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Synthesis and Biological Activities of 3-Carboxy-7-Methoxy-1-Tetralone Derivatives: Part-I

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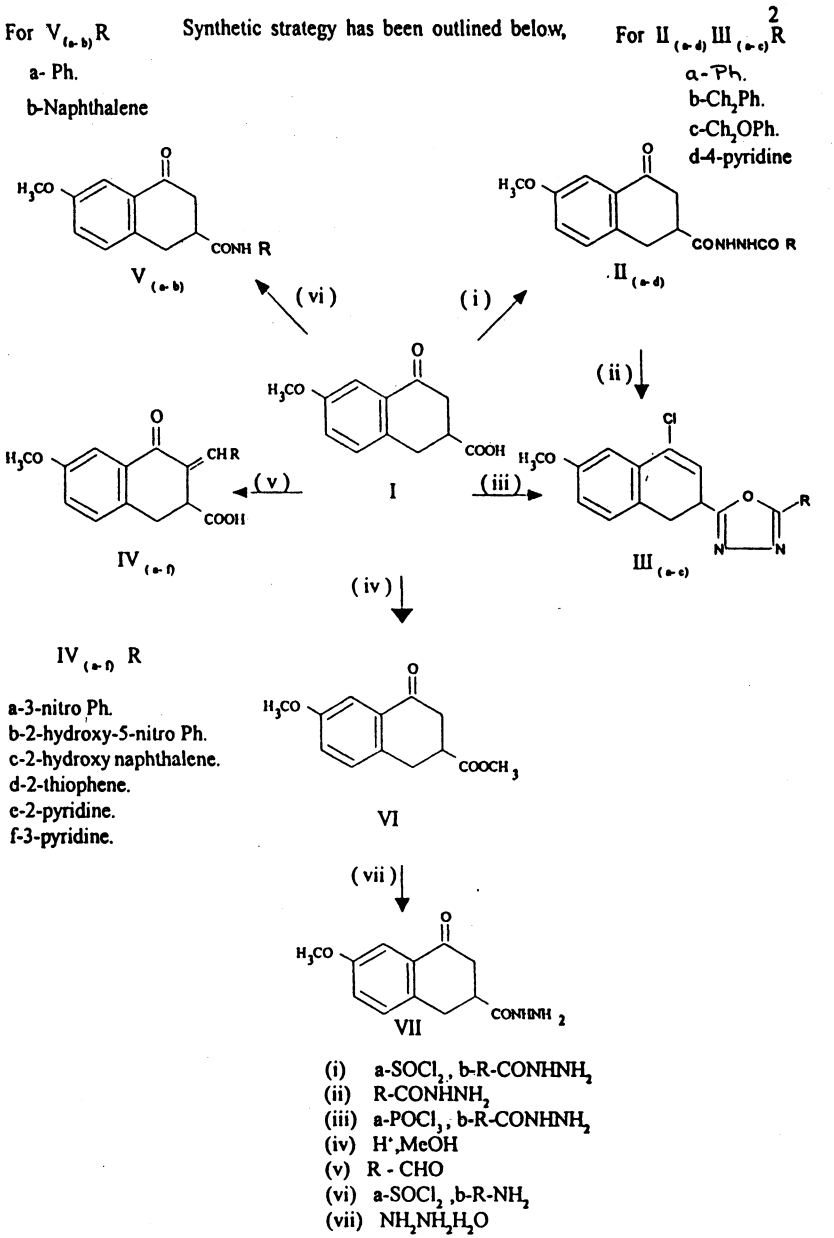
The acid chloride of 3-carboxy-7-methoxy-1-tetralone (I) was condensed with various benzhydrazides to yield substituted oxadiazoles *via* dioxobutane derivatives. I, when reacted with aromatic aldehydes produced the corresponding benzylidene derivatives. Treatment of I with thionyl chloride, phosphorus oxychloride and primary amine gave the corresponding 3-anilide derivatives. Treatment of II with hydrazine hydrate produced 3-hydrazocarbonyl-7-methoxy-1-tetralone VII. VII with acylating reagents *viz.*, acetyl chloride, gave 3-N-(β-monoacetyl) hydrazocarbonyl-7-methoxy-1-tetralone. Synthesis of substituted imidazolines from the condensation of VII and substituted oxazolinones. Synthesis of substituted quinazolin-4(3H)-ones from the condensation of VII and substituted benzoxazones. Condensation of VII with aldehydes gave the corresponding 3-arylidene hydrazocarbonyl-7-methoxy-1-tetralone. Treatment of VII with potassium thiocyanate in dilute hydrochloric acid gave thiosemicarbazide derivative.

