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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and anti-inflammatory activity evaluation of novel 3-alkyl-6-(4*H*-1,2,4-triazol-4-yl)-3,4-dihydro-2*H*-benzo[*e*][1,3]oxazine derivatives

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Abstract To discover new compounds with anti-inflammatory activity, a series of novel 3-alkyl-6-(4*H*-1,2,4-triazol-4-yl)-3,4-dihydro-2*H*-benzo[*e*][1,3]oxazine derivatives were synthesized and their structures were confirmed by spectroscopic techniques. In vivo anti-inflammatory activity of the synthesized compounds was determined using the xylene-induced mouse ear edema model. 3-Heptyl-6-(4*H*-1,2,4-triazol-4-yl)-3,4-dihydro-2*H*-benzo[*e*] [1,3]oxazine and 3-p-tolyl-6-(4*H*-1,2,4-triazol-4-yl)-3,4-dihydro-2*H*-benzo[*e*][1,3]oxazine demonstrated higher anti-inflammatory activity (74.04 % and 64.99 %, respectively) at 0.5 h after intraperitoneal administration than the reference drug ibuprofen (62.65 %). Further, the time of peak effect after oral administration was 4 h for both compounds. Our results identify new compounds with anti-inflammatory activity in vivo that may have improved safety/side effect profiles relative to the currently approved nonsteroidal anti-inflammatory drugs.

Keywords Synthesis · Anti-inflammatory · Mannich reaction · 4-Aminophenol

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Introduction

Inflammation is part of the complex biological reaction in vascular tissues to protect from injury or harmful stimuli including pathogens, damaged cells, or irritation (Ferrero-Miliani et al., 2007). However, prolonged inflammation can cause serious diseases such as diabetes, cancer, and atherosclerosis (Lyman et al., 2014; Momi et al., 2012). Nonsteroidal anti-inflammatory drugs (NSAIDs) are currently the most commonly administered medicines to reduce acute and chronic inflammation (Sng and Schug, 2009), fever (Eccles, 2006), and pain (Zahradnik et al., 2010; Kraemer and Rose, 2009). Recently, many studies have shown that long-term oral administration of NSAIDs is frequently associated with gastrointestinal (Botting, 2006; Naesdal and Brown, 2006; Cryer, 2005; Lazzaroni and Bianchi, 2004; James and Hawkey, 2003), hepatic (Adebayo and Bjarnason, 2006), and renal (Schneider et al., 2006; Mounier et al., 2006) side effects in patients. Therefore, the discovery of new compounds with enhanced safety profiles remains an area of unmet medical need.

Literature reports suggest that 1,2,4-triazoles exhibit a wide spectrum of therapeutic properties, including antibacterial (Demirbas et al., 2005; Sharma et al., 2008; Turan-Zitouni et al., 2005), antiviral (Kritsanida et al., 2002; Abdel-Aal et al., 2008), analgesic (Turan-Zitouni et al., 2001), anti-inflammatory (Tozkoparan et al., 2007; Rabea et al., 2006; Labanauskas et al., 2004), anticonvulsant (Almasirad et al., 2004; Kucukguzel et al., 2004), antidepressant (Varvaresou et al., 1998), and anticancer (Holla et al., 2003; Duran et al., 2002). Further, derivatives containing oxazine also exhibit anti-mycobacterial (Sindhu et al., 2014), anticancer (Kalirajan et al., 2012), anti-inflammatory (Liu et al., 2010), antimicrobial, and antifungal (EI Azab et al., 2015) activities.

In this study, we designed and synthesized 3-alkyl-6-(4*H*-1,2,4-triazol-4-yl)-3,4-dihydro-2*H*-benzo[*e*][1,3]oxazine derivatives (Fig. 1) and evaluated their anti-inflammatory activity in a xylene-induced mouse ear edema model of inflammation.

Results and discussion

Chemistry

Target compounds **2a–y** were prepared by a two-step synthesis (Scheme 1). In the first step, compound 1 was prepared by the Michael method (Stocks et al., 2004): dimethylformamide dimethylacetal (DMF-DMA) and formohydrazide were reacted in acetonitrile at 50 °C for 30 min, and then 4-aminophenol was added to the mixture to obtain compound **1**, which was catalyzed by ice water. Structures of all synthesized compounds were confirmed by infrared (IR), proton nuclear magnetic resonance (^{1}H-NMR), ^{13}C-NMR and high resolution-mass spectrometry (HRMS) techniques.

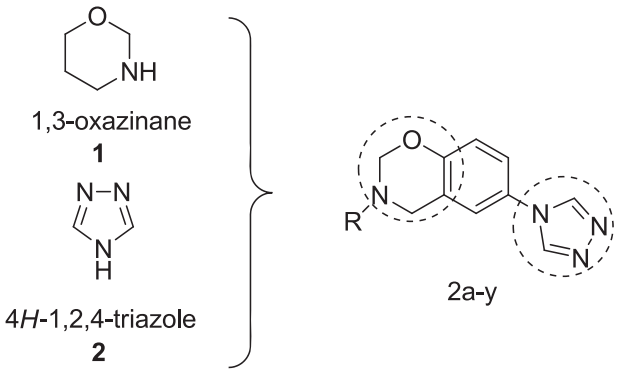
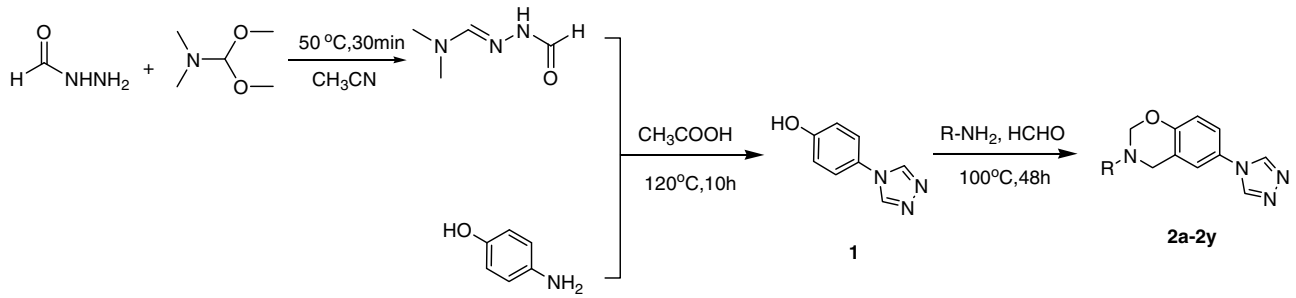


