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ORIGINAL RESEARCH

Synthesis and pharmacological evaluation of isoxazole derivatives containing 1,2,4-triazole Moiety

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ABSTRACT: A new class of isoxazole derivatives containing 1,2,4-triazole moiety were synthesized to meet structural requirements essential for antibacterial, antimycobacterial and anticancer activity. 1-(3,5-dipheny-1H-1,2,4-triazole-1-yl) ethanone (compound 2) was treated with different aromatic aldehydes to get substituted chalcones (3a-g) then subsequently cyclized with hydroxyl amine hydrochloride to yield 1-[5-(substituted aryl)-1,2-oxazol-3-yl]-3,5-diphenyl-1H-1,2,4-triazoles (4a-g). IR, ^{1}H-NMR, Mass spectra and elemental analysis were recorded to confirm the structures of target compounds. Compound 3a-g and 4a-g were screened for in vitro antimicrobial activity against B. subtillis NCIM 2063, E. coli NCIM 2065, C. albicans NCIM 3471 and A. niger NCIM 1196. MIC values were determined by liquid broth method. Chloro, nitro, methoxy substituted derivatives exhibited significant antibacterial and fungicidal potential. The in vitro antimycobacterial activity of the compounds 4a-g against Mycobacterium tuberculosis H37Rv was evaluated. The highest inhibition was observed through compound 4f as 76% at >6.25 μg/ml. Among the synthesized isoxazole derivatives, five compounds have been selected and evaluated for their anticancer activity at the National Cancer Institute for testing against a panel of approximately 60 different human tumor cell lines derived from nine neoplastic cancer types. The most efficient anticancer compound 4e was found to be active with selective influence on leukemia cancer cell lines, especially on SR with a growth % of 71.72.

KEY WORDS: Isoxazole, antimicrobial, antimycobacterial.

INTRODUCTION

1, 2, 4-triazoles has received substantial attention due to their effective biological importance like anticancer (1), antibacterial (2, 3), anticonvulsant (4), antiinflammatory, analgesic (5), antifungal (6,7), antidepressant (8), antitubercular (9), antimalarial (10) and hypoglycemic (11) activities. The isoxazole nucleus is well known for its medicinal importance and a number of related compounds are known to exhibit antifungal (12), antimicrobial (13), anticancer (14), analgesic, antiinflammatory (15), antituberculine (16), antiviral (17), antipsychotic (18), and hypoglycemic (19) activities.

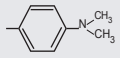
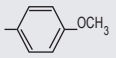
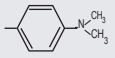
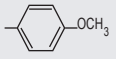
In appraisal of the above mentioned facts we describe herein the synthesis of some new isoxazole derivatives bearing 1, 2, 4-triazole moiety (Figure 1) and evaluation of their in vitro antimicrobial, antitubercular and anticancer activities.

EXPERIMENTAL

Chemistry

The melting points of compounds were determined by open tube capillary using Thermonik precision apparatus in Celsius scale and uncorrected. IR spectra were recorded using KBr pellets on PERKIN ELMER 8201 PC IR spectrophotometer, ^{1}H-NMR spectra of the final compound were recorded on BRUKER DRX NMR spectrometer (400 MHz). All spectra were obtained in DMSO. Mass spectra (FAB-MS) were recorded on 70V on JEOL D-300 spectrophotometer (Jeol Ltd., Tokyo, Japan). Elemental analysis for C, H and N were performed on a PERKIN ELMER 240 elemental analyzer.

TABLE 1. Physical and analytical data of compound 3a-g and 4a-g.

