



Synthetic studies of Alkoxy isoindole-1,3-diones tetra-azabenzof[azulenes and their Antibacterial activity

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Abstract: 3-Methylpyrazol-5-one **3** reacts with substituted benzaldehydes **4a-d** in the presence of anhydrous sodium acetate to produce the corresponding 4-arylidene-5-methyl-2,4-dihydro-pyrazol-3-ones **5a-d** and the condensation of **5a-d** with 2-bromoalkoxy-1H-isoindole-1, 3-(2H)-diones **2a-c** furnished corresponding 2-[2-(4-arylidene-3-methyl-5-oxo-4,5-dihydro-pyrazol-1-yl)alkoxy]-isoindole-1,3-diones **6a-l**, which on cyclisation with o-phenyldiamine give titled compounds **7a-l**. All the synthesized compounds have been characterized by elemental analysis and spectral data and screened for their antibacterial properties against various bacterial strains in order to obtain chemotherapeutic properties.

Key words: Synthetic studies, antibacterial activity

Introduction

A great deal of synthesis work has been done in last few years on various compounds having a condensed diazepine nucleus, especially benzodiazepin have attracted the attention of several chemist and biologists because of their valuable therapeutic properties like tranquillizer¹⁻³, neuroleptic agents⁴, antineoplastic^{5,6}, HIV-1 RT inhibitors^{7,8} antileukemic⁹ and antifungal¹⁰ etc. It is interesting to note that pyrazoles are also reported as well known pharmacophores¹¹⁻¹⁴. As a part of our studies aimed to synthesis of various heterocyclic imidoxy derivatives and in continuation to our work¹⁵⁻¹⁸ it seems interesting to integrate structural features from different biological active compounds in a single molecule. Consequently there have been many efforts for designing of novel, hybrid molecules possessing significant bioactivity. In the present work, we report the synthetic efforts to

synthesize alkoxy isoindole-1,3-dionestetra-azabenzof[*f*]azulenes containing benzodiazepine, pyrazole and imidoxy moieties.

Experimental

Melting points were determined in open capillary tubes and are uncorrected. The time required for completion of the reaction was monitored by TLC using Silica gel-G plates and spots were exposed in iodine chamber. IR spectra were recorded on a Perkin Elmer 1800 (FTIR) spectrometer ¹H NMR spectra (CDCl₃) were taken on a DRX-300 spectrometer (300 MHz) using TMS as internal standard and chemical shifts are expressed in δ ppm. Mass spectra were taken on a jeol SX-102/DA-6000 spectrometer. 2-Hydroxy-1H-isoindole-1,3-dione²⁰ **1**, 2-Bromoalkoxy-1H-isoindole-1,3-(2H)-diones²¹ **2a-c** and 3-methylpyrazol-5-one²² **3** were prepared by the reported methods.

Synthesis of 4-(4'-methoxybenzylidene)-5-methyl-2,4-dihydro-pyrazol-3-one 5a.

A mixture of 3-methylpyrazol-5-one **3** (0.98 g, 0.01 mole), anisaldehyde **4a** (1.12 ml, 0.01 mole) and anhydrous sodium acetate (0.82 g, 0.01 mole) were suspended in acetic acid (30 ml) and refluxed for 10 hours. The reaction mixture was filtered and the filtrate was poured on crushed ice. The solid obtained, was crystallised from ethanol. Compounds **5b-d** were also synthesized by the similar method using appropriate reactants with required change in reflux time.

