Available online at www.sciencedirect.com
ScienceDirect
European Journal of Medicinal Chemistry 44 (2009) 794–799
EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY
http://www.elsevier.com/locate/ejmech

Original article

Synthesis, analgesic and anti-inflammatory activities of novel 3-(4-acetamido-benzyl)-5-substituted-1,2,4-oxadiazoles

Mazahar Farooqui [a,*], Rajesh Bora [a,b], C.R. Patil [c]

[a] Department of Chemistry, Aurangabad College for Women, Navkhanda, Aurangabad 431001, India
[b] Wockhardt Research Centre, Chikalthana, Aurangabad 431 210, India
[c] R.C. Patel College of Pharmacy, Shirpur 425 405, India

Received 27 January 2008; received in revised form 17 May 2008; accepted 22 May 2008
Available online 14 July 2008

Abstract

A series of 3-(4-acetamido-benzyl)-5-substituted-1,2,4-oxadiazoles (**7a–7n**) were synthesized and screened for analgesic and *in vivo* anti-inflammatory activities using acetic acid writhing in mice model and carrageenan-induced paw oedema method in mice, respectively. The analgesic activity of compounds **7i** and **7m** is superior while that of **7d**, **7c**, **7f** and **7j** is equal to the reference standard, diclofenac sodium. The anti-inflammatory activity of compounds **6**, **7c**, **7e**, **7f**, **7i**, **7l**, **7m** and **7n** is found to be superior than that of diclofenac sodium which is used as a reference, while compounds **7d** and **7g** are found to be equipotent with the reference compound.

Keywords: Hydroxycarbamidoylmethyl; 1,2,4-Oxadiazoles; Anti-inflammatory activity; Analgesic activity; Diclofenac sodium

1. Introduction

Inflammation is a complex phenomenon involving interrelationships of humoral and cellular reactions through a number of inflammatory mediators. It is a usual symptom covering different pathologies, and there are still many questions to be answered in order to understand the inflammatory process as well as a need for better-tolerated and more efficient nonsteroidal anti-inflammatory drugs [1]. Nonsteroidal anti-inflammatory drugs (NSAIDs) are important therapeutic agents for the treatment of pain and inflammation. However, their therapeutic use is often limited by the common side effects, such as gastrointestinal (GI) haemorrhage and ulceration and also affects the functioning of platelets [2]. NSAIDs work by inhibiting the cyclooxygenase (COX), a key enzyme [3,4] so preventing the formation of inflammatory prostaglandins from metabolism of arachidonic acid. Since prostaglandins have dual functions, mediation of inflammation and cytoprotection in the stomach and intestine, and possible dissociation of anti-inflammatory effects from GI toxicity is suggested by recent discovery that COX exists in two isoforms, COX-1 and COX-2, which are encoded by two distinct genes. COX-1 is thought to provide cytoprotection; COX-2 inhibitor might have selective anti-inflammatory properties and lack of GI side effects [5].

1,2,4-Oxadiazoles are well known compounds which exhibit diversified biological activities [6–9]. Oxadiazoles have often been described as bio-isosteres for amides and esters [10]. Due to increased hydrolytic [11] and metabolic stabilities of the oxadiazole ring, improved pharmacokinetic and *in vivo* performance is often observed, which make these heterocycles an important structural motif for the pharmaceutical industry. As a consequence of these characteristics, oxadiazoles have impacted numerous drug discovery programs including muscarinic agonists [12], benzodiazepine receptor partial agonists [13], dopamine transporters [14], anti-rhinovirals [15], growth hormone secretogogues [16], 5-HT agonists [17], antispasmodics [18], nematocidal, fungicidal and microbicides [19], analgesics [20], anti-inflammatory agents [21], Fab I inhibitors as antibacterial agents [22], immunosuppressants [23], and also antiplatelet and antithrombotic agents

* Corresponding author.
E-mail address: mazahar_64@rediffmail.com (M. Farooqui).

0223-5234/$ - see front matter © 2008 Elsevier Masson SAS. All rights reserved.
doi:10.1016/j.ejmech.2008.05.022