Cmpd	Ar	Molecular Formula	M.P. (°C)	Yield (%)	Elemental Analysis (found) %C	%H	%N	IR(KBr) cm^{-1}
3a		$C_{23}H_{16}ClN_3O$	96-98	85	71.59 (71.56)	4.18 (4.22)	10.89 (10.80)	2932,3080 (Ar-CH),1625(C=N), 1664(C=O),783 (C-Cl)
3b		$C_{23}H_{16}N_4O_3$	95-97	87	69.69 (69.74)	4.07 (4.11)	14.13 (14.12)	2941,3091(ArCH),1620(C=N), 1660(C=O),1553(C-NO_2)
3c		$C_{25}H_{22}N_4O$	103-105	74	76.12 (76.18)	5.62 (5.59)	14.20 (14.20)	2945,3023(Ar-CH),1619(C=N), 1666(C=O), 3152,3144(N-CH_3)
3d		$C_{24}H_{19}N_3O_2$	94-96	79	75.57 (75.50)	5.02 (4.99)	11.02 (11.09)	2953,3089(Ar-CH),1617(C=N), 1662(C=O), 1156(O-CH_3)
3e		$C_{21}H_{15}N_3O_2$	90-92	82	73.89 (73.83)	4.43 (4.47)	12.31 (12.36)	2956,3075(Ar-CH),1618(C=N), 1667(C=O), 1221(C-O-C)
3f		$C_{23}H_{16}ClN_3O$	100-102	89	71.59 (71.55)	4.18 (4.19)	10.89 (10.86)	2944,3092(Ar-CH),1610(C=N), 1657(C=O),773 (C-Cl)
3g		$C_{23}H_{17}N_3O$	90-92	85	78.61 (78.66)	4.88 (4.86)	11.96 (11.93)	2942,3080(Ar-CH),1623(C=N), 1669(C=O)
4a		$C_{23}H_{15}ClN_4O$	122-124	74	69.26 (69.00)	3.79 (3.13)	14.05 (14.13)	3019,3132,3222(Ar-CH), 1697(C=Nstr),1596(C=C),789 (C-Cl)
4b		$C_{23}H_{15}N_5O_3$	116-118	68	67.48 (67.44).	3.69 (3.69)	17.11 (17.01)	3022,3041,3073,3176(Ar-CH), 1665(C=N),1552(C=C),1556 (C-NO_2)
4c		$C_{25}H_{21}N_5O$	115-117	76	73.69 (73.60)	5.19 (5.11)	17.19 (17.79)	3009,3037,3069,3196(Ar-CH),1670(C=N),1570(C=C),3131,3153(N-CH_3)
4d		$C_{24}H_{18}N_4O_2$	125-127	72	73.08 (73.88)	4.60 (4.02)	14.20 (14.22)	3013,3042,3081,3120(Ar-CH),1660(C=N),1565(C=C), 1166(OCH_3)
4e		$C_{21}H_{14}N_40_2$	118-120	69	71.18 (71.00)	3.98 (3.93)	15.81 (15.11).	3036,3080,3108,3195(Ar-CH) 1661(C=N), 1574(C=C)
4f		$C_{23}H_{15}ClN_4O$	130-132	70	69.26 (69.00)	3.79 (3.59)	14.05 (14.45)	3024,3064,3121,3151(Ar-CH), 1509(C=N),1659(C=C),765 (C-Cl)
4g		$C_{23}H_{16}N_4O$	127-129	79	75.81 (75.98)	4.43 (4.56)	15.38 (15.44)	3036,3073,3108, 3133, 3213(Ar- CH), 1532 (C=N), 1560 (C=C)

General procedure for synthesis of 1-(3,5-diphenyl-1H-1, 2, 4-triazol-1-yl)-3-(substituted aryl)prop-2-en-1-one (Chalcones, 3a-g)

Compound 2 (0.05mol) in methanol was treated with substituted aromatic aldehydes (0.05 mol) and 2% 10 ml NaOH afterward stirred the reaction mixture for 7-8 hours at room temp. Then mixture was poured in ice cold water to get precipitate of compound 3a-g then recrystalised by dioxane-ethanol mixture. Percentage yield, melting point, elemental data and IR spectral data were recorded in Table 1.

General procedure for synthesis of 1-[5-(substituted aryl)-1,2-oxazol-3-yl]-3,5-diphenyl-1H-1,2,4-triazole (4a-g)

Compound 3a-g (0.02 mol) in 1, 4-dioxane were treated with hydroxyl amine hydrochloride (0.02 mol) and 40% 10 ml KOH then refluxed the reaction mixture for 7-8 hours on water bath. The mixture was poured in ice cold water to get precipitate of compounds 4a-g then recrystalised by dioxane-ethanol mixture. Melting point, percent yield elemental data and IR spectral data of each compound are mentioned in Table 1. ^{1}H-NMR and Mass spectral data stated in Table 2.

