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Original Research Article

Synthesis, pharmacological evaluation and structure-activity relationship study of hydrazones

Keyur M. Pandya[a,*], Bhavesh P. Dave[b], Arpan H. Patel[c], Rajesh J. Patel[d], Jignesh T. Patel[e], Piyush S. Desai[a,*]

[a] *Department of Chemistry, Arts, Science, and Commerce College, Veer Narmad South Gujarat University, Surat, Gujarat, India*

[b] *Department of Chemistry, M.B. Patel Science College, Sardar Patel University, Anand, Gujarat, India*

[c] *Department of Clinical Development, Immunocore LLC, 181 Washington Street, Conshohocken, Pennsylvania-19428, USA*

[d] *Department of Organic Chemistry, Shri A.N. Patel P.G. Institute of Science and Research, Anand, Gujarat, India*

[e] *Department of Pathology and Laboratory Medicine, Northshore University Healthsystem, Evanston, Illinois-60201, USA*

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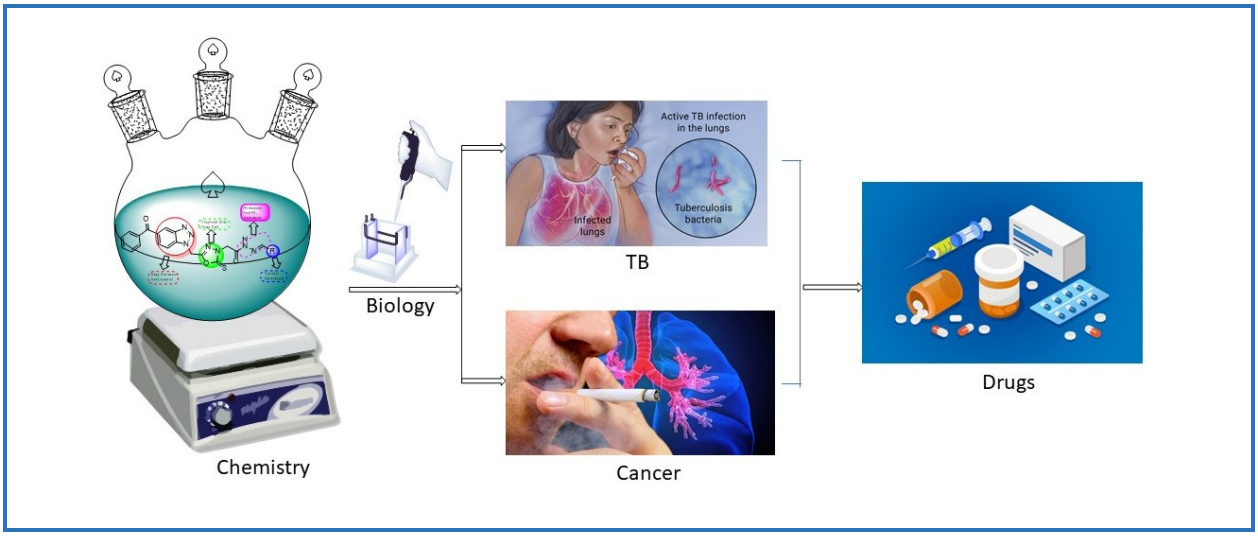
ABSTRACT

The development of novel compounds, hydrazones have shown that they possess a wide variety of biological activities. Hydrazones/azomethines/imines possess -NHN=CH- and constitute an important class of compounds for new drug development. We have undertaken a library synthesis of (1H-benzo[d][1,2,3]triazole-5-yl)(phenyl) methanone clubbed 1,3,4-oxadiazole derivatives bearing substituted hydrazone moiety were synthesized. We have synthesized a collection of 14 compounds and characterized by elemental analysis, MS, ^{1}H NMR, and ^{13}C NMR spectral data and were screened, against the anticancer and antituberculosis activity. Where the majority of these compounds showed good anticancer and antitubercular activities against the tested strains of *M. tuberculosis* H37Rv and lung NCI H-522, ovary PA-1, liver Hep G2 compared with the reference drugs. Compounds **5d, 5e, 5g,** and **5n** showed excellent potency against *M. tuberculosis* H37Rv strain compares to standard drugs whereas, against lung NCI H-522 cancer cell lines compounds **5e,** against ovary PA-1 cancer cell line compound **5i,** and against liver Hep G2 cell line compound **5n** showed excellent activity compared to standard drug thus, these studies suggest that (1H-benzo[d][1,2,3]triazol-5-yl)(phenyl)methanone clubbed 1,3,4-oxadiazole derivatives bearing hydrazone moiety are interesting scaffolds for the development of novel antitubercular and anticancer agents.

Corresponding author, email: scientistatwork@outlook.com (K.M. Pandya); psdesai69@gmail.com (P.S. Desai).
Tel.: +91 9427166199.

Graphical Abstract

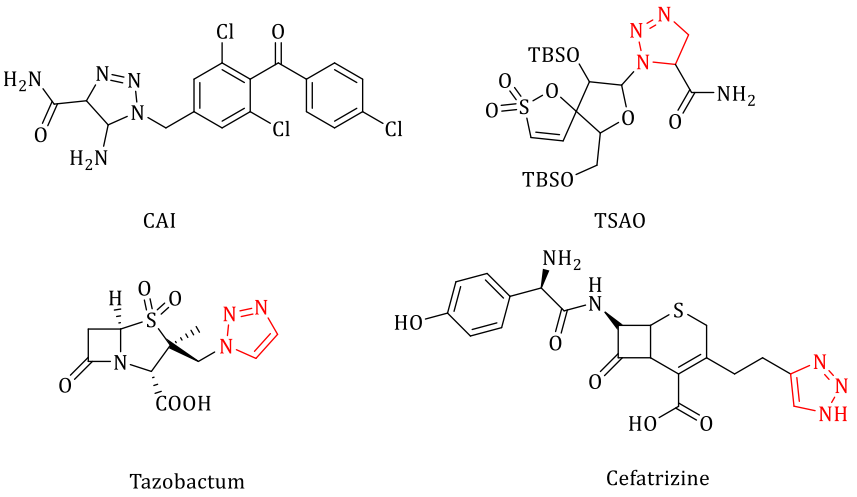


Introduction

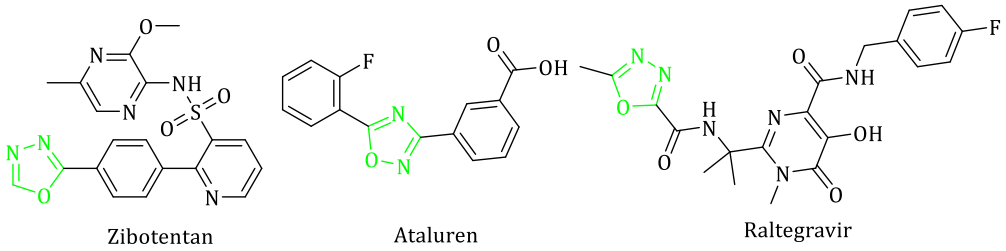
The great challenge for chemists is the discovery of new efficient compounds with minimal side effects and use of small doses, and many studies have been conducted for the development of new selective drugs. Heterocyclic systems play an important role in the discovery of new bioactive substances since they are present in various natural bioactive compounds [1]. Due to the high number of deaths [2], cancer treatment has attracted much attention from researchers and industries for the synthesis of new, more selective anticancer agents. Undesirable effects, toxicity, drug resistance, and reduced bioavailability are known for current anticancer available agents [3]. Therefore, the discovery of new anticancer agents, more efficient and more selective is urgent.