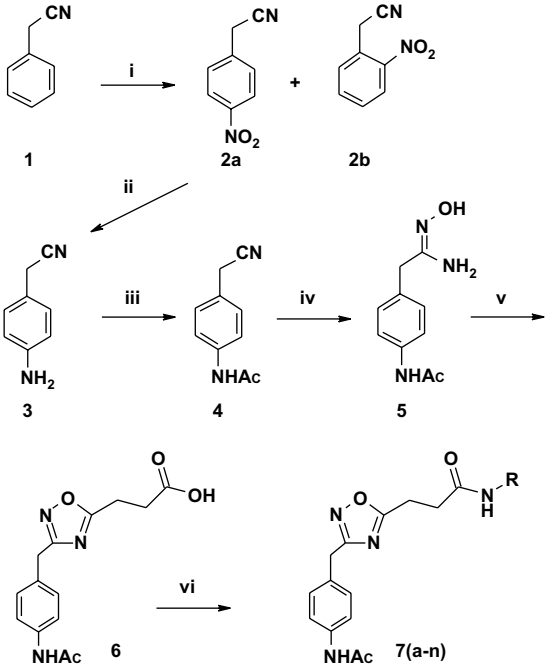
[24]. 3-Aryl-5-substituted 1,2,4-oxadiazoles have also shown the activity against kinetoplastid parasites [25] and interleukin-8 (IL-8) receptor antagonists and thereby leading to unique anti-inflammatory agents [26].

2. Chemistry

Based on these understandings we have undertaken the synthesis of 3,5-disubstituted [1,2,4]-oxadiazoles with amide functionality at C′5 terminal as novel compounds as a part of our research programme. These are then screened for analgesic and anti-inflammatory activities in different animal models.

Many synthetic methodologies are known in the literature for the synthesis of 3,5-disubstituted-[1,2,4]-oxadiazoles. Herein we have synthesized from *N*-[4-(*N*-hydroxycarbamidoylmethyl)-phenyl]-acetamide (**5**) intermediate, which was prepared as per the procedure reported in our earlier publication [27].

When compound **5** was reacted with succinic anhydride [28] in high boiling solvents such as xylene it afforded 3-[3-(4-acetylamino-benzyl)-[1,2,4]oxadiazol-5-yl]-propionic acid (**6**). This step is thermal cyclization in which open chain amidoxime undergoes *in situ* cyclodehydration yielding substituted oxadiazole compound with free carboxylic acid group. This substituted acid amidoxime when reacted with substituted aromatic amines afforded 3,5-disubstituted oxadiazole amide derivatives. The amide bond formation was carried out by using *N*-ethyl-*N*′-(3-dimethylaminopropyl)-carbodiimide hydrochloride [WSC, EDCI] and 1-hydroxy benzotriazole as a coupling reagent in solvent such as THF. All the compounds were synthesized in good to excellent yield (Scheme 1).



Scheme 1. Conditions and reagents: (i) conc. HNO_3/H_2SO_4, 0 °C; (ii) Pd/C, H_2/rt, THF; (iii) acetyl chloride/Et_3N/THF, 0 °C; (iv) $NH_2OH\cdot HCl$/$NaHCO_3$/MeOH/reflux; (v) succinic anhydride/xylene/120 °C; (vi) substituted amine/EDC·HCl/DIEA/THF, rt.

3. Biology

3.1. In vivo anti-inflammatory activity

Carrageenan footpad edema [29]. The acute anti-inflammatory activity of the synthesized compounds was determined following the carrageenan-induced paw oedema method in mice. Carrageenan solution (1% w/v) was prepared by dissolving 100 mg of carrageenan (Marine Colloidal Div., Springfield, NJ) in 10 ml of sterile saline (0.9%) solution. Male C57BL/6 mice were orally dosed with compound (at dose of 100 mg/kg *p.o.* as a suspension in 5% carboxymethylcellulose) 1 h before carrageenan challenge. Diclofenac sodium given at 100 mg/kg *p.o.* was used as a standard drug. Foot paw oedema was induced by injecting 0.05 ml of the carrageenan solution subcutaneously into the planter portion of the right hind paw of each mice under light anesthesia. Initial foot paw volume was measured immediately by digital plethysmometry (Ugo Basile Digital Plethysmometer, Model-7140, Italy) following carrageenan challenge. Oedema was measured 4 h after carrageenan administration. The swelling in each test group of animals was used to calculate the percent inhibition ± SEM of edema achieved by the compound at the test dose compared with the vehicle control group. The results are summarized in Table 1.

3.2. Analgesic activity [30]

For this test, male C57BL/6 mice were used. The drug treatment was same as stated above. The treatments were administered 1 h prior to acetic acid injection. For induction of pain, 0.25 ml of 0.6% v/v acetic acid was injected *i.p.* Total number of writhings were counted along the period of 30 min following acetic acid injection.

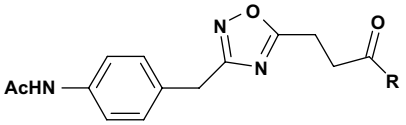
Average numbers of writhings in the control group were used to calculate percentage inhibition of writhings in other groups. The results are summarized in Table 1.

4. Results and discussion

Acute anti-inflammatory activity. Compounds **7d** and **7g** showed activity equipotent to that of reference standard, diclofenac, while compounds **6**, **7c**, **7e**, **7i**, **7l**, **7m**, and **7n** are more potent than diclofenac sodium in inhibiting the inflammation induced by carrageenan.

