1H-1,2,3-triazol-1-yl)propyl)-2H-benzo[b][1,4]oxazin-3(4H)-one (***5b***)

Light brown solid (83% yield): m.p: 114–118 °C; IR (KBr, ν): 3552, 3102, 2957, 2925, 2854, 1662, 1604, 1591, 1503, 1415, 1322, 1281, 1234, 1159, 1129, 1056, 976, 872, 740 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.36–2.41 (m, 5H, CH_2, CH_3), 4.07 (t, J = 6.9 Hz, 2H, CH_2), 4.47 (t, J = 6.7 Hz, 2H, CH_2), 4.62 (s, 2H, CH_2), 6.90–6.93 (m, 1H, Ar–H), 6.99–7.04 (m, 3H, Ar–H), 7.24 (d, J = 7.9 Hz, 2H, Ar–H), 7.73 (d, J = 8.2 Hz, 2H, Ar–H), 7.87 (s, 1H, N–N–CH; ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.25, 27.78, 38.29, 47.81, 67.52, 114.61, 117.33, 119.89, 123.05, 124.22, 125.62, 127.66, 127.90, 129.49, 138.00, 145.32, 147.86, 164.71; MS (ESI): m/z 349 [M+H]$^+$; HRMS: Calcd for $C_{20}H_{20}N_4O_2$: 349.16590, Found: 349.16527.

4.6.3. 4-(3-(4-pentylphenyl)-1H-1,2,3-triazol-1-yl)propyl)-2H-benzo[b][1,4]oxazin-3(4H)-one (***5c***)

White solid (64% yield)): m.p: 110–112 °C; IR (KBr, ν): 3366, 3097, 2954, 2933, 2854, 1692, 1602, 1497, 1459, 1397, 1321, 1274, 1233, 1162, 1127, 1054, 846, 816, 764 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.89 (t, J = 6.9 Hz, 3H, CH_3), 1.32–1.37 (m, 4H, $2CH_2$), 1.62–1.67 (m, 2H, CH_2), 2.35–2.42 (m, 2H, CH_2), 2.60 (t, J = 7.7 Hz, 2H, CH_2), 4.06 (t, J = 6.9 Hz, 2H, CH_2), 4.47 (t, J = 6.7 Hz, 2H, CH_2), 4.62 (s, 2H, CH_2), 6.90–6.92 (m, 1H, Ar–H), 6.99–7.03 (m, 3H, Ar–H), 7.24 (d, J = 8.1 Hz, 2H, Ar–H), 7.74 (d, J = 8.1 Hz, 2H, Ar–H), 7.87 (s, 1H, N–N–CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.03, 22.53, 27.80, 29.68, 31.08, 31.46, 35.70, 38.29, 47.83, 67.54, 114.63, 117.35, 119.93, 123.09, 124.25, 125.64, 127.84, 128.89, 143.15, 152.09, 164.75; MS (ESI): m/z 405[M+H]$^+$; HRMS: Calcd for $C_{24}H_{28}N_4O_2$: 405.22850, Found: 405.22786.

4.6.4. 4-(3-(4-(6-methoxynaphthalen-1-yl)-1H-1,2,3-triazol-1-yl) propyl)-2H-benzo [b] [1,4] oxazin-3(4H)-one (***5d***)