Fig. 1 Structure of compounds **1**, **2**, and **2a–y**

Pharmacology

Xylene-induced ear edema in kunming mice is a reliable model to evaluate the in vivo anti-inflammatory activity of test compounds (Sowemimo et al., 2013; Da Silva et al., 2010). ibuprofen was used as a reference drug. As a primary screen, the anti-inflammatory activity for each of the newly synthesized compounds was evaluated at a dose of 100 mg/kg administered by intraperitoneal injection. Since most anti-inflammatory medications are administered orally in the clinical setting, we chose two of the compounds with the highest anti-inflammatory activity in the primary screen (**2d**, **2h**) for further assessment by oral (p.o.) administration. Compounds **2d** and **2h** were administered at multiple time points (1, 2, 3, 4, 5, and 6 h) prior to xylene application. The time of peak anti-inflammatory effect for compounds **2d** and **2h** was 4 h after p.o. administration.

In the primary screen, all of the synthesized compounds were administrated intraperitoneally to assess their anti-inflammatory activity in the xylene-induced mouse ear edema model. Anti-inflammatory activity was expressed as the inhibition percentage compared to the control group. As shown in Table 1, most compounds exhibited some degree



R:

2a -C_4H_9	**2h** -C_6H_4(*p*-CH_3)	**2o** -$CH_2C_6H_5$	**2v** -$CH_2C_6H_4$(*m*-Cl)
2b -C_5H_{11}	**2i** -C_6H_4(*p*-OCH_3)	**2p** -$CH_2C_6H_4$(*p*-CH_3)	**2w** -$CH_2C_6H_4$(*p*-Cl)
2c -C_6H_{11}	**2j** -C_6H_4(*o*-F)	**2q** -$CH_2C_6H_4$(*p*-OCH_3)	**2x** -$CH_2C_6H_4$(*o*-Br)
2d -C_7H_{15}	**2k** -C_6H_4(*m*-F)	**2r** -$CH_2C_6H_4$(*m*-F)	**2y** -$CH_2C_6H_4$(*p*-Br)
2e -C_8H_{17}	**2l** -C_6H_4(*p*-F)	**2s** -$CH_2C_6H_4$(*p*-F)	
2f -$C_{12}H_{23}$	**2m** -C_6H_4(*m*-Cl)	**2t** -$CH_2C_6H_4$(2,4-2F)	
2g -C_6H_5	**2n** -C_6H_4(*p*-Br)	**2u** -$CH_2C_6H_4$(*o*-Cl)	

Scheme 1 Synthesis of the target compounds **2a-2y**

Table 1 Anti-inflammatory activity of compounds **2a–y** after intraperitoneal administration ($n = 8$)

Comp.	*R*	Dose (mg/kg)	Edema mean Mean ± S.E.M. (mg)	Inhibition Rate(%)
2a	$-C_4H_9$	100	$5.03 \pm 1.53^{**}$	49.41
2b	$-C_5H_{11}$	100	$3.85 \pm 0.52^{***}$	61.31
2c	$-C_6H_{13}$	100	$3.82 \pm 1.05^{***}$	61.64
2d	$-C_7H_{15}$	100	$2.58 \pm 1.05^{***}$	74.04
2e	$-C_8H_{17}$	100	$3.87 \pm 0.63^{***}$	61.14
2f	$-C_{12}H_{23}$	100	$4.25 \pm 1.55^{***}$	57.29
2g	$-C_6H_5$	100	$5.58 \pm 3.48^{*}$	43.89
2h	$-C_6H_4(p\text{-}CH_3)$	100	$3.48 \pm 1.31^{***}$	64.99
2i	$-C_6H_4(p\text{-}OCH_3)$	100	$4.68 \pm 2.24^{**}$	52.93
2j	$-C_6H_4(o\text{-F})$	100	6.65 ± 1.15	33.17
2k	$-C_6H_4(m\text{-F})$	100	$4.07 \pm 1.58^{***}$	59.13
2l	$-C_6H_4(p\text{-F})$	100	$4.33 \pm 1.90^{***}$	56.45
2m	$-C_6H_4(m\text{-Cl})$	100	6.92 ± 2.42	30.49
2n	$-C_6H_4(p\text{-Br})$	100	$5.12 \pm 1.32^{**}$	48.58
2o	$-CH_2C_6H_5$	100	$3.90 \pm 1.13^{***}$	60.80
2p	$-CH_2C_6H_4(p\text{-}CH_3)$	100	$3.73 \pm 1.42^{***}$	62.56
2q	$-CH_2C_6H_4(p\text{-}OCH_3)$	100	6.75 ± 1.87	32.16
2r	$-CH_2C_6H_4(m\text{-F})$	100	6.18 ± 2.75	37.86
2s	$-CH_2C_6H_4(p\text{-F})$	100	$4.42 \pm 1.96^{**}$	55.61
2t	$-CH_2C_6H_4$(2,4-2F)	100	$5.03 \pm 2.20^{**}$	49.41
2u	$-CH_2C_6H_4(o\text{-Cl})$	100	6.87 ± 1.63	30.99
2v	$-CH_2C_6H_4(m\text{-Cl})$	100	$4.38 \pm 2.41^{**}$	55.95
2w	$-CH_2C_6H_4(p\text{-Cl})$	100	$4.58 \pm 0.99^{**}$	53.94
2x	$-CH_2C_6H_4(o\text{-Br})$	100	$5.53 \pm 0.73^{*}$	44.39
2y	$-CH_2C_6H_4(p\text{-Br})$	100	7.37 ± 2.34	25.96
DMSO	—	100	9.95 ± 0.58	–
Ibuprofen	—	100	$3.72 \pm 0.75^{***}$	62.65

— No anti-inflammatory activity

$^{*}0.01 < p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$ compared to the vehicle group at corresponding time

of anti-inflammatory activity when administered intraperitoneally. Compounds **2d** and **2h** showed the highest inhibition percentage, 74.04 % and 64.99 %, respectively, and outperformed the reference drug ibuprofen in the assay (62.65 %). Among the tested compounds, compounds **2a**, **2f**, **2i**, **2n**, **2s**, **2t**, and **2v–x** showed 5–20 % anti-inflammatory activity compared to the control group. However, their anti-inflammatory activities were lower than that of ibuprofen. Compounds **2b**, **2c**, **2e**, **2f**, **2k**, **2l**, **2o**, and **2p** were not significantly different from ibuprofen. The remaining compounds did not exhibit significant differences compared to vehicle.

