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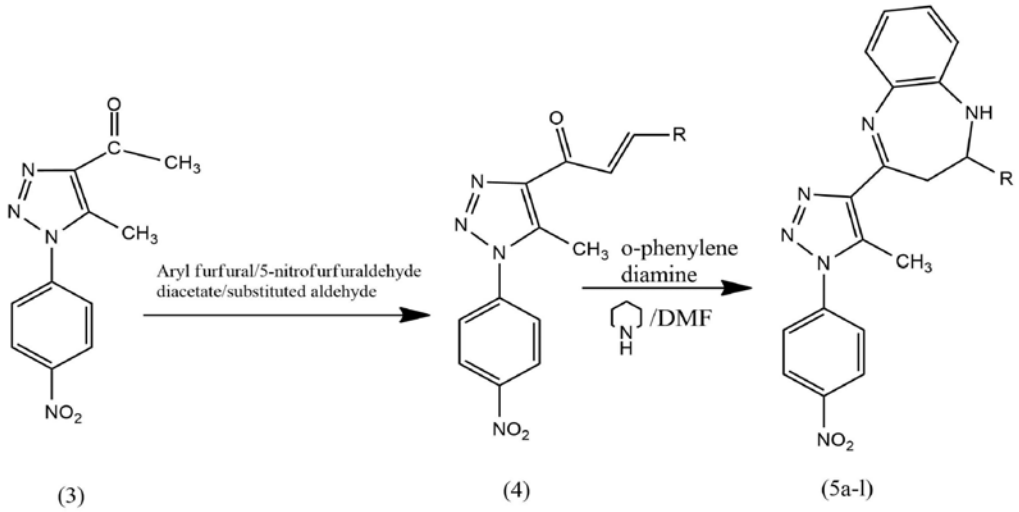
SYNTHESIS AND BIOLOGICAL ACTIVITY OF SOME NEW TRIAZOLYLBENZODIAZEPINES

B. Kalluraya*, Sahana Mallya, Asma, K. Aparna and B.R. Kaushik
Department of Studies in Chemistry, Mangalore University,
Mangalagangothri-574199 Karnataka, India

ABSTRACT A novel series of 4-[5-methyl-1-(4-nitrophenyl)-1H-1,2,3-triazol-4-yl)-2-[5-(substituted phenyl/arylfuryl/nitrofuryl)]-2,3-dihydro-1H-1,5-benzodiazepines was prepared by cyclocondensation of 3-[4-substituted phenyl/arylfuryl/nitrofuryl-2-yl]-1-(5-methyl-1-(4-nitrophenyl)-1H-1,2,3-triazole-4-yl)prop-2-en-1-one with *o*-phenylenediaamine. Structures of newly synthesized compounds were confirmed by spectral and analytical data. The newly synthesized compounds were screened for their antibacterial activity against Gram +ve and Gram –ve bacteria.



KEYWORDS Antibacterial activity, Benzodiazipines, 1,3-Dipolar cycloaddition, Triazolylchalcones

INTRODUCTION

1,5-Benzodiazepines and their derivatives constitute an important class of heterocyclic compounds which have proven their medicinal identity as anticancer, antioxidant, anticonvulsant, analgesic, anti-anxiety and hypnotic agents[1-2]. 1,5-Benzodiazepines exert biological activity similar to that of the well-known 1,4-derivatives and has demonstrated considerable activity not only in CNS-drug design, but also as peptidomimetic scaffolds[3] and key intermediates for the preparation of other fused ring components[4].

Keeping in view of the biological importance of benzodiazepine moiety and the potential bioactivity exhibited by 1,2,3-triazole and in continuation of our search for the synthesis of biologically potent molecules[5-7], we herein report a novel series of 1,5-benzodiazepines carrying 1,2,3-triazole nucleus.