Over the past years, benzotriazole derivatives have been widely studied for their antiviral [4], antibacterial [5], antioxidant [6], anti-inflammatory [7], antifungal activity [8], and anticancer activities [9]. The biological potential of these heterocycles against cancer cells has been reported with different mechanisms of action, such as inhibition of tubulin, blocking endothelin A receptor involved in apoptosis, mitogenesis, angiogenesis and metastasis in tumors, focal adhesion kinase inhibition, telomerase inhibition, interacting with several receptors involved in proliferation, cell growth and DNA biosynthesis [10, 11]. The presence of the azole group in their structures makes them more lipophilic and, therefore, more susceptible to passage through the cell membrane [12]. Potential pharmaceuticals (Scheme 1) based on 1,2,3-triazoles include the anticancer compound carboxyamidotriazole (CAI) [13], the nucleoside derivative non-nucleoside reverse transcriptase inhibitor tertbutyldimethylsilylspiroaminooxathioledioxide (known as TSAO), β-lactum antibiotic tazobactum and cefatrizine.

Within drug discovery and development, a number of compounds containing an oxadiazole moiety are in late-stage clinical trials, including zibotentan as an anticancer agent [14] and ataluren for the treatment of cystic fibrosis (Scheme 2) [15]. So far, one oxadiazole containing a compound, raltegravir [16], an antiretroviral drug for the treatment of HIV infection, has been launched onto the marketplace. It is clear that oxadiazoles are having a large impact on multiple drug discovery programs across a variety of disease areas, including diabetes [17], obesity [18], inflammation [19], cancer [20], and infection [21]. Therefore, there is a high demand for the development of easily accessible methods for the preparation of 1,3,4-oxadiazole derivatives.



Scheme 1. Potential pharmaceuticals based on 1,2,3-triazoles



Scheme 2. Structures of oxadiazole containing compounds in late-stage clinical development

Hydrazones, related to ketones and aldehydes belong to a class of organic compounds with the structure, $R_1NHN=CR_2$ [22] These compounds possess diverse biological (Scheme 3) and pharmacological properties [23]. These compounds contain C=N bond, which is conjugated with a lone pair of electrons of the functional nitrogen atom [24]. The nitrogen atoms of the hydrazones are nucleophilic and the carbon atom has both electrophilic and nucleophilic nature [25]. The α-hydrogen of hydrazones is more potent than that of acidic ketones [26]. The combination of

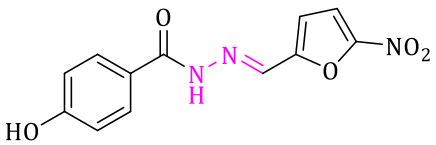
hydrazones with other functional group leads to compounds with unique physical and chemical character [27]. Owing to their biological and pharmacological properties, they are considered important for the synthesis of heterocyclic compounds [28].

Tuberculosis (TB) is a sort of lung infection, which is mainly caused by *Mycobacterium tuberculosis* (MTB). Some other species of bacteria causing tuberculosis include *M. africanum*, *M. pinnipedii*, *M. bovis*, *M. canettii*, *M. microti*, and *M. caprae* [29, 30]. Along with the HIV infection, TB is nowadays one of the biggest risks to human beings. It is believed to be one of the most infectious and fatal diseases and is a major threat to public health. There has been a continuous rise in new TB cases mostly in developing countries [31]. The TB situation may become even worse with the appearance of multi-drug resistant (MDR-TB) and the extensive drug-resistant (XDR-TB) strains. In 1882, Robert Koch achieved the isolation of the bacteria responsible for TB and received noble Prize for this finding [32].

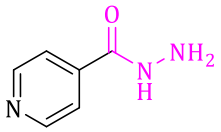
According to the WHO (world health organization), more than 75% of tuberculosis patients belong to economically productive age, which brings about a tremendously affecting economic and social crisis [33]. Though the six to nine-month multidrug protocol employed currently in the treatment of TB is extremely effective with drug-susceptible TB, the non-compliance of economically poor patients promote the growth of drug resistance [34]. Even though the existing method of treatment is highly effective against tuberculosis, the side effects, the long duration of treatment and the potential for drug-drug interactions are issues that highlight the requirement of new anti-TB drugs [35, 36]. Besides, MTB is resistant to some of the first and second-line drugs [37]. Hence, some efficient new drugs and advanced strategies are necessary to treat tuberculosis [38, 39].

In this paper, we designed (Scheme 4) and synthesized 14 benzotriazole 1,3,4-oxadiazole compounds bearing substituted hydrazones and evaluated their antimycobacterial and anticancer activities. The results of this study may be useful to researchers attempting to find new potential antimycobacterial and anticancer agents.