5a: (c.f. Table 2); **IR (KBr) (cm⁻¹):** 3435 (N-H), 3076 (Ar-H), 2964 (C-H, CH₃), 1690 (C=O), 1602 (C=N); **¹H NMR (CDCl₃):** 8.2 (s, 1H, N-H), 7.4-7.0 (m, 4H, Ar-H), 6.1 (s, 1H, C=CH), 3.7 (s, 3H, OCH₃), 1.7 (s, 3H, CH₃). **5b:** **IR (KBr) (cm⁻¹):** 3412 (N-H), 3080 (Ar-H), 2952 (C-H, CH₃), 1718 (C=O), 1612 (C=N), 728 (Ar-Cl); **¹H NMR (CDCl₃):** 8.0 (s, 1H, N-H), 7.3-6.9 (m, 4H, Ar-H), 6.2 (s, 1H, C=CH), 1.8 (s, 3H, CH₃). **5c:** **IR (KBr) (cm⁻¹):** 3396 (N-H), 3062 (Ar-H), 2946 (C-H, CH₃), 1705 (C=O), 1612 (C=N); **¹H NMR (CDCl₃):** 8.1 (s, 1H, N-H), 7.4-7.1 (m, 5H, Ar-H), 6.3 (s, 1H, C=CH), 1.8 (s, 3H, CH₃). **5d:** **IR (KBr) (cm⁻¹):** 3410 (N-H), 3070 (Ar-H), 2950 (C-H, CH₃), 1710 (C=O), 1626 (C=N); **¹H NMR (CDCl₃):** 8.1 (s, 1H, N-H), 7.6-7.2 (m, 4H, Ar-H), 6.2 (s, 1H, C=CH), 2.0 (s, 3H, CH₃), 1.7 (s, 3H, pyrazole-CH₃).

Synthesis of 2-[2-{4-(4'-methoxybenzylidene)-3-methyl-5-oxo-4,5-dihydro-pyrazol-1-yl}] ethoxy]-isoindol-1,3-dione 6a.

A mixture of compound **5a** (2.16 g, 0.01 mole), with 2-bromoethoxy-1H-isoindole-1,3-(2H)-dione **2a** (2.70 g, 0.01 mole) and pyridine (2 ml) were refluxed in absolute alcohol (30 ml) for 11 hrs. Excess of the solvent from the filtrate was removed under reduced pressure. On cooling, the solid separated was crystallized from ethanol. Compounds **6b-l** were also synthesized by the similar method using appropriate reactants and minor modification in reaction conditions.

6a: (c.f. Table 2); **IR (KBr) (cm⁻¹):** 3072 (Ar-H), 2932 (C-H, CH₃), 2837 (C-H, CH₂), 1755 (C=O, CO-N-CO), 1722 (C=O, pyrazole ring), 1603 (C=N), 1270 (C-N); **¹H NMR (CDCl₃):** 7.6-7.0 (m, 8H, Ar-H), 6.7 (s, 1H, C=CH), 3.6 (s, 3H, OCH₃), 3.4 (t, 2H, OCH₂CH₂N), 2.8 (t, 2H, OCH₂CH₂N), 1.9 (s, 3H, CH₃). **6c:** (c.f. Table 2); **IR (KBr) (cm⁻¹):** 3068 (Ar-H), 2946 (C-H, CH₃), 2848 (C-H, CH₂), 1776 (CO-N-CO), 1698 (C=O, pyrazole ring), 1620 (C=N), 1280 (C-N); **¹H NMR (CDCl₃):** 7.7-7.2 (m, 9H, Ar-H), 6.8 (s, 1H, C=CH), 3.4 (t, 2H, OCH₂CH₂N), 2.8 (t, 2H, OCH₂CH₂N), 1.9 (s, 3H, CH₃). **6f:** (c.f. Table 2); **IR (KBr) (cm⁻¹):** 3066 (Ar-H), 2940 (C-H, CH₃), 2842 (C-H, CH₂), 1770 (CO-N-CO), 1705 (C=O, pyrazole ring), 1616 (C=N), 1283 (C-N), 746 (Ar-Cl); **¹H NMR (CDCl₃):** 7.5-7.1 (m, 8H,

