ORIGINAL RESEARCH

Synthesis and biological evaluation of new sulfonamidoindoles

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ABSTRACT: A new series of sulfonamidoindole derivatives which are expected to demonstrate antiviral, anticancer and antimycobacterial properties have been designed and synthesized. Thus 3-phenyl-5-sulfonamido-1*H*-indole-2-carbohydrazide (5) was treated with sodium nitrite and hydrochloric acid to yield 3-phenyl-5-sufonamido-1*H*-indole-2-carbonylazide (6). Refluxing 6 with absolute ethanol led to N-(3-phenyl-5-sufonamido-1*H*-indol-2-yl)carbamic acid ethyl ester (7). Hydrazinolysis of 7 gave 4-(3-phenyl-5-sufonamido-1*H*-indol-2-yl) semicarbazide (8) which was condensed with aromatic aldehydes to afford 4-(3-phenyl-5-sufonamido-1*H*-indol-2-yl)-1-(un)substituted benzylidenesemicarbazides (9). Compounds 9a-c, 9e, 9f and 9h were evaluated against some DNA and RNA viruses in CRFK, VERO, HEL and HeLa cell cultures. Most of the compounds showed varying degrees of inhibition below 50% cytotoxic concentration (CC_{50}) or minumum cytotoxic concentration (MCC), but no specific antiviral effects (i.e. minimal antivirally effective concentration ≥5-fold lower than minimal cytotoxic concentration) were noted for any of the compounds against any of the viruses. 9e and 9f were selected for anticancer screening by the National Cancer Institute (NCI). 9e demonstrated the highest cytotoxicity against leukemia cell line SR (55.48%) and colon cancer cell line KM-12 (41.99%) in the primary screen. 9a-e, 9g and 9h were screened for antimycobacterial activity against *Mycobacterium tuberculosis* H37Rv using the microplate alamar blue assay (MABA), but none showed inhibition at 100 μg/ml.

KEYWORDS: indole, semicarbazone, antiviral activity, anticancer activity, antimycobacterial activity

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INTRODUCTION

Viral diseases, cancer and although a curable and a preventable disease tuberculosis are continuing to cause serious morbidity and mortality worldwide. Despite significant advances especially in antiviral and anticancer therapy, search for new agents continues in the attempt to develop drugs capable of overcoming toxicity and resistance. Delavirdine (**I**), methisazone (**II**) and sunitinib (**III**) are among indole derived drugs that are being used for the treatment of viral or neoplastic diseases (1,2). A thiosemicarbazone, thiacetazone (**IV**) is an antitubercular agent (2).

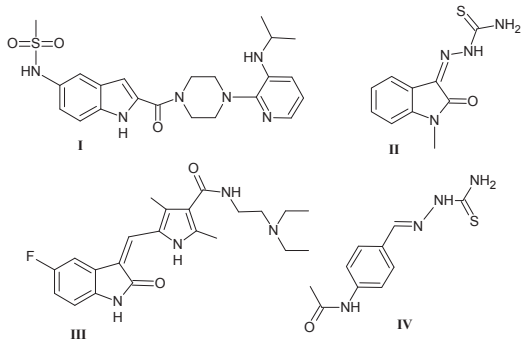


FIGURE 1. Antiviral, anticancer and antimycobacterial agents

Several indoles were found to be effective as inhibitors of human immunodeficiency virus reverse transcriptase (HIVrt) or histone deacetylase, inhibition of which might offer new therapies for AIDS and malignant cell growth (3-6). Furthermore, indole-2-carboxyclic acid benzylidene hydrazides were reported to be potent inducers of apoptosis (7). Very recently, derivatives of 5-sulfonamido-3-phenyl-1*H*-indole-2-carbohydrazide were found to be inhibitors of tumor associated isoforms IX and XII of carbonic anhydrase and mycobacterial β-carbonic anhydrases (8,9).

A series of investigations on 1*H*-indole-2,3-dione-3-thiosemicarbazones and variously substituted semicarbazones revealed promising antiviral, cytotoxic and antimycobacterial properties where

the antiviral effect was attributed to the presence of an intact NHC(=S)NH or NHC(=O)NH grouping (10-13).

In view of these observations, we report here the synthesis, structural determination and antiviral, anticancer and antimycobacterial evaluation of 4-(3-phenyl-5-sufonamido-1*H*-indol-2-yl)-1-(un)substituted benzylidenesemicarbazides .