Pale brown solid (79% yield)): m.p: 148–152 °C; IR (KBr, ν): 3559, 3125, 2956, 1663, 1610, 1503, 1467, 1416, 1327, 1280, 1260, 1223, 1165, 1055, 894, 861, 820, 781, 748 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.39–2.45 (m, 2H, CH_2), 3.94 (s, 3H, OCH_3), 4.09 (t, J = 6.9 Hz, 2H, CH_2), 4.51 (t, J = 6.6 Hz, 2H, CH_2), 4.63 (s, 2H, CH_2), 6.92–6.95 (m, 1H, Ar–H), 7.00–7.05 (m, 3H, Ar–H), 7.14–7.19 (m, 2H, Ar–H), 7.78–7.81 (m, 2H, Ar–H), 7.89–7.91 (m, 1H, Ar–H), 7.99 (s, 1H, N–N–CH), 8.27 (s, 1H, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 29.02, 38.00, 47.63, 53.67, 67.25, 105.51, 114.43, 117.08, 119.06, 120.15, 122.83, 124.00, 124.14, 125.49, 127.13, 127. 62,128.69, 129.41, 134.08, 145.07, 147.59, 157.64, 164.53; MS (ESI): m/z 415[M+H]$^+$; HRMS: Cacld for $C_{24}H_{22}N_4O_3$: 415.17647, Found: 415.17485.

4.6.5. 4-(3-(4-(Phenanthren-10-yl)-1H-1,2,3-triazol-1-yl)propyl)-2H-benzo[b][1,4]oxazin-3 (4H)-one (***5e***)

Brown solid (79% yield)): m.p: 140–144 °C; IR (KBr, ν): 3365, 3121, 3077, 2926, 2851, 1682, 1603, 1500, 1451, 1404, 1319, 1277, 1230, 1129, 1054, 921, 851, 759, 728 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.46–2.52 (m, 2H, CH_2), 4.15 (t, J = 6.9 Hz, 2H, CH_2), 4.59 (t, J = 6.8 Hz, 2H, CH_2), 4.64 (s, 2H, CH_2), 6.96–6.98 (m, 1H, Ar–H), 7.02–7.06 (m, 3H, Ar–H), 7.61–7.65 (m, 2H, Ar–H), 7.67–7.72 (m, 2H, Ar–H), 7.92 (s, 1H, N–N–CH), 8.02 (s, 2H, Ar–H), 8.40 (d, J = 8.2 Hz, 1H, Ar–H), 8.72 (d, J = 8.2 Hz, 1H, Ar–H), 8.78 (d, J = 8.0 Hz, 1H, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 27.86, 38.28, 47.94, 67.53, 114.58, 117.39, 122.53, 122.98, 123.09, 123.45, 124.26, 126.08, 126.70,126.86, 126.94,127.10, 128.39, 128.87, 130.05, 131.25, 144.26, 146.81, 164.75; MS (ESI): m/z 435[M+H]$^+$; HRMS: Calcd for $C_{27}H_{22}N_4O_2$: 435.18155, Found: 435.17951.

4.6.6. 4-(3-(4-(Methoxyphenyl)-1H-1,2,3-triazol-1-yl)propyl)-2H-benzo[b][1,4]oxazin-3 (4H) -one (***5f***)

White solid (89% yield)): m.p: 84–88 °C; IR (KBr, ν): 3435, 3137, 3083, 3021, 2986, 2932, 2857, 2833, 2429, 2087, 1604, 1589, 1489, 1358, 1323, 1306, 1291, 1222, 1160, 1130, 1037, 994, 847, 792, 690 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.34–2.44 (m, 2H, CH_2), 3.88 (s, 3H, OCH_3), 4.07 (t, J = 6.7 Hz, 2H, CH_2), 4.48 (t, J = 6.7 Hz, 2H, CH_2), 4.62 (s, 2H, CH_2), 6.88–6.93 (m, 2H, Ar–H), 7.02 (s, 3H, Ar–H), 7.31–7.39 (m, 2H, Ar–H), 7.47 (s, 1H, Ar–H), 7.91 (s, 1H, N–N–CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 27.77, 38.23, 47.85, 55.33, 67.49, 110.67, 114.27, 114.58, 117.34, 118.09, 120.48, 123.05, 124.23, 127.85, 129.85, 131.76, 145.29, 147.61, 159.97, 164.71; MS (ESI): m/z 365 [M+H]$^+$; HRMS: Calcd for $C_{20}H_{20}N_4O_3$: 365.16082, Found: 365.16056.

