Available online at www.sciencedirect.com
ScienceDirect
Chinese Chemical Letters 22 (2011) 508–510
CHINESE CHEMICAL LETTERS
www.elsevier.com/locate/cclet

Microwave mediated synthesis of non-carboxylic analogues of ibuprofen with improved pharmacological activity

K.V. Sujith [a], Balakrishna Kalluraya [a,*], Adithya Adhikari [a], J. Ravikumar [b]

[a] Department of Studies in Chemistry, Mangalore University, Mangalagangothri 574199, Karnataka, India
[b] Department of Pharmacology, NGSM Institute of Pharmaceutical Science, Deralakkatte 574160, Karnataka, India

Received 24 August 2010
Available online 3 March 2011

Abstract

A series of 1,2,4-triazolo[3,4-b]-thiadiazoles were synthesized following microwave irradiation method and also by conventional method. Newly synthesized compounds were evaluated for their anti-inflammatory and analgesic activities.

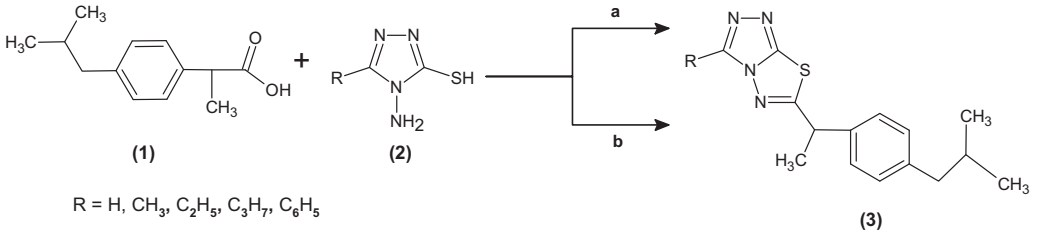
Keywords: Ibuprofen; Microwave; Thiadiazole; Anti-inflammatory; Analgesic

Ibuprofen is an important class of drug belongs to NSAIDs with anti-inflammatory and analgesic activity [1]. Long term use of NSAIDs like ibuprofen has been associated with gastrointestinal complications ranging from stomach irritation to life-threatening GI ulceration bleeding and nephrotoxicity [2,3]. In this perspective ibuprofen has been exploited, in fact this molecule has a carboxylic group as functional group, common to most NSAIDs which is responsible for its local irritation [4]. It has been reported that the derivatization of the carboxyl function of representative NSAIDs, resulted in an increased anti-inflammatory activity with reduced ulcerogenic effect [5–7]. Keeping in view of these observations and in continuation of our search for non-carboxylic derivatives of ibuprofen having improved pharmacological activity [8] we prepared a novel series of triazolothiadiazoles. Retaining the ibuprofen core and replacing its carboxylic group by a triazolothiadiazole moiety. Similarly the development of environmental friendly process has become a focal point in chemical research in recent years [9,10]. Particularly the more efficient use of energy and reduction in the amount of solvents and hazardous substance grab the attention. The microwave induced organic reaction received considerable attention due to their simplicity and operational convenience [11–13]. So we also developed newer eco friendly methods for the synthesis of target molecules namely triazolothiadiazole and the microwave induced reactions were found to be more efficient than the conventional method.

Melting points were determined in open capillary tubes and are uncorrected. IR spectra were recorded by dispersing the compounds in KBr pellets on a Shimadzu FT-IR 157 spectrophotometer. ^{1}H NMR spectra were recorded on a 400 MHz Bruker Avance spectrometer and all the chemical shift values were reported as δ. Mass spectra were recorded on a JEOL SX-102 (FAB) mass spectrometer. Microwave reactions were performed on a godrej domestic oven, with rotating platform tray.

* Corresponding author.
E-mail address: bkalluraya@gmail.com (B. Kalluraya).

1001-8417/$ – see front matter
doi:10.1016/j.cclet.2010.12.013



Scheme 1. Synthetic route for compound **3**. Conditions: (a) $POCl_3$, microwave irradiation at 160 W for 5 min; (b) $POCl_3$, reflux 16 h.