BIOLOGICAL METHODS

Antibacterial Activity

Determination of Minimal Inhibitory Concentration (MIC)

The Minimum Inhibitory Concentration (MIC) of the test compounds against gram positive bacteria B. subtillis (NCIM 2063), gram negative bacteria E. coli (NCIM 2065), yeast C. albicans (NCIM 3471) and mold A. niger (NCIM 1196) was determined by liquid broth method of two fold serial dilution technique (20). In this assay, the minimum concentration of

TABLE 2. ^{1}H-NMR and Mass spectral data of compound 4a-g.

Compound	^{1}H-NMR (δ ppm)	MS (FAB, positive ion mode) *m/z* [M+1]$^+$
4a	7.06 (1H, d, J=8.4Hz,Isoxazole), 7.52-8.45 (14H, m, Ar-H)	399
4b	7.05 (1H,d,J=8.5Hz,Isoxazole), 7.84-8.52 (14H, m, Ar-H)	410
4c	7.06 (1H,d,J=8.4Hz, Isoxazole), 6.72-8.51(14H,m,Ar-H), 3.19 (6H, s, -N(CH_3)2)	408
4d	7.08 (1H,d,J=8.3Hz, Isoxazole), 7.12-8.48 (14H,m,Ar-H), 3.86 (3H, s, OCH_3),	395
4e	7.11 (1H,d,J=8.2Hz, Isoxazole), 6.46-8.42 (13H, m, Ar-H)	355
4f	7.09 (1H,d,J=8.8Hz, Isoxazole), 6.84-8.34 (14H, m, Ar-H)	399
4g	δ7.10 (1H,d,J=8.6Hz, Isoxazole), 7.75-8.39 (15H, m, Ar-H)	365

each test substance required to inhibit the growth of microorganism was determined. The final concentration of test compounds ranged from 250 to 3.90 µg/ml. Standard antifungal drug Fluconazole and standard antibacterial drug Ampicillin was tested at concentrations ranging from 100 to 3.12 µg/ml respectively. The tubes were inspected visually to determine the growth of the organism as indicated by turbidity. MIC values of each tested compound recorded in Table 3.

Antitubercular activity

The antitubercular evaluation was carried out at Tuberculosis and Antimicrobial Acquisition Coordinating Facility (TAACF) USA. The resazurin colourometric MIC assay was used to determine antimycobacterial activity of the target compounds 4a-g against *Mycobacterium tuberculosis* H_{37}Rv. Antitubercular activity was evaluated at 6.25 µg/ml concentrations against Mycobacterium tuberculosis in Middlebrook 7H9 broth medium. The antimycobacterial activity data were compared with standard drug Rifampin at 0.25 µg/ml concentration which showed 98% inhibition. The screening data of target compounds are recorded in Table 4.

Anticancer activity

In the present study, newly synthesized 1-[5-(substituted aryl)-1,2-oxazol-3-yl]-3,5-diphenyl-1H-1,2,4-triazole (4a-g) have been evaluated for anticancer screening. Compound 4a, 4c, 4d, 4e and 4f were submitted to NCI for in vitro human tumor cell lines screening. The compounds were evaluated at single concentration of 10^{-5}M towards the panel of approximately 60 cancer cell lines derived from nine different cancer types: leukemia, lung, colon, CNS, melanoma, ovarian, renal, prostrate and breast cancers. Preliminary anticancer assay was performed according to the US NCI protocol. All the compounds were added to a previously prepared cell culture at a single concentration. The cell culture was incubated for 48 h. End point determinations were made with a protein binding dye, sulforhodamine B (SRB). The results for each compound were reported as the percent growth of treated cell lines or panel when compared to untreated control cells. The mean growth %, range of growth % and growth % relative to most sensitive cell line is depicted in Table 5.

TABLE 3. Antimicrobial activity of compound 3a-g and 4a-g.

Compound	Minimum Inhibitory Concentration (MIC) µg/ml			
	B. Subtillis	*E. coli*	*C. albicans*	*A. niger*
3a	62.5	62.5	125	125
3b	31.25	15.62	125	62.5
3c	250	125	125	250
3d	125	125	62.5	62.5
3e	250	125	125	62.5
3f	125	62.5	62.5	125
3g	250	250	125	250
4a	31.25	15.62	15.62	31.25
4b	31.25	31.25	62.5	31.25
4c	125	125	125	62.5
4d	62.5	15.62	31.25	31.25
4e	62.5	125	125	250
4f	15.62	7.81	15.62	62.5
4g	62.5	62.5	125	62.5
Ampicillin	6.25	6.25	-	-
Fluconazole	-	-	6.25	6.25

TABLE 4. Antitubercular screening result of compound 4a-g.