The structure–anti-inflammatory activity relationship of the synthesized compounds revealed that the activity is dependant on the basic molecular skeleton. Compound **6** is one of the most potent compounds. But having one or more lipophilic substituents on the aromatic ring further enhances the activity. This may be due to better partitioning of the molecule in the lipid bilayer of the cell membrane. Compound **7i** is the most

Table 1
The anti-inflammatory and analgesic activities of 3,5-disubstituted-[1,2,4]-oxadiazoles



S. no.	Entry	R	% Rise in paw volume	% Inhibition of inflammation	% Decrease in writhing
1	**6**	−OH	18 ± 2	75.34 ± 3.4	46.43 ± 1.39
2	**7a**	−Aniline	48 ± 3	34.24 ± 4.7	−13.10 ± 1.94
3	**7b**	-*m*-Anisidine	47 ± 3	35.61 ± 4.5	−7.14 ± 2.35
4	**7c**	−*o*-Anisidine	9 ± 1	87.67 ± 1.6	73.81 ± 0.49
5	**7d**	−*p*-Anisidine	37 ± 3	49.31 ± 4.2	67.26 ± 1.20
6	**7e**	2-Fluoroaniline	24 ± 5	67.12 ± 7.3	−23.21 ± 1.40
7	**7f**	4-Fluoroaniline	26 ± 4	64.38 ± 5	67.86 ± 1.07
8	**7g**	2,4-Fluoroaniline	34 ± 4	52.05 ± 6.7	−0.60 ± 0.91
9	**7h**	3-*F*-4-methoxy-aniline	29 ± 5	60.27 ± 7.3	36.90 ± 3.17
10	**7i**	3,4-D-Methoxy-aniline	3 ± 1	95.89 ± 1.9	80.36 ± 0.43
11	**7j**	*m*-Toludine	61 ± 1	16.43 ± 1.9	67.26 ± 1.01
12	**7k**	4-Trifluomethylaniline	46 ± 4	36.98 ± 5.7	31.55 ± 4.32
13	**7l**	3-Ethynyl aniline	11 ± 1	84.93 ± 1.6	61.31 ± 0.79
14	**7m**	Pyridine	9 ± 1	87.67 ± 1.9	80.95 ± 0.42
15	**7n**	Benzylamine	17 ± 5	76.71 ± 6.2	−0.60 ± 1.58
16	Control	Control	73 ± 7	0	−2.38 ± 1.33
17	Std	Diclofenac	36 ± 7	50.68 ± 9	77.38 ± 0.49

potent being two methoxy groups are present at *ortho* and *para* compared to one methoxy substituent present in compound **7c** revealing the importance of electron-donating group like methoxy substituents at *ortho* and *para* positions in the aromatic ring.

4.1. Analgesic activity

Compounds **7i** and **7m** are more potent analgesic than diclofenac sodium, while compounds **7d**, **7c**, **7f**, and **7j** are equipotent as analgesic with respect to the reference standard.

Presence of two methoxy groups in aromatic ring at *ortho* and *para* positions is highly effective for the analgesic and anti-inflammatory activities. It may be speculated that hydrophilicity of two amide groups is balanced by methoxy groups and therefore its pharmacokinetic behaviour is better than rest of the compounds. Hence compound **7i** is found to be the most active compound among the series in both the animal models. Therefore, compound **7i** can be considered as lead molecule for further development.

5. Experimental

Melting points were taken on a Precision melting point apparatus (DBK Instruments) and are uncorrected. IR spectra were obtained in potassium bromide (KBr) disks on a Bruker IR spectrophotometer, and ^{1}H NMR spectra were obtained on deuteriochloroform ($CDCl_3$) and or DMSO-d_6 solution on a Varian 400 MHz spectrophotometer. Elemental analyses were performed on Fissons micro CHN analyzer. Mass spectra were recorded on a MicroMass spectrometer by Waters. The yields unless otherwise mentioned are for the pure product. All the raw materials, reagents and solvents used were of commercial grade only.

5.1. Synthesis of 3-[3-(4-acetylamino-benzyl)-[1,2,4]oxadiazol-5-yl]-propionic acid (*6*)

To a stirred solution of *N*-[4-(*N*-hydroxycarbamidoylmethyl)-phenyl]-acetamide **5** (10.0 g; 0.048 M) in xylene (60 ml) was added succinic anhydride (4.8 g; 0.048 M). The resulting reaction mixture was then heated at 120 °C for 2 h and then cooled to room temperature. Xylene was then decanted and sticky brown solid left in the flask was triturated in ice-cold water to afford free solid. The resulting solid was filtered and triturated in diethyl ether to afford cream-colored solid **6** (11.0 g, 80%).