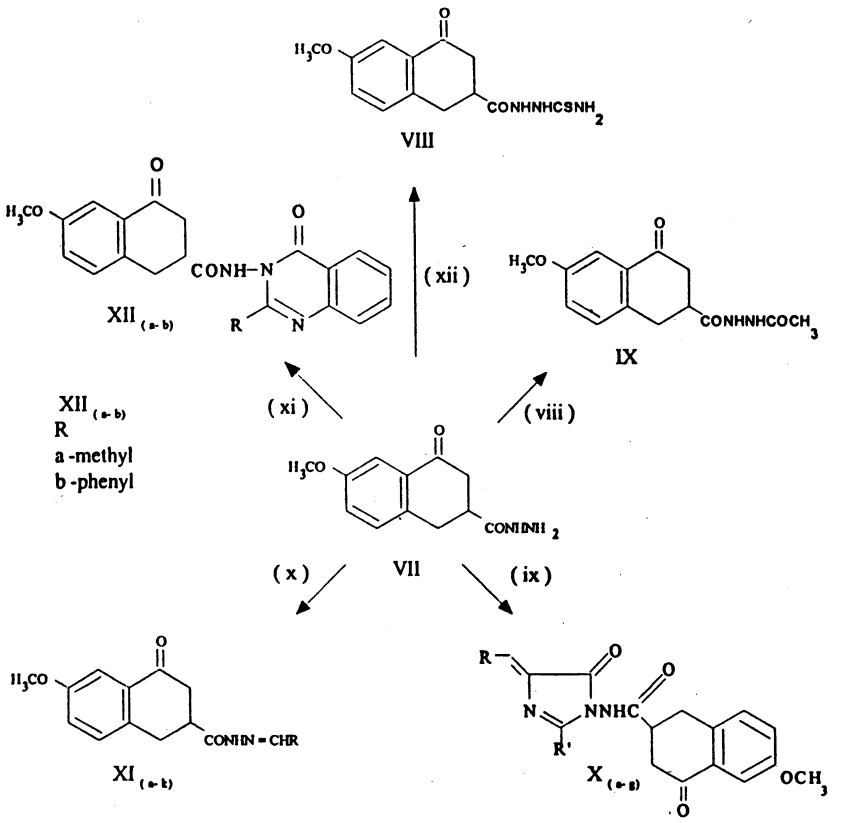
INTRODUCTION

A large number of substituted hydrazides and their condensation products, including heterocyclic compounds having 5- or 6-membered rings, are known for various biological activities[1]. The present paper reports the synthesis of hydrazide and its condensation products from 3-carbmethoxy-7-methoxy-1-tetralone[2] **(VI).** With a view to synthesis of analogous compounds with possible antibacterial properties, the acid chloride of 3-carboxy-7-methoxy-1-tetralone **(I)** was condensed with various benzhydrazides to yield substituted oxadiazoles $\mathbf{III_{a-c}}$ via dioxobutane derivatives $\mathbf{II_{a-d}}$. Benzylidene derivatives were synthesized from **I** and aromatic aldehydes such as 3-nitrobenzaldehyde, 2-hydroxy-5-nitrobenzaldehyde, 2-hydroxy-1-naphthaldehyde, pyridine-2-aldehyde, pyridine-3-aldehyde, thiophene-2-aldehyde. **I** was refluxed with thionyl chloride followed by addition of primary amine (aniline and 1-naphthylamine) to give 3-anilide- and 3-naphthanilide-7-methoxy-1-tetralone $\mathbf{V_{a-b}}$ respectively. The same products were synthesized in better yields through one pot procedure, on treament of $POCl_3$ with amine followed by addition of **I** at room temperature.