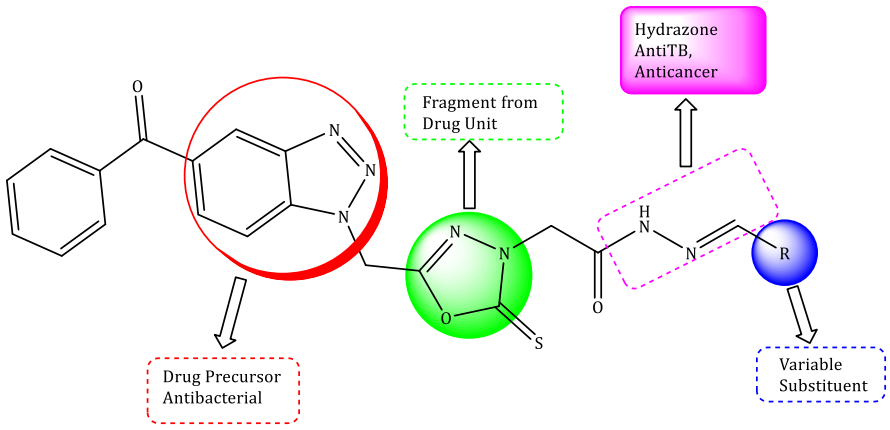
Scheme 3. Structures of hydrazones containing biologically active compounds



Nifuroxazide



Isoniazide



Scheme 4. Design of proposed hydrazone molecules for antimycobacterial and anticancer potential based on literature

Experimental

Materials and mthods

All chemicals (reagent grade) used were purchased from Aldrich. All solvents were used without further drying or purification and were of ACS grade purchased from local market. Separation of the compounds by column chromatography was carried out with silica gel 60 (200–300 mesh ASTM, E. Merck, Germany). The quantity of silica gel used was 50–100 times the weight charged on the column. Thin-layer chromatography (TLC) was run on the silica gel coated aluminum sheets (silica gel 60 GF_{254}, E. Merck, Germany) and visualized in ultraviolet (UV) light (254 nm).

Instrumentation

Melting points were determined in open capillary tubes on a stuart SMP 10 melting point apparatus and are uncorrected. Elemental analysis data were obtained with PerkinElmer C, H, N analyzer model 2400. Nuclear magnetic spectroscopy (NMR) spectra were produced using the varian 300 MHz spectrometer. The instrument was maintained at 25 °C operating at 300 MHz for ^{1}H NMR, and 75 MHz for ^{13}C NMR. The chemical shifts are given in parts per million (ppm) on the delta (δ) scale. Coupling constants are reported in hertz (Hz). The spectra were recorded in solutions of deuterated dimethyl sulfoxide (DMSO-d_6) with residual chloroform (δ 7.26 ppm for ^{1}H NMR, δ 77.23 for ^{13}C NMR) as the internal reference or in solutions of deuterated dimethyl sulfoxide (DMSO-d_6) with residual dimethyl sulfoxide (δ 2.50 ppm for ^{1}H NMR, δ 39.51 for ^{13}C NMR) as the internal reference. Data are reported as follows: (s = singlet; d = doublet; t = triplet; q = quartet; p = pentet; sep = septet; dd = doublet of doublets; dt = doublet of triplets; td = triplet of doublets; tt = triplet of

triplets; qd = quartet of doublets; ddd = doublet of doublet of doublets; br s = broad singlet). Mass spectra were recorded on a Shimadzu spectrometer.

Procedure for the synthesis of 2-(5-benzoyl-1H-benzo[d][1,2,3]triazol-1-yl)acetohydrazide 2 [40, 41]

To the solution of (1H-benzo[d][1,2,3]triazol-5-yl)(phenyl)methanone (22.4 mmol, 5 g) in absolute methanol (60 cm^3), methyl chloroacetate (22.4 mmol, 1.96 cm^3), hydrazine monohydrate (22.4 mmol, 1.09 cm^3) and anhydrous K_2CO_3 (26.9 mmol, 3.7 g) were added and the reaction mixture was heated under reflux for 16 hrs. Progress of the reaction was noticed by TLC technique. After completion of the reaction, the potassium salt was filtered off and the excess of ethanol was removed. The residue solidified on cooling wash with cold water, dried and recrystallized by EtOH to collect the final product **2** in good yields (5.3 g, 80.13%). Mp 145-147 °C, ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.14 (t, J = 4.3 Hz, 1H), 8.33 (d, J = 1.6 Hz, 1H), 7.90 (dd, J = 7.5, 1.5 Hz, 1H), 7.84-7.74 (m, 3H), 7.63-7.43 (m, 3H), 4.90 (s, 2H), 4.19 (d, J = 4.3 Hz, 2H).

Procedure for the synthesis of phenyl(1-((5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)methyl)-1H-benzo[d][1,2,3]triazol-5-yl)methanone [42]

A mixture of compound **2** (10.2 mmol, 3 g) was added in MeOH (100 cm^3), potassium hydroxide (5.34 mmol, 0.3 g) and heated with $CSCl_2$ (5.21 mmol, 0.38 cm^3) and refluxed for about 12 hrs at 65 °C. Progress of the reaction was monitored by TLC technique. After completion of the reaction, the separated solid was filtered, dried in vacuum and purified over a column of silica gel, eluted with C_6H_6: $CHCl_3$ (2:8 v/v) mixture to give a final product **3** with yield of (2.81 g, 81.92%). mp 177–179 °C, ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.39 (s, 1H), 8.31 (d, J = 1.6 Hz, 1H), 7.91 (dd, J = 7.5, 1.5 Hz, 1H), 7.85-7.77 (m, 3H), 7.63-7.56 (m, 1H), 7.54-7.48 (m, 2H), 4.74 (s, 2H).

Procedure for the synthesis of 2-(5-((5-benzoyl-1H-benzo[d][1,2,3]triazol-1-yl)methyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)acetohydrazide [43, 44]

To the solution of reactant 3 (7.11 mmol, 2.4 g) in absolute methanol (60 cm^3), methyl chloroacetate (7.11 mmol, 0.4 cm^3), hydrazine monohydrate (7.11 mmol, 0.65 cm^3) and anhydrous K_2CO_3 (8.54 mmol, 1.2 g) were added and the reaction mixture was heated under reflux for 16 hrs. Progress of the reaction was noticed by TLC technique. After completion of the reaction, the potassium salt was filtered off and the excess of ethanol was removed. The residue solidified on cooling wash with cold water, dried and recrystallized by EtOH to collect the final product **4** in good yields (2.4 g, 82.39%). mp 186–188 °C, ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.23 (t, J = 5.1 Hz, 1H), 8.22

(d, *J* = 1.6 Hz, 1H), 7.92 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.83-7.75 (m, 3H), 7.63-7.54 (m, 1H), 7.54-7.46 (m, 2H), 4.82 (s, 2H), 4.32 (s, 2H), 4.23-4.10 (m, 2H).

Procedure for the synthesis of (E)-N'-(substituted methylene)-2-(5-((5-benzoyl-1H-benzo[d][1,2,3]triazol-1-yl)methyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)acetohydrazide [45]

Take the compound **4** and aromatic aldehyde (listed in scheme 1) in a molar ratio (1:1 or 1:2) and make soluble in the EtOH (100 cm^3) and reflux in for about 4-5 hrs at 79 °C with a catalytic amount of glacial acetic acid (1-2 drops) on a water bath. The reaction was monitored by TLC. The mixture was evaporated under reduced pressure to give a residue. The residue was dissolved in DCM, and the organic layer were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel chromatography (PE/EtOAc = 1:1) and recrystallized from PE/EtOAc to afford products **5a–n**.