In the design of new compounds, development of hybrid molecules through the combination of different pharmacophores in one structure may lead to compounds with increased biological activity. These observations prompted us to synthesize new 1,2,4-triazolo[3,4-b]thiadiazoles derivatives carrying ibuprofen moiety at 6th position. Both ibuprofen and 1,2,4-triazoles are two important pharmacophores. When they combine to form fused triazolothiadiazole ring system, their synergism towards bio-active properties are studied.

Synthetic pathway for 3-substituted-6-[1-(4-isobutylphenyl)ethyl]-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazoles (**3**) is summarized in Scheme 1. An equimolar mixture of substituted triazoles (**2**) and ibuprofen were dissolved in phosphorus oxychloride. This mixture was then heated conventionally for about 16 h or by employing microwave irradiation for about 5 min at 160 W. The reaction mixture was then cooled to room temperature and poured into ice cold water and treated with saturated solution of sodium bicarbonate. It was then filtered, dried and recrystallized from ethanol to obtain compound **3**. Formation of the compounds was confirmed by spectral and analytical data [14]. Anti-inflammatory activity was determined by the carrageenan-induced paw edema method in Wistar albino rats by using plethysmography following the method of Winter *et al*. [15]. Diclofenac at an oral dose of 20 mg/kg served as the standard drug for comparison and Ibuprofen is used as a second reference for further comparison. The compounds showed anti-inflammatory activity ranging from 41% to 62% (Table 1), whereas standard drugs diclofenac and ibuprofen showed 75% and 42% inhibition after 3 h, respectively. Except compound **3a** all the other tested compounds exhibited more significant anti-inflammatory activity compared to the starting compound ibuprofen. Analgesic activities were evaluated on Swiss albino mice by hot plate method [16]. The reaction time of the animals on the hot plate at 60 and 120 min after drug administration (10 mg/kg) are noted. A dose level of 10 mg/kg diclofenac served as the standard drug for comparison. Compounds showed analgesic activity ranging from 39.28% to 61.84%, whereas the standard drug diclofenac showed 79.24% and ibuprofen showed 30.04% inhibition after 2 h (Table 2). All the tested compounds exhibited more significant analgesic activity compared to ibuprofen. Among the five compounds tested for biological activity, compound **3c**, carrying methyl group at sixth position exhibited significant anti-inflammatory and analgesic properties.

Discovery of mild and practical routes for the synthesis of heterocycles continues to attract the attention of researchers. To accomplish this, we employed microwave irradiation, which has been extensively used for the rapid synthesis of a variety of heterocyclic compounds. The newly synthesized analogues of ibuprofen exhibited increased biological potency compared to the parent drug, ibuprofen.

Table 1
Anti-inflammatory activity of ibuprofen derivatives.

Compounds (R)	Change in paw volume in mL ± SEM (% inhibition)		
	1 h	2 h	3 h
Diclofenac	0.5 ± 1.01 (65)	0.8 ± 4.18 (76)	1 ± 0.89 (75)
Ibuprofen	1.15 ± 2.67 (18)	2.11 ± 3.74 (36)	2.26 ± 2.35 (42)
3a (H)	0.98 ± 2.32 (30)	2.22 ± 3.14 (32)	2.3 ± 2.96 (41)
3b (CH_3)	1.14 ± 1.88 (19)	2 ± 1.21 (39)	1.98 ± 3.45 (49)
3c (C_2H_5)	1.1 ± 1.22 (22)	1.4 ± 2.11 (58)	1.5 ± 1.15 (62)
3d (C_3H_7)	1.22 ± 1.18 (13)	1.64 ± 1.17 (50)	2.05 ± 2.77 (47)
3e (C_6H_5)	0.9 ± 1.69 (36)	1.7 ± 1.36 (49)	1.68 ± 1.88 (57)

Table 2
Analgesic activity of ibuprofen derivatives.

