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Synthesis and Biological Evaluation of New 2-(5-fluoro-2-methyl-lH-inden-3-yl) Acetohydrazide Derivatives

R. B. Kawde[1], D. V. Patil[2], J. K. Patil[3] and V. D. Jadhav[4]

Associate Professor, Department of Chemistry, Kirti M. Doongursee College, Dadar (W), Mumbai, India[1]

Assistant Professor, Department of Chemistry, Kirti M. Doongursee College, Dadar (W), Mumbai, India[2]

Research Scholar, Department of Chemistry, Kirti M. Doongursee College, Dadar (W), Mumbai, India[3]

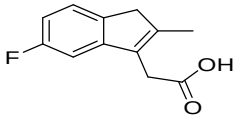
Research Scholar, Department of Chemistry, Kirti M. Doongursee College, Dadar (W), Mumbai, India[4]

ABSTRACT: Compound 2-(5-fluoro-2-methyl-1H-inden-3-yl) acetohydrazide was reacted with various substituted aldehydes at elevated temperature in methanol to yield substituted N-benzylidene-2-(2-methyl-1H-inden-3-yl) acetohydrazide as sole product. It is also observed that reaction went to completion during 8-10 hrs at reflux condition without adding any acid or base catalyst. The reaction condition found general for all the substituted benzaldehyde. These derivatives are found more than 80% in yield. These new compounds are studied for the antimicrobial activity.

KEYWORDS: Acetohydrazide, methanol , antimicrobial activity.

I. INTRODUCTION

The literature survey shows the utility of indene-acetic acid compounds as the pharmaceutical as well as fungicide and herbicide activity[1]. The Fluorinated organic molecules are familiar for a wide range of biological functions[2-4]. In the present paper the imino derivatives of hydrazide of 5-fluoro-2-methyl indene-3-acetic acid are prepared and studied for the biological evaluation. Acetohydrazides show anti-tuberculosis activity[5]. This Information provoked us to synthesise fluorine substituted Indene-3-aceticacid and its relative derivatives which could possibly show enhanced biological activity. Due to its versatile nature work was initiated from compound-1 which is the key raw material of Sulindac.

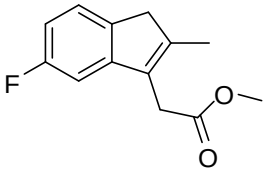


Compound-1

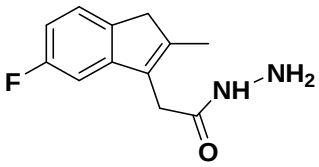
II. MATERIALS AND METHODS

A. R. grade or purified L. R. grade chemicals were used for the synthesis of 2-(5-fluoro-2- methyl-1H-inden-3-yl)acetohydrazide.

Synthesis of Methyl-5-fluoro-2-methyl-1H-3-indenylacetate: The esterification of 2-(5-fluoro-2-methyl-1H-inden-3-yl) acetic acid (1) was carried out by refluxing compound-1 in excess of methanol in presence of the catalytic amount of sulphuric acid to form compound-2.



Compound-2



Compound-3

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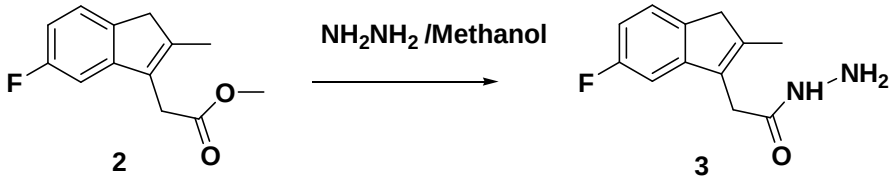
The hydrazinolysis of compound-2 was carried out in hydrazine hydrate in methanol to form compound-3 which is further used for the preparation of Schiff bases with substituted aldehydes.