*Corresponding author: Email: bkalluraya@gmail.com

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RESULTS AND DISCUSSION

Chemistry

1,5-Benzodiazepines **(5a-l)** were obtained by the cyclocondensation of triazolylchalcones **(4a-l)** with o-phenylenediamine **(Scheme 1)**. Chalcones carrying triazole nucleus **(4a-l)** were prepared by base catalyzed Claisen Schmidt condensation of triazolyl ketone[8] **(3)** with 5-nitrofurfuraldehyde diacetate/arylfurfuraldehyde/ substituted aldehyde[9] . The triazolyl ketone **(3)** was synthesized by 1,3-dipolar cycloaddition of p-azidonitrobenzene**(2)** with acetylacetone as dipolarophile[10]. p-Azidonitrobenzene **(2)** in turn was synthesized by diazotization of p-nitroaniline followed by treatment with sodium azide as per the literature procedure[11].

The IRspectrum of compound **5a** showed an absorption band at 1611 cm^{-1} corresponding to the stretching vibration of the C=N group, the C-H stretching was observed at 2851 cm^{-1} and N-H stretching was seen at 3560 cm^{-1}.

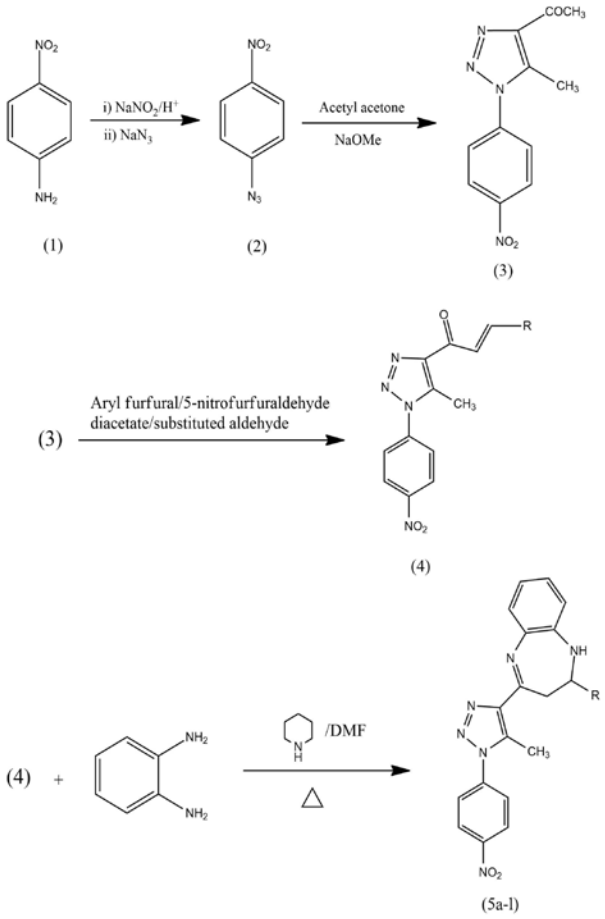
In the ^{1}H-NMR spectrum of compound **5a** the methyl protons attached to the triazole ring appeared as a singlet at δ 2.33 integrating for three protons. A doublet of doublets was observed at δ 3.35 integrating for one proton corresponding to CH_2 group of benzodiazepine ring and another doublet of doublets at δ 3.76 for the other proton, thereby indicating the magnetic non-equivalency of these two protons. The CH proton of benzodiazepine ring also appeared as a doublet of doublets at δ 4.67 integrating for one proton. A broad singlet was observed at δ 5.30 corresponding to NH proton and a multiplet was observed in the range of δ 7.64-8.51 integrating for twelve protons of aromatic ring. The furfural protons were observed as two doublets at δ 7.13 and 7.22.