M.p. 162–163 °C. IR (cm^{-1}, KBr): 3400, 3312, 3100, 1716, 1659, 1601 and 1542. ^{1}H NMR (DMSO-d_6): δ 2.1 (s, 3H, CH_3), 2.7 and 3.1 (each t, each 2H, each $-CH_2-$), 4.0 (s, 2H, $-CH_2Ph$), 7.15 and 7.45 (each 2 d, each 2H, each Ar–H), 9.95 (s, 1H, NH), 12.4 (broad s, 1H, −COOH). Mass (*m*/*z*): 290 (M^+1). Anal. Found: C, 58.50; H, 5.63; N, 14.90. Calcd for $C_{14}H_{15}N_3O_4$: C, 58.13; H, 5.23; N, 14.53%.

5.2. 3-[3-(4-Acetylamino-benzyl)-[1,2,4]oxadiazol-5-yl]-N-phenyl-propionamide (*7a*)

To a stirred solution of 3-[3-(4-acetylamino-benzyl)-[1,2,4]oxadiazol-5-yl]-propionic acid **6** (0.10 g, 0.35 mmol) and aniline (0.035 ml, 0.35 mmol, 1.0 equiv) in THF were added EDC·HCl (0.085 g, 0.42 mmol, 1.2 equiv), 1-hydroxy benzotriazole (0.012 mg, 0.09 mmol, 0.25 equiv) and ethyl *N*,*N*-diisopropylamine (0.075 ml, 0.42 mmol, 1.2 equiv).

Reaction mixture was then stirred at room temperature for 2 h. On completion of reaction organic solvent was evaporated under vacuum to afford crude sticky mass. On triturating in 10% $NaHCO_3$ solution yellow solid separated was then filtered under vacuum. It was then recrystallized from 95% ethanol to afford pale yellow solid (0.1 g, 90%).

M.p. 179–180 °C. IR (cm^{-1}, KBr): 3283, 3123, 1685, 1645, 1614 and 1578. ^1H NMR (DMSO-d_6): δ 2.0 (s, 3H, CH_3), 2.95 and 3.25 (each t, each 2H, each $-CH_2-$), 4.0 (s, 3H, $-CH_2Ph$), 7.2 and 7.4 (each 2 d, each 2H, each Ar-H), 9.95 (broad s, 1H, −NH), 12.4 (broad s, 1H, −COOH). Mass (*m/z*): 365 (M^+1). Anal. Found: C, 66.35; H, 5.91; N, 15.75. Calcd for $C_{20}H_{20}N_4O_3$: C, 65.92; H, 5.53; N, 15.37%.

*5.3. 3-[3-(4-Acetylamino-benzyl)-[1,2,4]oxadiazol-5-yl]-N-(3-methoxy-phenyl)-propionamide (**7b**)*

Prepared from *m*-anisidine (0.10 g, 0.35 mmol) and compound **6** (0.10 g, 0.35 mmol) by using the same procedure as mentioned in **7a** to afford **7b** as off-white solid (110 mg, 81%).

M.p. 137–138 °C. IR (cm^{-1}, KBr): 3263, 3118, 1670, 1614, 1595 and 1577. ^1H NMR (DMSO-d_6): δ 2.0 (s, 3H, CH_3), 2.85 and 3.25 (each t, each 2H, each $-CH_2-$), 3.7 (s, 3H, $-OCH_3$), 4.0 (s, 2H, $-CH_2Ph$), 6.6 and 7.05 (each d, each 1H, each Ar-H), 7.15 (s, 1H, −Ar), 7.2 and 7.45 (each 2 d, each 2H, each Ar-H), 7.22 (m, 2H, Ar-H), 9.9 (s, 1H, −NH), 10 (s, 1H, −NH). Mass (*m/z*): 395 (M^+1). Anal. Found: C, 64.30; H, 5.99; N, 14.55. Calcd for $C_{21}H_{22}N_4O_4$: C, 63.95; H, 5.62; N, 14.20%.

*5.4. 3-[3-(4-Acetylamino-benzyl)-[1,2,4]oxadiazol-5-yl]-N-(4-methoxy-phenyl)-propionamide (**7d**)*

Prepared from *p*-anisidine (0.10 g, 0.35 mmol) and compound **6** (0.10 g, 0.35 mmol) by using the same procedure as mentioned in **7a** to afford **7d** as yellow solid (105 mg, 78%).