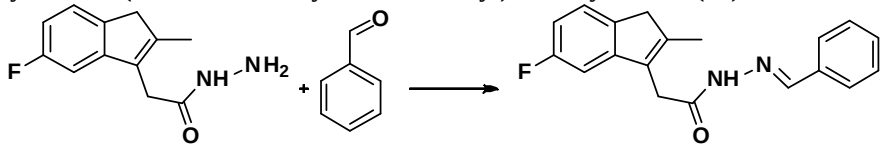
Preparation of 2-(5-fluoro-2-methyl-1H-inden-3-yl) acetohydrazide (3):



2 3

In one litre three neck flask was a Methyl-5-fluoro-2-methyl-1H-3-indenylacetate(**2**) (100 g, 0.45 mol) containing methanol (500 mL) at room temperature and stirred for 10 min. Hydrazine hydrate (10 g, 0.31mol) was then added drop wise and resulting mixture was refluxed for 10 hrs. Progress of the reaction was monitored by TLC (20 % Ethyl acetate in Hexane). After completion of the reaction, the content was cooled to 10°C for 2 hrs and filtered. Crude solid material was further recrystallized from ethanol to obtain 2-(5-fluoro-2-methyl-1H-inden-3-yl)acetohydrazide (**3**) as white solid (85g, 85 %). (Melting Point:175-178^{0}C). The structure of the compound (3) was confirmed by spectroscopic techniques like IR, ^{1}H NMR, ^{13}C NMR and mass spectroscopy.

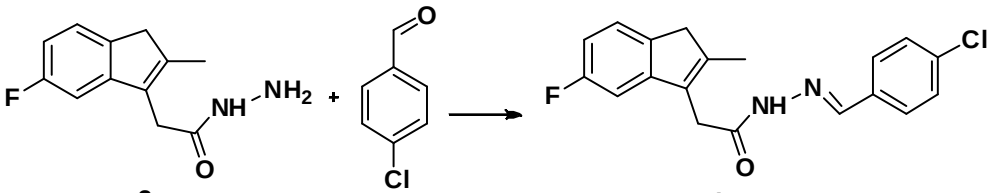
Preparation of N-benzylidene-2-(5-fluoro-2-methyl-1H-inden-3-yl) acetohydrazide (4a)



3 4a

To a well stirred suspension of compound-3 (5g, 22.7 mmol) in methanol (50 ml), benzaldehyde (2.53g, 23.84mmol) was added in one lot and refluxed for 10 hrs with constant stirring. Initially, reaction mass was clear. After 4 hrs solid material started precipitating out through the solution. This reaction mass was then cooled between 5- 10°C for about 1 hrs & filtered. Crude solid material was recrystallized from ethanol to yield as white crystals 4a (5.95g, 85%). (Melting Point: 210-213°C). The structure of this compound (**4a**) was confirmed by IR, ^{1}H NMR, ^{13}C NMR and mass spectroscopy .

Preparation of N-(4-chlorobenzylidene)-2-(5-fluoro-2-methyl-1H inden-3-yl) acetohydrazide (4b):



3 4b

To a well stirred suspension of compound-3 (5g, 22.7 mmol) in methanol (50 ml), 4-chloro benzaldehyde (3.2g, 22.7mmol) was added in one lot and refluxed for 10 hrs with constant stirring. Initially, reaction mass was clear. After 6 hrs solid material started was precipitated out through the solution. This reaction mass was then cooled between 5-10°C for about 1 hrs & filtered. Crude solid material was recrystallized from ethanol to yield as white crystals **4b** (6.5g, 84%).(Melting Point: 256-257^{o}C). The structure of this compound (**4b**) was confirmed by IR, ^{1}H NMR and mass spectroscopy.