Similarly in the ^{13}C-NMR spectrum of compound **5a**, the chemical shifts observed are as follows: δ 21.65(CH_3), 40.22(CH_2), 78.87(CH), 99.50, 119.60, 124.88, 125.85, 126.18, 128.99, 131.76, 138.74, 140.00, 143.66 and 154.75

Further in the mass spectrum of compound **5a** the molecular ion (M^++1) peak was observed at m/z, 525 and 527 in 3:1 ratio consistent with its molecular formula $C_{28}H_{21}ClN_4O_3$.

Antibacterial activity

The newly synthesized compounds were screened for their antibacterial activity against Gram positive and Gram negative strains of bacteria by Agar diffusion well-variant serial plate dilution method. The results showed that none of the tested compounds exhibited any activity comparable with the standard drug. However compound **5e** carrying 2, 4-diflurophenylfuryl moiety showed somewhat significant activity against *S.typhi*, *K.pneumonia* and *P.florida* , comparable with the standard drug.



R=a) 5-(p-Chloro phenyl)furyl, b) 5-(2,4-dinitro phenyl)furyl, c) 5-(o-nitro phenyl)furyl, d) 5-(p-nitro phenyl)furyl, e) 5-(2,4-difluro phenyl)furyl, f) 5-(3,4-dichlorophenyl)furyl, g) 5-(p-bromo phenyl)furyl, h) 5-nitro furyl, i) p-nitro phenyl, j) p-methyl phenyl, k) 3,4-dimethoxy phenyl, l) 2-chloro phenyl

Scheme

EXPERIMENTAL SECTION

The melting points of the newly synthesized compounds were determined using apparatus Innovative DTC-967A and are uncorrected. The IR spectra were recorded on a Shimadzu-ATR 157 spectrophotometer. The ^{1}H-NMR spectra were recorded on a BrukerAvance -II 400MHz NMR spectrometer using $CDCl_3$ as solvent and TMS as an internal standard. All the chemical shift values are expressed in δ scale down field from TMS. Mass spectra were recorded on Waters Micromass Q-Tof mass

Table 1: Characterization data of 4-{5-methyl-1-(4-nitrophenyl)-1H-1,2,3-triazol-4-yl}-2-(5-(substituted phenyl/ arylfuryl/nitrofuryl)-2,3-dihydro-1H-1,5-benzodiazepine (5a-l)

Compd. No.	R	M.P. (^{0}C) Yield (%)	Mol. Formula (Mol. Wt)	C H N analysis found (Calc.) C	H	N
5a	5-((p-chloro)	240-2	$C_{28}H_{21}ClN_6O_3$	64.1	4.1	16.0
		78	524.957	(64.06)	(4.03)	(16.01)
5b	5-((2,4-dinitro)	213-4	$C_{28}H_{20}N_8O_7$	57.9	3.5	19.3
	phenyl)furyl	79	580.51	(57.93)	(3.47)	(19.30)
5c	5-((o-nitro)	145-7	$C_{28}H_{21}N_7O_5$	62.8	3.9	18.3
	phenyl)furyl	81	535.51	(62.80)	(3.95)	(18.31)
5d	5-((p-nitro)	255-7	$C_{28}H_{21}N_7O_5$	62.8	4.0	18.3
	phenyl)furyl	81	535.51	(62.80)	(3.95)	(18.31)
5e	5-((2,4-difluoro)	215-7	$C_{28}H_{20}F_2N_6O_3$	63.9	3.8	15.9
	phenyl)furyl	80	526.493	(63.88)	(3.83)	(15.96)
5f	5-((3,4-dichloro)	170-2	$C_{28}H_{20}Cl_2N_6O_3$	60.1	3.60	15.1
	phenyl)furyl	79	559.40	(60.12)	(3.60)	(15.02)
5g	5-((p-bromo)	225-7	$C_{28}H_{21}BrN_6O_3$	59.1	3.7	14.8
	phenyl)furyl	82	569.408	(59.06)	(3.72)	(14.76)
5h	5-nitrofuryl	206-7	$C_{22}H_{17}N_7O_5$	57.5	3.7	21.3
		78	459.41	(57.52)	(3.73)	(21.34)
5i	p-nitrophenyl	255-7	$C_{24}H_{19}N_7O_5$	61.4	4.1	20.9
		79	469.45	(61.40)	(4.08)	(20.89)
5j	p-methylphenyl	224-5	$C_{25}H_{22}N_6O_2$	68.5	5.1	19.2
		80	438.48	(68.48)	(5.06)	(19.17)
5k	3,4-dimethoxy- phenyl	246-8	$C_{26}H_{24}N_6O_4$	64.5	5.0	17.4
		81	484.506	(64.45)	(4.99)	(17.35)
5l	2-chlorophenyl	179-80	$C_{24}H_{19}ClN_6O_2$	62.8	4.2	18.3
		79	458.899	(62.81)	(4.17)	(18.31)

