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THE SYNTHESIS OF SOME INDAZOLE DERIVATIVES AND THEIR ANTIMICROBIAL ACTIVITY

BAZI INDAZOL TÜREVLERİNİN SENTEZİ VE ANTİMİKROBİAL ETKİLERİ

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Some 1-[(N-substituted aminothio carbonylthio)acetyl]indazole derivatives were synthesized by reacting 1-(chloroacetyl)substituted indazoles with secondary amine dithiocarbamate derivatives in acetone. The structures elucidation of the compounds were performed by IR, ^{1}H-NMR and MS-FAB spectral data and elemental analyses. The substances were tested for their antimicrobial activity.

Bazı 1-[(N-sübstitüe aminotiyokarbonil tiyo)asetil]indazol türevleri, sekonder amin ditiyokarbamat türevleri ve sübstitüe 1-(kloroasetil)indazol türevleri ile aseton içinde reaksiyona sokularak elde edilmişlerdir. Bileşiklerin yapıları , IR, ^{1}H-NMR ve MS-FAB spektroskopik verileri ve elemental analiz sonuçları yardımı ile aydınlatıldı. Bileşiklerin antimikrobial etkileri araştırılmıştır.

Keywords : *1-(Chloroacetyl)indazole,1-[(N-Substituted aminothiocarbonylthio) acetyl]indazole, antimicrobial activity*

Anahtar Kelimeler: *1-(Kloroasetil)indazol, 1-[(N-sübstitüe aminotiyokarboniltiyo) asetil] indazol, antimikrobial aktivite.*

Introduction

It is well known that N-mono and N,N-disubstituted dithiocarbamate derivatives show diverse biological activities (antifungal,antiviral, herbicide and anticholinergic activities)(1-6)

Some indazoles derivatives have been reported to possess antihelmintic and antiallergic activities (7-9).

In view of these observations, we synthesized new 1-[(N-substituted aminothiocarbonylthio)acetyl]indazoles and tested them for antibacterial and antifungal activities.

Materials and Methods

Melting points were determined by using a Gallenkamp apparatus. Spectroscopic data were recorded by the following instruments: IR, Shimadzu IR-435 spectrophotometer; ^{1}H-NMR, Bruker 250 MHz NMR spectrometer; MS, Fast atom bombardment mass spectra (MS-FAB$^+$) were obtained by VG Quattro Mass spectrometer; Microanalyses, Leco CHNS elemental analyses apparatus.

General Procedure for Synthesis of the Compounds
1-(Chloroacetyl)substituted indazoles 2a-d:

Substituted indazole (0.01 mol) and triethylamine (0.01 mol) were dissolved in benzene (50 ml) with constant stirring. After, the mixture was cooled in an ice bath and chloroacetyl chloride (0.01 mol) was added dropwise with stirring. The reaction mixture thus obtained was further agitated for 1 h at room temperature. The precipitate was filtrated, the solvent was evaporated to dryness under reduced pressure and the products were recrystallized from ethanol.

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1-[(N-Substituted aminothiocarbonylthio)acetyl] indazoles 3a-v:

A mixture of 1-(chloroacetyl) substituted indazole (0.01 mol) and appropriate secondary amine dithiocarbamate sodium (0.01 mol) was treated in acetone at room temperature for 4 h. The solvent was evaporated, washed with water and recrystallized from ethanol.

These compounds showed characteristic IR bands at 1680 cm^{-1} (C=O) and 1245 cm^{-1} (C=S).

2a: (R_1=R_2=R_3=H) M.p.: 81°C.

^{1}H-NMR (DMSO-d_6, δ, ppm): 5.2 (2H, s, $COCH_2$), 7.50 (1H, t, 5-H of indazole), 7.65 (1H, t, 6-H of indazole), 7.95 (1H, d J=7.9 Hz, 7-H of indazole), 8.30 (1H, d J= 8.33 Hz, 4-H of indazole), 8.60 (1H, s, 3-H of indazole).

2b: (R_1=NO_2, R_2=R_3=H) M.p: 157°C

2c: (R_1=R_3=H, R_2=NO_2) M.p.:153°C.

2d: (R_1=R_2=H, R_3=OH) M.p.: 132°C.

3a: ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.30-1.45 (6H, d t, CH_3), 4.00-4.20 (4H, d q, CH_2-N-CH_2), 5.10 (2H, s, $COCH_2$), 7.80-8.75 (5H, m, aromatic protons).