Compound	MIC (µg/ml)	% Inhibition
4a	> 6.25	34
4b	> 6.25	64
4c	> 6.25	40
4d	> 6.25	62
4e	> 6.25	24
4f	> 6.25	76
4g	> 6.25	54
Rifampin	0.25	98

RESULT AND DISCUSSION

1,2,4-triazole contains cyclic secondary amino group. 3,5-diphenyl-1*H*-1,2,4-triazole (compound 1) being a secondary amine was acetylated to compound 2 by acetic anhydride and conc.

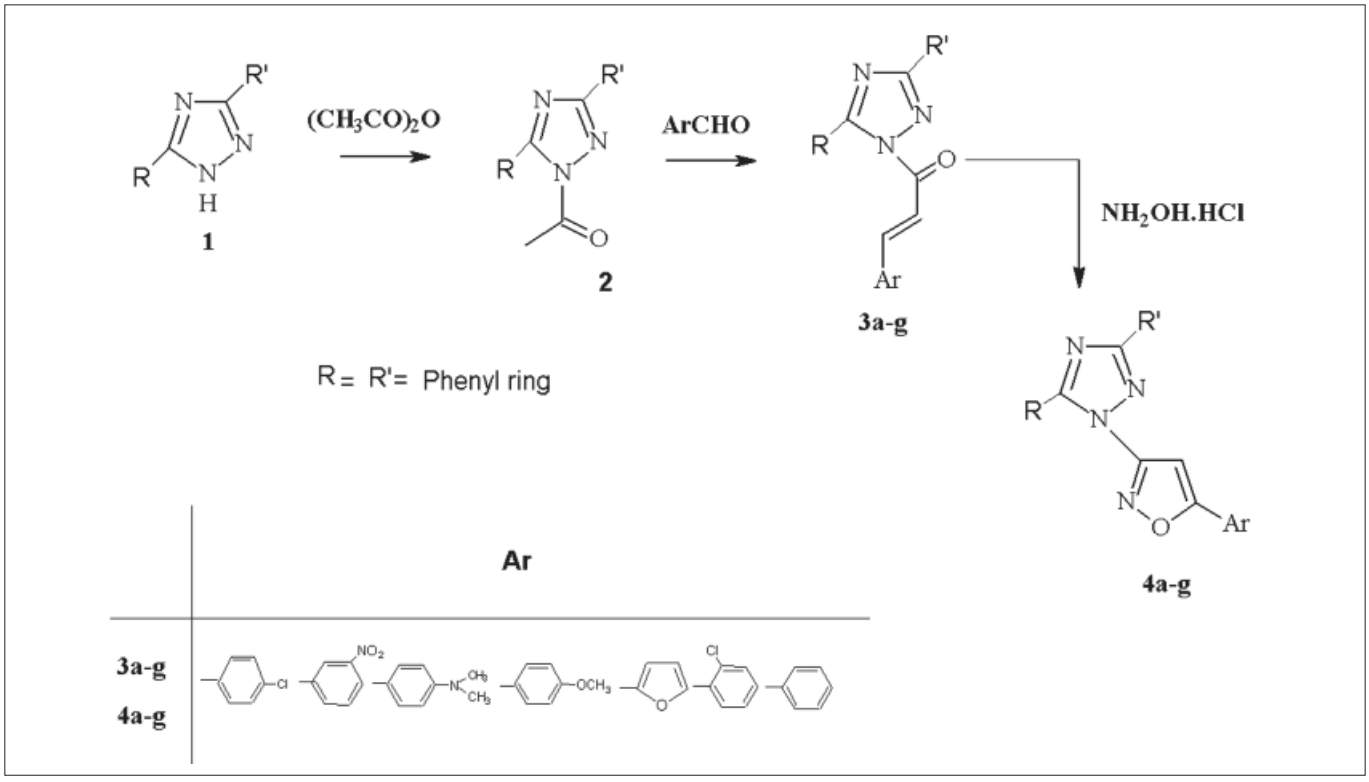


FIGURE 1. Synthesis of compound 3a-g and 4a-g.

