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SYNTHESIS OF NOVEL OXADIAZOLE DERIVATIVES WITH QUINAZOLINONE MOIETY AS POTENT ANALGESIC AGENTS

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ABSTRACT

A novel series of N-(6-bromo-2-methyl-4-oxaquinazolin-3(4H)-yl)-2-(5-(substituted phenyl)-1,3, 4-oxadiazol-2-ylthioacetamide (10-12) have been synthesized from 2-(5-(substituted phenyl)-1,3,4-oxadiazol-2-ylthio) acetyl chloride (7-9) with the aim to get better analgesic agents with minimum side effects. Structure the newly synthesized compounds were supported by means of elemental analysis and IR and ^{1}HNMR spectral analysis. Title compounds were evaluated for their analgesic activity and compared with standard drug phenylbutazone. In this series compound 12 showed better analgesic activities than standard drug.

KEYWORDS: Oxadiazole, quinazolinone, analgesic activity, phenylbutazone.

INTRODUCTION

Heterocyclic compounds have been an interesting area for the study of synthesis and biological activity. Oxadiazoles are the heterocyclic compounds containing are oxygen and two nitrogen atoms in a five member ring possessing a diversity of useful biological effects. Substituted oxadiazole derivatives have been reported to possess antibacterial[1,2], anti-inflammatory[3], antimicrobial,[4,5] analgesic[6] and anticancer[7], antidepressant[8], antioxidant[9] activities. Literature indicates that compounds containing quinazolinone nucleus have wide range of pharmacological activities include antimicrobial[10], analgesic[11,12], anti-inflammatory.[13,14] Keeping view of this, we have synthesized novel oxadiazole derivatives with quinazolinone moiety to investigate their analgesic activity.

MATERIALS AND METHODS

All reagents and solvents were of analytical grade and used directly. The melting points were determined in open glass capillaries tubes. The homogeneity of all newly synthesized compounds was routinely checked by thin layer chromatography (TLC). Elemental analysis (C, H, N) of all the synthesized compounds were determined by perkin-Elmer 2400 elemental analyzer. The IR spectra were recorded on a Beckman Acculab-10 spectrometer (ν max in cm^{-1}) and the ^{1}H NMR spectra were recorded by Brucker DPX-300 MHz using $CDCl_3$ as solvent. The animal research study was approved by the animal ethical committee (CPCSEA). The synthesis of the target compounds was accomplished according to the reaction sequence illustrated in Scheme 1.

RESULTS AND DISCUSSION

Analgesic activity

The analgesic activity of various synthesized compounds was screened by using acetic acid induced writhing test[15] in mice. Mice of either sex weighing between 60-70 gm were divided into group of six animals each. A 1% aqueous acetic acid solution (i.p. injection, 0.1 ml) was used as a writhing inducing agent. Mice were kept individually in the test cage before acetic acid injection and habituated for 60 min. screening of analgesic activity was performed after i.p. administration of test compounds and the reference drug Phenylbutazone at dose of 50 mg/kg (giving in table 1). The characteristic feature of this series was substituted phenyl moiety at fifth position of oxadiazole nucleus. We have observed that compound 12 showed maximum analgesic activity than standard drug at the three graded doses of 25, 50 and 100 mg/kg.

Table 1: **Analgesic activity of compounds 4-12.**

Compounds	Dose (mg/kg p.o.)	Analgesic activity % decrease of writhes in 60 min. after treatment relative to control
4	50	7.5
5	50	9.8
6	50	10.5
7	50	17.6
8	50	19.9
9	50	22.8
10	50	27.4
11	50	32.1
12	25 50 100	16.3 35.4 69 2
Phenylbutazone	25 50 100	18.4 34.1 68.8

Chemistry

Preparation of benzohydrazide (1)

Dissolved the ethyl benzoate (0.1 mol) in 30 ml of ethanol and hydrazine hydrate (0.1 mol) was added drop wise to mixture with stirring and reflux for 8 hr. Excess of ethanol was distilled out and the content was allowed to cool. The crystal formed was filtered, washed thoroughly with water, dried and recrystallized from ethanol to yield compound 1 (74%), m.p.: >134^{0}C. IR (KBr) v $_{max}$ in cm^{-1}: 3238 (NH), 3059 (aromatic CH stretching), 1687 (C=O), 1630 (C=C of aromatic ring). ^{1}HNMR ($CDCl_3$ + DMSO-d_6)δ in ppm: 7.20-8.21(m, 5H, Ar-H), 6.54 (s, 2H, NH_2 exchangeable with D_2O), 6.12 (s, 1H, NH). Anal. Calcd. For $C_7H_8N_2O$: C, 61.75; H, 5.92; N, 20.58; Found: C, 61.72; H, 5.87; N, 20.56%.

