DOI 10.1007/s11094-019-02031-x
Pharmaceutical Chemistry Journal, Vol. 53, No. 6, September, 2019 (Russian Original Vol. 53, No. 6, June, 2019)

N-(5-(TRIFLUOROMETHYL)-1,3,4-THIADIAZOL-2-YL)BENZAMIDE AND BENZOTHIOAMIDE DERIVATIVES INDUCE APOPTOSIS VIA CASPASE-DEPENDENT PATHWAY

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Original article submitted June 8, 2016.

New 1,3,4-thiadiazole-based compounds were designed, synthesized, and their anticancer effects were assessed by MTT assay against PC3 (prostate cancer), HT-29 (colon cancer), and SKNMC (neuroblastoma) cell lines. The results were compared to that of doxorubicin. According to MTT assay, some of the synthesized compounds exhibit higher cytotoxic activity (IC_{50}, μM range) than doxorubicin against PC3 and SKNMC cells but not HT29 cells. According to the analysis of structure – activity relationship, compounds with methoxy group as an electron donating moiety rendered higher activity than nitro group as an electron withdrawing group. Compound **4d** with *ortho* position of methoxy moiety activated caspases 3 and 9 in both PC3 and HT-29 cell lines.

Keywords*:* synthesis, bioisosteric change, 1,3,4-thiadiazole, MTT, caspase activity.

1. INTRODUCTION

Chemotherapy involves the use of low-molecular-weight drugs to selectively destroy tumor cells or at least prevent their proliferation [1]. Survey for the identification and discovery of new chemical structures that can act as more effective and reliable anticancer agents is still a major challenge to medicinal chemists. Despite of important advances achieved over recent decades in the research and development of various anticancer agents, current anticancer drugs still have major limitations such as drug resistance, lack of selectivity, and unwanted side effects. Hence, there is strong demand for the discovery and development of new effective cancer therapies devoid of mentioned limitations [2 – 7].

1,3,4-Thiadiazole is a heterocyclic five-membered ring that has gained prominence by exhibiting a wide variety of biological activities. The lower toxicity and *in vivo* stability of 1,3,4-thiadiazole nucleus is attributed to its aromaticity. It has interesting pharmacophores that display a broad spectrum of biological activity. 1,3,4-Thiadiazole exhibited potential antiglaucoma, antiinflammatory, antitumor, antiulcer, antibacterial, antiviral, analgesic, antiepileptic, antifungal and radioprotective properties. Some marketed drugs like acetazolamide (diuretic), sulfaethidole (antibacterial), cefazolin (antibacterial), etc. contain 1,3,4-thiadiazole ring [8 – 12].

Diverse chemical structure containing 1,3,4-thiadiazole have been reported with potential anticancer activity (Fig. 1). The 1,3,4-thiadiazole ring in anticancer agents performs its role in pharmacophores of apoptosis inducers and caspase activators, tyrosine kinase inhibitors, carbonic anhydrase inhibitors, etc. [13 – 27]. Therefore, various mechanisms could be imagined for anticancer chemical structures containing the 1,3,4-thiadiazole ring.

In the present work, we designed and synthesized new *N*-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)benzamide and

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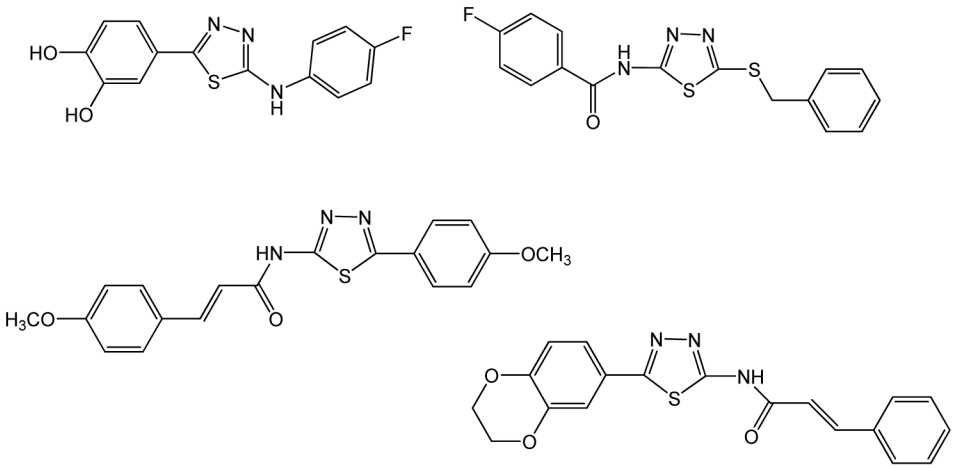


Fig. 1. Structure of some 1,3,4-thiadiazole-based compounds with anticancer activity.

