Indian Journal of Chemistry
Vol. 47B, March 2008, pp. 460-462

Evaluation of anticancer activity of some 1,3,4-oxadiazole derivatives

Pinaki Sengupta, Deepak Kumar Dash, Veerendra C Yeligar, K Murugesh,
D Rajalingam, Jagadish Singh & T K Maity*

Department of Pharmaceutical Technology, Division of Pharmaceutical Chemistry, Jadavpur University, Kolkata 700 032, India

E-mail: jutkmaity@yahoo.com

Received 21 July 2006; accepted (revised) 12 December 2007

Carboxymethyl derivatives of various *para* substituted/unsubstituted oxadiazole-2-thione have been evaluated for their potential anticancer activity. Male Swiss albino mice have been used as test animal. The anti-cancer activity has been evaluated by comparing the ability of the test compound (25 mg/kg) to inhibit the tumor weight as well as tumor cell count with that of the control. The results suggest that all the studied compounds show significant reduction in both tumor weight and tumor cell count with respect to that of the control. Compound **3** is found to the most potent. The standard compound used is Mitomycin C (1mg/kg).

Keywords: 1, 3, 4-Oxadiazole, anticancer activity, cell count, tumor weight inhibition

Research laboratories and academic institutions are still deeply involved in basic research for developing and optimization of newer drugs despite the extensive efforts of the research based pharmaceutical industry in this field. Product development involves applicaion of the existing products to meet the emerging therapeutic needs in addition to the discovery of new chemical entities. In the last three to four decades the investigations in the field of oxadiazole have intensiied due to the large number of uses of oxadiazoles in the most diverse areas. Oxadiazole derivatives are well known for their wide range of biological activity namely anti-inflamatory[1], analgesic[2], antipyretic[3,4], anticonvulsant[3,4], antiungal[5-7], antiparasitic[8], anti-acterial[9-13], antimycobacterial[14], *etc*. 1,3,4-oxadiazoles have been shown to be effective as bioisosteres of the carboxamide moiety in benzodiazepine receptor agonists, muscarinic receptor agonists and NK1 receptor antagonists[15]. The cytotoxicity of mono- and di-substituted oxadiazole derivatives and their precursors was evaluated on macrophages and on tumor cell lines[16]. A novel series of 3, 5-diaryl-oxadiazoles was identified as apoptosis-inducing agents through the cell and chemical genetics-based screening assay for compounds that induce apoptosis using a chemical genetics approach[17]. In the present study, is reported the anticancer potential of some carboxymethyl derivatives of substituted 1,3,4-oxadiazole-2-thiones **1-5** (**Figure 1**).

Result and Discussion

Tumor cells used for anticancer activity were EAC cells which originated from human breast carcinoma by spontaneous passaging. Results for anticancer activity as shown in **Table I** were reported as the percentage of tumor weight inhibition (% TWI) and percentage inhibition of ascitic cells or percentage of tumor cell count inhibition (%TCI) of the treated EAC cells when compared to untreated control cells. Compounds **1-5** having anticancer potential are shown in the **Table I**, where the growth percent inhibition of the EAC cells is from 37.86 to 58.25%. Compound **3** showed highest cancerous cell growth inhibition activity as compared to the others. The results of the present study are encouraging because a significant reduction in tumor weight and tumor cell count was observed. The carboxymethyl derivatives of various *para* substituted/unsubstituted oxadiazole-2-thione compounds significantly reduced the tumor weight and tumor cell count as compared to that of the EAC control group.

Experimental Section

All the reagents and solvents used were of analytical grade.