The following compounds (2, 3) were prepared using a similar procedure described for compound 9. The physical and spectral data of compounds 2 and 3 are giving below.

2-Hydroxy benzohydrazide (2)

(68%), m.p.: >157 ^{0}C. IR (KBr) v $_{max}$ in cm^{-1}: 3410 (OH), 3233 (NH), 3055 (aromatic CH stretching), 1690 (C=O), 1636 (C=C of aromatic ring). ^{1}HNMR ($CDCl_3$ + DMSO-d_6) δ in ppm: 11.85 (s, 1H, OH), 7.22-8.20(m, 4H, Ar-H), 6.57 (s, 2H, NH_2 exchangeable with D_2O), 6.18 (s, 1H, NH). Anal. Calcd. For $C_7H_8N_2O_2$: C, 55.26; H, 5.30; N, 18.41; Found: C, 55.22; H, 5.34; N, 18.43%.

2-Methoxy benzohydrazide (3)

(65%), m.p.: >169 ^{0}C. IR (KBr) v $_{max}$ in cm^{-1}: 3230 (NH), 3065 (aromatic CH stretching), 1680 (C=O), 1639 (C=C of aromatic ring). ^{1}HNMR ($CDCl_3$ + DMSO-d_6) δ in ppm: 7.22-8.23(m, 4H, Ar-H), 6.58 (s, 2H, NH_2 exchangeable with D_2O), 6.15 (s, 1H, NH), 4.12 (s, 3H, OCH_3). Anal. Calcd. For $C_7H_{10}N_2O_2$: C, 57.82; H, 6.07; N, 16.86; Found: C, 57.80; H, 6.10; N, 16.88%.

Preparation of 5-phenyl-1,3,4-oxadiazole-2-thiol (4)

In methanolic solution of benzohydrazide (0.1 mol), alcoholic potassium hydroxide (0.4 mol) and carbondisulfide (0.1 mol) were added and stirred for 4hr. and refluxed for 5 hr. The completion of the reaction, reaction mixture was checked by TLC. Thus obtained product was filtered, washed with water and recrystallized from methanol to yield compound 4 (63%), m.p.:> 189^{0}C. IR (KBr) v $_{max}$ in cm^{-1}: 3055 (aromatic CH stretching), 2683 (SH), 1680 (C=O), 1632 (C=C of aromatic ring), 1245 (N-N). ^{1}HNMR ($CDCl_3$ + DMSO-d_6) δ in ppm: 11.34 (s, 1H, SH exchangeable with D_2O), 7.20-8.20(m, 5H, Ar-H). Anal. Calcd. For $C_8H_6N_2OS$: C, 61.75; H, 5.92; N, 20.58; Found: C, 61.72; H, 5.87; N, 20.56%.

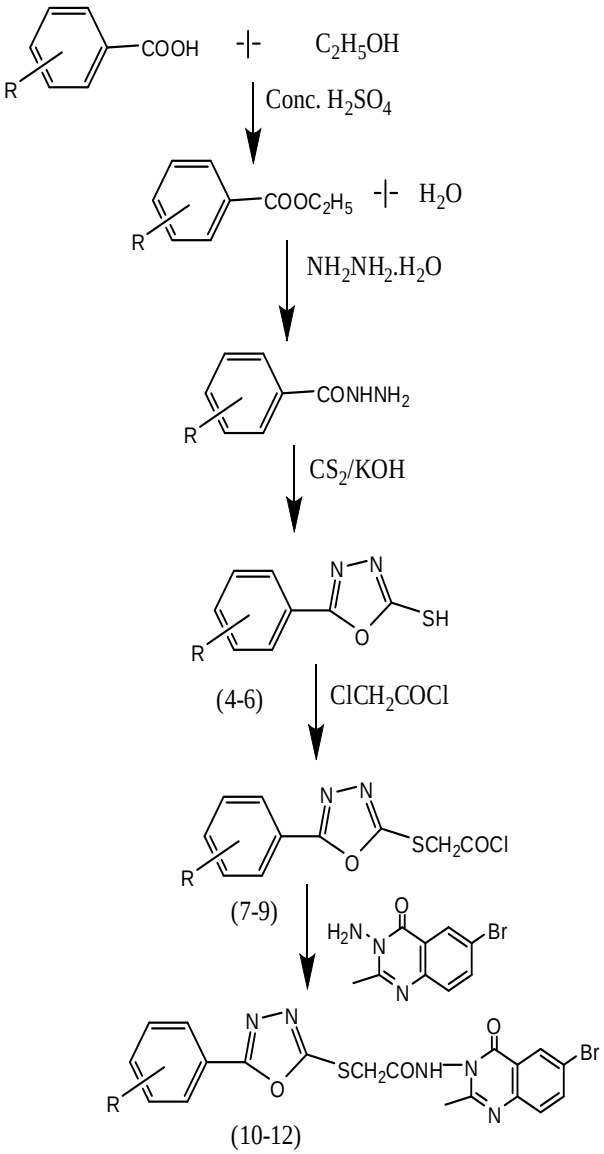
The following compounds (5, 6) were prepared using a similar procedure described for compound 9. The physical and spectral data of compounds 5 and 6 are giving below.