Most of the alkyl chain-substituted derivatives investigated exhibited at least modest anti-inflammatory activity in the xylene-induced ear edema assay. As the carbon chain lengthened, the anti-inflammatory activity of tested compounds first increased and then decreased, suggesting that C-7 is the appropriate length of the alkyl chain, and that appropriate lipophilic property is essential to the anti-inflammatory activity of the compounds (Li et al., 2009; Kroll et al., 1998).

For aromatic ring-substituted derivatives, electron-donating groups seemed to be a more beneficial structural feature than electron-withdrawing groups for anti-inflammatory activity. For compounds **2g–n**, the order of activity for different electron-withdrawing substituents was *m*-F > *p*-F > *p*-Br (>*o*-F > *m*-Cl), while the order of activity for electron-donating substituents was *p*-CH_3 > *p*-OCH_3. For compounds **2o–y**, the order of activity for electron-withdrawing substituents was *m*-Cl > *p*-F > *p*-Cl> 2,4-2F > *o*-Br (>*m*-F > *o*-Cl > *p*-Br), and the order of activity for electron-donating substituents was *p*-CH_3 > *p*-OCH_3. In addition, comparing compounds **2g-n** with compounds **2o–y** suggested that differences existed for compounds substituted at the phenyl ring; however, an all-inclusive rule for the effect of phenyl ring substitutions on anti-inflammatory activity was not clear.

Based on the results from our primary screen, compounds **2d** and **2h** were chosen to be further evaluated at multiple time points after oral administration (1, 2, 3, 4, 5, and 6 h). As shown in Table 2, the anti-inflammatory effects of **2d**, **2h**, and ibuprofen first increased and then declined over this time period. The time of peak effect was 4 h for all three compounds. Moreover, derivative **2d** showed higher activity than the reference drug at all time points.

Experimental

Chemistry

Reactions were monitored by thin-layer chromatography on silica gel plates precoated with F_{254} gel. Developed plates

Table 2 Anti-inflammatory activity of compounds **2d** and **2h** administered o.p. at different times before xylene application

Time (h)	Dose (mg/kg)	Inhibition		
		2d	**2h**	Ibuprofen
1	100	18.05	31.56	10.26
2	100	49.48*	33.90	24.03
3	100	68.57***	38.70	44.68*
4	100	80.52***	52.34*	56.63**
5	100	62.73**	36.75	15.71
6	100	53.64**	29.87	9.22

$^{*}0.01 < p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$ compared to the vehicle group at corresponding dose

were examined under an ultraviolet lamp (254 nm). Melting points were determined in open capillary tubes and were uncorrected. IR spectra were recorded (in KBr) using an fourier transform infrared spectroscopy1730 Spectrometer (PerkinElmer, Waltham, MA, USA). ^{1}H-NMR and ^{13}C-NMR spectra were recorded using an AV-300 Spectrometer (Bruker Daltonik, Bremen, Germany), and all chemical shifts were described in parts per million relative to that of tetramethylsilane. High-resolution mass spectra were measured using a matrix-assisted laser desorption/ionization-time of flight (MALDI-TOF) mass spectrometer (Bruker Daltonik, Germany). Chemicals were purchased from Aldrich Chemical Corporation.

General procedure for the synthesis of compound **1** (Deng et al., 2014) Dimethoxy-*N*,*N*-dimethylmethanamine (DMF-DMA; 6.5 g, 55 mmol) was added to a solution of 3.3 g (55 mmol) formohydrazide in acetonitrile (30 ml) in a 100 ml round-bottomed flask equipped with a reflux condenser. The reaction mixture was warmed to 50 °C for 30 min and then 5.5 g (50 mmol) of 4-aminophenol in acetonitrile (10 ml) was added with 5 ml acetic acid. The reaction temperature was increased to 120 °C for 9 h. After being cooled and concentrated, the product was added to ice water. The precipitate was collected via filtration and vacuum dried to produce the product at a moderate yield. The average of the yield was shown in the text.

4-(4H-1,2,4-Triazol-4-yl)phenol(**1**) M.p. 288–290 °C, yield: 76 %. ^{1}H-NMR (dimethyl sulfoxide (DMSO), 300 MHz) δ: 6.90 (d, 2H, $J = 8.5$ Hz, Ar–H), 7.46 (d, 2H, $J = 8.5$ Hz, Ar–H), 8.96 (s, 2H, $J = 7.5$ Hz, Triazole-H), 9.92 (s, 1H, –OH).

General procedure for the synthesis of compounds **2a–y** (Wen et al., 2015) Formaldehyde (18 mmol) was added to a solution of 6 mmol amine in 20 ml ethanol in a 50 ml round-bottomed flask. Compound **1** (1.0 g, 6 mmol) was added portion-wise to the mixture over 15 min with stirring at 0 °C, followed by addition of 1 ml triethylamine as a catalyst. The temperature of the mixture was gradually increased to 100 °C and stirred at 100 °C for 48 h. The reaction mixture was concentrated under reduced pressure, diluted with 30 ml dichloromethane, washed with 30 ml (1 mol/L) sodium hydroxide and 30 ml distilled water, and then saturated with 30 ml sodium chloride. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford brown oil. The oil was purified on a silica gel column with methanol and dichloromethane [V(methanol):V(dichloromethane) = 1:50] and collected as eluent fractions to yield target compounds **2a–y.**

3-Butyl-6-(4H-1,2,4-triazol-4-yl)-3,4-dihydro-2H-benzo[e][1,3]oxazine (**2a**) M.p. 111–112 °C, yield: 34 %. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 0.94 (t, 3H, $J = 7.2$ Hz, $–CH_3$), 1.31–1.43 (m, 2H, $–CH_2–$), 1.51–1.61 (m, 2H, $–CH_2–$), 2.75(t, 2H, $J = 6.0$ Hz, $–CH_2–$), 4.05 (s, 2H, –N–CH_2–Ar), 4.93 (s, 2H, –O–CH_2–N–), 6.90 (d, 1H, $J = 8.6$ Hz, Ar–H), 7.00 (s, 1H, Ar–H), 7.13 (d, 1H, $J = 6.7$ Hz, Ar–H), 8.38 (s, 2H, Triazole-H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 13.93, 20.28, 30.13, 49.97, 51.17, 82.98, 117.90, 121.97, 122.22, 126.37, 141.83, 154.96. IR (KBr) cm^{-1}: 1525 (C=N), 1223, 1092 (C–O–C). ESI-HRMS calcd. for $C_{14}H_{19}N_4O^+$ ([M + H]$^+$): 259.1553; found: 259.1560.