4.6.7. 4-(3-(4-Hexyl-1H-1,2,3-triazol-1-yl)propyl)-2H-benzo[b][1,4]oxazin-3(4H)-one (***5g***)

Pale brown solid (73% yield)): m.p: 80–85 °C; IR (KBr, ν): 3546, 3342, 3111, 3060, 2989, 2954, 2923, 2854, 2425, 1682, 1604, 1501, 1461, 1404, 1281, 1237, 1219, 1129, 1056, 1032, 785, 743 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.88 (t, J = 7.1 Hz, 3H, CH_3), 1.29–1.32 (m, 4H, $2CH_2$), 1.34–1.40 (m, 2H, CH_2), 1.64–1.70 (m, 2H, CH_2), 2.30–2.35 (m, 2H, CH_2) 2.72 (t, J = 7.7 Hz, 2H, CH_2), 4.01 (t, J = 7.1 Hz, 2H, CH_2), 4.40 (t, J = 6.8 Hz, 2H, CH_2), 4.61 (s, 2H, CH_2), 6.87–6.89 (m, 1H, Ar–H), 6.99–7.03 (m, 3H, Ar–H), 7.38 (s, 1H, N–N–CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.05, 22.54, 25.64, 27.73, 28.91,29.44, 31.55, 38.32, 47.57, 67.51, 114.59, 117.29, 121.13, 123.03, 124.18, 127.91, 135.73, 145.28, 164.65; MS (ESI): m/z 343 [M+H]$^+$; HRMS: Calcd for $C_{19}H_{26}N_4O_2$: 343.21285, Found: 343.21166.

4.6.8. 4-(3-(4-(Pyridin-2-yl)-1H-1,2,3-triazol-1-yl)propyl)-2H-benzo[b][1,4]oxazin-3(4H)-one (***5h***)

Light red liquid (70% yield): IR (KBr, ν): 3422, 2924, 2854, 1680, 1501, 1405, 1053, 771 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.38–2.43 (m, 2H, CH_2), 4.07 (t, J = 6.8 Hz, 2H, CH_2), 4.51 (t, J = 6.7 Hz, 2H, CH_2), 4.61 (s, 2H, CH_2), 6.92–6.96 (m, 1H, Ar–H), 6.99–7.04 (m, 4H, Ar–H), 7.37–7.40 (m, 1H, N–N–CH), 8.07 (s, 1H, Ar–H), 8.21 (d, J = 7.9 Hz, 1H, Ar–H), 8.57 (s, 1H, Ar–H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 27.26, 37.73, 49.09, 66.99, 114.23, 116.86, 120.80, 122.57,

123.49, 124.20, 126.48, 127.37, 132.77, 144.85, 146.13, 148.28, 164.31; MS (ESI): *m/z* 336[M+H]$^+$; HRMS: Calcd for $C_{18}H_{17}N_5O_2$: 336.14550, Found: 336.14493.

*4.6.9. 4-(3-(4-(Pyridin-3-yl)-1H-1,2,3-triazol-1-yl)propyl)-2H-benzo[b][1,4]oxazin-3(4H)-one (**5i**)*

Light red liquid (68% yield)): IR (KBr, ν): 3419, 2924, 2854, 1681, 1501, 1466, 1407, 1279, 1231, 1128, 1053, 807, 755, 708 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.37–2.43 (m, 2H, CH_2), 4.07 (t, J = 6.8 Hz, 2H, CH_2), 4.51 (t, J = 6.7 Hz, 2H, CH_2), 4.61 (s, 2H, CH_2), 6.93–6.95 (m, 1H, Ar–H), 7.00–7.04 (m, 3H, Ar–H), 7.37–7.40 (m, 1H, N–N–CH), 8.07 (s, 1H, Ar–H), 8.21 (d, J = 7.9 Hz, 1H, Ar–H), 8.57 (s, 1H, Ar–H), 9.01 (s, 1H, Ar–H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 28.91, 33.78, 49.15, 69.16, 114.28, 116.86, 120.89, 123.550, 124.26, 127.42, 132.82, 143.95, 144.87, 146.22, 148.33, 164.36; MS (ESI): *m/z* 336 [M+H]$^+$; HRMS: Calcd for $C_{18}H_{17}N_5O_2$: 336.14550, Found: 336.14468.