-benzothioamide derivatives and evaluated their anticancer activity *in vitro*. 1,3,4-Thiadiazole derivatives containing nitro group as electron withdrawing moiety and methoxy group as electron donating moiety were synthesized and the related structure activity relationship was defined. These derivatives categorized in two, benzamide and benzothioamide, derivatives. Finally, *in vitro* cytotoxicity of all benzamide and benzothioamide derivatives containing nitro and methoxy substituents were evaluated against three cancerous cell lines, PC3 (prostate cancer), HT-29 (colon cancer), and SKNMC (neurobalstoma) by MTT assay, and caspase activation by these compounds was also explored.

2. EXPERIMENTAL COMPUTATIONAL PART

In 2008, Hu, et al. [29] reported the synthesis and cytotoxicity of a series of benzanilides and thiobenzanilides [29]. In the present project, we decided to synthesize new 1,3,4-thiadiazole-based analogs of these compounds via bioisosteric replacement (Fig. 2) and evaluate their anticancer properties *in vitro*. It was supposed that 1,3,4-thiadiazole ring with two nitrogen atoms could be a better pharmacophoric portion than phenyl ring. Nitrogen atoms in this ring enhance the solubility and also increase the capability of the structure for binding and interaction to the related receptors through hydrogen bonding (nitrogen as hydrogen bond acceptor) and electrostatic (protonated state in biological media) interactions. Replacement of the phenyl ring with a 1,3,4-thiadiazole structure was performed to explore the impact of this hypothesis.

3. EXPERIMENTAL CHEMICAL PART

3.1. General

All target compounds **4a – 4f** and **5a – 5e** were synthesized with an average yield. According to Scheme 1, compound **3** was prepared via a solvent free condition reaction. Adding the liquid trifluoroacetic anhydride (**1**) through a dropping funnel to the stirring powder thiosemicarbazide (**2**) and refluxing in an oil bath at 60 – 70°C for 3 h and the following alkalization by ammonia solution afforded the creamy-white powder of 5-(trifluoromethyl)-1,3,4-thiadiazol-2-amine (**3**). Direct amidation of amine **3** with various nitrobenzoic acid as well as methoxybenzoic acid derivatives in acetonitrile solvent led to formation of the corresponding compounds **4a – 4f**. Direct amidation benefits from using the *N*-ethyl-*N*′-dimethylaminopropyl carbodiimide (EDC) as coupling agent. In addition, nydroxybenzotriazole (HOBt) was introduced into the reaction medium to facilitate reaction and prevent the formation of *N*-acylureas as side products. The obtained **4b – 4f** derivatives were treated with Lawesson's reagent in refluxing toluene solvent for 48 h con-