3i: ^{1}H-NMR (DMSO-d_6, δ, ppm): 3.65-3.75 (4H, m, CH_2-N-CH_2), 4.00 and 4.15(4H, two br, CH_2-O- CH_2), 5.15 (1H, s, $COCH_2$), 7.80-7.95 (1H, t, 6-H of indazole), 8.35 (1H, d J=7.83 Hz, 7-H of indazole), 8.70 (1H, d J=8.41 Hz, 5-H of indazole), 8.95 (1H, s, 3-H of indazole) MS(FAB$^+$): M+1: m/z:367.

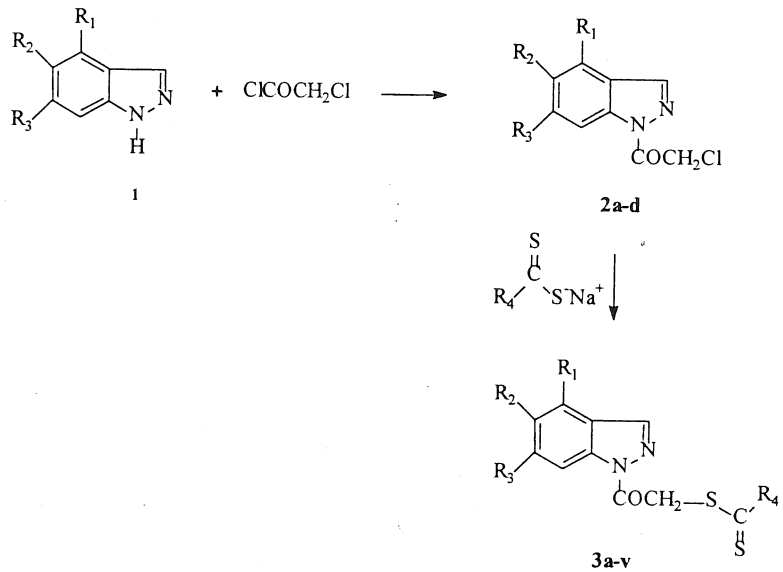
3m: ^{1}H-NMR (DMSO-d_6, δ, ppm):1.55-1.75(6H, br, 3-H, 4-H, 5-H of piperidine), 4.00 and 4.20 (4H, two br, CH_2-N- CH_2), 5.15 (2H, s, $COCH_2$), 8.40-8.55 (2H, m, 6-H and 7-H of indazole), 8.85 (1H, s, 3-H of indazole), 8.95 (1H, d J=1.52 Hz, 4-H of indazole). MS(FAB$^+$): M+1: m/z: 364

3o: ^{1}H-NMR (DMSO-d_6, δ, ppm): 2.75 (4H, br, CH_2-S-CH_2), 4.30 and 4.45 (4H, two br, CH_2-N-CH_2), 5.15 (2H, s, $COCH_2$), 8.35-8.50 (2H, m, 6-H and 7-H of indazole), 8.80 (1H, s, 3-H of indazole), 8.95 (1H, d J= 1.45 Hz, 4-H of indazole). MS(FAB$^+$): M+1: m/z:383

3p: ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.20 and 1.35 (6H, d t, CH_3), 3.85 and 4.00 (4H, d q, CH_2-N-CH_2), 5.15 (2H, s, $COCH_2$), 6.90 (1H, dd J= 8.64 and 2.08 Hz, 5-H of indazole), 7.65 (1H, d J=1.73 Hz, 7-H of indazole), 7.70 (1H, d J=8.62 Hz, 4-H of indazole), 8.45(1H, s, 3-H of indazole).

Antimicrobial Activity

Antimicrobial activities of the compounds were determined using the microdulition technique (10). MIC values were calculated as μg/ml. Standard bacteria and fungi strains were used: 1. Escherichia coli B, 2. Bacillus cereus NRRL B-3711, 3. Pseudomonas aeroginosa NRRL B-23, 4. Staphylococcus aureus NRRL B-767 and 5. Candida albicans and 6. Candida globrata.



Scheme 1.