*4.6.10. 4-(3-(4-(Hydroxymethyl)-1H-1,2,3-triazol-1-yl)propyl)-2H-benzo[b][1,4]oxazin-3 (4H)-one (**5j**)*

Pale brown liquid (80% yield); IR (KBr, ν): 3418, 2973, 2928, 1682, 1504, 1403, 1280, 1219, 1180, 1145, 1056, 952, 913, 756 cm^{-1}; ^{1}H NMR (500 MHz,$CDCl_3$): δ 1.86–1.92 (m, 1H, OH), 2.00–2.04 (m, 2H, CH_2), 4.42–4.44 (m, 2H, CH_2), 4.57–4.61 (m, 2H, CH_2), 4.79 (s, 4H, 2CH_2), 6.83–7.05 (m, 4H, Ar–H), 7.72 (s, 1H, N–N–CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 27.77, 38.23, 47.85, 55.33, 67.49, 114.58, 117.34, 118.00, 120.48, 123.05, 124.23, 129.85, 145.29, 159.97; MS (ESI): *m/z* 289 [M+H]$^+$; HRMS: Calcd for $C_{14}H_{16}N_4O_3$: 289.12952, Found: 289.12878.

*4.6.11. 4-(3-(4-Butyl-1H-1,2,3-triazol-1-yl)propyl)-2H-benzo[b][1,4]oxazin-3(4H)-one (**5k**)*

White solid (74% yield): m.p: 65–68 °C; IR (KBr, ν): 3444, 3111, 3060, 2956, 2925, 2856, 1682, 1604, 1501, 1461, 1403, 1328, 1281, 1238, 1216, 1184, 1146, 1056, 923, 784, 743 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.94 (t, J = 7.3 Hz, 3H, CH_3), 1.37–1.42 (m, 2H, CH_2), 1.63–1.69 (m, 2H, CH_2), 2.29–2.35 (m, 2H, CH_2), 2.73 (t, J = 7.5 Hz, 2H, CH_2), 4.02 (t, J = 6.2 Hz, 2H, CH_2), 4.41 (t, J = 6.5 Hz, 2H, CH_2), 4.60–4.62 (m, 2H, CH_2), 6.89–6.92 (m, 1H, Ar–H), 7.00–7.03 (m, 3H, Ar–H), 7.46 (s, 1H, N–N–CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.05, 22.54, 25.64, 29.44, 31.55, 38.32, 47.57, 67.51, 114.59, 117.29, 121.13, 123.03, 124.18, 127.91, 145.33. 164.65; MS (ESI): *m/z* 315[M+H]$^+$; HRMS: Cacld for $C_{17}H_{22}N_4O_2$: 315.18155, Found: 315.18050.

*4.6.12. 4-(3-(4-Propyl-1H-1,2,3-triazol-1-yl)propyl)-2H-benzo[b][1,4]oxazin-3(4H)-one (**5l**)*