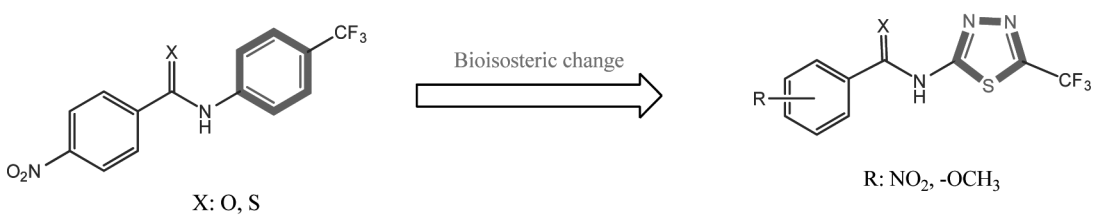
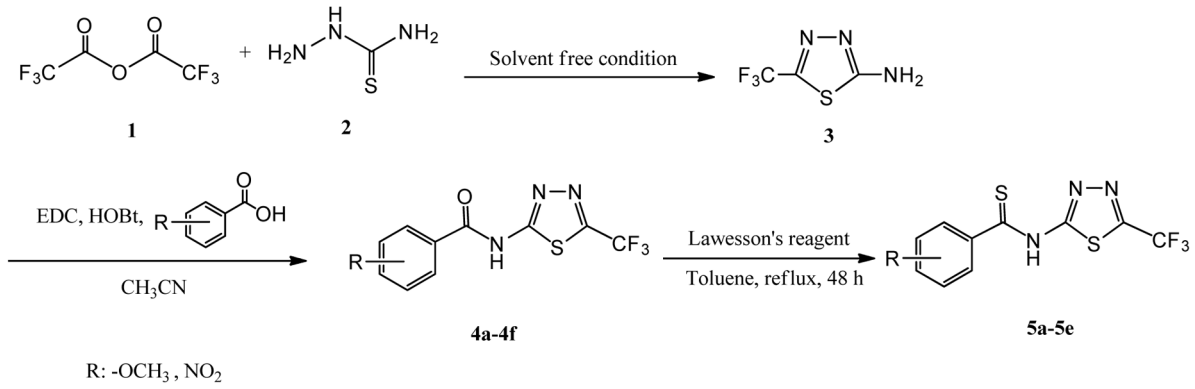


Fig. 2. Design of new 1,3,4-thiadiazole-based analogs through the bioisosteric replacement of phenyl ring.



Scheme 1. Synthesis of compounds **4a – 4f** and **5a – 5e.**

version to the related thioamide derivatives **5a – 5e**. Termination of all reactions was determined by thin layer chromatography (TLC) using appropriate mobile phase. Final purification was achieved by column chromatography or recrystallization from diethyl ether and/or *n*-hexane.

All chemical substances including initial materials, reagents and solvents were purchased from commercial suppliers like Merck and Sigma-Aldrich companies. Purity of the prepared compounds was proved by TLC using various solvents of different polarities. Merck silica gel 60 F_{254} plates were applied for analytical TLC. Column chromatography was performed on Merck silica gel (70 – 230 mesh) for purification of intermediate and final compounds. The ^{1}H-NMR spectra were recorded using Varian 400 spectrometer, and the chemical shifts are expressed as ä (ppm) with tetramethylsilane (TMS) as internal standard. The IR spectra were obtained on a Shimadzu 470 spectrophotometer in potassium bromide disks. Melting points (m.p.) were determined using elemental analyzer apparatus and remained uncorrected. The mass spectra (MS) were recorded on Finnigan TSQ-70 spectrometer (Finnigan, USA) at 70 eV. All cell lines were purchased from the Pasteur Institute of Iran. All intermediate and final compounds were prepared according to Scheme 1.

Synthesis of 5-(trifluoromethyl)-1,3,4-thiadiazol-2-amine (3). Compound **3** was prepared according to the literature [27, 31]: m.p., 224°C; yield, 73 %; IR (KBr; ν, cm^{-1}): 3302, 3128, 2958, 2924, 2854, 1639, 1519, 1327, 1192, 1149, 1037, 744, 686, 621; MS (*m/z*, %): 169 (M^+).

3.2. General Procedure for the Synthesis of Compounds **4a – 4f**

Equivalent amounts of EDC, HOBt and appropriate benzoic acid derivative were mixed in acetonitrile solvent and the mixture was stirred in room temperature for 30 min. Then, 5-(trifluoromethyl)-1,3,4-thiadiazol-2-amine (**3**) was added to the reaction medium and stirring was continued for 24 h in room temperature. The termination of reaction was proved by TLC. Acetonitrile was evaporated under reduced pressure and ethyl acetate/water mixture was added to the residue. The aqueous phase was removed and the organic phase was washed two times by dilute sulfuric acid, sodium bicarbonate, and brine. After separation of the organic layer, anhydrous sodium sulfate was added for drying. Then, sodium sulfate was removed by filtration and ethyl acetate was evaporated using rotary evaporator apparatus. Column chromatography or crystallization was applied if needed. All target compounds **4a – 4f** were obtained in the form of creamy powders [25 – 28, 32 – 34].