Treatment of **VI** with hydrazine hydrate gave the corresponding 3-hydrazocarbonyl-7-methoxy-1-tetralone **VII.** Treatment of **VII** with potassium thiocy-

anate in dilute hydrochloric acid gave thiosemicarbazide derivative **VIII**. Refluxing **VII** with acetyl chloride/acetic anhydride gave 3-N-(β-monoacetyl) hydrazocarbonyl-7-methoxy-1-tetralone **IX**. Synthesis of substituted imidazolines $\mathbf{X}_{a-g}$ from the condensation reaction of **VII** and substituted oxazolinones.[3] Condensation of **VII** in ethanol with aldehydes (benzaldehyde, *p*-anisaldehyde, piperonal, 4-dimethylaminobenzaldehyde, octonaldehyde, vanillin, salicylaldehyde, 2-hy-





XI a-k	R
a	-Ph.
b	2-hydroxy Ph.
c	4-dimethyl amino Ph.
d	4-methoxy Ph.
e	3,4-methylene dioxy Ph.
f	4-CH(CH$_2$)$_6$CH$_3$
g	4-hydroxy-3-methoxy Ph.
h	2-hydroxy-5-nitro Ph.
i	2-hydroxy naphthalene.
j	2-thiophene.
k	3-pyridine.

(viii) CH_3COCl / $(CH_3CO)_2O$
(ix) subs. oxazazolinone
(x) R-CHO
(xi) subs. benzoxazone
(xii) KSCN, dil. HCl.

X a-g	R	R'
a	-Ph.	-CH$_3$
b	-Ph.	-Ph.
c	2-Br-Ph.	-Ph.
d	4-CH(CH$_2$)$_6$CH$_3$	-Ph.
e	3-NO$_2$-Ph.	-Ph.
f	2-thiophene.	-Ph.
g	3,4-methylene--dioxy Ph.	-Ph.

droxy-5-nitrobenzaldehyde, 2-hydroxy-1-napthaldehyde, pyridine-3-aldehyde and thiophene-2-aldehyde), gave the corresponding 3-arylidene hydrazocarbonyl-7-methoxy-1-tetalone **XI$_{a-k}$**. Synthesis of substituted quinazolin-4(3H)-ones **XII$_{a-b}$** from the condensation reaction of **VIII** and substituted benzoxazones.[4]

EXPERIMENTAL

All melting points of the compounds synthesized are uncorrected. Micro analyses of the compounds were carried out on a Colemn instrument IR spectra (KBr) were recorded on a Perkin-Elmer Paragon-2000 instrument. NMR spectra were recorded on an AMX-500 Bruker instrument (500 Hz) and Varian instrument (300 Hz) using TMS as the internal standard. All the compounds gave satisfactory C, H and N analyses.

***1-Aryl-4-(7-methoxy-1-tetralone)-2,3-diaza-1,4-dioxobutane* (IIa–d)**

A mixture of **I** (2.17 g, 0.01 mol) and $SOCl_2$ (10 mL) was refluxed for 4 h. $SOCl_2$ was removed by distillation, the residue was dissolved in benzene and added dropwise to a solution containing aryl hydrazide (0.01 mol) in benzene (10 mL) and stirred for 3–4 h. The solid separated out was crystallised from DMF-methanol (1 : 1).

***2-Aryl-5-(7-methoxy-1-tetralone)-1,3,4-oxadiazole* (IIIa–c)**

Method I: *1-aryl-4-(4-chloro-6-methoxy-1,2-dihydro naphthalene)-2,3-diaza-1,4-dioxobutane* **(IIa–d)** (0.01 mol) and $POCl_3$ (0.05 mol) were heated for 4–5 h on a steam bath. The reaction mixture was then poured into ice-cold water and the resulting solid was crystallised from DMF-methanol (1 : 1).