Brown liquid (77% yield); IR (KBr, ν): 3438, 2925, 2854, 1682, 1502, 1465, 1404, 1278, 1128, 1054, 752 cm^{-1}; ^{1}H NMR (500 MHz,$CDCl_3$): δ 0.88 (t, J = 7.1 Hz, 3H, CH_3), 1.64–1.70 (m, 2H, CH_2), 2.30–2.35 (m, 2H, CH_2), 2.72 (t, J = 7.7 Hz, 2H, CH_2), 4.01 (t, J = 7.1 Hz, 2H, CH_2), 4.40 (t, J = 6.8 Hz, 2H, CH_2), 4.61 (s, 2H, CH_2), 6.87–6.89 (m, 1H, Ar–H), 7.00–7.03 (m, 3H, Ar–H), 7.38 (s, 1H, N–N–CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.05, 25.64, 31.55, 38.32, 47.57, 67.51, 114.59, 117.29, 121.13, 123.03, 124.18, 127.91, 135.73, 145.28, 164.65; MS (ESI): *m/z* 301 [M+H]$^+$; HRMS: Calcd for $C_{16}H_{20}N_4O_2$: 301.16590, Found: 301.16479.

*4.6.13. 4-(3-(4-(3-Chloropropyl)-1H-1,2,3-triazol-1-yl)propyl)-2H-benzo[b][1,4]oxazin-3 (4H)-one (**5m**)*

Brown solid (74% yield)): m.p: 71–79 °C; IR (KBr, ν): 3545, 3112, 3062, 2926, 2853, 1657, 1605, 1503, 1456, 1419, 1329, 1280, 1234, 1185, 1131, 1057, 926, 826, 749, 703 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.64–1.69 (m, 2H, CH_2), 2.30–2.36 (m, 4H, 2CH_2), 4.01 (t, J = 7.1 Hz, 4H, 2CH_2), 4.40 (t, J = 6.8 Hz, 2H, CH_2), 4.61 (s, 2H, CH_2), 6.87–6.89 (m, 1H, Ar–H), 7.00–7.02 (m, 3H, Ar–H), 7.38 (s, 1H, N–N–CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.64, 27.73, 31.55, 38.32, 47.57, 67.51, 114.59, 117.29, 121.13, 124.18, 123.03, 135.73, 145.28, 164.65; MS (ESI): *m/z* 335[M+H]$^+$; HRMS: Calcd for $C_{16}H_{19}N_4O_2Cl$: 335.12693, Found: 335.12569.

*4.6.14. 4-(3-(4-(1-Hydroxycyclohexyl)-1H-1,2,3-triazol-1-yl)propyl)-2H-benzo[b][1,4] oxazin-3(4H)-one (**5n**)*

White solid (62% yield)): m.p: 125–130 °C; IR (KBr, ν): 3367, 3138, 3069, 2921, 2856, 1605, 1500, 1459, 1446, 1433, 1335, 1295, 1237, 1210, 1175, 1163, 1144, 1129, 1070, 1035, 1001, 984, 833, 739 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.26 (s, 1H, CH), 1.38 (s, 1H, CH), 1.54–1.59 (m, 2H, CH_2), 1.72–1.80 (m, 2H, CH_2), 1.86–1.91 (m, 2H, CH_2), 1.96–2.02 (m, 3H, CH_2, OH), 2.31–2.37 (m, 2H, CH_2), 4.03 (t, J = 7.0 Hz, 2H, CH_2), 4.42 (t, J = 6.8 Hz, 2H, CH_2), 4.61 (s, 2H, CH_2), 6.87–6.90 (m, 1H, Ar–H), 6.99–7.04 (m, 3H, Ar–H), 7.57 (s, 1H, N–N–CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.95, 25.31, 27.66, 29.32, 29.63,38.06, 38.22, 47.68, 67.45, 69.43, 114.53, 117.30, 120.21, 123.00, 124.19, 127.82, 145.23, 155.57, 164.64; MS (ESI): *m/z* 357 [M+H]$^+$; HRMS: Cacld for $C_{19}H_{24}N_4O_3$: 357.19212, Found: 357.19106.

Acknowledgements

The authors gratefully acknowledge the financial support through the project: DST-SERB/EMEQ-078/2013 and the Council of Scientific and Industrial Research (CSIR), New Delhi for the award of fellowship to RB.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2014.10.051.