2-Nitro-*N*-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)-benzamide (4a): m.p., 158 – 160°C; yield, 79%; ^{1}HNMR ($CDCl_3$, 400 MHz; δ, ppm): 7.64 (t, 1H, J = 8 Hz, H_4-2-Nitrophenyl), 8.02 (d, 1H, J = 8Hz, H_6-2-Nitrophenyl), 8.35 (d, 1H, J = 8 Hz, 2-Nitrophenyl), 8.57(d, 1H, J = 8Hz, H_3-2-Nitrophenyl); IR (KBr; ν, cm^{-1}): 3298, 1730, 1668, 1517, 1489, 1479, 1456, 1419, 1330, 1301, 1232, 1190, 1136, 1035, 750; MS (*m/z*, %): 284 (40), 150 (100), 134 (95), 104 (30), 76 (85), 51 (45).

3-Nitro-*N*-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)-benzamide (4b): m.p., 183°C; yield, 66%; ^{1}HNMR ($CDCl_3$, 400 MHz; δ, ppm): 7.83 (t, 1H, J = 8 Hz, H_5-3-Nitrophenyl), 8.55 (d, 1H, J = 8 Hz, H_6-3-Nitrophenyl), 8.67 (d, 1H, J = 8 Hz, H_4-3-Nitrophenyl), 9.00 (s, 1H, H_2-3-Nitrophenyl); IR (KBr; ν, cm^{-1}): 3111, 1732, 1535, 1490, 1458, 1421, 1369, 1342, 1332, 1301, 1190, 1136, 1037, 705.

4-Nitro-*N*-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)-benzamide (4c): m.p., 245 – 249°C; yield, 80%; ^{1}HNMR ($CDCl_3$, 400 MHz; δ, ppm): 8.44 (d, 1H, J = 8 Hz, $H_{3,5}$-4-Nitrophenyl), 8.50 (d, 1H, J = 8 Hz, $H_{2,6}$-4-Nitrophenyl); IR (KBr; ν, cm^{-1}): 3111, 1732, 1681, 1533, 1490, 1458, 1421, 1348, 1332, 1303, 1190, 1138, 1037, 705; MS (*m/z*, %): 318 (45), 317 (65), 290 (65), 150 (100), 104 (80), 76 (60).

2-Methoxy-*N*-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)benzamide (4d): m.p., 104 – 106°C; yield, 74%; ^{1}H NMR ($CDCl_3$, 400 MHz; δ, ppm): 4.15 (s, 3H, $-OCH_3$), 7.12 (d, 1H, J = 8 Hz, H_3-2-Methoxyphenyl), 7.20 (t, 1H, J = 8 Hz, H_5-2-Methoxyphenyl), 7.64 (t, 1H, J = 8 Hz, H_4-2-Methoxyphenyl), 8.29 (d, 1H, J = 8 Hz,

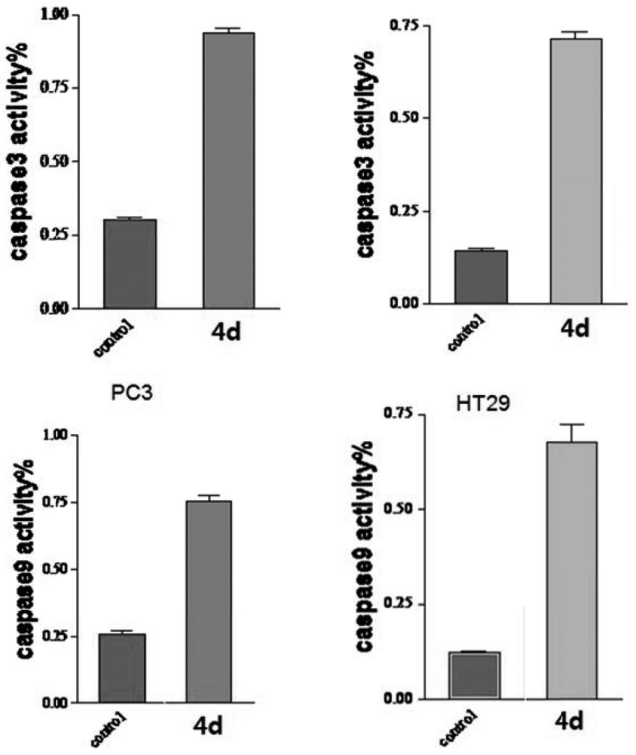


Fig. 3. Caspase activation by compound **4d** in PC3 and HT-29 cell lines.