spectrometer. Elemental analysis was carried out on ElementarVario-EL-Elementar III model analyser. The homogeneity of the compounds was checked by TLC silica gel plates, (MERCK) using petroleum ether : ethyl acetate.

General procedure for the preparation of 4-{5-methyl-1-(4-nitrophenyl)-1H-1,2,3-triazol 4-yl}-2-(5-(substituted phenyl/aryl/nitrofuryl)-2,3-dihydro-1H-1,5-benzodiazepines (5a-l):

To a mixture of o-phenylenediamine (0.108g, 2 mmol) and appropriate propenone (2 mmol) dissolved in 10mL of DMF was added piperidine (0.1 mL, 0.2 mmol), and the contents were refluxed at 80ºC for 5-6 hours. After completion of the reaction (TLC analysis), the reaction mixture was diluted with water, and extracted with dichloromethane (2x10 mL). The combined organic layer was dried over sodium sulfate, concentrated to dryness in vacuum, and the residue was purified by column chromatography (eluted with 2:8 EtOAc –petroleum ether) to afford the pure 1, 5-benzodiazepines **(5a-l). (Table 1)**

IR and ^{1}H-NMR spectral data for selected compounds:

5b: IR(KBr) :1616(C=N), 2851(C-H), 3540(NH), 1333 & 1530 (NO_2 symmetric and asymmetric); **^{1}H-NMR**(DMSO-d_6): 2.23(s, 3H,CH_3), 3.29 (d,d, 1H), 3.81(d,d,1H) benzodiazepine CH_2 protons which are magnetically non-equivalent, 4.53 (d,d,1H, benzodiazepine CH), 5.29(br, 1H, NH), 7.58-8.76(m, 11H, Ar-H), 7.08(d, 1H, furan-3H), 7.31(d,1H, furan-4H). Mass m/z, 581(M^++1) (M.F:$C_{28}H_{20}N_8O_7$).

5d: IR(KBr): 1621(C=N), 2951(C-H), 3531(NH), 1330(NO_2sym) & 1539 (NO_2 asym); **^{1}H-NMR**(DMSO-d_6)**:** 2.18(s, 3H,CH_3), 3.31 (d,d, 1H), 3.78(d,d,1H) benzodiazepine CH_2 , 4.38(d,d,1H, benzodiazepine CH), 5.41(br,1H, NH), 7.66-8.43(m, 12H, Ar-H), 7.11(d, 1H, furan-3H), 7.28(d,1H, furan-4H). Mass m/z, 536(M^++1) (M.F:$C_{28}H_{11}N_7O_5$).

5f: IR(KBr): 1612(C=N), 2946(C-H), 3490(NH), 1328(NO_2sym) & 1544 (NO_2 asym); **^{1}H-NMR**(DMSO-d_6): 2.20(s, 3H,CH_3), 3.28 (d,d, 1H), 3.81(d,d,1H) benzodiazepine CH_2 , 4.41(d,d,1H, benzodiazepine CH), 5.28(br, 1H, NH), 7.21-8.56(m, 13H, Ar-H & furan 3H & 4H), Mass m/z, 560,562 & 564 (M^+, M^++2 & M^++4) (M.F:$C_{28}H_{20}Cl_2N_6O_3$).