References

[1] D.J. Abraham, in: fifth ed.Burgers Medicinal Chemistry and Drug Discovery, vol. 1, John Wiley and Sons, 1995, pp. 3–4.
[2] Y. Sugimoto, T. Otani, S. Oie, K. Wierzba, Y. Yamada, Mechanism of action of a new macromolecular antitumor antibiotic, J. Antibiot. 43 (1990) 417–421.
[3] R. Frechette, M. Beach, Ortho Pharm Corp, 2-Substituted amino and thio-alkylbenzoxazine antimicrobial agents, WO Patent 972816. 1997 Aug 7.
[4] R. Frechette, W. M. A. Weindner, Ortho Pharm Corp, Benzoxazine antimicrobial agents, WO Patent 9717333. 1997 May 15.
[5] D. H. Miles, K. O. Petrovna, S. Naser, S. S. Yurjevich, E. A. Goun, S. V. Michailovich, 2-Oxo-1,4-benzoxazine compounds for treatment of tuberculosis, U. S. Patent 6,649,610. 2003 Nov 18.
[6] M. Hori, I. Watanabe, H. Ohtaka, K. Harada, J. Maruo, T. Morita, Kanebo Ltd, 1,4-Benzoxazine derivatives, pharmaceutical composition containing the same and use thereof, EP Patent 0719766. 2000 Apr 12.
[7] D. Bhuniya, S. K. Das, G. R. Madhavan, J. Iqbal, R. Chakrabarti, DR. Reddy's Lab Ltd, Benzoxazine and benzothiazine derivatives and pharmaceutical compositions containing them, WO Patent 03033481, 2003 Apr 24.
[8] M. B. Fleury, M. Largeron, P. Lestage, B. Lockhart, Adir Et Compagnie, Noval 8-amino-1,4-Benzoxazine compounds, preparation method and pharmaceutical compositions containing them, WO Patent 062889. 1999 Dec 9.
[9] G. A. Burton, M. Hillmann, P. Hoelscher, S. Jaroch, R. Jautelat, F.M Mcdonald, H. Rehwinkel, D. Sulzle, The benzoxazine and the benzothiazine derivatives and their properties inhibition as antioxydation, WO Patent 081324. 2001 Nov 1.
[10] K. A. Berryman, D. M. Downing, D. A. Dudley, J. J. Edmunds, L. S. Narasimhan, S. T. Rapundalo, Benzoxazinones/benzothiazinones as serine protease inhibitors, WO Patent 050257. 1999 Oct 7.
[11] G. A. Burton, M. Hillmann, P. Hoelscher, S. Jaroch, F.M Mcdonald, H. Rehwinkel, D.Sulzle, Benzoxazine and benzothiazine derivativs and their use in medicines, WO Patent 017173. 2000 Mar 30.
[12] H.C. Kolb, K.B. Sharpless, The growing impact of click chemistry on drug discovery, Drug Discov. Today 8 (2009) 1128–1137.
[13] S.G. Agalave, S.R. Maujan, V.S. Pore, Click chemistry: 1,2,3-Triazoles as pharcophores, Chem. Asian J. 6 (2011) 2696–2718.
[14] V.V. Rostovtsev, K.B. Sharpless, A Stepwise Huisgen Cycloaddition Process: copper(I)-catalyzed Regioselective "Ligation" of azides and Terminal alkynes, Angew. Chem. Int. Ed. 41 (2002) 2596–2599.
[15] H. Saqlain, A. Mohammad Sarwar, H. Hinna, S. Syed, D. Abhijeet, H. Firasat, A. Perwez, U. Sadiq, M.A.Q. Pasha, B. Sameena, N. Syed, A. Yakub, K. Chetna, Synthesis of novel 2-mercaptobenzoxazole based 1,2,3-triazoles as inhibitors