Ar-H), 6.6 (s, 1H, C=CH), 3.5 (t, 2H, OCH₂CH₂CH₂N), 2.8 (t, 2H, OCH₂CH₂CH₂N), 2.5 (quint, 2H, OCH₂CH₂CH₂N), 1.8 (s, 3H, CH₃). **6l**: (c.f. Table 2); **IR (KBr) (cm⁻¹)**: 3076 (Ar-H), 2950 (C-H, CH₃), 2838 (C-H, CH₂), 1750 (CO-N-CO), 1700 (C=O pyrazole ring), 1602 (C=N), 1286 (C-N); **¹H NMR δ (CDCl₃)**: 7.3-6.8 (m, 8H, Ar-H), 6.7 (s, 1H, C=CH-Ar), 3.4 (t, 2H, OCH₂CH₂CH₂CH₂N), 2.8 (t, 2H, OCH₂CH₂CH₂CH₂N), 2.2 (s, 3H, CH₃), 1.8 (s, 3H, Pyrazole CH₃).

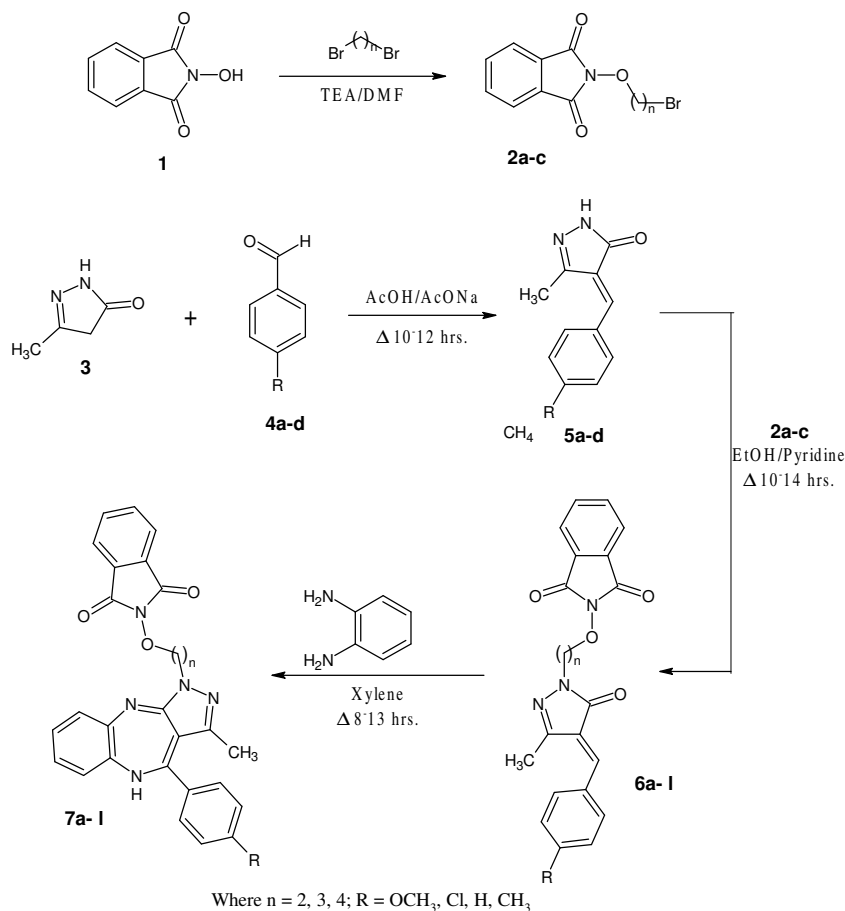
Synthesis of 2-[2-{10-(4'-methoxyphenyl)-1-methyl-10,10a-dihydro-9H-2,3,4,9-tetra-azabenzofuran-3-yl}ethoxy]-isoindol-1,3-dione 7a.

Compound **6a** (4.05 g, 0.01 mole) was dissolved in 80 ml hot xylene in round bottomed flask and o-phenylenediamine (1.08 g, 0.01 mole) was also dissolved in 20 ml boiling xylene. Now the boiling solution of o-phenylenediamine was added in small installments to the solution of **6a** and refluxed for 8-10 h. During the reaction water formed was separated by Dean-stark apparatus. Excess of solvent was then removed under reduced pressure. The residue was titrated with light petroleum ether and benzene (9:1) to give final product. It was filtered and recrystallized from light petroleum benzene. Compounds **7b-l** were also synthesized by the similar method using appropriate reactants.