MATERIALS AND METHODS

Sulfanilamide (**1**), ethyl 2-benzyl-3-oxobutanoate and the aromatic aldehydes were commercially available. **2-5** were synthesized as previously reported (14). M.p.'s were determined on a Büchi 530 or a Büchi 540 apparatus in open capillaries and are uncorrected. Elemental analyses were performed on a Carlo Erba 1106 or Thermo Finnigan Flash EA 1112 elemental analyzer. IR (KBr) and ^{1}H-NMR (DMSO-d_6) spectra were run on Perkin Elmer 1600 FT-IR, Bruker AC 200 (200 MHz) and Varian^{UNITY} INOVA (500 MHz) instruments. (bs=broad/singlet, ind.=indole, ar.= aromatic)

3-Phenyl-5-sulfonamido-1H-indole-2-carbonyl azide (6)

To a suspension of **5** (0.01 mol) in dioxane (10 ml) and acetic acid (10 ml) sodium nitrite (0.70 g) in water (3 ml) was added dropwise with stirring at 0-5 ^{0}C. A pale yellow solid separated out immediately and stirring continued for 20 minutes more. The crude azide separated was filtered, washed successively with ice-cold water (10 ml) and dioxane (5 ml), dried and used without further purification.

N-(3-phenyl-5-sufonamido-1H-indol-2-yl)carbamic acid ethyl ester (7)

A mixture of **6** (0.005 mol) and absolute ethanol (40 ml) was heated on a water bath under until dissolution. The reaction mixture was refluxed for 5 h in a mantle, cooled and left aside to stand overnight. Evaporation of the solvent under vacuum and cooling afforded **7** as a yellow solid which was used without further purification.

4-[3-Phenyl-5-sulfonamido-1H-indol-2-yl]semicarbazide (8)

7 (0.005 mol) was refluxed in 2.5 ml of hydrazine (98%) for 3 h. The precipitate formed after cooling was filtered, washed with ethanol (96%).

IR υ = 3377, 3300 (N-H), 1672 (C=O), 1306,1151 (SO_2) cm^{-1} . **^{1}H-NMR** δ = 11.69 (s, 1H, NH ind.), 8.06 (bs, 1H, N2-H), 7.96 (s, 1H, C4-H ind.), 7.59 (d J= 8.9 Hz, 1H, C6-H ind.) 7.51-7.54 (m, 4H ar), 7.47 (dd J= 8.3, 2.0 Hz, 1H, C7-H ind.) 7.30-7.43 (m, 1H ar), 7.02 (s, 2H, SO_2NH_2), 4.59 (bs, 2H, NH_2) ppm.

4-(3-Phenyl-5-sufonamido-1H-indol-2-yl)-1-(un)substituted benzylidenesemicarbazides (9)

8 (0.0025 mol) and an appropriate aromatic aldehyde (0.0025 mol) was refluxed in 25 mL of abs. EtOH (96%) for 5 h. The solid that separated was filtered and washed with hot ethanol (96%).

9a: IR υ = 3377, 3254, 3138 (N-H), 1695 (C=O), 1627 (C=N), 1316, 1149 (SO_2) cm^{-1} . **- ^{1}H-NMR** δ = 11.85 (s, 1H, NH ind.), 11.17 (s, 1H, N2-H), 9.30 (s, 1H, N4-H), 8.07 (s, 1H, N=CH), 7.97 (s, 1H, C4-H ind.), 7.64-7.69 (m, 4H ar), 7.54-7.61 (m, 4H ar), 7.36-7.44 (m, 4H ar), 7.08 (s, 2H, SO_2NH_2) ppm.

9d: IR υ = 3389, 3245 (N-H), 1697 (C=O), 1627 (C=N), 1323, 1156 (SO_2) cm^{-1} **- ^{1}H-NMR** δ = 11.82 (s, 1H, NH ind.), 11.15 (s, 1H, N2-H), 9.28 (s, 1H, N4-H), 8.09 (s, 1H, N=CH), 7.96 (s, 1H, C4-H ind.), 7.35-7.74 (m, 11H ar), 7.05 (s, 2H, SO_2NH_2) ppm.

9e: IR υ = 3381, 3256, 3209, 3138 (NH), 1694 (C=O), 1628 (C=N), 1315, 1149 (SO_2) cm^{-1} **- ^{1}H-NMR** δ = 11.80 (s,1H,NH ind.), 11.10 (s, 1H, N2-H), 9.22 (s, 1H, N4-H), 8.07 (s, 1H, N=CH), 7.95 (s, 1H, C_4-H ind.), 7.20-7.66 (m, 11H, ar), 7.03 (s, 2H, SO_2NH_2), 2.34(s, 3H, CH_3) ppm.