of proinflammatory cytokines and supressors of COX-2gene expression, Eur. J. Med. Chem. 81 (2014) 204–217.
[16] X. Jin-Mei, Z. En, S. Xiao-Jing, W. Yan-Cha, Y. Bin, J. Wei-Wei, G. Ya- Zhuo, L. Hong-Min, Synthesis and preliminary biological evaluation of 1,2,3-triazole-Jaspine B hybrids as potential cytotoxic agents, Eur. J. Med. Chem. 80 (2014) 593–604.
[17] D.M. Reddy, J. Srinivas, G. Chashoo, A.K. Saxena, H.M.S. Kumar, 4β-[(4-Alkyl)-1,2,3-triazol-1-yl] podophyltoxins as anticancer compounds: design, synthesis and biological evaluation, Eur. J. Med. Chem. 46 (2011) 1983–1991.
[18] K. Odlo, J. Hentzen, J.F.D. Chabert, S. Ducki, O.A.B.S.M. Gani, I. Sylte, 1,5-Disubstituted 1,2,3-triazoles as cis-restricted analogues of combretastation A-4: synthesis, molecular modeling and evaluation as cytotoxic agents and inhibitors of tubulin, Bioorg. Med. Chem. 16 (2008) 4829–4838.
[19] P. Singh, R. Raj, V. Kumar, M.P. Mahajan, P.M.S. Bedi, T. Kaur, A.K. Saxena, 1,2,3-Triazole tethered β-lactam-Chalcone bifunctional hybrids: synthesis and anticancer evaluation, Eur.J. Med. Chem. 47 (2012) 594–600.
[20] J.A. Stefely, R. Palchaudhuri, P.A. Miller, R.J. Peterson, G.C. Moraski, P.J. Hergenrother, M.J. Miller, N-((1-Benzyl-1H-1,2,3-triazol-4-yl)methyl)arylamide as a new scaffold that provides rapid access to antimicrotuble agents: synthesis and evaluation of antiproliferative activity against select cancer cell lines, J. Med. Chem. 53 (2010) 3389–3395.
[21] T. Belliotti, L. D. Wise, D. J. Wustrow, Benzoxazinone dopamine d4 receptor antagonists, WO Pat.ent Appl. 97045419, 1997.
[22] R.W. Brueggemeir, J.C. Hackett, Aromatase inhibitors in the treatment of breast cancer, Endocr. Rev. 26 (2005) 331–345.
[23] T.W. Moody, J. Chiles, E. Moody, CAI inhibits the growth of small cell lung cancer cells, Lung Cancer 39 (2003) 279–288.
[24] B. Yang, Q.J. He, D.Y. Zhu, Y.J. Lou, R.Y. Fang, Antiproliferative activity of contragestazol(DL111-IT) in murine and human tumor models in vitro and in vivo, Cancer Chemother. Pharmacol. 57 (2006) 268–273.
[25] M. Ilic, D. Kikelj, J. Ilas, Fluorinated dual antithrombotic compounds based on 1,4- benzoxazine scaffold, Eur. J. Med. Chem. 50 (2012) 255–263.
[26] Z. Xue-Wen, M. Han-Lin, Z. Xuan, J. Shi-Yao, M. Jun-Ying, Z. Bao-Xiang, Synthesis of 6-cinamoyl-2-H-benzo[b][1,4]oxazin-3(4H)-ones and their effects on A549 lung cancer cell growth, Eur. J. Med. Chem. 79 (2014) 95–101.
[27] D. ZhiWu, C. YiZhe, Z. Jing, S. Le, Z. BaoXiang, Z. Yun, Z. ShangLi, M. JunYing, Discovery of a benzoxazine derivative promoting angiogenesis invitro and invivo, J. Cell. Physiol. 223 (2010) 202–208.