10 Weeks old male Swiss albino mice with an average body weight of 18 to 20 g were used. All mice were kept on basal metabolic diet with water *ad*

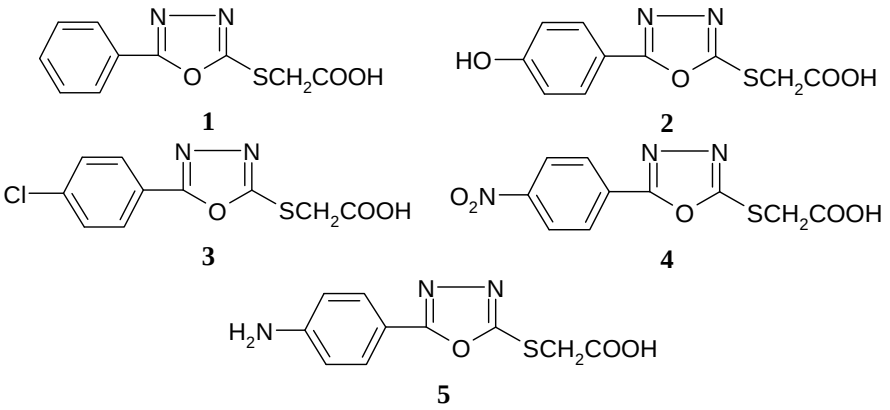

Figure 1 — Structure of compounds 1-5 synthesized and evaluated for anticancer activity

Table I — Results of anticancer activity of the tested compounds

Group	Dose of drug (mg /kg)	Average tumor weight (g)	% TWI	Average cell coun (number)	% TCI
I	-	-	-	-	-
II	-	2.90	0.00	103	0.00
III	25	1.80	37.93	64	37.86
IV	25	1.40	51.72	49	52.43
V	25	1.10	62.07	43	58.25
VI	25	1.30	55.17	47	54.36
VII	25	1.70	41.38	61	40.78
VIII	1	0.00	100.00	0	100.00

libitum. Male Swiss albino mice were divided into 8 groups (n = 8). EAC cells were collected from the donor mice and were suspended in sterile isotonic solution (0.9% w/v NaCl). The number of tumor cells per mL of this suspension were counted under microscope with the help of haemocytometer. All the groups were treated with EAC cells (0.2 mL of 2×10^6 cells/mouse) intraperitoneally except the normal group. This was taken as day zero. In this instance, the tumor cells multiplied relatively freely within the peritoneal cavity and ascites developed. A day of incubation was allowed for establishing the disease in the body before starting the drug administration. On the first day, 5mL/kg body weight of normal saline (0.9% w/v NaCl) was administered in group I (Normal). Phosphate buffer (*p*H 7.2), 5mL/kg body weight per day was administered in group II (EAC control). The synthesized compounds (**1-5,** 25 mg/kg body weight/day) and the standard drug Mitomycin C (1mg/kg body weight/day) were administered in groups (III-VII) and (VIII), respectively for 7 days at 24 hr intervals intraperitoneally. Thus 7 doses of the drug were administered to each mouse in the test group. On the 9th day food and water was withdrawn 18 hr before starting the testing operation. The weights of all the animals were recorded before they were sacrificed. The peritoneal cavity was dissected and the ascitic fluid was withdrawn by a syringe to a suitable volume, collected in sterile ice-cold saline and preserved in ice bath. The total number of living cells/mL in the peritoneal fluid of the 6 mice in a group was calculated. The fluid was sucked by adsorbent cotton. The weight of the 6 mice after sacrifice was recorded.

The evaluation of the test drug was made by comparing the cell count of the test with that of the control. The percentage inhibition of cell count was obtained by the following expression:

Percentage inhibition of Ascitic cells

$(TCI) = (1\text{-}T/C) \times 100$

where T is the average number of Ascitic cells/mL in test animals and C is the average number of the Ascitic cells/mL in control animals.

The groups and the design of the experiment were as follows:

Group-I: Normal saline (0.9 % NaCl w/v; 5 mL/kg, body weight).

Group-II: EAC (2×10^6 cells/mice) + Phosphate buffer (vehicle; 5mL/kg, body weight).

Group-III: EAC (2×10^6 cells/mice) + compound **1** (25 mg/kg, body weight).