Method II: A mixture of **I** (2.17 g, 0.01 mol), aryl hydrazide (0.01 mol) and $POCl_3$ (0.05 mol) were heated for 4–5 h on a steam bath. The reaction mixture was then poured into ice-cold water and the resulting solid was crystallised from DMF-methanol (1 : 1).

***2-Benzylidene-3-carboxy-7-methoxy-1-tetralone* (IVa–f)**

A mixture of **I** (2.18 g, 0.001 mol) and each of aromatic aldehyde (0.01 mol) were dissolved in ethanol (15 mL) and KOH solution (15 g in 7.5 mL water). The reaction mixture was shaken for 2 h; it was then acidified with dilute HCl. The solid separated out was crystallised from ethyl acetate.

***3-Anilide-7-methoxy-1-tetralone derivatives* (Va–b).**

By using $SOCl_2$*:* A mixture of **I** (2.17 g, 0.01 mol) and $SOCl_2$ (10 mL) was refluxed for 4 h. $SOCl_2$ was removed by distillation; the residue was dissolved in benzene and added dropwise to a cooled (10°C) solution containing primary amine (0.01 mol) in benzene. The solid separated out was crystallised from methanol (75%).

By using $POCl_3$*:* To a stirred solution of $POCl_3$ (0.75 g, 0.005 mol) was added gradually dry ethanol (0.3 mL, 0.005 mol) followed by primary amine (0.01 mol) and the mixture was stirred for 30 min. **I** (2.17 g, 0.01 mol) in triethylamine (1.5 g, 0.01 mol) and dry methylene chloride (25 mL) was slowly added at room temperature for 2 h. The reaction mixture was then poured in water and extracted from methylene chloride. After drying over anhydrous sodium sulphate, it was evaporated to dryness to give anilide derivative, which was crystallised from methanol (75%).

***3-Hydrazocarbonyl-7-methoxy-1-tetralone* (VII)**

A mixture of VI (4.68 g, 0.02 mol) and hydrazine hydrate (98%, 1.5 mL, 0.03 mol) in absolute ethanol (50 mL) were refluxed for 4 h. The reaction mixture was cooled and the separated solid was crystallised from ethanol.

***3-Thiosemicarbazide carbonyl-7-methoxy-1-tetralone* (VIII)**

A mixture of **VII** (0.01 mol) and dil. HCl (10 mL in 50 mL water) were refluxed for 4 h. The reaction mixture was cooled the separated solid was crystallised from ethanol.

***3-N-(β-monoacetyl) hydrazocarbonyl-7-methoxy-1-tetralone* (IX)**

A mixture of **VII** (2.34 g, 0.01 mol) and acetyl chloride (0.78 g, 0.01 mol) in dry pyridine (10 mL) were refluxed for 0.5 h and kept overnight at 10°C. The separated solid was crystallised from ethyl acetate.

***4-Benzylidene-1-(3-carboxamidyl-7-methoxy-1-tetralone)-2-substituted-5-oxo - 2-imidazoline derivatives* (Xa–g)**

A mixture of **VII** (0.234 g, 0.001 mol) and substituted oxazolinone derivative (0.001 mol) in pyridine (5 mL) were refluxed for about 6–8 h (TLC). After the completion of the reaction, the reaction mixture was cooled and the solid that separated was crystallised from ethanol-DMSO (1 : 1) mixture.

***3-Arylidene hydrazocarbonyl-7-methoxy-1-tetralone* (XIa–k)**

A mixture of **VII** (0.234 g, 0.001 mol) and aldehyde (0.001 mol) in ethanol (5 mL) and a few drops of piperidine were refluxed for about 3–6 h (TLC). After the completion of the reaction, the reaction mixture was cooled and the solid that separated was crystallised from ethanol-DMSO (1 : 1) mixture.