M.p. 188–190 °C. IR (cm^{-1}, KBr): 3256, 3108, 1677, 1624, 1590 and 1567. ^1H NMR (DMSO-d_6): δ 2.0 (s, 3H, CH_3), 2.8 and 3.1 (each t, each 2H, each $-CH_2-$), 3.75 (s, 3H, $-OCH_3$), 3.95 (s, 2H, $-CH_2Ph$), 6.8 (d, 2H, Ar-H), 7.16 (d, 2H, Ar-H), 7.41 and 7.46 (each 2 d, each 2H, each Ar-H), 9.86 (s, 1H, −NH). Mass (*m/z*): 395 (M^+1). Anal. Found: C, 64.35; H, 6.00; N, 14.60. Calcd for $C_{21}H_{22}N_4O_4$: C, 63.95; H, 5.62; N, 14.20%.

*5.5. 3-[3-(4-Acetylamino-benzyl)-[1,2,4]oxadiazol-5-yl]-N-(2-methoxy-phenyl)-propionamide (**7c**)*

Prepared from *o*-anisidine (0.10 g, 0.35 mmol) and compound **6** (0.10 g, 0.35 mmol) by using the same procedure mentioned in **7a** to obtain **7c** as pale yellow solid (90 mg, 66%).

M.p. 193–194 °C. IR (cm^{-1}, KBr): 3244, 3095, 1659, 1604, 1597 and 1577. ^1H NMR (DMSO-d_6): δ 2 (s, 3H, CH_3), 2.9 and 3.1 (each t, each 2H, each $-CH_2-$), 3.8 (s, 3H, $-OCH_3$), 4 (s, 2H, CH_2-Ph), 6.85 (d, 1H, Ar-H), 7 (m, 2H, Ar-H), 7.15 (d, 2H, Ar-H), 7.45 (d, 2H, Ar-H), 7.9 (broad d, 1H, Ar-H), 9.24 (s, 1H, −NH), 9.87 (s, 1H, −NH). Mass *m/z*: 395 (M^+1). Anal. Found: C, 64.315; H, 5.97; N, 14.55. Calcd for $C_{21}H_{22}N_4O_4$: C, 63.95; H, 5.62; N, 14.20%.

*5.6. 3-[3-(4-Acetylamino-benzyl)-[1,2,4]oxadiazol-5-yl]-N-(2,4-dimethoxy-phenyl)-propionamide (**7i**)*

Prepared from 2,4-dimethoxyaniline (0.10 g, 0.35 mmol) and compound **6** (0.10 g, 0.35 mmol) by using the same procedure mentioned as in **7a** to afford **7i** as pale yellow solid (115 mg, 78%).

M.p. 168–169 °C. IR (cm^{-1}, KBr): 3235, 3085, 1649, 1624, 1587 and 1569. ^1H NMR (DMSO-d_6): δ 2.0 (s, 3H, CH_3), 2.9 and 3.15 (each t, each 2H, each $-CH_2-$), 3.9 (s, 3H, $-OCH_3$), 4.0 (s, 2H, CH_2-Ph), 4.1 (s, 3H, OCH_3), 6.85 (d, 1H, Ar-H), 7.05 (m, 1H, Ar-H), 7.25 (m, 1H, Ar-H), 7.2 and 7.4 (each 2 d, each 2H, each Ar-H), 9.9 (s, 1H, −NH), 10.1(s, 1H, −NH). Mass (*m/z*): 425 (M^+1). Anal. Found: C, 62.60; H, 6.05; N, 13.60. Calcd for $C_{22}H_{24}N_4O_5$: C, 62.25; H, 5.70; N, 13.20%.

*5.7. 3-[3-(4-Acetylamino-benzyl)-[1,2,4]oxadiazol-5-yl]-N-(3-fluoro-4-methoxy-phenyl)-propionamide (**7h**)*

Prepared from 3-fluoro-4-dimethoxyaniline (0.10 g, 0.35 mmol) and compound **6** (0.10 g, 0.35 mmol) by using the same procedure mentioned in **7a** to obtain **7h** as pale yellow solid (100 mg, 68.5%).

M.p. 197–198 °C. IR (cm^{-1}, KBr): 3235, 3110, 1675, 1620, 1589 and 1570. ^1H NMR (DMSO-d_6): δ 2.0 (s, 3H, CH_3), 2.8 and 3.2 (each t, each 2H, each $-CH_2-$), 3.8 (s, 3H, $-OCH_3$), 4.0 (s, 3H, OCH_3), 7.05 (t, 2H, Ar-H), 7.15 (m, 2H, A), 9.9 (s, 1H, −NH), (10.1 (s, 1H, −NH). Mass (*m/z*): 425 (M^+1). Anal. Found: C, 61.52; H, 5.52; N, 13.95. Calcd for $C_{21}H_{24}FN_4O_4$: C, 61.16; H, 5.13; N, 13.58%.