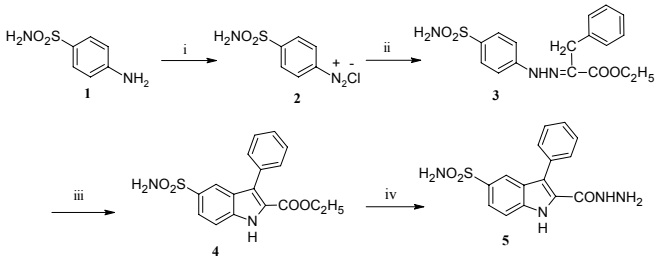
9g : IR υ = 3359, 3253, 3210, 3136 (N-H), 1691 (C=O), 1628 (C=N), 1319, 1148 (SO_2) cm^{-1} **- ^{1}H-NMR** δ = 11.78 (s, 1H, NH ind.), 10.98 (s, 1H, N2-H), 9.24 (s, 1H, N4-H), 8.07 (s, 1H, N=CH), 7.92 (s, 1H, C4-H ind.), 7.53-7.65 (m, 8H, ar), 7.36-7.43 (m, 1H, ar), 7.03 (s, 2H, SO_2NH_2), 6.98 (d J= 8.7 Hz, 2H, ar), 3.81 (s, 3H, OCH_3) ppm.

9h : IR υ = 3398, 3376, 3239 (NH), 1702 (C=O), 1625 (C=N), 1569 (NO_2), 1345, 1324 (SO_2/NO_2), 1158 (SO_2) cm^{-1} **- ^{1}H-NMR** δ = 11.84 (s, 1H, NH ind.), 11.35 (s, 1H, N2-H), 9.36 (s, 1H, N4-H), 8.27 (s, 1H, N=CH), 8.22 (s, 1H, C4-H ind.), 8.09 (d J= 7.3 Hz, 2H, ar), 7.98 (d J= 7.30 Hz, 2H, ar), 7.51-7.66 (m, 6H, ar), 7.33-7.46 (m, 1H, ar), 7.05 (s, 2H, SO_2NH_2) ppm.

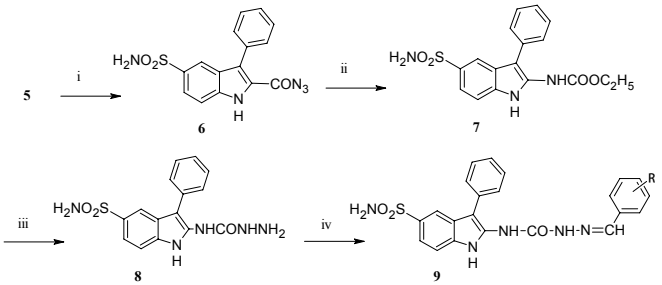
RESULTS AND DISCUSSION

The key intermediate 3-phenyl-5-sulfonamido-1*H*-indole-2-carbohydrazide (**5**) was prepared using a previously described method as outlined in Scheme 1 (14). Thus **2**, obtained from the reaction of **1** with $NaNO_2$ and HCl, was reacted with ethyl 2-benzyl-3-oxobutanoate to afford **3** via the Japp-Klingemann reaction. The Fischer-indole procedure was employed to cyclize **3** into ethyl 3-phenyl-5-sulfonamido-1*H*-indole-2-carboxylate (**4**). Subsequent exposure of **4** to an excess of hydrazine hydrate yielded **5**.

Further treatment of **5** with $NaNO_2$/HCl yielded 3-phenyl-5-sufonamido-1*H*-indole-2-carbonyl azide (**6**)(15). Refluxing **6** with absolute ethanol led to N-(3-phenyl-5-sufonamido-1*H*-



SCHEME 1. Reagents and conditions: (i) $NaNO_2$/HCl, 0-5°C (ii) ethyl-2-benzyl-3-oxobutanoate, KOH, H_2O (iii) HCl (37%), reflux (iv) NH_2NH_2 (98%), reflux.



SCHEME 2. Reagents and conditions: (i) $NaNO_2$/HCl, 0-5°C (ii) abs. C_2H_5OH, reflux (iii) NH_2NH_2 (98%), reflux (iv) RC_6H_4CHO, abs. C_2H_5OH , reflux.