(E)-2-(5-((5-benzoyl-1H-benzo[d][1,2,3]triazol-1-yl)methyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)-N'-(4-chlorobenzylidene)acetohydrazide (5a)

Colorless solid, yield 81%, mp 144−146 °C, ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.62 (s, 1H), 8.45-8.39 (m, 1H), 8.23 (s, 1H), 8.14-8.04 (m, 1H), 7.89 (dd, *J* = 10.2, 2.3 Hz, 1H), 7.85-7.76 (m, 4H), 7.65-7.49 (m, 3H), 7.49-7.42 (m, 3H), 4.57 (s, 2H), 4.50 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 197.9, 181.4, 163.1, 149.1, 143.3, 142.6, 138.5, 137.6, 133.6, 133.3, 133.3, 131.9, 129.8, 129.8, 129.7, 128.9, 128.49, 118.1, 110.1, 48.1, 44.8. ESIMS: *m/z* calculated for $C_{25}H_{18}ClN_7O_3S$ $(M+H)^+$ 531.09 found 532.10, Anal. Calc. for $C_{25}H_{18}ClN_7O_3S$: C, 56.45; H, 3.41; N, 18.43; found: C, 56.30; H, 3.46; N, 18.41%.

(E)-2-(5-((5-benzoyl-1H-benzo[d][1,2,3]triazol-1-yl)methyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)-N'-(4-fluorobenzylidene)acetohydrazide (5b)

Colorless solid, yield: 79%, mp 121−123 °C, ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.42 (dd, *J* = 2.2, 0.5 Hz, 1H), 8.23 (d, *J* = 0.6 Hz, 1H), 8.09 (dd, *J* = 10.2, 0.5 Hz, 1H), 7.89 (dd, *J* = 10.2, 2.2 Hz, 1H), 7.84-7.75 (m, 4H), 7.64-7.56 (m, 1H), 7.54-7.46 (m, 2H), 7.32-7.24 (m, 2H), 4.57 (s, 2H), 4.50 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 197.9, 181.3, 163.1, 155.8, 152.4, 149.0, 143.3, 142.6, 137.6, 133.6, 133.3, 131.9, 130.9, 130.8, 129.9, 129.8, 129.7, 128.9, 128.5, 118.0, 115.9, 115.7, 110.1, 48.1, 44.8. ESIMS: *m/z* calculated for $C_{25}H_{18}FN_7O_3S$ $(M+H)^+$ 516.12 found 516.08, Anal. Calc. for $C_{25}H_{18}FN_7O_3S$: C, 58.25; H, 3.52; N, 19.02%; found: C, 58.31; H, 3.51; N, 19.0%.

(E)-2-(5-((5-benzoyl-1H-benzo[d][1,2,3]triazol-1-yl)methyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)-N'-(4-methylbenzylidene)acetohydrazide (5c)

Colorless solid, yield 66%, mp 189–191 °C, ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.62 (s, 1H), 8.44-8.40 (m, 1H), 8.23 (s, 1H), 8.13-8.05 (m, 1H), 7.96-7.85 (m, 1H), 7.84-7.78 (m, 1H), 7.64-7.55 (m, 1H), 7.54-7.45 (m, 1H), 7.40 (dq, J = 7.8, 0.8 Hz, 1H), 4.57 (s, 1H), 4.50 (s, 1H), 2.39 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 197.8, 181.4, 163.1, 149.1, 143.3, 142.6, 139.1, 137.6, 133.6, 133.3, 131.9, 131.1, 129.7, 128.9, 128.5, 128.3, 127.4, 118.1, 110.1, 48.1, 44.8, 21.8. ESIMS: *m/z* calculated for $C_{26}H_{21}N_7O_3S$ $(M+H)^+$ 512.14 found 512.17, Anal. Calc. for $C_{26}H_{21}N_7O_3S$: C, 61.05; H, 4.14; N, 19.17%; found: C, 61.22; H, 4.19; N, 19.18%.

(E)-2-(5-((5-benzoyl-1H-benzo[d][1,2,3]triazol-1-yl)methyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)-N'-(4-hydroxybenzylidene)acetohydrazide (5d)

Colorless solid, yield 61%, mp 180–182 °C, ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.62 (s, 1H), 9.90 (s, 1H), 8.45-8.39 (m, 1H), 8.23 (s, 1H), 8.14-8.04 (m, 1H), 7.89 (dd, J = 10.2, 2.3 Hz, 1H), 7.84-7.76 (m, 2H), 7.65-7.44 (m, 5H), 6.82-6.72 (m, 2H), 4.57 (s, 2H), 4.50 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 197.8, 181.4, 163.1, 152.5, 149.1, 143.3, 142.6, 137.6, 133.6, 133.3, 133.1, 131.9, 129.7, 128.9, 128.5, 126.1, 118.1, 112.7, 110.1, 48.1, 44.8. ESIMS: *m/z* calculated for $C_{25}H_{19}N_7O_4S$ $(M+H)^+$ 514.12 found 514.19, Anal. Calc. for $C_{25}H_{19}N_7O_4S$: C, 58.47; H, 3.73; N, 19.09%; found: C, 58.46; H, 3.75; N, 19.12%.

(E)-2-(5-((5-benzoyl-1H-benzo[d][1,2,3]triazol-1-yl)methyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)-N'-(4-(dimethylamino)benzylidene)acetohydrazide (5e)

Colorless solid, yield 78%, mp 171–173 °C, ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.62 (s, 1H), 8.45-8.39 (m, 1H), 8.23 (s, 1H), 8.14-8.04 (m, 1H), 7.94-7.76 (m, 3H), 7.65-7.44 (m, 5H), 6.77-6.67 (m, 2H), 4.57 (s, 2H), 4.50 (s, 2H), 3.00 (s, 6H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 197.9, 181.4, 163.1, 151.4, 149.1, 143.3, 142.6, 137.6, 133.6, 133.3, 131.9, 130.4, 129.7, 128.9, 128.5, 120.1, 118.1, 111.4, 110.1, 48.1, 44.8, 39.9. ESIMS: *m/z* calculated for $C_{27}H_{24}N_8O_3S$ $(M+H)^+$ 541.23 found 540.10, Anal. Calc. for $C_{27}H_{24}N_8O_3S$: C, 59.99; H, 4.48; N, 20.73%; found: C, 59.91; H, 4.44; N, 20.72%.