*5.8. 3-[3-(4-Acetylamino-benzyl)-[1,2,4]oxadiazol-5-yl]-N-(4-fluoro-phenyl)-propionamide (**7f**)*

Prepared from 4-fluoroaniline (0.10 g, 0.35 mmol) and compound **6** (0.10 g, 0.35 mmol) by using the same procedure mentioned in **7a** to afford **7f** as pale yellow solid (105 mg, 80%).

M.p. 196–197 °C. IR (cm^{-1}, KBr): 3245, 3105, 1665, 1610, 1595 and 1560. ^1H NMR (DMSO-d_6): δ 2.0 (s, 3H, CH_3), 2.81 and 3.13 (each t, each 2H, each $-CH_2-$), 3.95 (s, 2H, $-CH_2-Ph$), 7.0 (t, 2H, Ar-H), 7.15 (d, 2H, Ar-H), 7.45 (d, 2H, Ar-H), 7.52 (m, 2H, Ar-H), 9.87 (broad s, 1H, −NH), 10.08 (s, 1H, −NH). Mass (*m/z*): 383 (M^+1). Anal. Found: C, 63.18; H, 5.35; N, 15.00. Calcd for $C_{21}H_{19}FN_4O_4$: C, 62.82; H, 5.01; N, 14.65%.

*5.9. 3-[3-(4-Acetylamino-benzyl)-[1,2,4]oxadiazol-5-yl]-N-(2-fluoro-phenyl)-propionamide (**7e**)*

Prepared from 2-fluoroaniline (0.10 g, 0.35 mmol) and compound **6** (0.10 g, 0.35 mmol) by using the same procedure mentioned in **7a** to afford **7e** as cream-colored solid (95 mg, 72%).

M.p. 147–148 °C. IR (cm^{-1}, KBr): 3265, 3095, 1662, 1605, 1599 and 1575. ^1H NMR (DMSO-d_6): δ 2.0 (s, 3H, CH_3), 2.95 and 3.13 (each t, each 2H, each $-CH_2-$), 3.95 (s, 2H, $-CH_2-Ph$), 7.10 (m, 2H, Ar-H), 7.16 (d, 2H, Ar-H d), 7.21 (m, 1H, Ar-H), 7.46 (d, 2H, Ar-H), 7.78 (1H, broad s, Ar-H), 9.82 (s, 1H, −NH) and 9.86 (s, 1H, −NH). Mass (*m/z*): 383 (M^+1). Anal. Found: 63.20; H, 5.39; N, 15.03. Calcd for $C_{21}H_{19}FN_4O_4$: C, 62.82; H, 5.01; N, 14.65%.

*5.10. 3-[3-(4-Acetylamino-benzyl)-[1,2,4]oxadiazol-5-yl]-N-(2,4-difluoro-phenyl)-propionamide (**7g**)*

Prepared from 2,4-difluoroaniline (0.10 g, 0.35 mmol) and compound **6** (0.10 g, 0.35 mmol) by using the same procedure mentioned in **7a** to obtain **7g** as pale yellow solid (110 mg, 80.3%).

M.p. 147–148 °C. IR (cm^{-1}, KBr): 3260, 3100, 1672, 1600, 1589 and 1555. ^1H NMR (DMSO-d_6): δ 2.0 (s, 3H, CH_3), 2.85 and 3.15 (each t, each 2H, each $-CH_2-$), 4.0 (s, 2H, $-CH_2-Ph$), 7 (t, 1H, Ar-H), 7.16 (d, 2H, Ar-H), 7.23–7.29 (m, 1H, Ar-H), 7.4 (d, 2H, Ar-H), 7.7 (m, 1H, Ar-H), 9.82 (m, 1H, N-H), 9.87 (s, 1H, −NH) Mass (*m/z*): 400 (M^+1). Anal. Found: C, 63.22; H, 5.41; N, 15.05. Calcd for $C_{21}H_{18}F_2N_4O_3$: C, 62.82; H, 5.01; N, 14.65%.

*5.11. 3-[3-(4-Acetylamino-benzyl)-[1,2,4]oxadiazol-5-yl]-N-(4-trifluoromethyl-phenyl)-propionamide (**7k**)*

Prepared from 4-trifluoromethylaniline (0.10 g, 0.35 mmol) and compound **6** (0.10 g, 0.35 mmol) by using the same procedure mentioned in **7a** to obtain **7k** as pale yellow solid (110 mg, 73.3%).