TABLE 1. Physicochemical data of 8 and 9

Comp.	R	Formula (M.W.)	Yield %	M.p. °C	Analysis Calculated / Found C %	H %	N %
8	-	$C_{15}H_{15}N_5O_3S.½H_2O$ (354.37)	52	231-234	50.79 50.92	4.51 4.41	19.75 19.01
9a	H	$C_{22}H_{19}N_5O_3S$ (433.48)	81	>300	60.95 60.20	4.41 3.97	16.15 15.82
9b	2-Cl	$C_{22}H_{18}ClN_5O_3S$ (467.92)	64	281-283	56.46 55.90	3.87 3.78	14.96 14.60
9c	3-Cl	$C_{22}H_{18}ClN_5O_3S$ (467.92)	73	>300	56.46 55.67	3.87 3.60	14.96 14.32
9d	4-Cl	$C_{22}H_{18}ClN_5O_3S$ (467.92)	86	>300	56.46 55.77	3.87 3.70	14.96 14.38
9e	3-CH_3	$C_{23}H_{21}N_5O_3S$ (447.51)	59	283	61.72 61.42	4.73 4.70	15.65 15.64
9f	4-CH_3	$C_{23}H_{21}N_5O_3S$ (447.51)	56	283	61.72 61.42	4.73 4.47	15.65 14.90
9g	4-OCH_3	$C_{23}H_{21}N_5O_4S.\ H_2O$ (481.49)	90	263-266 (dec.)	57.32 56.49	4.78 3.92	14.54 13.98
9h	4-NO_2	$C_{22}H_{18}N_6O_5S$ (478.48)	78	289	55.22 54.81	3.79 3.80	17.56 17.18

indol-2-yl)carbamic acid ethyl ester (**7**) via a rearrangement reaction (15). Hydrazinolysis of **7** gave 4-(3-phenyl-5-sufonamido-1*H*-indol-2-yl)semicarbazide (**8**) which was condensed with aromatic aldehydes to afford 4-(3-phenyl-5-sufonamido-1*H*-indol-2-yl)-1-(un)substituted benzylidenesemicarbazides (**9**) (Scheme 2 and Table 1) (15,16).

Compounds **8** and **9** were characterized by their combustion analyses, melting points and spectral data. The IR spectra of compounds **8** and **9** showed NH stretching bands of the indole ring, semicarbazide, semicarbazone and sulfonamide groups at 3398-3136 cm^{-1} (14-18). The presence of the carbonyl functionality was confirmed by the bands observed in the 1702-1672 cm^{-1} region (14-18). The C=N stretching band of compounds **9a-h** occurred at 1628-1625 cm^{-1}. Strong absorption bands observed in the 1345-1306 cm^{-1} and 1158-1148 cm^{-1} regions were attributed to the asymmetric and symmetric SO_2 stretching vibrations of the sulfonamide group (14,16).

The ^{1}H-NMR spectrum of compound **8** displayed the N-H, C4-H, C6-H and C7-H protons of the indole ring at 11.69 and 7.96, 7.59 and 7.47 ppm, respectively. Broad resonances observed at 8.06 and 4.59 ppm were assigned to the N2-H and N1-H of the semicarbazide (15). N4-H was not observed presumably due to deuterium exchange with DMSO-d_6. The SO_2NH_2 protons resonated at 7.02 ppm. The indole NH, N2-H, N4-H and the azomethine proton (N=CH) of **9a**, **9d**, **9e**, **9g** and **9h** exhibited the expected singlets at 11.85-11.78, 11.35-10.98, 9.36-9.22 and 8.27-8.02 ppm, respectively (14-18). The SO_2NH_2 protons resonated at 7.08-7.03 ppm (14,16). All the other protons were observed in the expected regions.

Compounds **9a-c**, **9e**, **9f** and **9h** were evaluated against feline corona virus (FIPV), feline herpes virus (FHV) in Crandell-Rees feline kidney (CRFK), parainfluenza-3 virus, rheovirus-1, sindbis virus, coxsackie virus B4, punto toro virus in VERO, herpes simplex virus-1 (KOS)(HSV-1), herpes simplex virus-2 (G)(HSV-2), vaccinia virus, vesicular stomatitis virus (VSV), herpes simplex virus-1 TK KOS ACV in human embroyonic lung (HEL) and vesicular stomatitis virus, coxsackie virus B4 and respiratory syncytial virus (RSV) in Henrietta Lacks (HeLa) cell cultures. As can be seen in Tables 2 and 3, most of the compounds showed varying degrees of inhibition below 50% cytotoxic concentration (CC_{50}) or minumum cytotoxic concentration (MCC), but no specific antiviral effects (i.e. minimal antivirally effective concentration ≥5-fold lower than minimal cytotoxic concentration) were noted for any of the compounds against any of the viruses.