***2-Substituted-3-(3-carboxamidyl-7-methoxy-1-tetralone)-quinazolin-4(3H)-ones* (XIIa–b)**

A mixture of VII (0.234 g, 0.001 mol) and substituted benzoxazone derivative (0.001 mol) in pyridine (5 mL) were refluxed for about 6–8 h (TLC). After the completion of the reaction the reaction mixture was cooled and the solid that separated was crystallised from ethanol-DMSO (1 : 1) mixture.

TABLE-1
PHYSICAL DATA OF THE PRODUCTS

Compound No.	m.p. (°C)	Colour	Yield (%)		m.f.
IIa	166–68	light brown	61.53		$C_{19}H_{18}N_2O_4$
IIb	154–55	light brown	56.81		$C_{20}H_{20}N_2O_4$
IIc	175–78	brown	60.32		$C_{20}H_{20}N_2O_5$
IId	190–92	brown	68.96		$C_{18}H_{17}N_3O_4$
IIIa	169–70	brown	Using methods		
			I	II	
			9.02	8.56	$C_{19}H_{15}ClN_2O_2$

Compound No.	m.p. (°C)	Colour	Yield (%)		m.f.
IIIb	193–94	brown	12.72	8.84	$C_{20}H_{17}ClN_2O_2$
IIIc	196–98	brown	10.28	9.16	$C_{20}H_{17}ClN_2O_3$
IVa	210–12	orange	75.54		$C_{19}H_{15}NO_6$
IVb	126–28	yellow	84.10		$C_{19}H_{15}NO_7$
IVc	197–99	yellow	61.70		$C_{23}H_{18}O_5$
IVd	215–16	pale yellow	76.75		$C_{17}H_{14}O_4S$
IVe	161–62	pale yellow	22.00		$C_{18}H_{15}NO_4$
IVf	195–96	pale yellow	55.66		$C_{18}H_{15}NO_4$
Va	189–90	colourless	using		
			$POCl_3$	$SOCl_2$	
			88.00	65.50	$C_{18}H_{17}NO_3$
Vb	140–41	violet	86.00	72.00	$C_{22}H_{19}NO_3$
VII	158–60	colourless	91.80		$C_{12}H_{14}N_2O_3$
VIII	140–42	colourless	81.22		$C_{13}H_{15}N_3O_3S$
IX	278–79	colourless	66.66		$C_{14}H_{16}N_2O_4$
Xa	185–86	pale yellow	45.23		$C_{23}H_{21}N_3O_4$
Xb	162–65	pale yellow	51.19		$C_{28}H_{23}N_3O_4$
Xc	216–17	pale yellow	38.46		$C_{28}H_{22}BrN_3O_4$
Xd	222–24	pale yellow	48.81		$C_{31}H_{29}N_3O_4$
Xe	238–39	pale yellow	68.20		$C_{28}H_{22}N_4O_6$
Xf	236–38	pale yellow	65.20		$C_{26}H_{21}N_3O_4S$
Xg	228–29	pale yellow	68.12		$C_{29}H_{23}N_3O_6$
XIa	220–22	pale yellow	86.90		$C_{19}H_{18}N_2O_3$
XIb	209–10	bright yellow	94.60		$C_{19}H_{18}N_2O_4$
XIc	215–16	yellow	65.70		$C_{21}H_{23}N_3O_3$
XId	200–03	yellow	85.20		$C_{20}H_{20}N_2O_4$
XIe	237–39	pale yellow	36.06		$C_{20}H_{18}N_2O_6$
XIf	230–34	yellow	53.03		$C_{20}H_{28}N_2O_3$
XIg	216–18	yellow	70.00		$C_{20}H_{20}N_2O_5$
XIh	224–25	yellow	83.50		$C_{19}H_{17}N_3O_6$
XIi	217–18	bright yellow	87.10		$C_{23}H_{20}N_2O_4$
XIj	180–82	light brown	80.48		$C_{17}H_{16}N_2O_3S$
XIk	240–42	pale yellow	73.91		$C_{18}H_{17}N_3O_3$
XIIa	190–91	light brown	77.18		$C_{21}H_{19}N_3O_4$
XIIb	178–80	light brown	73.34		$C_{26}H_{21}N_3O_4$

RESULTS AND DISCUSSION

The IR spectra of dioxobutane derivatives showed the absorption band in the region of 3300–3200 cm^{-1} due to —NH stretchings. The amido and cyclic carbonyl groups showed the absorption bands in the region of 1660–1640 cm^{-1}.