(E)-2-(5-((5-benzoyl-1H-benzo[d][1,2,3]triazol-1-yl)methyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)-N'-(2-nitrobenzylidene)acetohydrazide (5f)

Colorless solid, yield 68%, mp 113–115 °C, ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.62 (s, 1H), 8.57 (s, 1H), 8.45-8.39 (m, 1H), 8.14-8.04 (m, 2H), 8.00-7.76 (m, 4H), 7.69 (ddd, J = 7.8, 6.3, 1.7 Hz, 1H), 7.64-7.44 (m, 4H), 4.57 (s, 2H), 4.50 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 197.9, 181.4, 163.1, 154.1, 148.0, 143.3, 142.6, 137.6, 133.6, 133.3, 132.0, 130.0, 129.7, 129.7, 128.9, 128.5, 126.7, 126.4, 118.1, 110.1, 48.1, 44.8. ESIMS: *m/z* calculated for $C_{25}H_{18}N_8O_5S$ $(M+H)^+$ 543.11 found 542.10, Anal. Calc. for $C_{25}H_{18}N_8O_5S$: C, 55.35; H, 3.34; N, 20.65%; found: C, 55.39; H, 3.31; N, 20.70%.

(E)-2-(5-((5-benzoyl-1H-benzo[d][1,2,3]triazol-1-yl)methyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)-N'-(2-hydroxybenzylidene)acetohydrazide (5g)

Colorless solid, yield 73%, mp 125−127 °C, ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.62 (s, 1H), 8.74 (s, 1H), 8.45-8.39 (m, 1H), 8.14-8.02 (m, 2H), 7.89 (dd, J = 10.2, 2.3 Hz, 1H), 7.84-7.76 (m, 2H), 7.65-7.53 (m, 1H), 7.53-7.44 (m, 3H), 7.28 (ddd, J = 8.6, 7.3, 1.5 Hz, 1H), 6.98-6.85 (m, 2H), 4.57 (s, 2H), 4.50 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 197.8, 181.4, 163.1, 159.5, 159.5, 143.3, 142.6, 137.6, 133.6, 133.3, 133.0, 131.9, 131.7, 129.7, 128.9, 128.5, 120.7, 119.7, 118.0, 117.5, 110.1, 48.1, 44.8. ESIMS: *m/z* calculated for $C_{25}H_{19}N_7O_4S$ $(M+H)^+$ 514.12 found 514.17, Anal. Calc. for $C_{25}H_{19}N_7O_4S$: C, 58.47; H, 3.73; N, 19.09%; found: C, 58.49; H, 3.70; N, 19.09%.

(E)-2-(5-((5-benzoyl-1H-benzo[d][1,2,3]triazol-1-yl)methyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)-N'-(4-nitrobenzylidene)acetohydrazide (5h)

Colorless solid, yield 80%, mp 109−111 °C, ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.62 (s, 1H), 8.45-8.39 (m, 1H), 8.32-8.20 (m, 3H), 8.14-8.04 (m, 1H), 8.02-7.92 (m, 2H), 7.89 (dd, J = 10.2, 2.3 Hz, 1H), 7.84-7.76 (m, 2H), 7.65-7.53 (m, 1H), 7.50 (ddt, J = 7.7, 6.7, 0.9 Hz, 2H), 4.57 (s, 2H), 4.50 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 197.9, 181.4, 163.1, 149.1, 147.4, 143.3, 142.6, 139.1, 137.6, 133.6, 133.3, 131.9, 129.7, 128.9, 128.5, 127.7, 125.4, 118.1, 110.1, 48.1, 44.7. ESIMS: *m/z* calculated for $C_{25}H_{18}N_8O_5S$ $(M+H)^+$ 543.11 found 542.91, Anal. Calc. for $C_{25}H_{18}N_8O_5S$: C, 55.35; H, 3.34; N, 20.65%; found: C, 55.33; H, 3.30; N, 20.63%.

(E)-2-(5-((5-benzoyl-1H-benzo[d][1,2,3]triazol-1-yl)methyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)-N'-(pyridin-4-ylmethylene)acetohydrazide (5i)

Colorless solid, yield 74%, mp 157−159 °C, ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.60-8.52 (m, 2H), 8.45-8.39 (m, 1H), 8.20 (d, J = 0.8 Hz, 1H), 8.14-8.05 (m, 1H), 8.03 (s, 1H), 7.89 (dd, J = 10.2, 2.3 Hz, 1H), 7.86-7.76 (m, 2H), 7.76-7.68 (m, 2H), 7.65-7.53 (m, 1H), 7.50 (ddt, J = 7.7, 6.7, 0.8 Hz, 2H), 4.57 (s, 2H), 4.50 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 197.9, 181.4, 163.1, 149.2, 149.1, 143.3, 142.6, 139.9, 137.6, 133.6, 133.3, 131.9, 129.7, 128.97, 128.4, 122.4, 118.0, 110.1, 48.0, 44.7. ESIMS: *m/z* calculated for $C_{24}H_{18}N_8O_3S$ $(M+H)^+$ 499.12 found 498.87, Anal. Calc. for $C_{24}H_{18}N_8O_3S$: C, 57.82; H, 3.64; N, 22.48%; found: C, 57.81; H, 3.67; N, 22.50%.

(E)-2-(5-((5-benzoyl-1H-benzo[d][1,2,3]triazol-1-yl)methyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)-N'-(pyridin-2-ylmethylene) acetohydrazide (5j)

Colorless solid, yield 67%, mp 149−151 °C, ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.55 (dd, J = 4.5, 1.8 Hz, 1H), 8.45-8.39 (m, 1H), 8.18-8.05 (m, 2H), 8.03 (s, 1H), 7.89 (dd, J = 10.2, 2.3 Hz, 1H), 7.87-7.76

(m, 2H), 7.65-7.53 (m, 1H), 7.53-7.44 (m, 2H), 7.37 (ddd, *J* = 7.2, 4.5, 1.5 Hz, 1H), 4.57 (s, 2H), 4.50 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 197.8, 181.4, 163.1, 152.9, 148.1, 143.3, 142.6, 141.4, 137.6, 133.6, 133.3, 132.6, 131.9, 129.7, 128.9, 128.5, 122.5, 120.8, 118.1, 110.1, 48.1, 44.8. ESIMS: *m/z* calculated for $C_{24}H_{18}N_8O_3S$ $(M+H)^+$ 499.12 found 499.23, Anal. Calc. for $C_{24}H_{18}N_8O_3S$: C, 57.82; H, 3.64; N, 22.48%; found: C, 57.81; H, 3.62; N, 22.47%.