3-Pentyl-6-(4H-1,2,4-triazol-4-yl)-3,4-dihydro-2H-benzo[e][1,3]oxazine (**2b**) M.p. 129–130 °C, yield: 36 %. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 0.92 (t, 3H, $J = 6.0$ Hz, $–CH_3$), 1.31–1.39 (m, 4H, $–CH_2–$), 1.53–1.64 (m, 2H, $–CH_2–$), 2.75 (t, 2H, $J = 7.5$ Hz, $–CH_2–$), 4.06 (s, 2H, –N–CH_2–Ar), 4.94 (s, 2H, –O–CH_2–N–), 6.91 (d, 1H, $J = 8.7$ Hz, Ar–H), 7.00 (s, 1H, Ar–H), 7.13 (dd, 1H, $J_1 = 3.0$ Hz, $J_2 = 6.0$ Hz, Ar–H), 8.38 (s, 2H, Triazole-H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 14.02, 22.50, 27.70, 29.26, 49.95, 51.43, 82.95, 117.87, 121.96, 122.17, 126.36, 141.81, 154.93. IR (KBr) cm^{-1}: 1528 (C=N), 1200, 1093 (C–O–C). ESI-HRMS calcd. for $C_{15}H_{21}N_4O^+$ ([M + H]$^+$): 273.1710; found: 273.1706.

3-Hexyl-6-(4H-1,2,4-triazol-4-yl)-3,4-dihydro-2H-benzo[e][1,3]oxazine (**2c**) M.p. 131–133 °C, yield: 32 %. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 0.89 (t, 3H, $J = 6.7$ Hz, $–CH_3$), 1.27–1.39 (m, 6H, $–CH_2–$), 1.52–1.61 (m, 2H, $–CH_2–$), 2.74 (t, 2H, $J = 7.5$ Hz, $–CH_2–$), 4.05 (s, 2H, –N–CH_2–Ar), 4.93 (s, 2H, –O–CH_2–N–), 6.90 (d, 1H, $J = 8.7$ Hz, Ar-H), 7.00 (s, 1H, Ar–H), 7.13 (dd, 1H, $J_1 = 2.5$ Hz, $J_2 = 8.6$ Hz, Ar–H), 8.38 (s, 2H, Triazole-H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 14.03, 22.59, 26.80, 27.98, 31.65, 49.94, 50.24, 51.46, 82.94, 117.87, 121.96, 122.17, 126.35, 141.81, 154.92. IR (KBr) cm^{-1}: 1531 (C=N), 1223, 1095 (C–O–C). ESI-HRMS calcd. for $C_{16}H_{23}N_4O^+$ ([M + H]$^+$): 287.1866; found: 287.1881.

3-Heptyl-6-(4H-1,2,4-triazol-4-yl)-3,4-dihydro-2H-benzo[e][1,3]oxazine (**2d**) M.p. 129–131 °C, yield: 28 %. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 0.89 (t, 3H, $J = 6.7$ Hz, $–CH_3$), 1.31 (s, 10H, $–CH_2–$), 2.75 (t, 2H, $J = 7.5$ Hz, $–CH_2–$), 4.05 (s, 2H, –N–CH_2–Ar), 4.94 (s, 2H, –O–CH_2–N–), 6.91 (d,1H, $J = 8.7$ Hz, Ar–H), 7.00 (s, 1H, Ar–H), 7.13 (d, 1H, $J = 6.0$ Hz, Ar-H), 8.39 (s, 2H, Triazole-H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 14.07, 22.61, 27.10, 28.04, 29.13, 31.79, 49.97, 51.48, 82.97, 117.91, 121.97, 122.22, 126.36, 141.83, 154.96. IR (KBr) cm^{-1}:1531 (C=N), 1232, 1095 (C–O–C). ESI-HRMS calcd for $C_{17}H_{25}N_4O^+$ ([M + H]$^+$): 301.2023; found: 301.2020.

3-Octyl-6-(4H-1,2,4-triazol-4-yl)-3,4-dihydro-2H-benzo[e][1,3]oxazine (**2e**) M.p. 130–132 °C, yield: 31 %. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 0.88 (t, 3H, $J_1 = 6.0$ Hz, -CH_3),

1.27–1.32 (m, 12H, $-CH_2-$), 2.75 (t, 2H, $J_1 = 7.5$ Hz, $-CH_2-$), 4.05 (s, 2H, –N–CH_2–Ar), 4.94 (s, 2H, –O–CH_2–N–), 6.91 (d, 1H, $J = 8.7$ Hz, Ar–H), 7.00 (d, 1H, $J = 3.0$ Hz, Ar–H), 7.13 (dd, 1H, $J_1 = 3.0$ Hz, $J_2 = 9.0$ Hz, Ar–H), 8.39 (s, 2H, Triazole-H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 14.08, 22.63, 27.15, 28.05, 29.25, 29.43, 31.80, 49.97, 51.48, 82.98, 117.90, 121.97, 122.21, 126.37, 141.82, 154.97. IR (KBr) cm^{-1}: 1524 (C=N), 1223, 1091 (C–O–C). ESI-HRMS calcd for $C_{18}H_{27}N_4O^+$ ($[M + H]^+$): 315.2179; found: 315.2186.