7a: (c.f. Table 2); **IR (KBr) (cm⁻¹)**: 3432 (N-H), 3060 (Ar-H), 2928 (C-H, CH₃), 2836 (C-H, CH₂), 1750 (CO-N-CO), 1606 (C=N), 1267 (C-N); **¹H NMR (CDCl₃)**: 7.8-7.6 (m, 12H, Ar-H), 4.8 (s, 1H, NH), 3.9 (s, 3H, OCH₃), 3.2 (t, 2H, OCH₂CH₂N), 2.7 (t, 2H, OCH₂CH₂N), 1.9 (s, 3H, CH₃); m/z: 493 [M]⁺, 386, 204, 190, 162, 146, 132, 107, 104, 76. **7c**: (c.f. Table 2); **IR (KBr) (cm⁻¹)**: 3410 (N-H), 3070 (Ar-H), 2940 (C-H, CH₃), 2842 (C-H, CH₂), 1760 (CO-N-CO), 1620 (C=N), 1281 (C-N); **¹H NMR (CDCl₃)**: 7.8-7.6 (m, 13H, Ar-H), 4.8 (s, 1H, NH), 3.3 (t, 2H, OCH₂CH₂N), 2.8 (t, 2H, OCH₂CH₂N), 2.0 (s, 3H, CH₃); m/z: 463 [M]⁺, 387, 190, 162, 146, 132, 104, 76. **7f**: (c.f. Table II); **IR (KBr) (cm⁻¹)**: 3420 (N-H), 3068 (Ar-H), 2932 (C-H, CH₃), 2830 (C-H, CH₂), 1742 (CO-N-CO), 1618 (C=N), 1274 (C-N), 750 (Ar-Cl); **¹H NMR (CDCl₃)**: 7.8-7.6 (m, 12H, Ar-H), 4.9 (s, 1H, NH), 3.3 (t, 2H, OCH₂CH₂CH₂N), 2.9 (t, 2H, OCH₂CH₂CH₂N), 2.6 (quint., 2H, OCH₂CH₂CH₂N), 2.1 (s, 3H, CH₃); m/z: 513 [M⁺+2]⁺, 511[M]⁺, 204, 190, 162, 146, 132, 104, 76. **7l**: (c.f. Table 2); **IR (KBr) (cm⁻¹)**: 3422 (N-H), 3062 (Ar-H), 2942 (C-H, CH₃), 2848 (C-H, CH₂), 1756 (CO-N-CO), 1610 (C=N), 1283 (C-N); **¹H NMR (CDCl₃)**: 7.7-7.6 (m, 12H, Ar-H), 4.7 (s, 1H, NH), 3.7 (d, 1H, CH-Ar), 3.5 (d, 1H, CH), 3.2 (t, 2H, OCH₂CH₂CH₂CH₂N), 2.8 (t, 2H, OCH₂CH₂CH₂CH₂N), 2.3 (s, 3H, CH₃), 1.8 (s, 3H, Pyrazole CH₃); m/z: 505 [M]⁺, 218, 162, 146, 132, 104, 76.

Results and Discussion

4-Arylidene-5-methyl-2,4-dihydro-pyrazol-3-ones **5a-d** were synthesized by the reaction of 3-methylpyrazol-5-one **3** with substituted benzaldehydes **4a-d** in the presence of anhydrous sodium acetate and the formation of **5a** was characterized by ¹H NMR signal at δ 6.1 ppm for C=CH-Ar. Compounds **5a-d** were further condensed with 2-bromoalkoxy-1H-isoindole-1,3-(2H)-dione **2a-c** in the presence of pyridine to give 2-[2-(4-arylidene-3-methyl-5-oxo-4,5-dihydro-pyrazol-1-yl)alkoxy]-isoindole-1,3-diones **6a-l**. Absence of free stretching IR vibration band for NH group at 3435 cm⁻¹ and ¹H NMR signal for the proton of NH group at δ 8.2 ppm, which was present in its precursor **5a-d** confirms the formation of **6a-l**. Compounds **6a-l** were further cyclized with o-phenylenediamine in dry xylene to give final product **7a-l**. Structural assignments of compounds **7a-l** are based on IR, ¹H NMR, Mass spectral data and elemental analysis.