(E)-2-(5-((5-benzoyl-1H-benzo[d][1,2,3]triazol-1-yl)methyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)-N'-((2-chloropyridin-4-yl)methylene)acetohydrazide (5k)

Colorless solid, yield 69%, mp 195–197 °C, ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.45-8.39 (m, 1H), 8.20 (dd, *J* = 2.6, 1.9 Hz, 2H), 8.14-8.05 (m, 1H), 8.05-7.95 (m, 2H), 7.94-7.86 (m, 2H), 7.86-7.76 (m, 2H), 7.65-7.53 (m, 1H), 7.53-7.44 (m, 2H), 4.57 (s, 2H), 4.50 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 197.9, 181.4, 163.1, 149.8, 149.7, 146.3, 143.3, 142.6, 137.6, 133.6, 133.3, 131.9, 129.7, 128.9, 128.5, 123.1, 121.3, 118.1, 110.1, 48.1, 44.8. ESIMS: *m/z* calculated for $C_{24}H_{17}ClN_8O_3S$ $(M+H)^+$ 533.08 found 533.32, Anal. Calc. for $C_{24}H_{17}ClN_8O_3S$: C, 54.09; H, 3.22; N, 21.03%; found: C, 54.01; H, 3.25; N, 21.01%.

(E)-2-(5-((5-benzoyl-1H-benzo[d][1,2,3]triazol-1-yl)methyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)-N'-((2-bromopyridin-4-yl)methylene)acetohydrazide (5l)

Colorless solid, yield 70%, mp 160–162 °C, ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.45-8.39 (m, 1H), 8.35 (d, *J* = 4.4 Hz, 1H), 8.20 (d, *J* = 0.7 Hz, 1H), 8.14-8.05 (m, 1H), 8.05-7.98 (m, 2H), 7.94-7.86 (m, 2H), 7.86-7.76 (m, 2H), 7.65-7.53 (m, 1H), 7.50 (ddt, *J* = 7.7, 6.7, 0.9 Hz, 2H), 4.57 (s, 2H), 4.50 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 197.8, 181.4, 163.1, 149.7, 146.3, 145.3, 143.3, 142.6, 142.0, 137.6, 133.6, 133.3, 131.9, 129.7, 128.9, 128.5, 126.5, 122.1, 118.1, 110.1, 48.1, 44.8. ESIMS: *m/z* calculated for $C_{24}H_{17}BrN_8O_3S$ $(M+H)^+$ 577.03 found 577.27, Anal. Calc. for $C_{24}H_{17}BrN_8O_3S$: C, 49.92; H, 2.97; N, 19.41%; found: C, 50.02; H, 2.99; N, 19.44%.

(E)-2-(5-((5-benzoyl-1H-benzo[d][1,2,3]triazol-1-yl)methyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)-N'-((2-fluoropyridin-4-yl)methylene)acetohydrazide (5m)

Colorless solid, yield 74%, mp 134–136 °C, ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.55 (d, *J* = 5.3 Hz, 1H), 8.45-8.39 (m, 1H), 8.20 (d, *J* = 0.7 Hz, 1H), 8.14-8.05 (m, 1H), 8.03 (s, 1H), 7.97-7.76 (m, 5H), 7.65-7.53 (m, 1H), 7.53-7.44 (m, 2H), 4.57 (s, 2H), 4.50 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 197.8, 181.4, 163.1, 163.1, 159.7, 149.8, 149.7, 146.3, 146.1, 145.3, 145.2, 143.3, 142.6, 137.6, 133.6, 133.3, 131.9, 129.7, 128.9, 128.5, 118.1, 117.5, 117.4, 110.1, 103.5, 103.3, 48.1, 44.7. ESIMS: *m/z* calculated for $C_{24}H_{17}FN_8O_3S$ $(M+H)^+$ 517.11 found 517.29, Anal. Calc. for $C_{24}H_{17}FN_8O_3S$: C, 55.81; H, 3.32; N, 21.69%; found: C, 55.92; H, 3.31; N, 21.65%.

(E)-2-(5-((5-benzoyl-1H-benzo[d][1,2,3]triazol-1-yl)methyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)-N'-(thiophen-2-ylmethylene)acetohydrazide (5n)

colorless solid, yield 64%, mp 142−144 °C, ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.74 (s, 1H), 8.45-8.39 (m, 1H), 8.14-8.05 (m, 1H), 8.03 (s, 1H), 7.89 (dd, J = 10.2, 2.3 Hz, 1H), 7.81 (dt, J = 6.6, 1.6 Hz, 3H), 7.65-7.40 (m, 4H), 7.20 (t, J = 5.0 Hz, 1H), 4.57 (s, 2H), 4.50 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 197.8, 181.3, 163.1, 143.3, 142.6, 138.1, 137.6, 133.6, 133.3, 133.3, 131.9, 129.7, 128.9, 128.6, 128.5, 127.7, 127.6, 118.1, 110.1, 48.1, 44.7. ESIMS: *m/z* calculated for $C_{23}H_{17}N_7O_3S_2$ $(M+H)^+$ 504.08 found 504.21, Anal. Calc. for $C_{23}H_{17}N_7O_3S_2$: C, 54.86; H, 3.40; N, 19.47%; found: C, 53.99; H, 3.43; N, 19.46%.

Pharmacology

In vitro cytotoxicity

In vitro cytotoxicity against human cancer cell lines [46, 47]. The human cancer cell lines procured from the national cancer institute, India were used in this study. Cells were grown in tissue culture flasks in complete growth medium (RPMI-1640 medium with 2 mM glutamine, pH 7.4 supplemented with 10% fetal bovine serum, 100 μg/cm^3 streptomycin, and 100 units/cm^3 penicillin) in a carbon dioxide incubator (37 °C, 5% CO_2, 90% RH). The cells at a sub confluent stage were harvested from the flask by treatment with trypsin (0.05% in PBS (pH 7.4) containing 0.02% EDTA). Cells with viability of more than 98%, as determined by trypan blue exclusion, were used for determination of cytotoxicity. The cell suspension of 1 × 10^5 cells/cm^3 was prepared in complete growth medium. Stock 4 × 10^{-2} M compound solutions were prepared in DMSO. The stock solutions were serially diluted with complete growth medium containing 50 μg/cm^3 of gentamycin to obtain working test solution of required concentrations.

