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5-ACETYLINDAN ARYLOXYACETOHYDRAZONE DERIVATIVES: SYNTHESIS AND ANTITUBERCULOSIS ACTIVITY

5-ASETİLİNDAN ARİLOKSİASETOHİDRAZON TÜREVLERİ: SENTEZLERİ VE ANTİTÜBERKÜLOZ ETKİLERİ

GÜLHAN TURAN-ZITOUNI*, Z. ASIM KAPLANCIKLI

Department of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Anadolu, 26470-Eskişehir, Turkey

Some 5-acetylindan aryloxyacetohydrazone derivatives were synthesized by reacting 5-acetylindan with aryloxyacetohidrazide derivatives in butanol. The structure of the compounds obtained were performed by using IR, ^{1}H NMR, Mass (FAB$^+$) spectroscopy and elemental analysis results. The antituberculosis activity was examined by TAACF.

Bazı 5-asetilindan ariloksiasetohidrazon türevleri, 5-asetilindan ve ariloksiasetohidrazon türevlerinin bütanol içinde reaksiyonu ile sentezlendi. Bileşiklerin yapıları, IR, ^{1}H NMR, Mass (FAB$^+$) spektroskopisi ve elemental analiz sonuçları kullanılarak aydınlatıldı. Antitüberküloz etki TAACF tarafından denendi.

Keywords : *5-Acetylindan; Aryloxyacetohydrazone; Antituberculose Activity*

Anahtar kelimeler : *5-Asetilindan; Ariloksiasetohidrazon, Antitüberküloz Aktivite*

Introduction

It is well know that hydrazide/hydrazone derivatives show diverse biological activities (tuberculostatic(1-3), antibacterial and antifungal activities(4-6), monoamine oxidase inhibitor activity (7,8)).

In this work, we have synthesized some new 5-acetylindan aryloxyacetohydrazone derivatives by reacting 5-acetylindan with aryloxyacetohydrazides. (Figure)

The antituberculosis activities of the compounds were examined by TACCF (Tuberculosis Antimicrobial Acquisition and Coordinating Facility), Southern Research Institute, GWL Hansen's Disease Center, Colorado State University.

Materials and Methods

Melting points were determined by using a Gallenkamp apparatus and are uncorrected. Spectroscopic data were recorded by the following instruments: IR: Shimadzu IR-435 Spectrofotometer; ^{1}H-NMR: Bruker 250 MHz Spectrometer; MS: Fast atom bombardment mass spectra (FAB-MS) were obtained by VG Quattro Mass Spectrometer. Microanalytical data were obtained by Microanalytical Section of Service Central (CNRS, Ecole Normale Chimie de Montpellier, France).

General Procedure for the Synthesis of the Compounds
5-Acetylindan(1)

This compound was prepared according to the methode reported in literature(9,10).

Aryloxyacetohydrazides(2)

These compounds were prepared according to the previously reported method(1,11,12).

5-Acetylindan aryloxyacetohydrazones (3a-n)

A mixture of 5-acetylindan (0.005 mol) and an appropriate aryloxyacetohydrazide or α-aryloxypropiohydrazide (0.005 mol) in butanol was refluxed for 5h. The solid seperated upon cooling was filtered, dried and recrystallized (Table 1).

The Spectral Data Of The Compounds

3a: IR(KBr, cm^{-1}); 3205 (N-H), 1686 (C=O), 1665, 1560 (C=N, C=C), 1260 (C-O-C)

^{1}H-NMR (250 MHz) (DMSO -d_6 δ, ppm); 1.95-2.10 (2H, m, protons C_2 of indan), 2.20 and 2.25 (3H, two s, CH_3) 2.80-2.95 (4H, m, protons C_1 and C_3 of indan), 4.75 and 5.15 (2H, two s, $COCH_2$), 6.85-7.05 (3H, m, protons C_3,C_4 and C_5 of phenyl), 7.25-7.35 (3H, m, protons C_4, C_6, C_7 of indan), 7.55, 7.70 (2H, d(J=7.86 Hz), protons C_2 and C_6 of phenyl), 10.50 (1H, br, NH).