a	$R = \text{OCH}_3,$	$n = 2$	g	$R = \text{H},$	$n = 3$
b	$R = \text{Cl},$	$n = 2$	h	$R = \text{CH}_3,$	$n = 3$
c	$R = \text{H},$	$n = 2$	i	$R = \text{OCH}_3,$	$n = 4$
d	$R = \text{CH}_3,$	$n = 2$	j	$R = \text{Cl},$	$n = 4$
e	$R = \text{OCH}_3,$	$n = 3$	k	$R = \text{H},$	$n = 4$
f	$R = \text{Cl},$	$n = 3$	l	$R = \text{CH}_3,$	$n = 4$

Antibacterial Screening

In the present investigation all the synthesized compounds were screened at 100 $\mu\text{g/ml}$ against various bacterial strains viz. *Escherichia coli*, *Proteus mirabilis*, *Klebsiella pneumonia*, *Pseudomonas aureginosa*, *Salmonella typhi* and *Staphylococcus aureus* for their antibacterial activity using ampicillin as a standard drug by cup and well method developed by Collee, Fraser, Marmion and Simmons¹⁹. The screening results are summarized in Table 1 indicating that all the synthesized compounds have been manifested moderate to fairly good growth inhibition. Especially, compounds 7b, 7e, 7g, 7i, 7j and 7k have shown strong antibacterial activity as compared to standard.

Table 1. Antimicrobial activity of synthesized compounds 7a-l Zone of inhibition (mm)/(activity index)

Compd.	Antibacterial Activity (100µg/ml)					
	<i>E. coli</i>	<i>P. mirabilis</i>	<i>K. pneumonia</i>	<i>P. aureginosa</i>	<i>S. typhi</i>	<i>S. aureus</i>
7a	17/1.06	10/0.62	11/0.84	11/0.91	10/0.50	12/0.80
7b	13/0.81	17/1.06	15/1.15	09/0.75	16/0.80	14/0.90
7c	07/0.43	09/0.56	10/0.76	07/0.58	13/0.65	05/0.33
7d	12/0.75	07/0.43	08/0.61	11/0.91	09/0.45	11/0.73
7e	15/0.93	13/0.81	11/0.84	10/0.83	18/0.90	16/1.06
7f	09/0.56	11/0.68	10/0.76	07/0.58	13/0.65	12/0.80
7g	07/0.43	12/0.75	07/0.53	10/0.83	09/0.45	08/0.53
7h	13/0.81	09/0.56	09/0.69	08/0.66	11/0.55	06/0.40
7i	14/0.87	13/0.81	11/0.84	13/1.08	09/0.45	11/0.73
7j	12/0.75	08/0.50	14/1.07	09/0.75	17/0.85	13/0.86
7k	06/0.37	05/0.31	11/0.84	06/0.50	08/0.40	14/0.90
7l	10/0.62	12/0.75	07/0.53	09/0.75	12/0.60	09/0.60
Stand.	16	16	13	12	20	15

(Activity index) = Inhibition zone of the sample/Inhibition zone of the standard.
Standard used: Amicacin

Table-2. Physical and analytical data of compounds 5a-d, 6a-l and 7a-l.