5-(2-hydroxyphenyl-1,3,4-oxadiazole-2-thiol (5)

(74%), m.p.: >198 ^{0}C. IR (KBr) v $_{max}$ in cm^{-1}: 3413 (OH), 3059 (aromatic CH stretching), 2738 (SH), 1687 (C=O), 1639 (C=C of aromatic ring), 1250 (N-N). ^{1}HNMR ($CDCl_3$ + DMSO-d_6) δ in ppm: 12.15 (s, 1H, OH exchangeable with D_2O), 11.12 (s, 1H, SH), 7.21-8.22 (m, 4H, Ar-H). Anal. Calcd. For $C_8H_6N_2O_2S$: C, 49.47; H, 3.11; N, 14.42; Found: C, 49.45; H, 3.14; N, 14.42%.

5-(2-methoxyphenyl-1,3,4-oxadiazole-2-thiol (6)

(74%), m.p.:> 194 ^{0}C. IR (KBr) v $_{max}$ in cm^{-1}: 3068 (aromatic CH stretching), 2731 (SH), 1682 (C=O), 1637 (C=C of aromatic ring), 1248 (N-N). ^{1}HNMR ($CDCl_3$ + DMSO-d_6) δ in ppm: 11.16 (s, 1H, SH exchangeable with D_2O), 7.20-8.21(m, 4H, Ar-H), 4.41 (s, 3H, OCH_3). Anal. Calcd. For $C_9H_8N_2O_2S$: C, 51.91; H, 3.87; N, 13.45; Found: C, 51.92; H, 3.89; N, 13.42%.



R = H, 2-OH, 2-OCH_3

Scheme 1.

Preparation of 2-(5-phenyl-1,3,4-oxadiazol-2-ylthio)acetylchloride (7)

A mixture of compound 4 (0.1 mol) in dry diethylether (10 ml) and triethylamine (0.3 mol) was taking in a round bottom flask. The reaction was stirred an ice bath and when temperature below 10^0C, then chloroacetyle chloride (0.15mol) was added drop wise with stirring. After the completion of the reaction, reaction mixture was kept for 24 hr. at room temperature. The reaction mixture was added to ice cold water to obtain the compound 7. It was dried and purified by recrystallization from chloroform. (74%), m.p.: >210 ^{0}C. IR (KBr) v $_{max}$ in cm^{-1}: 3050 (aromatic CH stretching), 1680 (C=O), 1635 (C=C of aromatic ring)), 1244 (N-N), 710 (C-Cl). ^{1}HNMR ($CDCl_3$ + DMSO-d_6) in ppm: 7.20-8.23 (m, 5H, Ar-H), 4.92 (s, 2H, S- CH_2). Anal. Calcd. For $C_{10}H_7ClN_2O_2S$: C, 47.16; H, 2.77; N, 11.00; Found: C, 47.62; H, 2.79; N, 11.02%.

The following compounds (8, 9) were prepared using a similar procedure described for compound 9. The physical and spectral data of compounds 8 and 9 are giving below.

2-(5-(2-hydroxyphenyl-1,3,4-oxadiazol-2-ylthio)acetylchloride (8)

(74%), m.p.:> 229 ^{0}C. IR (KBr) v $_{max}$ in cm^{-1}: 3053 (aromatic CH stretching), 1685 (C=O), 1630 (C=C of aromatic ring), 1234 (N-N), 718 (C-Cl). ^{1}HNMR ($CDCl_3$ + DMSO-d_6) δ in ppm: 12.21 (s, 1H, OH), 7.23-8.20 (m, 4H, Ar-H), 4.96 (s, 2H, S- CH_2). Anal. Calcd. For $C_{10}H_7ClN_2O_3S$: C, 44.37; H, 2.61; N, 10.35; Found: C, 44.34; H, 2.63; N, 10.32%.