5g: IR(KBr) :1614(C=N), 3011 (C-H), 3546 (NH), 1513 (NO_2sym) & 1536 (NO_2 asym); **^{1}H-NMR**(DMSO-d_6): 2.16(s, 3H,CH_3), 3.27 (d,d, 1H), 3.81(d,d,1H) benzodiazepine CH_2, 4.53 B(d,d,1H, benzodiazepine CH), 5.38(br, 1H, NH), 7.02(d, 2H, J=8.1 Hz, ortho protons of p-bromo phenyl), 7.48(d, 2H, J=8 Hz, meta protons of p-bromo phenyl), 8.38(d,2H, J=7.58Hz, Ar-H), 8.1(d, 2H, J=7.4 Hz, ortho protons of p-nitro phenyl), 8.38(d, 2H, J=7.4 Hz, meta protons of p-nitro phenyl), 6.98(d,1H, furan-3H), 7.26(d,1H, furan-4H). Mass m/z, 569(M^+), 570(M^++2) (M.F:$C_{28}H_{21}BrN_6O_3$).

5j: IR(KBr) :1630(C=N), 2985(C-H), 3498(NH), 1318(NO_2sym) & 1346(NO_2asym); **^{1}H-NMR**($CDCl_3$): 2.36(s, 3H,CH_3 of p-tolyl), 2.41 (s,3H,CH_3 of triazolyl), 3.45(d,d,1H) & 3.87(d,d,1H) the magnetically non-equivalent benzodiazepine CH_2 protons , 4.72(d,d,1H, CH), 5.75(br, 1H, NH), 7.04-8.02(m, 12H, Ar-H).Mass m/z, 438 (M.F:$C_{25}H_{22}N_6O_6$).

Antibacterial activity

The newly synthesized 1,5-benzodiazepines were screened for antibacterial activity against Gram positive bacterial strains namely*Bacillus Subtilis* MTCC 441,*Staphylococcus aureus* MTCC 542 and Gram negative bacterial strains *Klebsiella pneumonia* MTCC 7028,*Salmonella sp*. MTCC 1169, *Pseudomonas florida* MTCC 668 and *Escherichia coli* MTCC 519, by Agar diffusion well-variant serial plate dilution method[12].In this method 24 hours nutrient broth cultures of bacterial inoculum were uniformly spread using sterile cotton swabs on a sterile petri dish containing solidified nutrient agar medium.Then wells of 6mm diameter were bored in the inoculated plates with the help of gel puncher.The test samples (50µg/20 µl DMSO),standard chloramphenicol (50µg/20 µl DMSO) and control(DMSO) were added into the labeled wells. The plates were incubated at 37ºC for 24 hours in an upright position and the zone of inhibition was recorded. The entire test was performed in triplicate. The results are summarized in **Table 2**.

Table-2: Antibacterial activity of compounds (5a-l) (Diameter of zone of inhibition in mm)

Compound No.	Gram +ve bacterial strains		Gram -ve bacterial strains			
	B.subtilis (MTCC 441)	S.aureus (MTCC 9542)	E.coli (MTCC 519)	S.typhi (MTCC 1169)	K.pneumoniae (MTCC 7028)	P.florida (MTCC 668)
5a	_	10	12	16	10	14
5b	14	_	_	_	14	_
5c	16	08	_	_	_	_
5d	08	_	_	_	10	_
5e	10	08	14	20	22	24
5f	14	08	10	18	20	10
5g	_	12	_	_	12	_
5h	_	_	_	_	12	_
5i	08	10	14	12	12	12
5j	16	_	8	_	14	14
5k	12	10	12	12	10	12
5l	10	08	12	12	10	10
Chloramphenicol	28	29	9	30	27	32
Solvent control	0	0	0	0	0	0

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