M.p. 201–202 °C. IR (cm^{-1}, KBr): 3267, 3090, 1677, 1625, 1589 and 1567. ^1H NMR (DMSO-d_6): δ 2.2 (s, 3H, CH_3), 2.95 and 3.2 (each t, each 2H, each $-CH_2-$), 4.0 (s, 2H, $-CH_2-Ph$), 7.15 (d, 2H, −NH), 7.45 (d, 2H, Ar-H), 7.63 and 7.72 (each d, each 2H, Ar-H), 9.86 and 10.39 (each s, each 1H, each −NH). Mass (*m/z*): 433 (M^+1). Anal. Found: C, 58.75; H, 4.80; N, 13.33. Calcd for $C_{21}H_{19}F_3N_4O_3$: C, 58.33; H, 4.43; N, 12.96%.

*5.12. 3-[3-(4-Acetylamino-benzyl)-[1,2,4]oxadiazol-5-yl]-N-m-tolyl-propionamide (**7j**)*

Prepared from *m*-toludine (0.10 g, 0.35 mmol) and compound **6** (0.10 g, 0.35 mmol) by using the same procedure mentioned in **7a** to obtain **7j** as white solid (115 mg, 88.5%).

M.p. 152–153 °C. IR (cm^{-1}, KBr): 3240, 3120, 1680, 1615, 1599 and 1570. ^1H NMR (DMSO-d_6): δ 2.0 (s, 3H, CH_3), 2.23 (s, 3H, $Ar-CH_3$), 2.81 and 3.12 (each t, each 2H, each $-CH_2-$), 3.95 (s, 2H, $-CH_2-Ph$), 6.8 (d, 1H, Ar-H), 7.3–7.17 (m, 3H, Ar-H), 7.29 (d, 1H, Ar-H), 7.35 (s, 1H, Ar-H), 7.46 (d, 2H, Ar-H), 9.8 (s, 1H, −NH), 9.93 (s, 1H, −NH). Mass (*m/z*): 379 (M^+1). Anal. Found: C, 67.05; H, 6.26; N, 15.20. Calcd for $C_{22}H_{22}N_4O_3$: C, 66.65; H, 5.86; N, 14.80%.

*5.13. 3-[3-(4-Acetylamino-benzyl)-[1,2,4]oxadiazol-5-yl]-N-(3-ethynyl-phenyl)-propionamide (**7l**)*

Prepared from 3-ethynylaniline (0.10 g, 0.35 mmol) and compound **6** (0.10 g, 0.35 mmol) by using the same procedure mentioned in **7a** to obtain **7l** as pale yellow solid (105 mg, 78.4%).

M.p. 194–195 °C. IR (cm^{-1}, KBr): 3257, 3111, 1666, 1607, 1586 and 1544. ^1H NMR (DMSO-d_6): δ 2.0 (s, 3H, CH_3), 2.85 (t, 2H, CH_2-), 4.15 (s, 1H, acetylene), 3.25 (t, 2H, CH_2-), 4.0 (s, 2H, $-CH_2-Ar$), 7.15 (m, 3H, Ar-H), 7.2–7.25 (m, 1H, Ar-H), 7.4–7.50 (m, 3H, Ar-H), 7.7 (s, 1H, Ar-H) 9.86, 10.13 (each s, each 1H, each −NH protons). Mass (*m/z*): 389 (M^+1). Anal. Found: C, 68.33; H, 5.49; N, 14.72. Calcd for $C_{22}H_{20}N_4O_3$: C, 68.03; H, 5.19; N, 14.42%

*5.14. 3-[3-(4-Acetylamino-benzyl)-[1,2,4]oxadiazol-5-yl]-N-pyridin-3-yl-propionamide (**7m**)*

Procedure. Prepared from 3-aminopyridine (0.10 g, 0.35 mmol) and compound **6** (0.10 g, 0.35 mmol) by using the same procedure mentioned in **7a** to obtain **7m** as cream-colored solid (100 mg, 79.4%).

M.p. 189–190 °C. IR (cm^{-1}, KBr): 3288, 3070, 1666, 1607, 1586 and 1544. ^1H NMR (DMSO-d_6) δ 2.0 (s, 3H, CH_3), 2.85 and 3.15 (each t, each 2H, each $-CH_2-$), 4.0 (s, 2H, $-CH_2-Ar$), 7.2–7.25 (d, 2H, Ar-H), 7.4 (d, 2H, Ar-H), 7.45 (m, 1H, Py-H), 8.4 (m, 1H, Py-H), 8.75 (dd, 1H, Py-H), 8.95 (d, 1H, Py-H), 9.8 (s, 1H, −NH) and 9.98 (s, 1H, −NH). Mass (*m/z*): 366 (M^+1). Anal. Found: C, 62.80; H, 5.60; N, 19.52. Calcd for $C_{19}H_{19}N_5O_3$: C, 62.46; H, 5.24; N, 19.17%.

*5.15. 3-[3-(4-Acetylamino-benzyl)-[1,2,4]oxadiazol-5-yl]-N-benzyl-propionamide (**7n**)*

Prepared from benzyl amine (0.10 g, 0.35 mmol) and **6** (0.10 g, 0.35 mmol) by using the same procedure mentioned in **7a** to obtain **7n** as white solid (120 mg, 92.3%).