3-Dodecyl-6-(4H-1,2,4-triazol-4-yl)-3,4-dihydro-2H-benzo[e][1,3]oxazine (**2f**) M.p. 116–117 °C, yield: 29 %. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 0.89 (t, 3H, $J_1 = 6.0$ Hz, $-CH_3$), 1.27 (s, 18H, $-CH_2-$), 1.52–1.63 (m, 2H, $-CH_2-$), 2.75(t, 2H, $J = 7.5$ Hz, $-CH_2-$), 4.05 (s, 2H, –N–CH_2–Ar), 4.94 (s, 2H, –O–CH_2–N–), 6.91 (d, 1H, $J = 8.7$ Hz, Ar–H), 6.99 (d, 1H, $J = 3.0$ Hz, Ar–H), 7.13 (dd, 1H, $J_1 = 3.0$ Hz, $J_2 = 9.0$ Hz, Ar–H), 8.38 (s, 2H, Triazole-H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 14.10, 22.66, 27.15, 28.05, 29.32, 29.48, 29.60, 31.89, 49.98, 51.49, 82.97, 117.89, 121.96, 122.20, 126.37, 141.81, 154.96. IR (KBr) cm^{-1}: 1519 (C=N), 1226, 1093 (C–O–C). ESI-HRMS calcd. for $C_{22}H_{35}N_4O^+$ ($[M + H]^+$): 371.2805; found: 371.2808.

3-Phenyl-6-(4H-1,2,4-triazol-4-yl)-3,4-dihydro-2H-benzo[e][1,3]oxazine (**2g**) M.p. 164–165 °C, yield: 25 %. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 4.70 (s, 2H, –N–CH_2–Ar), 5.43 (s, 2H, –O–CH_2–N–), 6.90–7.22 (m, 6H, Ar–H), 7.29 (t, 2H, $J = 7.5$ Hz, Ar–H), 8.36 (s, 2H, Triazole-H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 50.48, 79.89, 118.43, 118.52, 121.21, 122.08, 122.36, 122.41, 126.69, 129.41, 141.77, 147.85, 154.82. IR (KBr) cm^{-1}:1521 (C = N), 1232, 1078 (C–O–C), 1120 (C–N). ESI-HRMS calcd. for $C_{16}H_{15}N_4O^+$ ($[M + H]^+$): 279.1240; found: 279.1242.

3-p-Tolyl-6-(4H-1,2,4-triazol-4-yl)-3,4-dihydro-2H-benzo[e][1,3]oxazine (**2h**) M.p. 168–170 °C, yield: 27 %. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 2.29 (s, 3H, $-CH_3$), 4.67 (s, 2H, –N–CH_2–Ar), 5.41 (s, 2H, –O–CH_2–N–), 6.94(d, 1H, $J =$ 9.0 Hz, Ar–H), 7.02–7.14 (m, 6H, Ar–H), 8.37 (s, 2H, Triazole-H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 20.56, 50.84, 80.39, 118.47, 118.90, 121.26, 122.48, 126.63, 129.94, 131.88, 141.81, 145.53, 154.93. IR (KBr) cm^{-1}: 1517 (C=N), 1220, 1099 (C–O–C), 1100 (C–N). ESI-HRMS calcd. for $C_{17}H_{17}N_4O^+$ ($[M + H]^+$): 293.1397; found: 293.1393.

3-(4-Methoxyphenyl)-6-(4H-1,2,4-triazol-4-yl)-3,4-dihydro-2H-benzo[e][1,3]oxazine (**2i**) M.p. 133–135 °C, yield: 25 %. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 3.77 (s, 3H, $-OCH_3$), 4.63 (s, 2H, –N–CH_2–Ar), 5.37 (s, 2H, –O–CH_2–N–), 6.85 (d, 2H, $J = 8.9$ Hz, Ar-H), 6.95 (d, 1H, $J = 8.7$ Hz, Ar–H), 7.03 (s, 1H, Ar–H), 7.12 (t, 3H, $J = 8.9$ Hz, Ar–H), 8.38 (s, 2H, Triazole-H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 51.32, 55.50, 81.12, 114.61, 118.46, 120.96, 121.26, 122.51, 126.63, 141.82, 154.95, 155.40. IR (KBr) cm^{-1}: 1512 (C=N), 1241, 1085 (C–O), 1187 (C–N). ESI-HRMS calcd. for $C_{17}H_{17}N_4O_2^+$ ($[M + H]^+$): 309.1346; found: 309.1346.

3-(2-Fluorophenyl)-6-(4H-1,2,4-triazol-4-yl)-3,4-dihydro-2H-benzo[e][1,3]oxazine (**2j**) M.p. 153–154 °C, yield: 16 %. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 4.65 (s, 2H, –N–CH_2–Ar), 5.38 (s, 2H, –O–CH_2–N–), 6.97–7.25 (m, 7H, Ar–H), 8.39 (s, 2H, Triazole-H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 50.47, 80.59, 116.36, 116.63, 118.57, 121.22, 122.33, 122.58, 124.51, 124.61, 126.86, 136.17, 136.29, 141.80, 154.50. IR (KBr) cm^{-1}: 1523 (C=N), 1230, 1082 (C–O–C), 1183 (C–N). ESI-HRMS calcd. for $C_{16}H_{14}FN_4O^+$ ($[M + H]^+$): 297.1146; found: 297.1152.

3-(3-Fluorophenyl)-6-(4H-1,2,4-triazol-4-yl)-3,4-dihydro-2H-benzo[e][1,3]oxazine (**2k**) M.p. 164–165 °C, yield: 20 %. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 4.70 (s, 2H, –N–CH_2–Ar), 5.41 (s, 2H, –O–CH_2–N–), 6.65–7.25 (m, 7H, Ar–H), 8.38 (s, 2H, Triazole-H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 50.54, 79.39, 105.43, 105.76, 108.56, 108.84, 113.81, 118.71, 121.25, 122.15, 122.70, 126.94, 130.54, 130.67, 141.86, 154.73. IR (KBr) cm^{-1}: 1520 (C=N), 1233, 1081 (C–O–C), 1184 (C–N). ESI-HRMS calcd. for $C_{16}H_{14}FN_4O^+$ ($[M + H]^+$): 297.1146; found: 297.1142.

3-(4-Fluorophenyl)-6-(4H-1,2,4-triazol-4-yl)-3,4-dihydro-2H-benzo[e][1,3]oxazine (**2l**) M.p. 118–120 °C, yield: 22 %. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 4.66 (s, 2H, –N–CH_2–Ar), 5.38 (s, 2H, –O–CH_2–N–), 6.95–7.17 (m, 7H, Ar–H), 8.38 (s, 2H, Triazole-H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 51.26, 80.59, 115.83, 116.13, 118.58, 120.71, 120.82, 121.23, 122.16, 122.64, 126.79, 141.79, 144.33, 154.81. IR (KBr) cm^{-1}: 1519 (C=N), 1234, 1078 (C–O–C), 1185 (C–N). ESI-HRMS calcd. for $C_{16}H_{14}FN_4O^+$ ($[M + H]^+$): 297.1146; found: 297.1148.