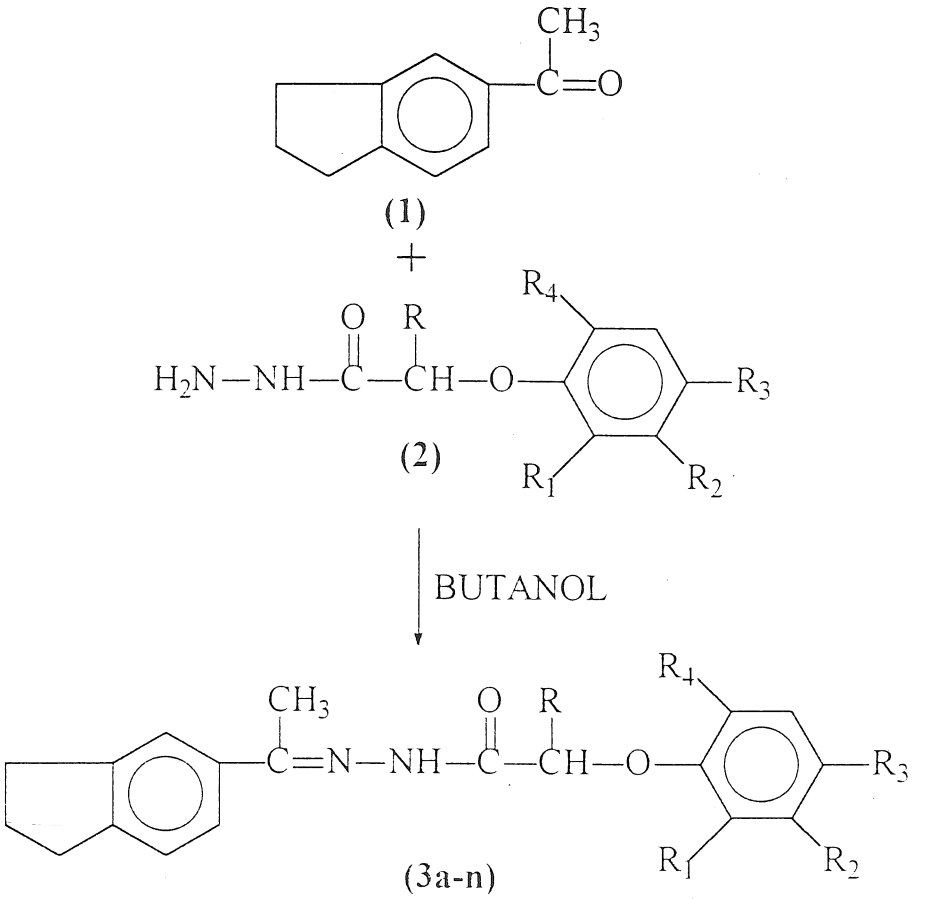
MASS(FAB)M+1: m/z: 309

Microanalytical Data: Anal. Calcd. for $C_{19}H_{20}N_2O_2$ (308.38): C, 74.00; H, 6.54; N, 9.08. Found: C, 73.87; H, 6.23; N, 9.00

3b: IR (KBr, cm^{-1}); 3195 (N-H), 1690 (C=O), 1670, 1575 (C=N, C=C), 1250 (C-O-C)

^{1}H-NMR (250 MHz) (DMSO -d_6 δ, ppm); 1.95-2.15 (2H, m, protons C_2 of indan), 2.20 and 2.25 (3H, two s, CH_3), 2.80-2.95 (4H,m protons C_1 and C_3 of indan) 4.75 and 5.20 (2H, two s, $COCH_2$), 6.95 (2H, d

*To whom correspondance should be adressed



Figure

(J=8.92 Hz) protons C_3 and C_5 of phenyl), 7.20-7.40 (3H, m, protons C_4, C_6, C_7 of indan), 7.60 (2H, d (J=7.20 Hz), protons, C_2 and C_6 of phenyl, 10.70 (1H, br, NH) *MASS(FAB) M+1*: m/z:343