Group-IV: EAC (2×10^6 cells/mice) + compound **2** (25 mg/kg, body weight).
Group-V: EAC (2×10^6 cells/mice) + compound **3** (25 mg/kg, body weight).
Group-VI: EAC (2×10^6 cells/mice) + compound **4** (25 mg/kg, body weight).
Group- VII: EAC (2×10^6 cells/mice) + compound **5** (25 mg/ kg, body weight).
Group-VIII: EAC (2×10^6 cells/mice) + Standard drug Mitomycin C (1mg/kg, body weight).

The anti-cancer activity of the compounds were measured in EAC treated animals with respect to the following parameters such as:
(i) T**umor weight**: The mice were dissected and the ascitic fluid was collected from the peritoneal cavity. The tumor weight was calculated from the difference in weight of mice before dissection and collection of ascitic fluid after dissection.
(ii)**Tumor cell count**: The ascitic fluid was taken in a WBC pipette and diluted 100 times. Then a drop of the diluted cell suspension was placed on the Neubauer counting chamber and the number of cells in the 64 small squares were counted.

Conclusion

The anticancer properties of the carboxymethyl derivative of 1,3,4-oxadiazole-2-thiones were evaluated by measuring their ability to inhibit cancer cell growth in ascitic fluid of Swiss albino mice. From the present study, it can be concluded that the oxadiazole compounds can potentially be developed into useful anticancer agents that can prompt future researchers to synthesize a series of oxadiazole derivatives containing a wide variety of substituents with the aim of obtaining novel heterocyclic systems with enhanced anticancer activity. Further work to develop and/or improve similar and related compounds and test them for a wide range of biological activity is in progress.

Acknowledgements

The author is grateful to Jadavpur University for providing the necessary facilities to carry out this research work and also to the University Grants Commission for providing fellowship.

References

1 Omar F A, Mahfouz N M & Rahman M A, *Eur J Med Chem*, 31, **1996**, 819.
2 Feray A, Zuhal T & Nuket O, *Turk J Chem*, 26, **2002**, 159.
3 Mishra L, Said M K, Itokawa H & Takeya K, *Bioorg Med Chem***,** 3(9), **1995**, 1241.
4 Suman S P & Bahel S C, *J Indian Chem Soc*, 56, **1979**, 712.
5 Goswami B N, Kataky J C S & Baruah J N, *J Heterocycl Chem*, 21, **1984,** 205.
6 Holla B S, Poojary K N, Kalluraya B & Gowda P V, *Indian J Heterocycl Chem*, 5, **1996**, 273.
7 Nicoladies D N, Fylaktakidou K C & Litinas K E, *J Heterocycl Chem*, 33, **1996**, 967.
8 Omar M T, *Arch Pharm Res (Seoul)*, 20, **1997**, 602.
9 Hamad M M, Said S A & El-Ekyabi Y M, *Monatsh Chem*, 127, **1996**, 549.
10 Matsumoto K Y, Yasuda Y, Tanimoto T, Matsumoto K, Yoshida T & Shoji J, *J Antibiotics (Tokyo)*, 42, **1998**, 1465.
11 Pakonstantinou G S, Markos P, Tsantili K A & Chytyroglon L A, *Pharmazie*, 53, **1998**, 300.
12 Shafi S S & Radhakrishnan T R, *Indian J Heterocycl Chem*, 5**,** **1995**, 133.
13 Talawr M B, Dejai S R, Sommanavar Y S, Marihal S C & Bennur S C, *Indian J Heterocycl Chem*, 5, **1996**, 215.
14 Wilder Smith A E, *Arzneim Forsch*, 16, **1966**, 1034.
15 Roffey J, Bioisostere in Medicinal Chemistry, Technical Notes for the Medicinal Chemist, *Maybridge Med Chem*, 1, **1997**, 6.
16 D' Souza A O, Pedrosa M T, Alderete J B, Cruz A F, Prado M A, Alves R B & Silva C L, *Pharmazie*, 60 (5), **2005**, 396.
17 Zhang H Z, Kasibhatla S, Kuemmerle J, Kemnitzer W, Ollis-Mason K, Qiu L, Crogan-Grundy C, Tseng B, Drewe J & Cai S X, *J Med Chem*, 48(16), **2005**, 5215.