3-(3-Chlorophenyl)-6-(4H-1,2,4-triazol-4-yl)-3,4-dihydro-2H-benzo[e][1,3]oxazine (**2m**) M.p. 154–156 °C, yield: 20 %. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 4.70 (s, 2H, –N–CH_2–Ar), 5.41 (s, 2H, –O–CH_2–N–), 6.94–7.25 (m, 7H, Ar–H), 8.39 (s, 2H, Triazole-H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 50.53, 79.28, 116.43, 118.46, 118.71, 121.24, 122.01, 122.12, 122.65, 126.89, 130.43, 135.08, 141.79, 149.04, 154.70. IR (KBr) cm^{-1}: 1518 (C=N), 1229, 1079 (C–O–C), 1182 (C–N). ESI-HRMS calcd. for $C_{16}H_{14}ClN_4O^+$ ($[M + H]^+$): 313.0851; found: 313.0849.

3-(4-Bromophenyl)-6-(4H-1,2,4-triazol-4-yl)-3,4-dihydro-2H-benzo[e][1,3]oxazine (**2n**) M.p. 164–166 °C, yield: 20 %. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 4.68 (s, 2H, –N–CH_2–Ar), 5.40 (s, 2H, –O–CH_2–N–), 6.96 (d, 1H, $J =$ 8.7 Hz, Ar–H), 7.00–7.05 (m, 3H, Ar–H), 7.15 (dd, 1H, J_1 = 3.0 Hz, $J_2 = 9.0$ Hz, Ar-H), 7.37–7.43 (m, 2H, Ar–H),

8.37 (s, 2H, Triazole-H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 49.34, 54.88, 82.46, 118.00, 121.38, 121.40, 121.90, 122.23, 126.61, 130.42, 131.58, 136.54, 141.66, 154.58. IR (KBr) cm^{-1}: 1510 (C=N), 1232, 1083 (C–O–C), 1188 (C–N). ESI-HRMS calcd. for $C_{16}H_{14}BrN_4O^+$ ($[M + H]^+$): 357.0346; found: 357.0353.

3-Benzyl-6-(4H-1,2,4-triazol-4-yl)-3,4-dihydro-2H-benzo[e][1,3]oxazine (**2o**) M.p. 134–136 °C, yield: 27 %. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 3.95 (s, 2H, –N–CH_2–Ar), 4.04 (s, 2H, –N–CH_2–Ar), 4.96 (s, 2H, –O–CH_2–N–), 6.97 (d, 2H, $J = 7.9$ Hz, Ar–H), 7.16 (dd, 1H, $J_1 = 3.0$ Hz, $J_2 = 9.0$ Hz, Ar–H), 7.32–7.38 (m, 5H, Ar–H), 8.38 (s, 2H, Triazole-H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 49.33, 55.59, 82.66, 118.00, 121.66, 122.00, 122.24, 126.59, 127.63, 128.56, 128.86, 137.52, 141.78, 154.76. IR (KBr) cm^{-1}: 1523 (C=N), 1219, 1067 (C–O–C), 1124 (C–N). ESI-HRMS calcd. for $C_{17}H_{17}N_4O^+$ ($[M + H]^+$): 293.1397; found: 293.1401.

3-(4-Methylbenzyl)-6-(4H-1,2,4-triazol-4-yl)-3,4-dihydro-2H-benzo[e][1,3]oxazine (**2p**) M.p. 154–156 °C, yield: 29 %. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 2.38 (s, 3H, –CH_3), 3.90 (s, 2H, –N–CH_2–Ar), 4.03 (s, 2H, –N–CH_2–Ar), 4.95 (s, 2H, –O–CH_2–N–), 6.97 (d, 2H, $J = 8.5$ Hz, Ar–H), 7.15–7.20 (m, 3H, Ar–H), 7.26 (d, 2H, $J = 8.0$ Hz, Ar–H), 8.39 (s, 2H, Triazole-H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 21.17, 49.22, 55.32, 82.65, 118.04, 121.71, 122.02, 122.30, 126.55, 128.87, 129.28, 134.38, 137.41, 141.82, 154.86. IR (KBr) cm^{-1}: 1520(C=N), 1220, 1000 (C–O–C), 1135 (C–N). ESI-HRMS calcd. for $C_{18}H_{19}N_4O^+$ ($[M + H]^+$): 307.1553; found: 307.1550.

3-(4-Methoxybenzyl)-6-(4H-1,2,4-triazol-4-yl)-3,4-dihydro-2H-benzo[e][1,3]oxazine (**2q**) M.p. 157–159 °C, yield: 28 %. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 3.85 (d, 5H, $J = 12.7$ Hz, –N–CH_2–Ar, –OCH_3), 4.03 (s, 2H, –N–CH_2–Ar), 4.94 (s, 2H, –O–CH_2–N–), 6.89 (s, 1H, Ar–H), 6.92 (s, 1H, Ar–H), 6.95–6.98 (m, 2H, Ar–H), 7.16 (dd, 1H, $J_1 = 3.0$ Hz, $J_2 = 9.0$ Hz, Ar–H), 7.28 (d, 2H, $J = 6.0$ Hz, Ar–H), 8.39 (s, 2H, Triazole-H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 49.14, 54.89, 55.22, 82.36, 113.86, 117.90, 121.64, 121.90, 122.14, 126.49, 129.41, 130.04, 141.70, 154.75, 159.06. IR (KBr) cm^{-1}: 1527 (C=N), 1242, 1093 (C–O–C), 1128 (C–N). ESI-HRMS calcd. for $C_{18}H_{19}N_4O_2^+$ ($[M + H]^+$): 323.1503; found: 323.1498.