Microanalytical Data: Anal. Calcd. for $C_{19}H_{19}ClN_2O_2$ (342.82): C, 66.56; H, 5.58; N, 8.17. Found: C, 66.23; H, 5.07; N, 8.02

3c: *IR (KBr, cm^{-1})*; 3189 (N-H), 1686 (C=O), 1667, 1570 (C=N, C=C), 1270- (C-O-C)

^{1}H-NMR (250 MHz) (DMSO -d_6 δ, ppm); 1.90-2.10 (2H, m, protons C_2 of indan), 2.25 2.30 (6H, two s, two CH_3), 2.80-2.95 (4H, m, protons C_1 and C_3 of indan), 4.70 and 5.10 (2H, two s, $COCH_2$), 6.75, 6.90 (2H, two d(J=8.41 Hz and J=8.46 Hz), protons C_3 and C_5 of phenyl), 7.00-7.25 (3H, m, protons C_4, C_6 and C_7 of indan), 7.50, 7.70 (2H, two d(J=7.85 Hz and 8.02 Hz), protons C_2 and C_6 of phenyl), 10.70 (1H, br, NH)

MASS (FAB) M+1: m/z: 323

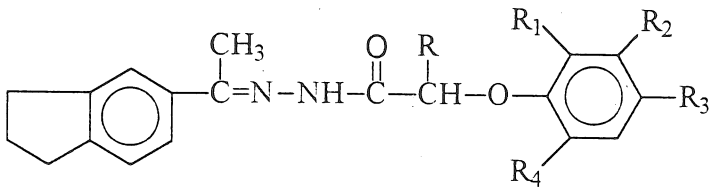
Microanalytical Data; Anal. Calcd. for $C_{20}H_{22}N_2O_2$ (322.40): C, 74.51; H, 6.87; N, 8.69. Found: C, 74.22; H, 6.88; N, 8.47

3d: *IR (KBr, cm^{-1})*; 3198 (N-H), 1691 (C=O), 1673, 1580 (C=N, C=C), 1285 (C-O-C)

^{1}H-NMR (250 MHz) (DMSO -d_6 δ, ppm); 1.95-2.15 (2H, m, protons C_2 of indan), 2.25 and 2.30 (3H, two s, CH_3), 2.80-2.95 (4H, m, protons C_1 and C_3 of indan), 4.70 and 5.40 (2H, two s, $COCH_2$), 7.00-7.40 (3H, m, protons C_4, C_6, C_7 of indan), 7.55 (2H, d (J=7.53 Hz), protons C_2 and C_6 of phenyl), 8.15, 8.30 (2H, two d (J=8.19 and 8.02 Hz) protons C_3 and C_5 of phenyl), 9.50 and 10.60 (1H, two s, NH) *MASS (FAB) M+1* :m/z: 354

Microanalytical Data; Anal. Calcd. for $C_{19}H_{19}N_3O$ (353.38): C, 64.57; H, 5.42; N, 11.89. Found: C, 64.55;

Table 1. Some Characteristics of Compounds



No	R	R_1	R_2	R_3	R_4	M.p.^{0}C	Yield %
3a	H	H	H	H	H	128	85
3b	H	H	H	Cl	H	161	67
3c	H	H	H	CH_3	H	135	80
3d	H	H	H	NO_2	H	148	77
3e	H	CH_3	H	H	CH_3	182	82
3f	CH_3	H	H	H	H	127	75
3g	CH_3	Cl	H	H	H	159	73
3h	CH_3	H	Cl	H	H	144	70
3ı	CH_3	H	H	Cl	H	153	69
3j	CH_3	NO_2	H	H	H	156	78
3k	CH_3	H	NO_2	H	H	121	76
3l	CH_3	H	H	NO_2	H	160	75
3m	CH_3	H	H	CH_3	H	119	69
3n	CH_3	H	H	OCH_3	H	126	82

H, 5.27; N, 11.92

3e: *IR (KBr, cm^{-1});* 3172 (N-H), 1689 (C=O), 1665, 1569 (C=N, C=C), 1280 (C-O-C)