TABLE 5. Anticancer screening data of tested compounds

Compound No.	60 Cell lines in assay in 1-dose 10 $^{-5}$M concentration			
(NSC code)	Mean growth (%)	Range growth (%)	Most sensitive cell line	Growth of most sensitive cell line (%)
4a:NSC:761075-O	103.27	-17.33-40.41	Renal Cancer (UO-31)	-17.33
4c:NSC:761077-Q	104.38	-15.01-39.18	Renal Cancer (UO-31)	-15.01
4d:NSC:761078-R	103.54	-26.80-63.92	Renal Cancer (UO-31)	-26.80
4e: NSC:761079-S	104.94	-28.28-57.93	Leukemia (SR)	-28.28
4f: NSC:761076-P	104.63	-20.22-55.07	Renal Cancer (UO-31)	-20.22

H_2SO_4. The yield of the compound 2 was found to be quantitative and it was readily converted to corresponding chalcones (3a-g) by treating them with different aromatic aldehydes and sodium hydroxide and hence seven different derivatives are synthesized. Then all Chalcones were subsequently cyclized with hydroxyl amine hydrochloride in basic medium to get required isoxazole derivatives (Figure 1) with good reaction yield.

Infrared spectrum of compound 3a-g and 4a-g showed a sharp absorption at 1553-1556, 765-789, 1156-1166, 3131-3153 and 2932-3222 cm^{-1} which is attributed to -NO_2, -Cl, -OCH_3, -N-$(CH_3)2$ and aromatic region. Synthesized target compounds 4a-g showed appropriate ^{1}H-NMR signals, 1-H (CH) proton of the isoxazole showed characteristic delta values of range at δ 7.05-7.11. Aromatic protons showed multiplets in the range of δ 6.46–8.52, the expected signals with appropriate multiplicities for different types of protons were observed for the derivatives. Mass spectra of the compounds 4a-g showed molecular ion peaks with high abundance at m/z in agreement with their molecular formula.

Newly synthesized derivatives 3a-g and 4a-g were tested for in vitro antimicrobial activity. Compound 4a and 4d exhibited fungicidal potential with MIC values 15.62 and 31.25 µg/ml respectively against *C. albicans* and *A. niger*. Compound 4f, 3d, 3f and 4b showed moderate inhibitory properties against both the fungi. Compound 4f exhibited antibacterial potential at 15.62 and 7.81 µg/ml against *B. Subtillis* and *E. coli* respectively and found to be most potent antibacterial agent. Compound 3b, 4a and 4b exhibited significant antibacterial activity. The superior antibacterial and antifungal activity is attributed to the presence of pharmaco-