3-(3-Fluorobenzyl)-6-(4H-1,2,4-triazol-4-yl)-3,4-dihydro-2H-benzo[e][1,3]oxazine (**2r**) M.p. 138-149 °C, yield: 23 %. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 4.03 (s, 4H, -N-CH_2-Ar), 4.94 (s, 2H, -O-CH_2-N-), 6.98 (t, 3H, $J = 10.8$ Hz, Ar-H), 7.10-7.18 (m, 3H, Ar-H), 7.31 (t, 1H, $J = 7.5$ Hz, Ar-H), 8.38 (s, 2H, Triazole-H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 49.37, 55.06, 82.63, 114.60, 118.02, 121.47, 121.99, 124.24, 124.25, 124.29, 126.65, 130.07, 140.28, 140.38, 141.74, 154.60, 161.36, 164.62. IR (KBr) cm^{-1}: 1524 (C=N), 1237, 1081 (C–O–C), 1125 (C–N). ESI-HRMS calcd for $C_{17}H_{16}FN_4O^+$ ($[M + H]^+$): 311.1303; found: 311.1305.

3-(4-Fluorobenzyl)-6-(4H-1,2,4-triazol-4-yl)-3,4-dihydro-2H-benzo[e][1,3]oxazine (**2s**) M.p. 153–154 °C, yield: 19 %. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 3.91 (s, 2H, –N–CH_2–Ar), 4.03 (s, 2H, –N–CH_2–Ar), 4.94 (s, 2H, –O–CH_2–N–), 6.96–6.99 (m, 2H, Ar–H), 7.07 (t, 2H, $J = 8.6$ Hz, Ar–H), 7.16 (dd, 1H, $J_1 = 2.5$ Hz, $J_2 = 8.6$ Hz, Ar–H), 7.35 (dd, 2H, $J_1 = 6.0$ Hz, $J_2 = 8.6$ Hz, Ar–H), 8.39 (s, 2H, Triazole-H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 49.33, 54.85, 82.45, 115.32, 115.60, 118.12, 121.54, 122.01, 122.38, 126.64, 130.39, 130.50, 133.16, 133.20, 141.80, 154.77. IR (KBr) cm^{-1}: 1510 (C=N), 1215, 1095 (C–O–C), 1122 (C–N). ESI-HRMS calcd. for $C_{17}H_{16}FN_4O^+$ ($[M + H]^+$): 311.1303; found: 311.1303.

3-(2,4-Difluorobenzyl)-6-(4H-1,2,4-triazol-4-yl)-3,4-dihydro-2H-benzo[e][1,3]oxazine (**2t**) M.p. 134–136 °C, yield: 18 %. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 3.94 (s, 2H, –N–CH_2–Ar), 4.05 (s, 2H, –N–CH_2–Ar), 4.94 (s, 2H, –O–CH_2–N–), 6.79–7.00 (m, 4H, Ar–H), 7.17 (dd, 1H, $J_1 = 2.7$ Hz, $J_2 = 8.7$ Hz, Ar–H), 7.40 (dd, 1H, $J_1 = 8.5$ Hz, $J_2 = 15.0$ Hz, Ar–H), 8.39 (s, 2H, Triazole-H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 48.42, 49.50, 82.48, 103.57, 103.91, 104.25, 111.24, 118.05, 121.36, 121.92, 122.33, 126.63, 131.71, 141.70, 154.58. IR (KBr) cm^{-1}: 1518 (C=N), 1228, 1076 (C–O–C), 1131 (C–N). ESI-HRMS calcd. for $C_{17}H_{15}F_2N_4O^+$ ($[M + H]^+$): 329.1208; found: 329.1213.

3-(2-Chlorobenzyl)-6-(4H-1,2,4-triazol-4-yl)-3,4-dihydro-2H-benzo[e][1,3]oxazine (**2u**) M.p. 150–152 °C, yield: 21 %. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 4.06 (d, 4H, $J = 8.1$ Hz, –N–CH_2–Ar), 4.99 (s, 2H, –O–CH_2–N–), 6.99 (d, 2H, $J = 8.8$ Hz, Ar–H), 7.18 (dd, 1H, $J_1 = 3.0$ Hz, $J_2 = 6.0$ Hz, Ar–H), 7.25–7.33 (m, 2H, Ar–H), 7.41 (dd, 1H, $J_1 = 3.0$ Hz, $J_2 = 6.0$ Hz, Ar–H), 7.47 (dd, 1H, $J_1 = 3.0$ Hz, $J_2 = 6.0$ Hz, Ar–H), 8.40 (s, 2H, Triazole-H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 49.55, 52.89, 82.97, 118.06, 121.56, 121.98, 122.29, 126.56, 126.82, 128.80, 129.70, 130.44, 134.35, 135.20, 141.71, 154.67. IR (KBr) cm^{-1}: 1524 (C=N), 1230, 1074 (C–O–C), 1130 (C–N). ESI-HRMS calcd. for $C_{17}H_{16}ClN_4O^+$ ($[M + H]^+$): 327.1007; found: 327.1012.

3-(3-Chlorobenzyl)-6-(4H-1,2,4-triazol-4-yl)-3,4-dihydro-2H-benzo[e][1,3]oxazine (**2v**) M.p. 163–165 °C, yield: 23 %. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 3.93 (s, 2H, –N–CH_2–Ar), 4.04 (s, 2H, –N–CH_2–Ar), 4.96 (s, 2H, –O–CH_2–N–), 6.98 (d, 2H, $J = 3.0$Hz, Ar–H), 7.18 (d, 1H, $J = 9.0$Hz, Ar–H), 7.30 (s, 3H, Ar–H), 7.41 (s, 1H, Ar–H), 8.40 (s, 2H, Triazole-H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 49.37, 55.03, 82.59, 118.02, 121.39, 121.94, 122.26,126.62, 126.78, 127.72, 128.67, 129.76, 134.40, 139.69, 141.68, 154.58. IR (KBr) cm^{-1}: 1517 (C=N), 1228,

1079 (C–O–C), 1129 (C–N). ESI-HRMS calcd. for $C_{17}H_{16}ClN_4O^+$ ($[M+H]^+$): 327.1007; found: 327.1003.