^{1}H-NMR (250 MHz) (DMSO-d_6 δppm); 1.90-2.05 (2H, m, protons C_2 of indan), 2.15, 2.20, 2.25 (9H, tree s, tree CH_3), 2.83-2.95 (4H, m, protons C_1 and C_3 of indan), 4.40 and 4.75 (2H, two s, $COCH_2$), 6.80-7.65 (6H, m, aromatic protons), 10.30 and 10.65 (1H, two s, NH)

MASS (FAB) M+1 :m/z: 337

Microanalytical Data: Anal. Calcd. for $C_{21}H_{24}N_2O_2$ (336.43): C, 74.97; H, 7.19; N, 8.32. Found: C, 74.90; H, 7.00; N, 8.57

3f: *IR (KBr, cm^{-1})*; 3165 (N-H), 1679 (C=O), 1665, 1575 (C=N, C=C), 1250 (C-O-C)

^{1}H-NMR (250 MHz) DMSO-d_6 δ, ppm); 1.55 (3H, d (J=6.61 Hz), CH_3-C-O), 1.95-2.05 (2H, m, protons C_2 of indan), 2.20, 2.25 (3H, two s, CH_3), 2.70-2.95 (4H, t, protons C_1 and C_3 of indan), 5.10 and 5.70 (1H, two q(J=6.54 and 6.55 Hz) COCH), 6.80-7.05 (3H, m, protons C_3, C_4 and C_5 of phenyl), 7.20-7.45 (3H, m, protons C_4, C_6, C_7 of indan), 7.55 and 7.65 (2H, two d(J=6.88 Hz and J=7.85 Hz), protons C_2 and C_6 of phenyl), 10.60 (1H, br, NH)

MASS (FAB) M+1: m/z: 323

Microanalytical Data: Anal. Calcd. for $C_{20}H_{22}N_2O_2$ (322.40): C, 74.51; H, 6.87; N, 8.69. Found: C, 74.73; H, 6.53; N, 8.79

3g: *IR (KBr, cm^{-1})*; 3201 (N-H), 1690 (C=O), 1661, 1568 (C=N, C=C), 1290 (C-O-C)

^{1}H-NMR (250 MHz) DMSO-d_6 δ, ppm); 1.50-1.60 (3H, m, CH_3-C-O), 1.90-2.05 (2H, m, protons C_2 of indan) 2.20 and 2.25 (3H, two s, CH_3), 2.70-2.90 (4H, m, protons C_1 and C_3 of indan), 5.10 and 5.60 (1H, two q (J=6.50 and 6.54 Hz) COCH), 6.70-7.65 (7H, m, aromatic protons), 10.45 and 10.60 (1H, two s, NH)

MASS (FAB) M+1: m/z: 357

Microanalytical Data; Anal. Calcd. for $C_{20}H_{21}ClN_2O_2$ (356.85); C, 67.31; H, 5.93; N, 7.85. Found: C, 67.37; H, 5.76; N, 7.98

3h:*IR (KBr, cm^{-1})*; 31.90 (N-H), 1685 (C=O), 1664-1575 (C=N, C=C), 1150 (C-O-C)

^{1}H-NMR (250 MHz) DMSO-d_6 δ, ppm); 1.50 (3H, d (J=6.55 Hz), CH_3-C-O), 1.90-2.10 (2H, m, protons C_2 of indan), 2.20 and 2.25 (3H, two s, CH_3), 2.75-2.90 (4H, t, protons C_1 and C_3 of indan), 5.10 and 5.60 (1H, two q (J=6.49 and 6.54 Hz) COCH), 6.70-7.00 (3H, m, protons C_4, C_6, C_7 of indan), 7.15-7.40 (2H, m, protons C_4 and C_5 of phenyl), 7.45, 7.65 (2H, two d (J=8.19 Hz and J=8.07 Hz), protons C_2 and C_6 of phenyl), 10.70 (1H, br, NH)

MASS (FAB) M+1: m/z: 357

Microanalytical Data; Anal. Calcd. for $C_{20}H_{21}ClN_2O_2$ (356.85); C, 67.31; H, 5.93; N, 7.85. Found: C, 67.67; H, 5.64; N, 7.94