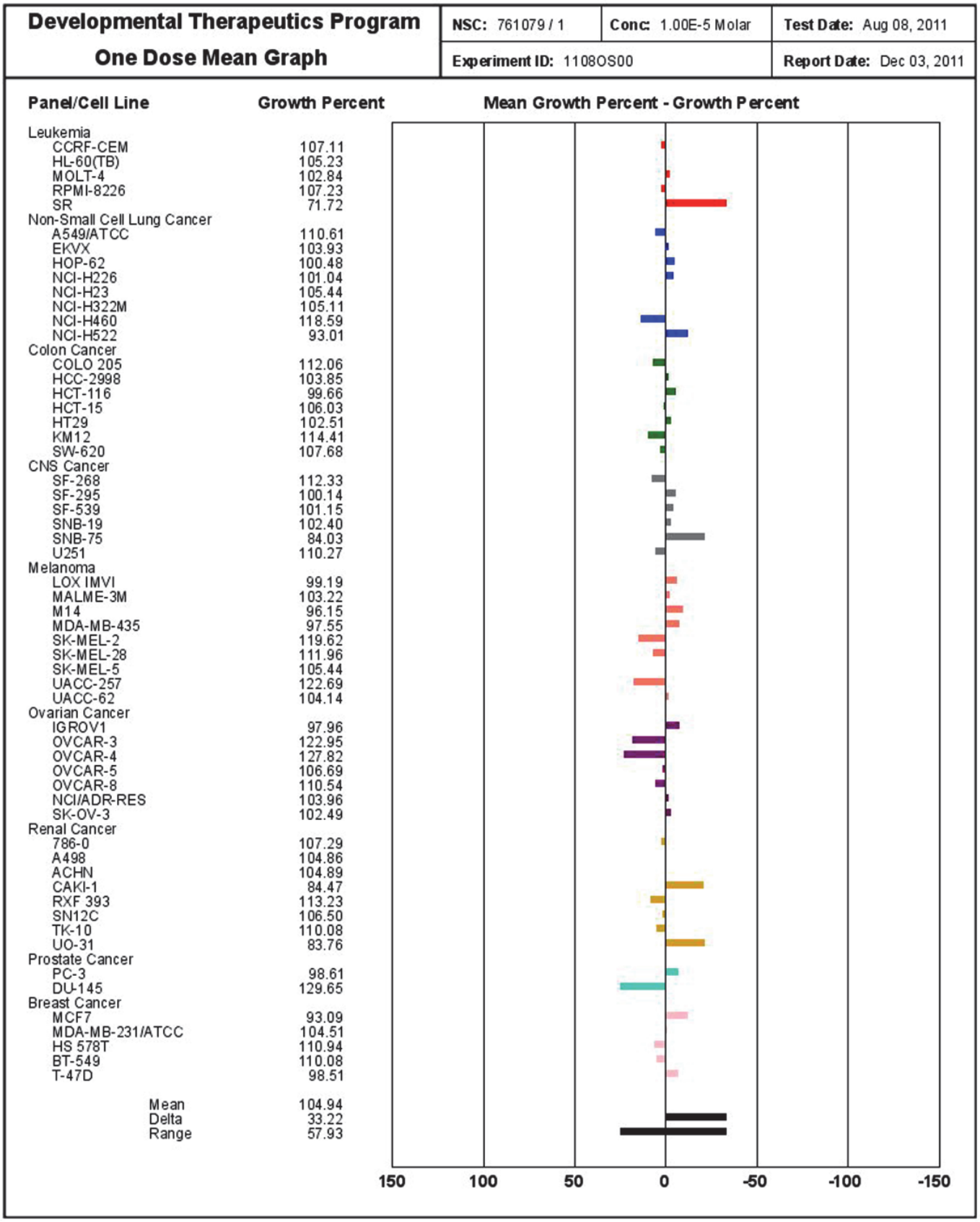


FIGURE 2. Selected NCI sixty cell screening data highlighting the potency of compound (4e: NSC:761079-S) against Leukemia cancer cell line (SR). Bars to the right of the mean line represent cell lines more sensitive to test compound compared to mean, whereas bars to the left represent less sensitive cell lines.

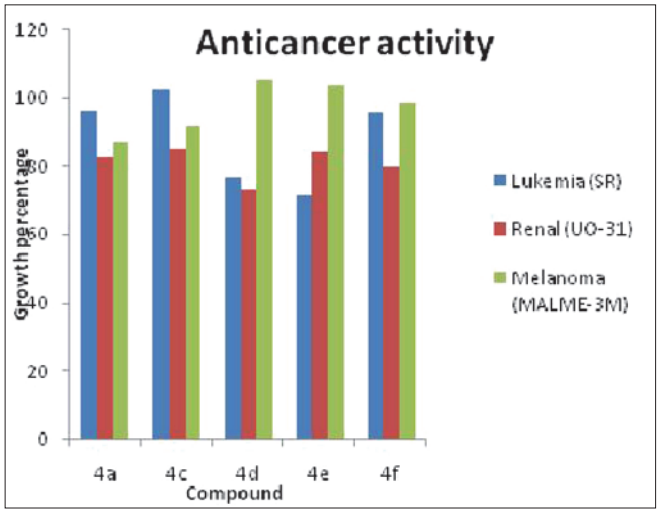


FIGURE 3. Anticancer activity of titled compounds against three cell lines.

logically active phenyl substituted chloro, nitro, methoxy group attached to isoxazole moiety. Compound 4a-g were tested for in vitro antitubercular activity and found in the range of 54% to 76% growth of inhibition. 2-chloro, 4-methoxy and 3-nitro group of derivatives exhibited maximum antimycobacterial activity. 2-Chloro substituted compound (4f) was found to be most potent antimycobacterial agent with 76% growth of inhibition.