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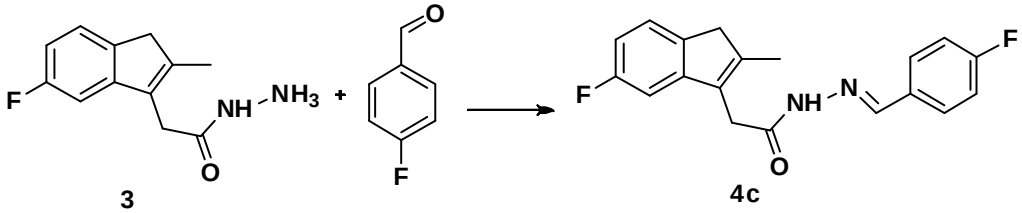
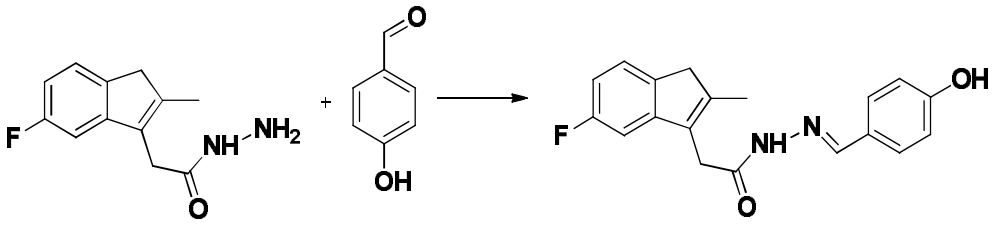
Preparation of N-(4-fluorobenzylidene)-2-(5-fluoro-2-methyl-1H-inden-3-yl) acetohydrazide (4c):



3 4c

To a well stirred suspension of compound-3 (5g, 22.6 mmol) in methanol (50 ml), 4-fluoro benzaldehyde (2.96g, 23.84mmol) was added in one lot and refluxed for 10 hrs with constant stirring. Initially, reaction mass was clear. After 5 hrs solid material was precipitated out through the solution. This reaction mass was then cooled between 5- 5- 10°C for about 1 hrs & filtered. Crude solid material was recrystallized from ethanol to yield as white crystals **4c** (6.3g, 86%). (Melting Point: 237-240°C). The structure of this compound (**4c**) was confirmed by IR,^{1}H NMR and mass spectroscopy.

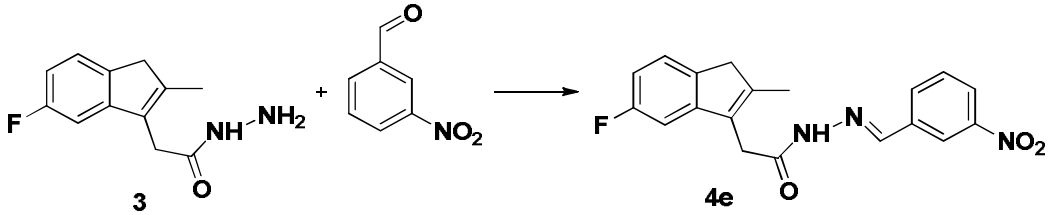
Preparation of N'-(4-hydroxybenzylidene)-2-(5-fluoro-2-methyl-1H-inden-3-yl)acetohydrazide (4d):



3 4d

To a well stirred suspension of compound-3 (5g, 22.7 mmol) in methanol (50 ml), 4-4-hydroxy benzaldehyde (2.91, 23.84 mmol) was added in one lot and refluxed for 12 hrs with constant stirring. Initially, reaction mass was clear. After 6 hrs. Solid material was precipitated out through the solution. This reaction mass was then cooled between 5-10°C for about 2 hrs & filtered. Crude solid material was recrystallized from ethanol to yield as white crystals **4d** (6.0g, 82%).(Melting Point: 220-222°C). The structure of this compound **(4d)** was confirmed by IR, ^{1}H NMR and mass spectroscopy.

