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ORIGINAL ARTICLE

Synthesis, characterization and anticancer activity of certain 3-{4-(5-mercapto-1,3,4-oxadiazole-2-yl)phenylimino}indolin-2-one derivatives

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Indole;
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Abstract A series of 5- or 7-substituted 3-{4-(5-mercapto-1,3,4-oxadiazol-2-yl)phenylimino}-indolin-2-one derivatives were synthesized by treating 5-(4-aminophenyl)-1,3,4-oxadiazole-2-thiol with different isatin derivatives. The newly synthesized compounds were characterized on the basis of spectral (FT-IR, ^{1}H NMR, MS) analyses. All the synthesized derivatives were screened for anticancer activity against HeLa cancer cell lines using MTT assay. All the synthetic compounds produced a dose dependant inhibition of growth of the cells. The IC_{50} values of all the synthetic test compounds were found between 10.64 and 33.62 μM. The potency (IC_{50} values) of anticancer activity of compounds **VIb–d** was comparable with that of known anticancer agent, Cisplatin. Among the synthesized 2-indolinones, compounds **VIb–d** with halogen atom (electron withdrawing groups) at C5 position showed the most potent activity. These results indicate that C5 substituted derivatives may be useful leads for anticancer drug development in the future.

1. Introduction

The development of new anticancer therapeutic agents is one of the fundamental goals in medicinal chemistry. Cytotoxicity and genotoxicity of anticancer drugs to the normal cells are major problems in cancer therapy and engender the risk of inducing secondary malignancy (Aydemir and Bilaloglu, 2003). A dose of anticancer drug sufficient to kill tumor cells is often toxic to the normal tissue and leads to many side effects, which in turn, limits its treatment efficacy. In recent years, there has been a concerned search for the discovery and development of novel selective anticancer agents, devoid of many of the unpleasant side effects of conventional

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anticancer agents. The synthesis of a newer class of anticancer agents is in need of time.

Literature survey revealed that isatin (1H-indole-2,3-dione) possesses diverse chemotherapeutic activities, such as anticancer (Gursoy and Karal, 2003), antiviral (Debra et al., 2006), anti-HIV (Pandeya et al., 1999a), anti-mycobacterial (Karal et al., 2007), antibacterial (Pandeya et al., 1999b), anti-inflammatory (Sridhar and Ramesh, 2001) and anticonvulsant (Verma et al., 2004). Among these properties, cytotoxic and antineoplastic activities of this moiety have been found to be interesting. It has been reported in the literature that compounds bearing 1,3,4-oxadiazole ring possess significant biological properties such as anticancer (Aboraia et al., 2006), anti-inflammatory (Nargund et al., 1994), hypoglycemic (Ladduwahetty et al., 1996), antifungal, antibacterial (Khanum et al., 2005), antitubercular (Mamolo et al., 2005), analgesic (Bhandari et al., 2008), antiviral (Kucukguzel et al., 2007) activities.

In view of the biological importance of these isatin and 1,3,4-oxadiazole moieties, it was planned to synthesize a new series of isatin derivatives containing 1,3,4-oxadiazole i.e. 5- or 7-substituted 3-{4-(5-mercapto-1,3,4-oxadiazol-2-yl) phenylimino}indolin-2-ones and were evaluated for *in vitro* anticancer activity against HeLa (cervical), IMR-32 (neuroblastoma) & MCF-7 (breast) cancer cell lines using MTT assay.

2. Materials and methods

2.1. General

Melting points (mp) were determined in open capillaries, using Toshniwal melting point apparatus, expressed in °C and are uncorrected. The IR spectra of the compounds were recorded on thermo Nicolet Nexus 670S series, FT-IR spectrometer using KBr disc. ^{1}H NMR was scanned on Avance-400 MHz instrument. Chemical shifts are expressed in δ (ppm) relative to TMS as an internal standard using DMSO-d_6 *as* solvent. Mass spectra were recorded on a LC-MSD-Trap-SL. The purity of the compounds was checked on silica gel-coated aluminum sheets (Merck, 1.005554, silica gel HF254–361, Type 60, 0.25 mm, Darmstadt, Germany) by thin-layer chromatography (TLC). TLC was performed on silica gel G for TLC (Merck) and spots were visualized by iodine vapor or by irradiation with ultraviolet light (short wave length, 254 nm). Column chromatography was performed by using Qualigen's silica gel for column chromatography (60–120 mesh).

2.2. Chemicals

All the solvents, reagents and catalysts used are of AR grade. Isatin, fetal bovine serum (FBS), Dulbecco's modified eagle's medium (DMEM), penicillin, amphotericin B, and streptomycin were purchase from Himedia (Mumbai, India). 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) was purchased from Sigma Chemical Company (St. Louis, MO, USA). Substituted isatins were prepared by the procedures reported in the literature (Bahl, 2004).