3-(4-Chlorobenzyl)-6-(4H-1,2,4-triazol-4-yl)-3,4-dihydro-2H-benzo[e][1,3]oxazine (**2w**) M.p. 164–166 °C, yield: 25 %. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 3.91 (s, 2H, –N–CH_2–Ar), 4.03 (s, 2H, –N–CH_2–Ar), 4.94 (s, 2H, –O–CH_2–N–), 6.98 (d, 2H, $J = 6.0$ Hz, Ar–H), 7.17 (dd, 1H, $J_1 = 3.0$ Hz, $J_2 = 9.0$ Hz, Ar–H), 7.34 (dd, 4H, $J_1 = 9.0$ Hz, $J_2 = 12.0$ Hz, Ar–H), 8.39 (s, 2H, Triazole-H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 49.38, 54.91, 82.53, 118.12, 121.49, 122.00, 122.37, 126.64, 128.74, 130.15, 133.42, 136.00, 141.77, 154.73. IR (KBr) cm^{-1}: 1519 (C=N), 1234, 1083 (C–O–C), 1134 (C–N). ESI-HRMS calcd. for $C_{17}H_{16}ClN_4O^+$ ($[M+H]^+$): 327.1007; found: 327.1013.

3-(2-Bromobenzyl)-6-(4H-1,2,4-triazol-4-yl)-3,4-dihydro-2H-benzo[e][1,3]oxazine (**2x**) M.p. 162–164 °C, yield: 24 %. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 4.05 (d, $J = 13.5$ Hz, 4H, –N–CH_2–Ar), 5.00 (s, 2H, –O–CH_2–N–), 7.01 (s, 2H, Ar–H), 7.20 (s, 2H, Ar–H), 7.31–7.41 (m, 1H, Ar–H), 7.48 (d, 1H, $J = 3.0$ Hz, Ar–H), 7.61 (d, 1H, $J = 6.0$ Hz, Ar–H), 8.40 (s, 2H, Triazole-H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 49.52, 55.36, 82.98, 118.09, 121.59, 122.01, 122.31, 124.65, 126.56, 127.44, 129.07, 130.56, 133.04, 136.84, 141.72, 154.70. IR (KBr) cm^{-1}: 1525 (C=N), 1224, 1083 (C–O–C), 1138 (C–N). ESI-HRMS calcd. for $C_{17}H_{16}BrN_4O^+$ ($[M+H]^+$): 371.0502; found: 371.0502.

3-(4-Bromobenzyl)-6-(4H-1,2,4-triazol-4-yl)-3,4-dihydro-2H-benzo[e][1,3]oxazine (**2y**) M.p. 166–168 °C, yield: 27 %. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 3.89 (s, 2H, –N–CH_2–Ar), 4.02 (s, 2H, –N–CH_2–Ar), 4.93 (s, 2H, –O–CH_2–N–), 6.95–6.98 (m, 2H, Ar–H), 7.17 (dd, 1H, $J_1 = 3.0$ Hz, $J_2 = 6.0$ Hz, Ar–H), 7.26 (d, 2H, $J = 9.0$ Hz, Ar–H), 7.49 (d, 2H, $J = 8.2$ Hz, Ar–H), 8.39 (s, 2H,Triazole-H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 49.34, 54.88, 82.46, 118.00, 121.38, 121.40, 121.90, 122.23, 126.61, 130.42, 131.58, 136.54, 141.66, 154.58. IR (KBr) cm^{-1}: 1523 (C=N), 1227, 1082 (C–O–C), 1135 (C–N). ESI-HRMS calcd. for $C_{17}H_{16}BrN_4O^+$ ($[M+H]^+$): 371.0502; found: 371.0504.

Pharmacology

The anti-inflammatory activity of each compound was evaluated by examining in vivo inhibition of xylene-induced ear edema (Pardridge, 2005) in kunming mice (22 ± 2 g, 8 animals per group). All of the animals were purchased from the Laboratory of Animal Research, Yanbian University. Mice were acclimated to the laboratory conditions (20–25 °C, relative humidity at 45–65 %) for more than 1 week prior to experimentation and fed a standard pellet diet with water.

Xylene-induced ear-edema model with intraperitoneally administered compounds All test compounds and ibuprofen were freshly prepared (dissolved with DMSO) prior to intraperitoneal administration at a dose of 100 mg/kg and volume of 0.1 mL/20 g of mice weight. Control mice were injected with vehicle (DMSO, 0.1 mL/20 g of mice weight) only. Thirty minutes after administration, 20 μL xylene was smeared evenly using a micropipette on the surface of the right ear of each mouse. Thirty minutes later, a circular tissue (7 mm diameter) was excised from both ears of treated mice using a cylindrical borer. Mice were restrained from struggling during the 30 min test period. The weights of the left (untreated) and right (treated) ear sections were recorded. Edema was quantified by analyzing the difference in weight between the left (untreated) and right (treated) ear sections. Anti-inflammatory activity was expressed as the inhibition percentage compared to the control group. Ibuprofen was used in parallel as a reference drug. Edema values, expressed as mean ± standard deviation, were compared statistically using one-way-ANOVA followed by Dunnet's post-hoc test. Differences with p values < 0.05 were considered statistically significant.

Xylene-induced ear-edema model with p.o. administered compounds Two of the compounds screened by intraperitoneal administration (compounds **2d** and **2h**) and ibuprofen were homogenized in 0.5 % sodium carboxymethylcellulose (CMC–Na) and administered orally at 100 mg/kg (0.4 mL/20 g body weight). Control mice received 0.5 % CMC–Na (0.4 mL/20 g body weight) only. To explore the peak activity of the test compounds, edema was quantified at different time intervals after oral administration (1, 2, 3, 4, 5, and 6 h).

Conclusion

In the present study, we described the syntheses and anti-inflammatory activities of evaluation of novel 3-alkyl-6-(4*H*-1,2,4-triazol-4-yl)-3,4-dihydro-2*H*-benzo[*e*][1,3]oxazine derivatives (**2a**–**2y**). The results showed that 3-heptyl-6-(4*H*-1,2,4-triazol-4-yl)-3,4-dihydro-2*H*-benzo[*e*][1,3]oxazine (**2d**) and 3-p-tolyl-6-(4*H*-1,2,4-triazol-4-yl)-3,4-dihydro-2*H*-benzo[*e*][1,3]oxazine (**2h**) displayed the highest inhibition percentage, 74.04 % and 64.99 % (intraperitoneal administration), respectively, which were a bit more potent than the reference drug Ibuprofen (62.65 %). Moreover, compound **2d** showed higher activity than the reference drug at all time points by oral administration.

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Compliance with ethical standards

Conflict of interest We declare that we have no conflict of interest with respect to this study.

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