The compound 4a, 4c, 4d, 4e and 4f were evaluated at single concentration of 10^{-5} M towards the panel of approximately 60 cancer cell lines derived from nine different cancer types. The mean growth %, range of growth % and growth % relative to most sensitive cell line is depicted in Table 5. The tested compounds showed a broad spectrum of growth inhibitory activity against human tumor cells, as well as some distinctive pattern of selectivity (Figure 2). Compound 4e was found to be a highly active growth inhibitor of the Leukemia cancer cell line (SR) with a growth % of most sensitive cell line to be -28.28, whilst least active over other cell lines. The mean growth % for compound 4e was observed 104.94 % and fall in a range of -28.28-57.93. Compounds 4a, 4c, 4d and 4f showed selectivity on renal cancer (UO-31) with a growth % of most sensitive cell line to be -17.33, -15.01, -26.80 and -20.22 respectively and found to be moderate growth inhibitor of the renal cancer cell line (UO-31). These compounds showed varying range of growth % -17.33 to 40.41 for compound 4a, -15.01 to 39.18 for compound 4c, -26.80 to 63.92 for compound 4d and -20.22 to 55.07 for compound 4f. The compound 4d possessed significant activity on renal cancer cell line (UO-31) from other tested compounds. The SAR study revealed that anticancer activity of compounds is sensitive to the nature of substituents on isoxazole ring. Among the compounds tested, compound with furyl and methoxy phenyl substitution on isoxazole ring shows most marked effect and possessed significant activity (Figure 3). Amongst all the compound p-dimethylaminophenyl substituted derivative (4c) was found to be least active anticancer agent. The results also states that heterocyclic ring isoxazole do not support pre eminently for the anticancer activity.

CONCLUSION

Antibacterial and antifungal studies revealed that compound containing -Cl, $-NO_2$ and $-OCH_3$ groups were found to be potent antimicrobial agents than other tested compounds. Compound 4a-g were showed significant antimicrobial activity than compound 3a-g (chalcones). Modification in the lead molecule via different stages changes the biological activity that was observed from present study. Compound 4f was found to be the most potent antimycobacterial agent among the novel series. In the present investigation five compounds were tested and most of them displayed antitumor activity on renal cancer and leukemia cancer cell lines. The most efficient anticancer compound 4e was found to be active with selective influence on leukemia cancer cell lines, especially on SR with a growth % of 71.72. The obtained result proves the necessity for further investigations to clarify the feature underlying the antitumor potential of tested compounds. Thus the present work provides new outline on the study of antimicrobial, antimycobacterial and anticancer activity of Isoxazole derivatives putting emphasis on assimilation with 1, 2, 4-triazole moiety.

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1,2,4-triazol içeren izoksazol türevlerinin sentezi ve farmakolojik etkisi

ÖZET: Antibakteriyal, antimikobakteriyal ve antikanser etki göstermesi tasarlanan 1,2,4-triazol artığı taşıyan izoksazol türevi bir seri yeni bileşik sentezlenmiştir. 1-(3,5-Difeni-1H-1,2,4-triazol-1-il)etanon'un (bileşik 2), değişik aromatik aldehitlerle tepkimesi sonucunda kazanılan sübstitüe şalkonlar'ın (3a-g) hidroksil amin hidroklorürle tepkimesinden 1-[5-(sübstitüe aril)-1,2-oksazol-3-il]-3,5-difenil-1H-1,2,4-triazol'ler (4a-g) kazanılmıştır. Hedef bileşiklerin yapıları IR ve 1H-NMR spektroskopisi, kütle spektrometrisi ve elementel analiz yöntemleri kullanılarak aydınlatılmıştır. 3a-g ve 4a-g bileşiklerinin in vitro antimikrobiyal etkileri B. subtillis NCIM 2063, E. coli NCIM 2065, C. albicans NCIM 3471 ve A. niger NCIM 1196 suşlarına karşı taranmış; MİK değerleri sıvı dilüsyon yöntemi kullanılarak saptanmıştır. Kloro, nitro, metoksi sübstitüe türevler yüksek antibakteriyal ve antifungal etki göstermiştir. 4a-g bileşiklerinin in vitro antimikobakteriyal etki potansiyali Mycobacterium tuberculosis H37Rv suşuna karşı araştırılmış; 4f bileşiği, >6.25 μg/ml derişimde %76 inbibisyon göstermiştir. Sentezlenen izoksazol türevi bileşiklerden beşinin antikanser etki potansiyali NCI'de (National Cancer Institute) dokuz neoplastik kanser türünden üretilmiş 60 faklı tümör hücre hattında çalışılmış; 4e bileşiğinin lösemi kanser hücre hatlarına karşı seçici etki gösterdiği ve özellikle SR hücre hattının gelişimini %71.72 oranında inhibe ettiği saptanmıştır.

ANAHTAR KELİMELER: Izoksazol; antimikrobiyal; antimikobakteriyel

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