H_6-2-Methoxyphenyl), 11.51 (brs, NH). IR (KBr, cm^{-1}): 3296, 1666, 1600, 1516, 1477, 1328, 1303, 1180, 1163, 1139, 1033, 1012, 756, 740, 667; MS (*m/z*, %): M^++1 (5), 272 (100), 135 (100), 92 (50), 107 (50), 77 (90), 63 (40), 52 (25).

3-Methoxy-*N*-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)benzamide (4e): m.p., 133°C; yield, 45%; ^{1}HNMR ($CDCl_3$, 400 MHz; δ, ppm): 3.89 (s, 3H, -OCH_3), 7.50 (m, 2H, aromatic), 7.66 (s, 1H, H_2-3-Methoxyphenyl), 7.86 (d, 1H, J = 8 Hz, H_5-3-Methoxyphenyl), 12.04 (brs, NH); IR (KBr; ν, cm^{-1}): 3170, 1670, 1600, 1516, 1489, 1330, 1303, 1267, 1195, 1180, 1136, 1035, 742.

4-Methoxy-*N*-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)benzamide (4f): m.p., 182°C; yield, 74%; ^{1}HNMR ($CDCl_3$, 400 MHz; δ, ppm): 3.94 (s, 3H, -OCH_3), 7.06 (d, 1H, J = 8 Hz, $H_{3,5}$-4-Methoxyphenyl), 8.24 (d, 1H, J = 8 Hz, $H_{2,6}$-4-Methoxyphenyl); IR (KBr; ν, cm^{-1}): 3309, 3128, 2931, 2850, 1770, 1604, 1516, 1327, 1242, 1172, 1087, 1037, 975, 756.

3.3. General Procedure for the Synthesis of Compounds **5a – 5e**

In a flat bottom flask were mixed 1.5 mole of Lawesson's reagent and 1 mole of appropriate amide derivatives (**4b – 4f**) obtained from the previous step. Toluene was added as solvent and the mixture was refluxed for 48 h. The completion of the reaction was proved by TLC. Then, toluene was evaporated by rotary evaporator, EtOAC/water mixture was added to the residue, and the aqueous phase was removed. The organic layer was washed two times by brine. Ethyl acetate phase was separated and dried using anhydrous sodium sulfate. Sodium sulfate was removed by filtration and ethyl acetate was evaporated under reduced pressure. All target compounds **5a – 5e** were obtained as yellowish powders and washed by diethyl ether and *n*-hexane for the removal of impurities [29, 30].

3-Nitro-*N*-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)-benzothioamide (5a): m.p., 123°C; yield, 52%; ^{1}HNMR ($CDCl_3$, 400 MHz; δ, ppm): 7.71 (m, 3-Nitrophenyl), 8.4 (dd, 1H, 3-Nitrophenyl), 8.57 (dd, 1H, 3-Nitrophenyl), 9.02 (s, H_2-3-Nitrophenyl); IR (KBr; ν, cm^{-1}): 3111, 2920, 1732, 1665, 1535, 1490, 1458, 1421, 1332, 1301, 1190, 1138, 1037, 705; MS (*m/z*, %): M^+ 34 (5), 290 (15), 256 (95), 160 (55), 150 (70), 113 (70), 96 (70), 74 (70), 64 (100), 57 (50), 43 (80).

4-Nitro-*N*-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)-benzothioamide (5b): m.p., 245 – 249°C; yield, 66%; ^{1}HNMR ($CDCl_3$, 400 MHz; δ, ppm): 8.33 (d, 1H, J = 8 Hz, $H_{3,5}$-4-Nitrophenyl), 8.36 (d, 1H, J = 8 Hz, $H_{2,6}$-4-Nitrophenyl); IR (KBr; ν, cm^{-1}): 3111, 2800, 1732, 1650, 1535, 1490, 1458, 1421, 1332, 1303, 1190, 1138, 1037, 705; MS (*m/z*, %): M^+ 334 (15), 317 (25), 290 (25), 150 (100), 120 (95), 104 (55), 92 (45), 76 (40).