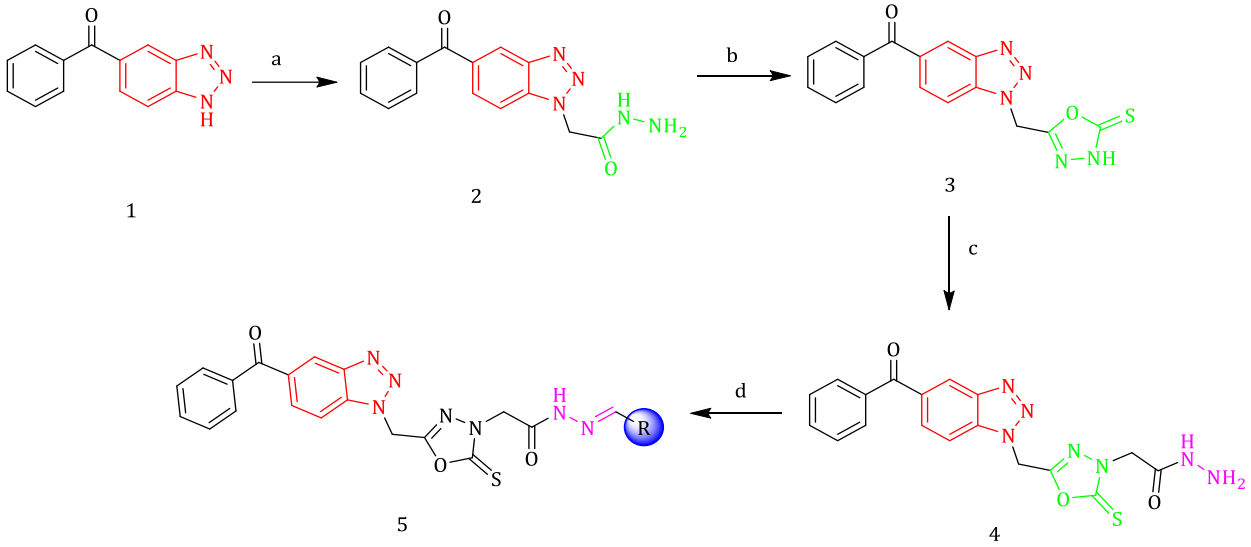
In vitro cytotoxicity against various human cancer cell lines was determined using 96-well tissue culture plates. The 100 mm^3 of cell suspension was added to each well of the 96-well tissue culture plates. The cells were allowed to grow in CO_2 incubator (37 °C, 5% CO_2, 90% RH) for 24 h. The test materials in complete growth medium (100 μL) were added after 24 h incubation to wells containing cell suspension. The plates were further incubated for 48 h (37 °C in an atmosphere of 5% CO_2 and 90% relative humidity) in a carbon dioxide incubator after addition of test material and then the cell growth was stopped by gently layering trichloroacetic acid (50% TCA, 50 mm^3) on top of the medium in all the wells. The plates were incubated at 4 °C for 1 h to fix the cells attached to the bottom of the wells. The liquid of all the wells was gently pipetted out and discarded. The plates were washed five times with distilled water to remove TCA, growth medium-low molecular weight metabolites, serum proteins, *etc*. were air-dried. Cell growth was measured by staining with sulforhodamine B dye. The

adsorbed dye was dissolved in Tris–HCl buffer (100 mm^3, 0.01 M, pH 10.4) and plates were gently stirred for 10 min using a mechanical stirrer.

Results and Discussion

Chemistry

Benzotriazole ring is the fundamental structure for the anticancer activities of benzotriazole derivatives. On the other hand, 1,3,4-oxadiazole and its derivatives have wide biological activities, such as antitubercular, and antitumor. Many of them have been used as active groups to designed anticancer drugs. In our present work, we tried to connect benzotriazole rings with 1,3,4-oxadiazole ring and substituted hydrazones to find some potential anticancer and antitubercular agents which were prepared as shown in Scheme 5 and Table 1.



Scheme 5. Reagents and conditions a) EtOH, $ClCH_2COOCH_3$, NH_2NH_2. H_2O, Anhy. K_2CO_3, reflux, 16 hrs, b) MeOH, KOH, $CSCl_2$, reflux, 12 hrs, c) EtOH, $ClCH_2COOCH_3$, NH_2NH_2. H_2O, Anhy. K_2CO_3, reflux, 16 hrs, d) R-CHO, EtOH, glacial AcOH (1-2 drops), 79 °C, 4-5 h, %

Table 1. Properties of the synthesized compounds (**5a-n**)

Compound	R	Compound	R
5a	*p*-ClC_6H_5-	**5h**	*p*-$NO_2C_6H_5$-
5b	*p*-FC_6H_5-	**5i**	4-pyridine
5c	*p*-$CH_3C_6H_5$-	**5j**	2-pyridine
5d	*p*-OHC_6H_5-	**5k**	2-chloropyridine
5e	*p*-$N(CH_3)_2C_6H_5$-	**5l**	2-bromopyridine
5f	*o*-$NO_2C_6H_5$-	**5m**	2-fluoropyrimidine
5g	*o*-OHC_6H_5-	**5n**	2-thienyl

Antitumor activity

Purified and fully characterized compounds **5a–n** (Scheme 5) were screened *in vitro* for anticancer activity against three human cancer cell lines consisting of the lung (NCl H-522), ovary (PA-1), and liver (Hep G2). Percentage (%) growth inhibition of compounds **5a–n** against various cancer cell lines was determined at a concentration of 1×10^{-5} M solution and results are summarized in Table 2. Compounds **5e** lung (NCl H-522), **5i** ovary (PA-1), and **5n** liver (Hep G2) exhibited good anticancer activity as compared to standard drugs *i.e.,* 5-fluorouracil, cyclophosphamide, and cycloheximide. Anticancer activity of a series of compounds **5a–n** derivatives are reported in Table 2. From the activity data, it is clear that derivatives **5e, 5i** and **5n** prepared compounds are useful in increasing the anticancer activity. The good anticancer activity is shown (Figure 1) by some of these molecules may be due to the fact that these molecules met the electronic and other stereochemical requirements on the target site in a better way as compared to other molecules which failed to act.