Compounds (R)	Before treatment ± SEM	After treatment ± SEM (% increase in reaction time)	
		1 h	2 h
Diclofenac	2.12 ± 0.18	3.14 ± 0.28 (48.11)	5.92 ± 0.21 (79.24)
Ibuprofen	2.13 ± 0.26	2.61 ± 0.38 (22.53)	2.77 ± 0.33 (30.04)
3a (H)	1.68 ± 0.64	2.18 ± 0.26 (29.76)	2.34 ± 0.12 (39.28)
3b (CH_3)	1.71 ± 0.17	2.2 ± 0.58 (28.65)	2.43 ± 0.18 (42.10)
3c (C_2H_5)	1.52 ± 0.25	2.24 ± 0.34 (47.36)	2.46 ± 0.22 (61.84)
3d (C_3H_7)	1.58 ± 0.21	2.04 ± 0.50 (29.11)	2.30 ± 0.23 (45.56)
3e (C_6H_5)	1.81 ± 0.23	2.36 ± 0.38 (30.38)	2.72 ± 0.18 (50.27)

Acknowledgment

The authors are thankful to UGC for the financial assistance and to the Head, SAIF, CDRI, Lucknow for providing mass and ^{1}H NMR spectral data.

References

[1] X.G. Zhao, X.Y. Tao, D.Z. Wei, et al. Eur. J. Med. Chem. 41 (2006) 1352.
[2] M.C. Allison, A. Howatson, C.J. Torrance, et al. Engl. J. Med. 327 (1992) 749.
[3] M.B. Kimmey, J. Rheumatol. 19 (1992) 68.
[4] C. Hawkey, L. Laine, T. Simon, et al. Arthritis Rheum. 43 (2000) 370.
[5] A.S. Kalgutkar, A.B. Marnett, B.C. Crews, et al. J. Med. Chem. 43 (2000) 2860.
[6] M. Duflos, M.R. Nourrisson, J. Brelet, et al. Eur. J. Med. Chem. 36 (2001) 545.
[7] M. Amir, S. Kumar, Acta Pharm. 57 (2007) 31.
[8] K.V. Sujith, J.N. Rao, P. Shetty, B. Kalluraya, Eur. J. Med. Chem. 44 (2009) 3697.
[9] K.D. Sharwan, Indian J. Chem. 45B (2006) 2337.
[10] K. Mogilaiah, J.U. Rani, Indian J. Het. Chem. 16 (2006) 187.
[11] B. Kalluraya, G. Rai, Synth. Commun. 34 (2004) 4055.
[12] B. Kalluraya, G. Rai, Indian J. Chem. 42B (2003) 2556.
[13] B. Kalluraya, G. Rai, Synth. Commun. 33 (2003) 3583.
[14] Analytical data **3a**. yield: 58%; m.p. 83–86 °C; IR (KBr) γ/cm^{-1}: 2925 (C–H), 1510 (C=N); ^{1}H NMR ($CDCl_3$): δ 0.82 (d, 6H, J = 6.54 Hz, $(CH_3)_2$), 1.66 (d, 3H, J = 7.12 Hz, $CHCH_3$), 1.77–1.81 (m, 1H, CH), 2.40 (d, 2H, J = 7.20 Hz, CH_2-Ar), 4.59 (q, 1H, $CHCH_3$), 7.09 (d, 2H, J = 8.00 Hz, ibu-Ar), 7.30 (d, 2H, J = 8.00 Hz, ibu-Ar); LC–MS (*m*/*z*): 287 (M^++1). Anal. calcd. for $C_15H_{18}N_4S$: C 63.96, H 6.71, N 18.64; Found: C 63.89, H 6.77, N 18.59. **3b**. yield: 64%; m.p. 122 °C; IR (KBr) γ/cm^{-1}: 2954 (C–H), 1535 (C=N); ^{1}H NMR ($CDCl_3$): δ 0.84 (d, 6H, J = 6.57 Hz, $(CH_3)_2$), 0.90 (s, 3H, CH_3), 1.69 (d, 3H, J = 7.02 Hz, $CHCH_3$), 1.77–1.80 (m, 1H, CH), 2.43 (d, 2H, J = 7.11 Hz, CH_2-Ar), 4.60 (q, 1H, $CHCH_3$), 7.16 (d, 2H, J = 7.92 Hz, ibu-Ar), 7.31 (d, 2H, J = 7.95 Hz, ibu-Ar); LC–MS (*m*/*z*): 301 (M^++1). Anal. calcd. for $C_{16}H_{20}N_4S$: C 64.93, H 7.05, N 17.81; Found: C 64.87, H 7.02, N 17.78. **3c**. yield: 69%; m.p. 96–98 °C; IR (KBr) γ/cm^{-1}: 2958 (C–H), 1561 (C=N); ^{1}H NMR ($CDCl_3$): δ 0.91 (d, 6H, J = 6.56 Hz, $(CH_3)_2$), 1.50 (t, 3H, CH_3),1.81 (d, 3H, J = 7.16 Hz, $CHCH_3$), 1.83–1.89 (m, 1H, CH), 2.49 (d, 2H, J = 7.20 Hz, CH_2-Ar), 3.08–3.14 (q, 2H, CH_2), 4.40 (q, 1H, $CHCH_3$), 7.17 (d, 2H, J = 8.16 Hz, ibu-Ar), 7.23 (d, 2H, J = 8.12 Hz, ibu-Ar); LC–MS (*m*/*z*): 315 (M^++1). Anal. calcd. for $C_{17}H_{22}N_4S$: C 65.81, H 7.36, N 17.05; Found: C 65.77, H 7.33, N 17.11. **3d**. yield: 56%; m.p. 101–103 °C; IR (KBr) γ/cm^{-1}: 2959 (C–H), 1488 (C=N); ^{1}H NMR ($CDCl_3$): δ 0.82 (d, 6H, J = 6.60 Hz, $(CH_3)_2$), 0.97 (t, 3H, CH_3), 1.69 (d, 3H, J = 7.08 Hz, $CHCH_3$), 1.75–1.82 (m, 1H, CH), 1.75–1.82 (m, 2H, CH_2), 2.43 (d, 2H, J = 7.17 Hz, CH_2-Ar), 2.98 (t, 2H, CH_2), 4.61 (q, 1H, $CHCH_3$), 7.17 (d, 2H, J = 8.04 Hz, ibu-Ar), 7.31 (d, 2H, J = 8.04 Hz, ibu-Ar); LC–MS (*m*/*z*): 329 (M^++1). Anal. calcd. for $C_{18}H_{24}N_4S$: C 69.53, H 6.08, N 15.41; Found: C 69.58, H 6.11, N 15.45. **3e**. yield: 51%; m.p. 115–118 °C; IR (KBr) γ/cm^{-1}: 2951 (C–H), 1578 (C=N); ^{1}H NMR ($CDCl_3$): δ 0.92 (d, 6H, J = 6.64 Hz, $(CH_3)_2$), 1.83–1.90 (m, 1H, CH), 1.89 (d, 3H, J = 7.12 Hz, $CHCH_3$), 2.50 (d, 2H, J = 7.16 Hz, CH_2-Ar), 4.50 (q, 1H, $CHCH_3$), 7.19 (d, 2H, J = 8.12 Hz, ibu-Ar), 7.27 (d, 2H, J = 8.08 Hz, ibu-Ar), 7.49–8.38 (m, 5H, Ar); LC–MS (*m*/*z*): 363 (M^++1). Anal. calcd. for $C_{21}H_{22}N_4S$: C 70.11, H 6.39, N 14.91; Found: C 70.17, H 6.42, N 14.88.
[15] C.A. Winter, E.A. Risley, G.W. Nuss, Proc. Soc. Exp. Biol. Med. III (1962) 544.
[16] N.B. Eddy, D. Leimbach, J. Pharmacol. Exp. Ther. 107 (1953) 385.