2-(5-(2-methoxyphenyl-1,3,4-oxadiazol-2-ylthio)acetylchloride (9)

(54%), m.p.: > 234 ^{0}C. IR (KBr) v $_{max}$ in cm^{-1}: 3238 (NH), 3059 (aromatic CH stretching), 1687 (C=O), 1630 (C=C of aromatic ring), 1256 (N-N), 720 (C-Cl). ^{1}HNMR ($CDCl_3$ + DMSO-d_6) δ in ppm: 7.20-8.21 (m, 4H, Ar-H), Anal. Calcd. For $C_{11}H_9N_2O_3S$: C, 46.40; H, 3.19; N, 9.84; Found: C, 46.42; H, 3.17; N, 9.82%.

Preparation of N-(6-bromo-2-methyl-4-oxoquinazoli-3-(4H)-yl)-2-(5-phenyl-1,3,4-oxadiazol-2-ylthio)acetamide (10)

The mixture of compound 7 (0.1 mol) and 3-amino-6-bromo-2-methyl-4-oxoquinazoline (0.1mol) in ethanol (50 ml) was refluxed for 10 hr. The solid thus obtained was filtered, dried and recrystallized from methanol to yield compound 10. (50%), m.p.: > 244 ^{0}C. IR (KBr) v $_{max}$ in cm^{-1}: 3236 (NH), 3054 (aromatic CH stretching), 2823 (CH_3), 1683 (C=O), 1630 (C=C of aromatic ring), 612 (C-Br). ^{1}HNMR ($CDCl_3$ + DMSO-d_6) δ in ppm: 7.22-8.20(m, 8H, Ar-H), 6.12 (s, 1H, NH), 4.96 (s, 2H, S- CH_2), 2.23 (s, 3H, CH_3). Anal. Calcd. For $C_{19}H_{14}BrN_5O_3S$: C, 48.32; H, 2.99; N, 14.83; Found: C, 48.35; H, 2.97; N, 14.85%.

The following compounds (11, 12) were prepared using a similar procedure described for compound 9. The physical and spectral data of compounds 11 and 12 are giving below.

N-(6-bromo-2-methyl-4-oxoquinazoli-3-(4H)-yl)-2-(5-(2-hydroxyphenyl)-1,3,4-oxadiazol-2-ylthio)acetamide (11)

(47%), m.p.: >253 ^{0}C. IR (KBr) v $_{max}$ in cm^{-1}: 3230 (NH), 3052 (aromatic CH stretching), 1682 (C=O), 1630 (C=C of aromatic ring), 614 (C-Br). ^{1}HNMR ($CDCl_3$ + DMSO-d_6) δ in ppm: 12.14 (s, 1H, OH exchangeable with D_2O), 7.20-8.23 (m, 7H, Ar-H), 6.12 (s, 1H, NH), 4.99 (s, 2H, S- CH_2), 2.27 (s, 3H, CH_3).. Anal. Calcd. For $C_{19}H_{14}BrN_5O_4S$: C, 46.73; H, 2.89; N, 14.34; Found: C, 46.70; H, 2.87; N, 14.32%.

N-(6-bromo-2-methyl-4-oxoquinazoli-3-(4H)-yl)-2-(5-(2-methoxyphenyl)-1,3,4-oxadiazol-2-ylthio)acetamide (12)

(44%), m.p.: > 264^{0}C. IR (KBr) ν_{max} in cm^{-1}: 3238 (NH), 3057 (aromatic CH stretching), 1685 (C=O), 1638 (C=C of aromatic ring), 620 (C-Br). ^{1}HNMR ($CDCl_3$ + DMSO-d_6) δ in ppm: 7.20-8.21(m, 7H, Ar-H), 6.12 (s, 1H, NH)), 4.96 (s, 2H, S- CH_2), 4.43 (s, 3H, OCH_3), 2.23 (s, 3H, CH_3).. Anal. Calcd. For $C_{20}H_{16}BrN_5O_4S$: C, 47.82; H, 3.21; N, 13.94; Found: C, 47.80; H, 3.25; N, 13.92%.

CONCLUSION

Analgesic activity results indicated that all the derivatives of this activity. Compound 12 having 2-methoxy group on fifth position of oxadiazole showed more potent analgesic activity which was more effective than standard drug phenyl butazone.

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