2-Methoxy-*N*-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)benzothioamide (5c): m.p., 118°C; yield, 44%; ^{1}HNMR ($CDCl_3$, 400 MHz; δ, ppm): 4.13 (s, 3H, -OCH_3), 7.10 (d, 1H, J = 8 Hz, H_3-2-Methoxyphenyl), 7.18 (t, 1H, J = 8 Hz, H_5-2-Methoxyphenyl), 7.63 (t, 1H, J = 8 Hz, H_4-2-Methoxyphenyl), 8.27 (d, 1H, J = 8 Hz, H_6-2-Methoxyphenyl), 11.49 (brs, NH); IR (KBr; ν, cm^{-1}): 3298, 2958, 2927, 2854, 1675, 1600, 1516, 1477, 1330, 1300, 1180, 1145, 1033, 929, 756, 671, 528; MS (*m/z*, %): M^+ 319 (5), 304 (100), 286 (20), 272 (100), 256 (20), 224 (35), 204 (40), 196 (30), 169 (40), 151 (100).

3-Methoxy-*N*-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)benzothioamide (5d): m.p., 155 – 160°C; yield, 45%; ^{1}HNMR ($CDCl_3$, 400 MHz; δ, ppm): 3.89 (s, 3H, -OCH_3), 7.21 (d, 1H, J = 8 Hz, H_4-3-Methoxyphenyl), 7.47 (t, 1H, J = 8 Hz, H_5-3-Methoxyphenyl), 7.63 (s, 1H, H_2-3-Methoxyphenyl), 7.78 (d, 1H, J = 8 Hz, H_6-3-Methoxyphenyl); IR (KBr; ν, cm^{-1}): 3217, 3174, 2924, 2850, 1674, 1600, 1516, 1330, 1265, 1176, 1141, 1080, 1037, 786.

4-Methoxy-*N*-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)benzothioamide (5e): m.p., 209°C; yield, 66%; ^{1}HNMR ($CDCl_3$, 400 MHz; δ, ppm): 3.92 (s, 3H, -OCH_3), 7.05 (d, 1H, J = 8 Hz, $H_{3,5}$-4-Methoxyphenyl), 8.23 (d, 1H, J = 8 Hz, $H_{2,6}$-4-Methoxyphenyl); IR (KBr; ν, cm^{-1}): 3294, 3151, 2924, 2854, 1670, 1600, 1504, 1330, 1300, 1253, 1184,1141, 1107, 1037, 744.

4. EXPERIMENTAL BIOLOGICAL PART

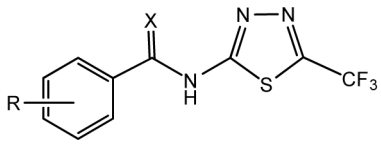
The *in vitro* cytotoxic activity of compounds **4a – 4f** and **5a – 5e** was assessed against three cancerous cell lines including PC3 (prostate cancer), HT29 (colon cancer) and SKNMC (neuroblastoma) using MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide) assay procedure. The test cells were seeded in 96-well plates and incubated for 48 h for the attachment. Then, the cells were incubated with various concentrations of synthesized compounds **4a – 4f** and **5a – 5e**, washed with PBS, and treated with MTT solution. The amount of produced purple formazan is proportional to the number of viable cells as determined by measuring the absorbance of each well by plate reader. Two independent experiments in triplicate were performed for determining the sensitivity to each compound, the IC_{50} (μM) values were calculated by linear regression analysis and expressed as mean ± SD. Doxorubicin was used as a standard drug [30]. The activity of caspases was also investigated according to the literature [27].

5. RESULTS AND DISCUSSION

Table 1 presents data for all compounds tested against three cancerous cell lines. PC3 (Prostate carcinoma), HT-29 (Colon carcinoma) and SKNMC (Neuroblastoma) cells were used in this assay by MTT procedure for a preliminary study. In this survey, methoxy- and nitro-containing derivatives were synthesized to explore the role of the electron releasing and electron donating properties of substituents. We also investigated replacement of the oxygen of carbonyl functional group by sulfur atom to render a thioamide moiety instead of the amide congener. Approximately, all compounds showed higher cytotoxic activity against PC3 cell line as compared to other cell lines. HT-29 cell line was the most resistant cell line in this series and SKNMC cells exhibited an average sensitivity to the test compounds in comparison to the response of PC3 and HT-29 cell lines.