M.p. 163–164 °C. IR (cm^{-1}, KBr): 3257, 3111, 1666, 1607, 1586 and 1544. ^1H NMR (DMSO-d_6): δ 2.0 (s, 3H, CH_3), 2.65 (t, 2H, CH_2-), 3.15 (t, 2H, CH_2-), 3.95 (s, 2H, $-CH_2-Ar$), 4.23 (s, 2H, Ar-CH_2) 7.15–7.22 (m, 5H, Ar-H), 7.25 (m, 2H, Ar-H), 7.47–7.49 (d, 2H, Ar-H), 8.4 (s, 1H, −NH) 9.88(s, 1H, -NH). Mass (*m/z*): 379 (M^+1). Anal. Found: C, 66.96; H, 6.24; N, 15.17. Calcd for $C_{21}H_{22}N_4O_3$: C, 66.65; H, 5.86; N, 14.80%.

Acknowledgement

Author is greatly thankful to Dr. Mahesh Patel, Director, Wockhardt Research Centre, Aurangabad for the technical support provided for carrying out this research work.

References

[1] Christos A. Kontogiorgis, J. Med. Chem. 48 (2005) 6400–6408.
[2] G. Habeeb Amgad, P.N. Praveen Rao, J. Med. Chem. 44 (2001) 2921–2927.
[3] W.L. Xie, J.G. Chipmann, Proc. Natl. Acad. Sci. U. S. A. 88 (1991) 2692–2696.
[4] M.C. Allison, A.C. Howatson, N. Engl. J. Med. 327 (1992) 749–754.
[5] J.H. Botting, Drugs Today 35 (1999) 225.
[6] A.W. Ricardo, Filho Neves, Molecules 11 (2006) 318–324.
[7] K. Hemming, J. Chem. Res. 216 (2001) 209–216.
[8] V.A. Glushkov, L.V. Anikina, Pharma. Chem. J. 38 (2004) 86–89.
[9] R.M. Srivastava, L.P.F. Morais, Heterocycl. Commun. 6 (2000) 41–48.
[10] R.Y. Jonathan, J.D. Robert, Tetrahedron Lett. 39 (1998) 3931.
[11] L.B. Clapp, Adv. Heterocycl. Chem. (1976) 65.
[12] B.S. Orlek, F.E. Balney, J. Med. Chem. 34 (1991) 2726.
[13] F. Watjen, R. Baker, J. Med. Chem. 32 (1989) 2282.
[14] F.L. Carroll, J.L. Gray, J. Med. Chem. 36 (1993) 2886.
[15] G.D. Diana, D.L. Volkots, J. Med. Chem. 37 (1994) 2421.
[16] M. Ankersen, B. Peschke, Bioorg. Med. Chem. Lett. 7 (1997) 1293.
[17] C. Chen, C.H. Senanayake, J. Org. Chem. 59 (1994) 3738.
[18] A.S. Sousa, French Patent 1,363,235, 1964 Chem. Abstr. 62 (1965) 5282.
[19] H. Ulrich, H.G. Wilfried, Ger Offen. DE 3,805,698, 1989.
[20] P. Afiatpour, R.M. Srivastava, Braz. J. Med. Biol. Res. 27 (1994) 1403.
[21] S.E. Dahlgren, T. Dalham, Acta Pharmacol. Toxicol. 31 (1972) 193.
[22] A. Dirk, George Chan Heerding, Bioorg. Med. Chem. Lett. 11 (2001) 2061.
[23] C.B. Vu, E.G. Corpuz, J. Med. Chem. 42 (1999) 20.
[24] K. Bethge, H.H. Pertz, Arch. Pharm. 78 (2005) 338.
[25] Denise M. Cottrell, Jaffery Capers, Bioorg. Med. Chem. 12 (2004) 2815–2824.
[26] Michele A. Weidner-Wells, Todd C. Henninger, Bioorg. Med. Chem. Lett. 14 (2004) 4307–4311.
[27] Rajesh Bora, M. Farooqui, J. Heterocycl. Chem. 44 (2007) 645.
[28] G. Leandri, L. Maioli, Boll. Sci. Fac. Chim. Ind., Bolgna 15 No. 3, (1957) 5762 Chem. Abstr. 52 (1958) 7291h.
[29] Maria Eugenia Alvarez, Alexandra Ester Rotelli, Lilian Eugenia Pelzer, José Roberto Saad, Oscar Giordano, Il Farmaco 55 (2000) 502–505.
[30] R. Kosher, M. Anderson, E.J. deBeer, Fed. Proc. 18 (1959) 412.