3i : *IR (KBr, cm^{-1})*; 3211 (N-H), 1691 (C=O), 1659, 1569 (C=N, C=C), 1275 (C-O-C)

^{1}H-NMR (250 MHz) DMSO-d_6 δ, ppm); 1.55 (3H, two d (J=6.55 Hz and J=6.44 Hz), CH_3-C-O), 2.00-2.15 (2H, m, protons C_2 of indan), 2.25-2.30 (3H, two s, CH_3), 2.80-2.95 (4H, t, protons C_1 and C_3 of indan), 5.10 and 5.65 (1H, two q (J=6.53 and 6.56 Hz) COCH), 6.80, 7.05 (2H, two d(J=8.98 Hz and J=8.96 Hz), protons C_3 and C_5 of phenyl), 7.25-7.45 (3H, m, protons C_4, C_6, C_7 of indan), 7.50-7.70 (2H, m, protons C_2 and C_6 of phenyl), 10.70 (1H, br, NH)

MASS (FAB) M+1: m/z: 357

Microanalytical Data; Anal. Calcd. for $C_{20}H_{21}ClN_2O_2$ (356.85); C, 67.31; H, 5.93; N, 7.85. Found: C, 67.43; H, 5.67; N, 7.72

3j : *IR (KBr, cm^{-1})*; 3266 (N-H), 1691 (C=O), 1665, 1577 (C=N, C=C), 1250 (C-O-C)

^{1}H-NMR (250 MHz) DMSO-d_6 δ, ppm); 1.60 (3H, d (J=6.63 Hz), CH_3-C-O), 1.95-2.10 (2H, m, protons C_2 of indan), 2.25, 2.30 (3H, two s, CH_3), 2.80-2.95 (4H, m, protons C_1 and C_3 of indan), 5.25 and 5.80 (1H, two q(J=6.54 and 6.54 Hz) COCH), 7.00-8.00 (7H, m, protons aromatic), 10.80 (1H, br, NH)

MASS (FAB) M+1: m/z: 368

Microanalytical Data: Anal. Calcd. for $C_{20}H_{21}N_3O_4$ (367.39): C, 65.38; H, 5.76; N, 11.43. Found: C, 65.73; H,5.52; N, 11.80

3k : *IR (KBr, cm^{-1})*; 3272 (N-H), 1677 (C=O), 1655, 1583 (C=N, C=C), 1250 (C-O-C)

^{1}H-NMR (250 MHz) DMSO-d_6 δ, ppm); 1.50-1.65 (3H, m, CH_3-C-O), 1.95-2.05 (2H, m, protons C_2 of indan), 2.25, 2.30 (3H, two s, CH_3), 2.80-2.95 (4H, m, protons C_1 and C_3 of indan), 5.20 and 5.90 (1H, two q(J=6.53 and 6.50) COCH), 7.20-7.90 (7H, m, aromatic protons), 9.50 and 10.70 (1H, two s, NH)

MASS (FAB) M+1: m/z: 368

Microanalytical Data: Anal. Calcd. for $C_{20}H_{21}N_3O_4$ (367.39): C, 65.38; H, 5.76; N, 11.43. Found: C, 65.02; H,5.57; N, 11.09

3l : *IR (KBr, cm^{-1})*; 3226 (N-H), 1697 (C=O), 1670, 1573 (C=N, C=C), 1280 (C-O-C)

^{1}H-NMR (250 MHz) DMSO-d_6 δ, ppm); 1.60 (3H, two s, CH_3-C-O), 1.90-2.05 (2H, m, protons C_2 of indan), 2.25, 2.30 (3H, two s, CH_3), 2.80-2.95 (4H, m, protons C_1 and C_3 of indan), 5.20 and 5.80 (1H, two q (J=6.55 and 6.52 Hz) COCH), 6.95-7.25 (3H, m, protons C_4, C_6, C_7 of indan), 7.50 and 7.60 (2H, two d (J=10.99 Hz and J=7.92 Hz), protons C_2 and C_6 of phenyl), 8.15, 8.25 (2H, two d(J=6.96 Hz and J=7.02 Hz), protons C_3 and C_5 of phenyl), 10.80 (1H, br, NH)