Preparation of N'-(3-nitrobenzylidene)-2-(5-fluoro-2-methyl-1H-inden-3-yl)acetohydrazide (4e):



3 4e

To a well stirred suspension of compound-3 (5g, 22.7 mmol) in methanol (50 ml), 4-nitro benzaldehyde (3.6g, 23.84mmol) was added in one lot and refluxed for 12 hrs with constant stirring. Initially, reaction mass was clear, but after 6hrs. Solid material was precipitated out through the solution. This reaction mass was then cooled between 5-10°C for about 2 hrs & filtered. Crude solid material was recrystallized from ethanol to yield as white crystals **4e (6.5, 81%). (**Melting Point: 210-212°C). The structure of this compound **(4e)** was confirmed by IR, ^{1}H NMR and mass spectroscopy.

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III. RESULTS AND DISCUSSIONS

The newly synthesised compounds are characterised by various analytical and spectroscopic methods as follows.

Table:1 Analytical Data

Compounds	Molecular formula	Molecular Weight	Colour	Observed/ (Calculated)					*m/z* $[M+1]^+$
				%C	%H	%Cl	%F	%N	
3	$C_{12}H_{13}FN_2O$	220.24	Off White	64.95 (65.44)	5.85 (5.95)	-	8.55 (8.63)	12.80 (12.72)	221.10
4a	$C_{19}H_{17}FN_2O$	308.35	White	73.85 (74.01)	5.40 (5.56)	-	6.0 (6.16)	8.91 (9.08)	309.07
4b	$C_{19}H_{16}ClFN_2O$	342.80	White	65.81 (66.57)	4.6 (4.70)	10.34 (10.28)	5.42 (5.55)	8.01 (8.17)	343.07
4c	$C_{19}H_{16}F_2N_2O$	326.34	White	68.87 (69.93)	4.86 (4.94)	-	11.43 (11.64)	8.41 (8.58)	327.07
4d	$C_{19}H_{17}FN_2O_2$	324.35	White	69.88 (70.36)	5.12 (5.28)	-	5.71 (5.86)	8.49 (8.64)	325.07
4e	$C_{19}H_{16}FN_3O_3$	353.35	White	63.98 (64.58)	4.39 (4.56)	-	5.24 (5.38)	11.78 (11.89)	355.06

Compound (3): ^{1}H NMR Spectrum (300 MHz, DMSO): δ 2.1(s, 3H,-CH_3), 3.2(s, 2H, CH_2), 3.3(s, 2H, CH_2), 4.2(s, 2H, NH_2), 6.8-7.3(m,3H,Ar-H) and 9.2 (s, 1H, -NH).
^{13}C NMR Spectrum (500 MHz, DMSO: 13.5, 31.3, 42.2, 106.6, 112.2, 125.6, 132.9, 138.7, 146.4, 150.0, 165.2 and 170.8 ppm.
IR Spectrum (KBr):- 786, 933, 1010, 1172, 1273, 1365, 1465, 1535(C=C), 1627(C=O), 2901(C-H), 3039 (-NH) and 3189(-NH_2)cm^{-1}.