TABLE 2. Antiviral evaluation of 9a-9c, 9e, 9f and 9h

Comp.	R	CRFK (EC_{50} μg/ml)[b] CC_{50} [a] (μg/ml)	Feline corona virus	Feline herpes virus	MCC [c] (μg/ml)	VERO (EC_{50} μg/ml) [b] Coxsackie virus B4	Parain-fluenza-3 virus	Reo-virus-1	Sindbis virus	Punto Toro virus
9a	H	>100	>100	>100	100	>20	>20	>20	>20	>20
9b	2-Cl	>100	>100	>100	20	>4	>4	>4	>4	>4
9c	3-Cl	>100	>100	>100	20	>4	>4	>4	>4	>4
9e	3-CH_3	>100	>100	>100	20	>4	>4	>4	>4	>4
9f	4-CH_3	>100	40.3	72.8	20	>4	>4	>4	>4	>4
9h	4-NO_2	>100	>100	>100	20	>4	>4	>4	>4	>4
HHA[d]		>100	17.6	16.9	-	-	-	-	-	-
UDA [d]		>100	12.4	30.2	-	-	-	-	-	-
Ganciclovir(mM)		>100	>100	7.4	-	-	-	-	-	-
Ribavirin(mM)		-	-	-	>250	>250	146	>250	250	50
(S)-DHPA(mM) [d]		-	-	-	>250	>250	>250	250	>250	>250
DS-5000 [d]		-	-	-	>100	50	>100	>100	100	20

[a] 50% cytotoxic concentration, as determined by mesuring cell viability by the colorimetric formazan based MTS assay.
[b] Required to reduce virus-induced cytopathogenicity by 50 %.
[c] Required to cause a microscopically detectable alteration of normal cell morphology.
[d] *Hippeastrum hybrid* (HHA), *Urtica dioica* (UDA), dextrane sulfate (DS-5000), S-dihydroxypropyladenine ((S)-DHPA).

TABLE 3. Antiviral evaluation of 9a-9c, 9e, 9f and 9h

		HEL (EC_{50} μg/ml) [b]						HeLa (EC_{50} μg/ml) [b]			
Comp.	R	MCC [a] (μg/ml)	HSV-1 KOS	HSV-1 KOS ACV^r	HSV-2 G	Vaccinia virus	VSV	MCC [a] (μg/ml)	VSV	Coxsackie B4	RSV
9a	H	>100	>100	>100	>100	>100	>100	100	>20	>20	>20
9b	2-Cl	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
9c	3-Cl	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
9e	3-CH_3	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
9f	4-CH_3	>100	>100	>100	>100	>100	>100	100	>20	>20	>20
9h	4-NO_2	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
Ganciclovir(mM)		>100	0.5	20	0.2	>100	>100	-	-	-	-
Brivudin(mM)		>250	0.04	250	29	22	>250	-	-	-	-
Cidofovir(mM)		>250	1	2	2	6	>250	-	-	-	-
Ribavirin(mM)		>250	>250	>250	10	95	>250	>250	29	124	29
(S)-DHPA(mM)		-	-	-	-	-	-	>250	146	>250	>250
DS-5000		-	-	-	-	-	-	>100	2	>100	12

[a]Required to cause a microscopically detectable alteration of normal cell morphology.
[b]Required to reduce virus-induced cytopathogenicity by 50 %.

Compounds **9e** and **9f** were selected for anticancer screening by the National Cancer Institute (NCI) and screened against 60 different human tumor cell lines, representing leukemia, melanoma and cancers of the lung, colon, brain, ovary, breast, prostate, and kidney at a single dose of 10^{-5} M (19). **9e** demonstrated the highest cytotoxicity (55.48%) against leukemia cell line SR and colon cancer cell line KM-12 (41.99%) in the primary screen conducted at 10^{-5} M (Figure 2). **9f** displayed the highest cytotoxicity against non small cell lung cancer cell line HOP-92 (30.46 %). **9a-e**, **9g** and **9h** were screened for antimycobacterial activity against *Mycobacterium tuberculosis* H37Rv using the microplate alamar blue assay (MABA), but none showed inhibition at 100 μg/ml [20].