The NMR spectra showed multiplet in the region of δ 2.1–2.6 ppm, of five methylene protons. A sharp singlet was observed at δ 3.9–4.0 ppm, attributed to three protons of the methoxy group. Aromatic protons showed multiplet at δ 7.0–7.5 ppm; the two amido protons showed singlet at δ 8.6–8.7 ppm.

The IR spectra of oxadiazole derivatives did not show the absorprtion band in the region of 3300–3200 cm^{-1} and 1660–1640 cm^{-1} due to —NH stretchings and carbonyl groups present in the starting meterial **(IIa–c)** which confirmed that cyclisation has taken place.

The anilide derivatives show absorption band at 3350–3300 cm^{-1} for —CONH stretching vibration.

The IR spectra of 3-hydrazocarbonyl-7-methoxy-1-tetralone **VII** showed the absorption band in the region of 3300–3200 cm^{-1} due to —NH stretchings. The amido and cyclic carbonyl groups showed the absorption bands in the region of 1660–1640 cm^{-1}.

The IR spectra of 3-thiosemicarbazidecarbonyl-7-methoxy-1-tetralone **VIII** showed the absorption band in the region of 3300–3200 cm^{-1} due to —NH stretchings. The amido and cyclic carbonyl groups showed the absorption bands in the region of 1660–1640 cm^{-1}.

The IR spectra of 3-N-(β-monoacetyl) hydrazocarbonyl-7-methoxy-1-tetralone **IX** showed the absorption band in the region of 3200 cm^{-1} due to —NH stretchings. The carbonyl groups showed the absorption bands in the region of 1705 (—$COCH_3$), 1660 (cyclic) and 1640 cm^{-1} (amido). The NMR spectra showed a sharp singlet at δ 2.5 ppm, attributed to three protons of the acetyl group. The two amido protons showed singlet at δ 8.8 ppm.

The IR spectra of benzylidene derivatives showed absorption band for —C=CN— linkage at 1640–1620 cm^{-1} and absorption band at 1730–1700 cm^{-1} attributed to the —C=O group stretching frequency. The NMR spectra showed a sharp singlet at δ 8.6–8.7 ppm, attributed to the methylidene proton. The carboxylic acid proton showed a hump at δ 13.6 ppm.

The hydrazones of 3-carbmethoxy-7-methoxy-1-tetralone are crystalline in nature and stable under dry conditions. The strong intensity IR band present in the compounds at 3250–3150 cm^{-1} can be attributed to —NH stretching frequency. A moderately strong band at 1700–1660 cm^{-1} in the spectra of all hydrazones are attributed to the stretching frequency of —C=O group. Hydrazones exhibit —C=N stretching frequency at 1620–1600 cm^{-1}. NMR spectra showed a singlet at δ 8.0–8.5 ppm, attributed to —CH=N proton.

The IR spectra of quinazolinones showing the absorption band at 3250–3150 cm^{-1} can be attributed to —NH stretching frequency. The carbonyl groups showed the absorption bands in the region of 1700–1640 cm^{-1}. The NMR spectra showed singlet at δ 8.4 ppm of amido proton.

Antibactrial activity

All the compounds were subjected to M.I.C. (minimum inhibitory concentration) test. Strains of the following bacteria were used: *Staphylococcus aureus, Escherichia coli, Salmonella typhi* and *Klebsiella pneumoniae* and none of them showed any significant antibacterial activity.

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