Five compounds, **4d**, **4e**, **5a**, **5c** and **5d,** demonstrated higher cytotoxic activity against PC3 cell line compared to doxorubicin as reference drug. On the whole, methoxy substitution at *ortho* and *meta* positions of the phenyl ring enhanced the anticancer activity in compounds **4d**, **4e**, **5c** and **5d**. This means that methoxy in both benzamide and benzothioamide derivatives could play an effective role in increasing the cytotoxic properties. Compounds **4b**, **4f** and **5b** also showed an acceptable potency in PC3 cell line with IC_{50} equal to that of doxorubicin (IC_{50} = 8 μM). None of the tested compounds showed superior activity toward the HT-29 cell line and all of them exhibited a lower IC_{50} as compared to doxorubicin. Compounds **4c**, **4d**, **4f**, **5a** and **5b** exhibited significantly higher activity than doxorubicin against SKNMC cell line, while compound **4e** possessed IC_{50} value close to that of doxorubicin. Nitro moiety in compound **4c** at position 4 exerted an acceptable anticancer effect toward SKNMC cell line as compared to other positions in the phenyl ring for this moiety. High cytotoxicity against PC3 cell line observed for compounds **4d** and **4e** showed this

TABLE 1. Cytotoxicity (IC_{50} ± SEM, μM) of Compounds **4a – 4f** and **5a – 5e** against Selected Cancerous Cell Lines



Compound	R	X	PC3	HT-29	SKNMC
4a	2-NO_2	O	9.12 ± 0.11	180.12 ± 2.43	230.73 ± 3.41
4b	3-NO_2	O	8.21 ± 0.23	19.54 ± 0.76	188.14 ± 2.78
4c	4-NO_2	O	9.01 ± 0.12	60.57 ± 2.91	**28.07** ± 0.93
4d	2-OCH_3	O	**4.61 ± 0.21**	45.71 ± 1.01	**30.09 ± 0.91**
4e	3-OCH_3	O	**5.27 ± 0.95**	11.95 ± 0.31	39.24 ± 1.21
4f	4-OCH_3	O	8.46 ± 0.43	25.36 ± 0.78	**26.65 ± 0.96**
5a	3-NO_2	S	**5.11 ± 0.32**	148.13 ± 1.79	**20.78 ± 0.19**
5b	4-NO_2	S	8.01 ± 0.91	9.04 ± 0.03	**20.03 ± 1.01**
5c	2-OCH_3	S	**4.49 ± 0.83**	25.09 ± 0.98	73.34 ± 2.02
5d	3-OCH_3	S	**4.72 ± 0.35**	25.15 ± 1.03	49.90 ± 2.65
5e	4-OCH_3	S	9.26 ± 0.24	22.74 ± 0.09	102.23 ± 1.98
Doxorubicin	-	-	8.32 ± 0.86	8.64 ± 0.05	40.61 ± 3.09

rule to be also valid against SKNMC cell line, where these two compounds with methoxy moiety exhibited a strong anticancer activity. Compound **4f** with inserted *para* methoxy substituent was also active against SKNMC cell line. As mentioned above, compound **5a** with *meta* substitution of nitro group was active against PC3 cell line. This compound showed excellent cytotoxic effect toward SKNMC, while moving the nitro group to *para* position reserved the observed effect.

Compound **4d** was selected as one of the most cytotoxic derivatives for the caspase activity assay in these series. According to Fig. 3, compound **4d** was able to activate caspases 3 and 9 more significantly as compared to control. It could be conclude that compound **4d** probably induce apoptosis through both intrinsic and extrinsic pathways.

ACKNOWLEDGEMENTS

The authors acknowledge financial support from the research deputy of Kermanshah University of Medical Sciences. This manuscript has been deduced from the Pharm D Thesis of Mrs, Nazanin-Sadat Afnanzade as well as Mr. Mohammad Hossein Shafiee for submitting to the Faculty of Pharmacy.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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