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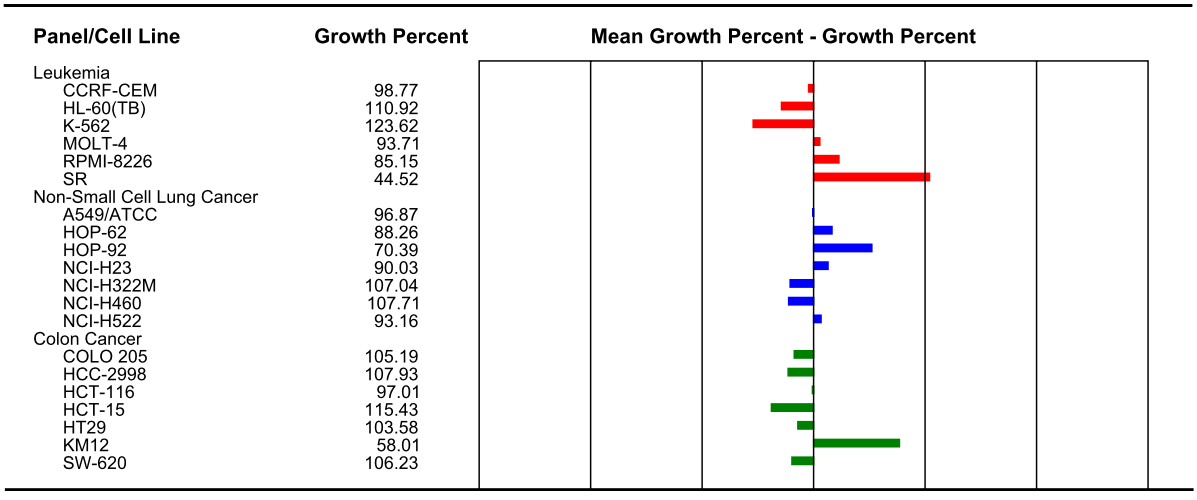

FIGURE 2. Cytotoxic activity of 9e against leukemia, non-small cell lung cancer and colon cancer cell lines. The One-dose data is reported as a mean graph of the percent growth of treated cells The growth percent is growth relative to the no-drug control, and relative to the time zero number of cells.

Yeni sülfonamidoindollerin sentezi ve biyolojik aktivitelerinin araştırılması

ÖZET: Antiviral, antikanser ve antimikobakteriyel aktivite göstermesi beklenen bir seri yeni sülfonamidoindol türevi tasarlanmış ve sentez edilmiştir. Bu amaçla 3-fenil-5-sülfonamido-1*H*-indol-2-karbohidrazidin (5) sodyum nitrit ve hidroklorik asitle tepkimesinden kazanılan 3-fenil-5-sülfonamido-1*H*-indol-2-karbonil azit (6) susuz etanollü ortamda ısıtılarak 3-fenil-5-sülfonamido-1*H*-indol-2-karbamik asit etil ester (7) oluşturulmuştur. 7 nin hidrazinolizi ile kazanılan 4-(3-fenil-5-sülfonamido-1*H*-indol-2-il)semikarbazid in (8) aromatik aldehitlerle kondensasyonundan 4-(3-fenil-5-sülfonamido-1*H*-indol-2-il)-1-(non)sübstitüe benziliden semikarbazidler (9) elde edilmiştir. Sentezlenen 9a-c, 9e, 9f ve 9h bileşiklerinin CRFK, VERO, HEL ve HeLa hücre kültürlerinde bazı DNA ve RNA virüslerine karşı etkileri incelenmiş, bileşiklerin çoğunda %50 sitotoksik konsantrasyon veya minimum sitotoksik konsantrasyon altında değişen düzeylerde inhibisyon gözlenmiş ancak hiçbir türev sitotoksik konsantrasyonun 5 kat altında ya da daha düşük efektif antiviral konsantrasyon sergilememiştir. Amerikan Ulusal Kanser Enstitüsü tarafından seçilen 9e ve 9f bileşiklerinde antikanser aktivite araştırılmış, ön denemede en yüksek sitotoksisiteyi 9e nin lösemi SR hücre dizisi (%55.48) ve kolon kanseri LM-12 hücre dizisine (%41.99) karşı gösterdiği saptanmıştır. 9a-e, 9g ve 9h bileşiklerinde *Mycobacterium tuberculosis* H37Rv ye karşı 100 μg/ml derişimde microplate alamar blue (MABA) yöntemiyle antimikobakteryel etki araştırılmış, ancak etki saptanmamıştır.

ANAHTAR KELİMELER: indol, semikarbazon, antiviral aktivite, antikanser aktivite, antimikobakteryel aktivite

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