Table I. Physicochemical Data of the Compounds

Comp.	R_1	R_2	R_3	R_4	M.p °C	Yield %	Molecular Formula (MW)
3a	H	H	H	diethylamine	92	82	$C_{14}H_{17}N_3OS_2$ 307
3b	H	H	H	pyrrolidine	163	78	$C_{14}H_{15}N_3OS_2$ 305
3c	H	H	H	piperidine	120	85	$C_{15}H_{17}N_3OS_2$ 319
3d	H	H	H	morpholine	160	85	$C_{14}H_{15}N_3O_2S_2$ 321
3e	H	H	H	thiomorpholine	145	80	$C_{14}H_{15}N_3OS_3$ 337
3f	NO_2	H	H	diethylamine	125	80	$C_{14}H_{16}N_4O_3S_2$ 352
3g	NO_2	H	H	pyrrolidine	186	65	$C_{14}H_{14}N_4O_3S_2$ 350
3h	NO_2	H	H	piperidine	145	82	$C_{15}H_{16}N_4O_3S_2$ 364
3i	NO_2	H	H	morpholine	195	87	$C_{14}H_{14}N_4O_4S_2$ 366
3j	NO_2	H	H	thiomorpholine	155	87	$C_{14}H_{14}N_4O_3S_3$ 382
3k	H	NO_2	H	diethylamine	152	70	$C_{14}H_{16}N_4O_3S_2$ 352
3l	H	NO_2	H	pyrrolidine	172	62	$C_{14}H_{14}N_4O_3S_2$ 350
3m	H	NO_2	H	piperidine	170	78	$C_{15}H_{16}N_4O_3S_2$ 364
3n	H	NO_2	H	morpholine	187	82	$C_{14}H_{14}N_4O_4S_2$ 366
3o	H	NO_2	H	thiomorpholine	193	82	$C_{14}H_{14}N_4O_3S_3$ 382
3p	H	H	OH	diethylamine	134	80	$C_{14}H_{17}N_3O_2S_2$ 323
3r	H	H	OH	pyrrolidine	158	70	$C_{14}H_{15}N_3O_2S_2$ 321
3s	H	H	OH	piperidine	228	75	$C_{15}H_{17}N_3O_2S_2$ 335
3t	H	H	OH	morpholine	245	80	$C_{14}H_{15}N_3O_3S_2$ 337
3v	H	H	OH	thiomorpholine	232	82	$C_{14}H_{15}N_3O_2S_3$ 353

Results and Discussion

In the present work, 1-(chloroacetyl)indazole derivatives **(2a-d)** was prepared by reacting substituted indazoles **(1)** with chloroacetyl chloride in accordance with the method described in the literature (11,12).

The reaction of the 1-(chloroacetyl)indazoles with secondary amine dithiocarbamates in acetone at the room temperature gave the 1-[(N-substituted aminothiocarbonylthio)acetyl] indazole derivatives **(3a-v)** (Scheme I) (Table I). It was pointed out that the above reaction was especially performed in low temperature, because; N-substituted dithiocarbamates can give isothiocyanates by elimination reaction at high tem-

perature (13-15).Analytical and spectral data (IR, ^{1}H-NMR, MS(FAB$^+$)) confirmed the structure of **2a-d** and **3a-v**. In the IR spectra , some significiant stretching bands du to C=O, C=N, C=C and C=S were found to be at 1680, 1620, 1580 and 1245 cm^{-1}, respectively. In the NMR spectra of the compounds, alkyl groups attached to the nitrogen of dithiocarbamoyl groups are not magnetically equivalent, their signals were observed separately in general. The 3-H proton of indazole resonated as a singlet at about 8.90 ppm.

Some of these compounds had appreciable activity for B.cereus and S. aureus(Table II).

Table 2. The Antimicrobial Activities of the Compounds

	E. coli B	B.cereus	P.aeroginosa	S.aureus	C.albicans	C.globrata
3a	250	0.48	250	62.5	250	250
3b	250	31.25	250	62.5	250	250
3c	250	7.81	250	0.48	250	250
3d	250	125	250	31.25	250	250
3e	250	31.25	250	0.48	250	250
3f	250	7.81	250	0.48	250	250
3g	250	31.25	250	0.48	250	250
3h	250	0.48	250	0.48	250	250
3i	250	7.81	250	0.48	250	250
3j	250	0.48	250	0.48	250	250
3k	250	31.25	250	31.25	250	250
3m	250	62.5	250	62.5	250	250
3n	250	0.48	250	31.25	250	250
3o	250	62.5	250	125	250	250
3p	250	0.48	250	62.5	250	250
3s	250	0.48	125	15.62	250	250
3t	250	0.48	250	15.62	250	250
3v	250	0.97	250	15.62	250	250
A	250	125	125	7.81	250	250
B	250	125	125	7.81	62.5	62.5

A: Chloramphenicole succinate B: Ketoconazole

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