MASS (FAB) M+1: m/z: 368

Microanalytical Data: Anal. Calcd. for $C_{20}H_{21}N_3O_4$ (367.39): C, 65.38; H, 5.76; N, 11.43. Found: C, 65.27; H,5.87; N, 11.72

3m : *IR (KBr, cm^{-1})*; 3207 (N-H), 1696 (C=O), 1664, 1598 (C=N, C=C), 1270 (C-O-C)

^{1}H-NMR (250 MHz) DMSO-d_6 δ, ppm); 1.50 (3H, d(J=6.65 Hz), CH_3-C-O), 1.95-2.10 (2H, m, protons C_2 of indan), 2.20, 2.35 (6H, m, two CH_3), 2.80-2.95 (4H, t, protons C_1 and C_3 of indan), 4.95 and 5.60 (1H, two q(J=6.55 and 6.51) COCH), 6.70, 6.85 (2H, two d (J=8.52 Hz and J=8.50 Hz), protons C_3, and C_5 of phenyl), 7.00 and 7.25 (2H, m, protons C_4, C_6, C_7 of indan), 7.55, 7.65 (2H, two d(J=9.27 Hz and J=8.90 Hz), protons C_2 and C_6 of phenyl), 10.50 and 10.70 (1H, two s, NH)

MASS (FAB) M+1: m/z: 337

Microanalytical Data: Anal. Calcd. for $C_{21}H_{24}N_2O_2$ (336.43): C, 74.97; H, 7.19; N, 8.32. Found: C, 75.32; H,6.98; N, 8.43

3n : *IR (KBr, cm^{-1})*; 3179 (N-H), 1691 (C=O), 1660, 1578 (C=N, C=C), 12750 (C-O-C)
^{1}H-NMR (250 MHz) DMSO-d_6 δ, ppm); 1.55 (3H, two d (J=6.54 and J=6.57 Hz), CH_3-C-O), 1.95-2.05 (2H, m, protons C_2 of indan), 2.25, 2.30 (3H, two s, CH_3), 2.80-2.95 (4H, m, protons C_1 and C_3 of indan), 3.75 and 3.80 (3H, two s, OCH_3), 5.00 and 5.65 (1H, two q (J=6.48 and 6.55 Hz) COCH) , 6.69-7.65 (7H, m, aromatic protons), 10.35 and 10.70 (1H, two s, NH)
MASS (FAB) M+1: m/z: 353
Microanalytical Data: Anal. Calcd. for $C_{21}H_{24}N_2O_3$ (352.43): C, 71.57; H, 6.86; N,7.95. Found: C, 71.90; H,6.88; N, 8.16

Antituberculosis Activity

Primary screening was conducted at 12.5 µg/ml against Mycobacterium tuberculosis H3 7 Rv in BACTED 12 B medium. Antituberculosis activities of the compounds were examined by TAACF according to the BACTED 460 radiometric system (13, 14).

Results and Discussion

In the present work, 14 new 5-acetylindan aryloxyacetohydrazone derivatives were synthesized by reacting 5-acetylindan with aryloxyacetohydrazides.

The structure of the compounds were elucidated by IR, ^{1}H-NMR, MASS spectra and elemental analyses. In the IR spectra of all the compounds N-H and C=O bands were observed at about 3450-3200 cm^{-1} and 1680 cm^{-1}, respectively. The ^{1}H-NMR spectra all of the compounds gave the peaks characteristic for protons C_1, C_2, C_3, of indan. We observed paired peaks for protons of CH_3-C=N, $COCH_2$, COCH and NH, corresponding to trans(E) and cis(Z) forms of the compounds. For each compound, the intensities of these paired peaks differed from others, due to the variable amounts of E and Z, which are usually unequal.

A low antituberculosis activity (MIC=12.5 µg/ml) was observed only for compounds 3a, 3b, 3d in the range 23.35 and 26% respectively. Rifampicine showed inhibition values (at 0.25 µg/ml) in the range 98%.

Acknowledgements

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