[28] L. Haiying, L. Ning, W. Shengqing, W. Li, Z. Jing, S. Le, Z. Yun, Z. Shangli, X. Zhigang, Z. Baoxiang, M. Junying, Identification of a small molecule targeting annexin A7, BBA-Molecular Cell Res. 1833 (2013) 2092–2099.
[29] W. Li, D. ZhiWu, H. Bin, Z. BaoXiang, W. Hua, Z. Jing, K. HsiangFu, Z. ShangLi, M. JunYing, Distinct patterns of autophagy evoked by two benzoxazine derivatives in vascular endothelial cells, Autophagy 6 (2010) 1115–1124.
[30] S. Le, Z. HongLing, S. ChunHui, Z. BaoXiang, Z. Jing, Z. ShangLi, S. Hua, M. JunYing, Role of Hmbox1 in endothelial differentiation of bone-marrow stromal cells by a small molecule, ACS Chem.Biol. 5 (2010) 1035–1043.
[31] L. Nagarapu, H.K. Gaikwad, K. Sirikonda, J. Mateti, R. Bantu, P.S. Raghu, K.M. Mahduri, S.V. Kalivendi, Synthesis and cytotoxicity evaluation of 1-[3-(9H-carbazol- 4-yloxy)-2-hydroxypropyl]-3-aryl-1H-pyrazole-5-carboxylic acid derivatives, Eur. J. Med. Chem. 45 (2010) 4720–4725.
[32] L. Nagarapu, J. Mateti, H.K. Gaikwad, R. Bantu, M. Sheebarani, N.J.P. Shubhasini, Synthesis and anti-inflammotory activity of some noval 3-phenyl-N-[3-(4-phenylpiperazin-1yl)propyl]1-H-pyrazole-5-carboxamide derivatives, Bioorg Med. Chem. Lett. 21 (2011) 4138–4140.
[33] L. Nagarapu, H.K. Gaikwad, R. Bantu, S.R. Manikonda, Chemoenzymatic synthesis with lipase catalyzed resolution and evaluation of antitumor activity of (R/S)-2-[2-hydroxy-3-(4-phenylpiperazin-1-yl)propyl]-1Hpyrralo[3,4-b]quinolin-3(2H)-one, Eur. J. Med. Chem. 46 (2011) 2152–2156.
[34] L. Nagarapu, V. Paparaju, A. Satyenar, Synthesis of novel analogues of (+)-varitriol via olefin cross-matathesis reaction, Biorg. Med. Chem. Lett. 18 (2008) 2351–2354.
[35] L. Nagarapu, A. Satyendar, B. Rajashaker, K. Srinivas, P. Ruparani, K. Radhika, G. Shubhashini, Synthesis and antimicrobial activity of noval C-linked imadazole glycoconjugates, Biorg. Med. Chem. Lett. 18 (2008) 1167–1171.
[36] L. Nagarapu, S. Vanaparthi, R. Bantu, C.G. Kumar, Synthesis of noval benzo[4,5]thiazolo[1,2-a]pyrimidine-3-carboxylate derivatives and biological evaluation as potential anticancer agents, Eur. J. Med. Chem. 69 (2013) 817–822.
[37] L. Nagarapu, B. Yadagiri, R. Bantu, C.G. Kumar, S. Pombala, J. Nanubolu, Studies on the synthetic and structural aspects of benzosuberones bearing 2,4-thiazolidenone moiety as potential anti-cancer agents, Eur. J. Med. Chem. 71 (2014) 91–97.
[38] B. Yadagiri, U.D. Holagunda, R. Bantu, L. Nagarapu, C.G. Kumar, S. Pombala, B. Sridhar, Synthesis of novel building blocks of benzosuberone bearing coumarine moieties and their evaluation as potential anticancer agents, Eur. J. Med. Chem. 79 (2014) 260–265.
[39] X. Huang, C. Cheng-Chu, Synthesis of 3-oxo-3,4-dihydro-2H-1,4-benzoxazines and 1,4-benzothiazines under phase-transfer catalysis, Communications (1984) 851–852.