Compound (4a) : ^{1}H NMR (Varian, 600MHz), (DMSO) δ 2.1(s, 3H,-CH_3), 3.3(s, 2H, CH2), 3.9(s, 2H, CH_2), 6.8-7.7(m,8H,Ar-H), 8.0and 8.2(s 1H,N=CH-) and 11.4 and 11.6(s,1H, -NH, two separate peaks appears due to *syn* and *anti* conformation).
^{13}C NMR Spectrum (600 MHz, DMSO): 15.2, 32.1, 42.8, 106.7, 110.4, 124.5, 126.9, 128.4, 129.0, 131.7, 136.1, 138.7, 143.6, 144.6, 148.9, 161.4, 163.6, 166.3 and 171.3 ppm.
IR (KBr, cm^{-1}) :752, 800, 869, 916, 1134, 1172, 1249, 1398, 1477, 1593, 1615(C=N), 1690(C=O), 2845,2889, 2962, (-CH), 3084, 3176 (-NH).
Compound(4b): ^{1}H NMR (Varian, 600MHz), (DMSO) δ 2.1(s, 3H,-CH_3),3.4(s, 2H, CH_2), 3.9(s, 2H,-CH_2), 6.8-7.8 (m,7H,Ar-H), 8.0and 8.25(s, 1H, N=CH-) and 11.5and 11.7(s,1H, -NH, two separate peaks appears due to *syn* and *anti* conformation).
IR (KBr, cm^{-1}):756, 800,821, 918, 1087, 1172, 1249, 1350, 1366, 1400, 1475, 1593, 1612(C=N), 1670(C=O), 2887, 2966(-CH), 3093, 3170 (-NH).
Compound(4c): ^{1}H NMR (Varian, 600MHz), (DMSO) δ 2.1(s, 3H,-CH_3),3.4(s, 2H, CH_2), 3.9(s, 2H,-CH_2), 6.8-7.7 (m,7H,Ar-H), 8.0and 8.25(s, 1H, N=CH-) and 11.5and 11.7(s,1H, -NH, two separate peaks appears due to *syn* and *anti* conformation).
IR (KBr, cm-1): 831, 909, 918, 1018, 1172, 1247, 1354, 1396, 1475, 1502, 1616(C=N), 1675(C=O), 2837,2889, 2968, 2966(-CH), 3082, 3165 (-NH).

Compound (4d): ^{1}H NMR (Varian, 600MHz), (DMSO) δ 2.1(s, 3H,-CH_3),3.4(s, 2H, CH_2), 3.9(s, 2H,-CH_2), 6.8-7.7 (m, 7H, Ar-H), 8.0and 8.25(s, 1H, N=CH-), 9.9(s, 1H, -OH), 11.2and 11.4(s,1H, -NH, two separate peaks appears due to *syn* and *anti* conformation).
IR (KBr, cm^{-1}) 837, 916, 1064, 1163, 1246, 1305, 1448, 1475, 1510, 1558, 1606(C=N), 1680(C=O), 2887, 2904, 2966(-CH), 3062, 3217 (-NH), 3311(-OH).
Compound (4e): ^{1}H NMR (500 MHz, DMSO) δ 2.1(s, 3H,-CH_3),3.3(s, 2H, CH_2), 4.0(s, 2H,-CH_2), 6.8-8.2 (m,7H,Ar-H), 8.3 and 8.4(s, 1H, N=CH-) and 11.7and 11.9(s,1H, -NH, two separate peaks appears due to *syn* and *anti* conformation).

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IR (KBr, cm^{-1}):- 790, 864, 1185, 1210, 1350(-NO_2, sym), 1392, 1473, 1533(-NO2, asym), 1610(C=N), 1680(C=O), 2883, 2972(-CH), 3178 (-NH).

Antimicrobial studies: The newly synthesized 2-(5-fluoro-2-methyl-l*H*-inden-3-yl)acetohydrazide derivatives were screened for their anti-microbial activities such as anti-bacterial and anti-fungal activity against selected microorganisms.

Table 2: Observations for antibacterial activity

Compound	Substituent on Aromatic Aldehyde	MIC(µg/mL)	
		E. coli	*S. aureus*
4a	H	100	120
4b	p-Cl	100	80
4c	p-F	140	100
4d	p-OH	22	20
4e	m-NO_2	60	70
Standard: Ciprofloxacin		<22	<18

Table 3: Observations for antifungal activity

Compound	Substituent on Aromatic Aldehyde	MIC(µg/mL)	
		C. albicans	*A. niger*
4a	H	80	90
4b	p-Cl	90	100
4c	p-F	80	90
4d	p-OH	24	28
4e	m-NO_2	24	28
Standard: Fluconazole		<22	<24

IV. ACKNOWLEDGEMENT

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