Compd.	m.p (°C)	Yield (%)	Molecular formula	% Found/Calcd		
				C	H	N
5a	168	62	C ₁₂ H ₁₂ N ₂ O ₂	66.58/66.66	5.49/5.55	12.91/12.96
5b	156	60	C ₁₁ H ₉ N ₂ OCl	59.74/59.86	4.04/4.08	12.72/12.69
5c	172	71	C ₁₁ H ₁₀ N ₂ O	70.92/70.96	5.31/5.37	15.01/15.05
5d	166	66	C ₁₂ H ₁₂ N ₂ O	71.60/72.00	5.70/6.00	13.96/14.00
6a	130	60	C ₂₂ H ₁₉ N ₃ O ₅	65.16/65.18	4.52/4.69	9.89/10.37
6b	141	64	C ₂₁ H ₁₆ N ₃ O ₄ Cl	61.48/61.53	3.87/3.90	10.19/10.26
6c	170	66	C ₂₁ H ₁₇ N ₃ O ₄	67.12/67.20	4.39/4.53	11.09/11.20
6d	120	60	C ₂₂ H ₁₉ N ₃ O ₄	68.59/67.86	4.81/4.88	10.72/10.79
6e	146	69	C ₂₃ H ₂₁ N ₃ O ₅	65.72/65.87	5.00/5.01	9.86/10.02
6f	159	64	C ₂₂ H ₁₈ N ₃ O ₄ Cl	62.29/62.33	4.14/4.25	9.72/9.91
6g	176	59	C ₂₂ H ₁₉ N ₃ O ₄	67.75/67.86	4.83/4.88	10.54/10.79
6h	144	61	C ₂₃ H ₂₁ N ₃ O ₄	68.40/68.48	5.11/5.21	10.03/10.42
6i	153	61	C ₂₄ H ₂₃ N ₃ O ₅	66.47/66.51	5.29/5.31	9.54/9.69
6j	182	68	C ₂₃ H ₂₀ N ₃ O ₄ Cl	63.00/63.08	4.34/4.57	9.56/9.60
6k	186	65	C ₂₃ H ₂₁ N ₃ O ₄	68.42/68.48	5.19/5.21	10.37/10.42
6l	194	56	C ₂₄ H ₂₃ N ₃ O ₄	69.02/69.06	5.31/5.51	10.00/10.07
7a	268	58	C ₂₈ H ₂₃ N ₅ O ₄	68.01/68.15	4.59/4.66	14.01/14.19
7b	290	60	C ₂₇ H ₂₀ N ₅ O ₃ Cl	64.95/65.12	3.91/4.02	13.92/14.07
7c	246	51	C ₂₇ H ₂₁ N ₅ O ₃	69.82/69.97	4.48/4.53	15.02/15.11
7d	305	52	C ₂₈ H ₂₃ N ₅ O ₃	70.40/70.44	4.75/4.82	14.61/14.67
7e	273	61	C ₂₉ H ₂₅ N ₅ O ₄	68.55/68.63	4.87/4.93	13.71/13.80
7f	287	56	C ₂₈ H ₂₂ N ₅ O ₃ Cl	65.61/65.68	4.23/4.30	13.61/13.68
7g	278	45	C ₂₈ H ₂₃ N ₅ O ₃	70.38/70.44	4.75/4.82	14.59/14.67

7h	270	52	C ₂₉ H ₂₅ N ₅ O ₃	70.79/70.87	5.00/5.09	14.21/14.25
7i	284	53	C ₃₀ H ₂₇ N ₅ O ₃	69.03/69.09	5.10/5.18	13.37/13.43
7j	254	59	C ₂₉ H ₂₄ N ₅ O ₃ Cl	66.16/66.22	4.50/4.56	13.23/13.32
7k	292	52	C ₂₉ H ₂₅ N ₅ O ₃	70.81/70.87	5.03/5.09	14.19/14.25
7l	315	58	C ₃₀ H ₂₉ N ₅ O ₃	71.19/71.28	5.29/5.34	13.79/13.86

Conclusion

In the present paper we have succeeded to synthesize alkoxy isoindole-1,3-diones tetraazabenzofazulenes in good yields which have been tested for antibacterial properties. Although compounds show moderate to good activity but some of the synthesized compounds have shown significant antibacterial activity which reveals the chemotherapeutic values of the synthetic compounds.

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