2.3. Cell cultures

The cell cultures like HeLa (cervical), IMR-32 (neuroblastoma) & MCF-7 (breast) cancer cell lines were purchased from the National Centre for Cell sciences (NCCS), Pune, India. These cell lines were grown and maintained using suitable (DMEM) media and were grown in culture medium supplemented with 10% fetal bovine serum, 1% L-glutamine and 1% penicillin-streptomycin-amphotericin B antibiotic solution. Cells were seeded in 25 cm^2 tissue culture flasks (tarsons, India), at 250,000 cells/flask in a total volume of 9 ml. When confluent, all the cells were trypsinized (using Trypsin-EDTA, HiMedia, Mumbai, India), and seeded in 96-well plates (tarsons, India).

2.4. Chemistry

2.4.1. Synthesis of isatin derivatives

The different (5- or 7-substituted) isatin derivatives were prepared as reported in the literature (Henry and Blatt, 1964).

2.4.2. Synthesis of N-(4-[hydrazinecarbonyl] phenyl) acetamide (**IV**)

N-(4-[Hydrazinecarbonyl] phenyl) acetamide (**IV**) was prepared from ethyl-*p*-acetamido benzoate (**III**) as reported in the literature (Varma and Chauhan, 1988).

2.4.3. Synthesis of 5-{4-(aminophenyl)-1,3,4-oxadiazol}-2-thiol (**V**)

5-{4-(Aminophenyl)-1,3,4-oxadiazol}-2-thiol (**V**) was synthesized from *N*-(4-[hydrazinecarbonyl] phenyl) acetamide (**IV**) by adopting the procedure mentioned by Khanum et al. (2005).

2.4.4. Synthesis of 3-{4-(5-mercapto-1,3,4-oxadiazol-2-yl) phenylimino}-5 or 7-substituted-indolin-2-one (**VI**)

5-{4-(Aminophenyl)-1,3,4-oxadiazol}-2-thiol (compound **V**; 1.93 g, 0.01 mol) and Isatin (1.47 g, 0.01 mol) were refluxed in 20 ml of ethanol in the presence of a catalytic amount of glacial acetic acid (2–3 drops) for 5–6 h and cooled. The solid separated was filtered and washed with cold alcohol and the product obtained was recrystallized from methanol (yield: 2.41 g, 75%), m.p. 268–270 °C)

2.4.5. Spectral data of synthesized compounds (**VIa–k**)

*2.4.5.1. 3-(4-[5-Mercapto-1,3,4-oxadiazole-2-yl] phenylimino)-indolin-2-one (**VIa**).* IR υ (cm^{-1}): 1264 (C═S), 1676 (C═O), 3432 (N–H of amide), 1533 (C═N) and 1184 (ether, C–O–C); ^{1}H NMR (DMSO-d_6) δ ppm: 7.45–7.62 (m, 4H, Ar–H), 7.75–7.85 (m, 4H, Ar–H), 7.81 (s, 1H, SH), 10.27 (s, 1H, indole NH), ESI: *m*/*z* value 323.2.

*2.4.5.2. 3-(4-[5-Mercapto-1,3,4-oxadiazole-2-yl] phenylimino)-5-flouro-indolin-2-one (**VIb**).* IR υ (cm^{-1}): 1261 (C═S), 1667 (C═O), 3220 (N–H of amide), 1547 (C═N), 1165 (ether, C–O–C) and 759 (C–F); ^{1}H NMR (DMSO-d_6) δ ppm: 6.99 (d, 1H, Ar–H), 7.3–7.6 (m, 5H, Ar–H), 7.65 (s, 1H, Ar–H), 7.89 (s, 1H, SH), 10.21 (s, 1H, indole NH), ESI: *m*/*z* value 341.0.

*2.4.5.3. 3-(4-[5-Mercapto-1,3,4-oxadiazole-2-yl] phenylimino)-5-bromo-indolin-2-one (**VId**).* IR υ (cm^{-1}): 1271 (C═S), 1682 (C═O), 3177 (N–H of amide), 1534 (C═N), 1151 (C–N), 1151 (ether, C–O–C) and 662 (C-Br); ^{1}H NMR (DMSO-d_6) δ ppm: 7.10 (d, 1H, Ar–H), 7.16–7.43 (m, 5H, Ar–H),7.52 (s, 1H, Ar–H), 7.88 (s, 1H, SH), 10.3 (s, 1H, indole NH), ESI: *m*/*z* value 411.1.