Table 2. *In vitro* anticancer activity of compounds **5a-n**

Entry	% growth inhibition at 1×10^{-5} M concentration		
	Lung NCI H-522	Ovary PA-1	Liver Hep G2
5a	10	18	22
5b	08	16	14
5c	05	13	17
5d	04	11	25
5e	33	17	26
5f	11	10	12
5g	03	05	16
5h	10	07	03
5i	09	41	21
5j	09	07	10
5k	06	11	18
5l	00	02	07
5m	01	04	08
5n	07	08	44
Cycloheximide	15	34	26
5-fluorouracil	24	22	18
Cyclophosphamide	11	12	18

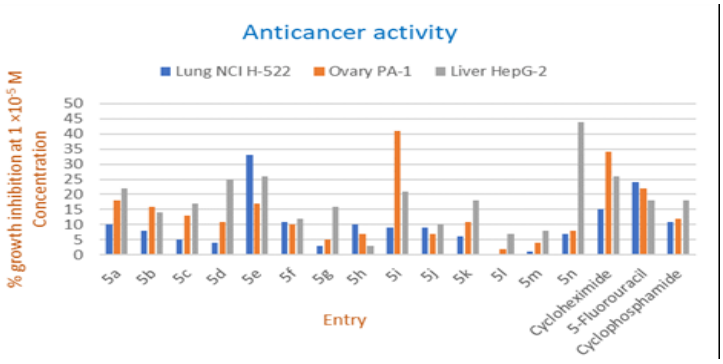


Figure 1. Graphical representation of the anticancer activity of synthesized compounds

Antimycobacterial screening

From literature survey impelled us to go for the screening of antitubercular activity. Thus, all the newly synthesized compounds were evaluated *in vitro*, to study its activity against *Mycobacterium tuberculosis* H37Rv. The primary screening was conducted at a concentration of 6.25 μg/mL in BACTEC MGIT system [41]. Compounds demonstrating 99% inhibition in the primary screen were described as most potent compounds (Figure 2). The preliminary results observed, indicated that compounds **5d** (97%), **5e** (99%), and **5g** (93%) showed the highest inhibition at a constant concentration level (6.25 μg/mL). The observed MICs and % inhibition of compounds are presented in Table 3. Isoniazid, rifampin, ethambutol, and pyrazinamide were used as the reference drug. All the active compounds were found to be non-toxic.

Table 3. *In vitro* antitubercular activity of compounds **5a-n** against *M. tuberculosis* H37Rv

Entry	BACTEC MGIT method	
	MIC (μg/mL)	% Inhibition
5a	>6.25	87
5b	>6.25	82
5c	>6.25	89
5d	6.25	97
5e	6.25	99
5f	>6.25	79
5g	6.25	93
5h	>6.25	75
5i	>6.25	88
5j	>6.25	82
5k	>6.25	80
5l	>6.25	81
5m	>6.25	84
5n	6.25	95
Ethambutol	3.13	99
Pyrazinamide	6.24	99
Isoniazid	0.20	99
Rifampicin	0.25	98

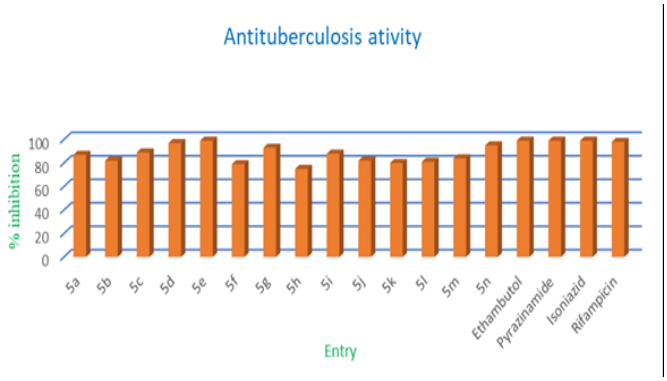


Figure 2. Graphical representation of the antitubercular activity of synthesized compounds

Structure-activity relationship (SAR) study

SAR studies revealed that the presence of the benzotriazole ring is essential for the anticancer activity. Substitution pattern on the benzotriazole clubbed thioxadiazole and hydrazone derivatives was carefully selected for considering electronic environments of the structure. Antimycobacterial and anticancer data of targeted compounds in Tables 2 and 3 has clearly shown that diverse electronic varieties are responsible for antimycobacterial and anticancer activity. The various substitution on hydrazone exhibited better anticancer and antimycobacterial activity and deduced the following SAR study Figure 3.

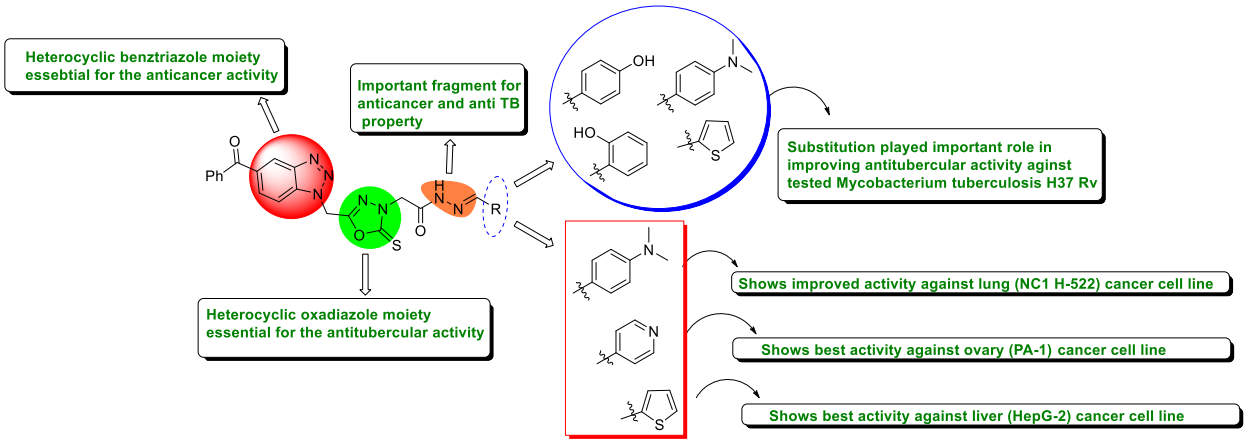


Figure 3. Structural activity relationship of synthesized hydrazones derivatives

Conclusions

A library of newly hydrazones (**5a–n**) were developed from benzotriazole and 1,3,4-oxadiazole. All synthesized compounds, characterized by analytical and spectral data (^{1}H NMR, ^{13}C NMR and mass spectroscopy) demonstrated compliance with the suggested structure. Hydrazone core structure derivatives were observed to have enhanced anticancer, and anti-mycobacterial activity, as evident from the anticancer and antimycobacterial evaluation results. Most of the compounds were found to be potent against tested cancer cell lines and bacteria with moderate to good activity. For the specific bacterial strains.

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Disclosure Statement

No potential conflict of interest was reported by the authors.

Ethics approval and consent to participate

This article does not contain any studies with human and animal subjects performed by any of the authors.

Orcid

Keyur M. Pandya 0000-0002-1282-7078

Piyush S. Desai 0000-0002-8813-1149

Caution

Thiophosgene ($CSCl_2$) may cause severe dermatitis if allowed to come in contact with the skin. This preparation should be carried out in a good hood, and rubber gloves should be worn throughout.
Harmful if swallowed.
Causes skin irritation.
Causes serious eye irritation.
Toxic if inhaled.
May cause respiratory irritation.
Wear protective gloves/protective clothing/eye protection/face protection.

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