INTERNATIONAL JOURNAL OF PHARMACEUTICAL, CHEMICAL AND BIOLOGICAL SCIENCES

Available online at www.ijpcbs.com

Research Article

NOVEL METHOD FOR THE SYNTHESIS OF DIAZEPINES AND TRIAZEPINES INVOLVING 8-BROMO/NITRONAPHTHO [2,1-B]FURAN AND THEIR ANTIMICROBIAL ACTIVITY

D. Ramesh[1*], MN. Kumaraswamy[1] and KM. Nagarsha[2]

[1]Department of PG Studies and Research in Industrial Chemistry and Chemistry, Sir. M.V. Government Science College, Bommanakatte, Bhadravathi-577302, Karnataka, Bangalore, India.
[2]Department of Chemistry Sahyadri Science College, Shimoga-577202, Karnataka, Bangalore, India.

ABSTRACT

The key starting material, 2-hydroxy-1-naphtholdoxime **1** was synthesized from naphtholdehyde and converted to ethyl -3-aminonaphtho[2,1-*b*]furan-2-carboxylate **2**. Similarly the reaction **1** with phenacyl bromide in the presence of anhydrous potassium carbonate in dimethyl formamide afforded 2-benzoyl-3-aminonaphtho[2,1-*b*]furan **6** by a known method**.** In this case condensation and Thorpe-Ziegler cyclization occurred in a single step.

2-Benzoyl-3-aminonaphtho[2,1-*b*]furan **6** on treatment with chloroacetyl chloride give corresponding a chloroacetamido compound **7** which on bromination and Nitration gave *N*-(2-benzoyl-8-substitutednaphtho[2,1-*b*]furan-1-yl)-2-chloroacetamide **8a-b.** The compounds **8a-b** underwent cyclization in methanolic ammonia to produce 5-phenyl-1H-2,3-dihydro-(8-substituted naphtho[2,1-*b*]furo[3,2-*e*])-1,4-diazepine-2-one **9a-b**.

Another method for the formation of 1,4-diazepine ring has been devised. In this method ethyl-3-aminonaphtho[2,1-*b*]furan-2-carboxylate **2** was converted into corresponding chloroacetyl compound **3** which on bromination and Nitration gaveethyl 1-[(chloroacetyl)amino]-8 substitutednaphtho[2,1-*b*]furan-2-carboxylate **4a-b.** The compounds **4a-b** underwent cyclization in methanolic ammonia to produce 1*H*-2,3,4,5-tetrahydro-(8-substitutednaphtho[2,1-**b**]furo[3,2-e])-1,4-diazepine-2,5-dione **5a-b.**

The condensation of **6** with ethyl chloroformate in the presence of anhydrous potassium carbonate in absolute ethanol to afford 2-benzoyl-3-carbethoxyaminonaphtho[2,1-*b*]furan **10.** The compounds 10 on bromination and nitration yields 2-benzoyl-3-carbethoxyamino-8-substitutednaphtho[2,1-*b*]furan**11a-b.**

The compound **11a-b** was further reacted with derivatives of hydrazine in refluxing ethanol. The products formed were identified as the hydrazones**12a-d.**

The cyclization of hydrazones**12a-d** was brought about by refluxing these compounds with acetic acid to obtain 5-phenyl-3-substituted-1*H*-2,3-dihydro-8-substituted naphtho[2,1-*b*]furo[3,2-*e*]-1,3,4-trizapin-2-ones **13a-d**.

The structures of the compounds are confirmed on the basis of IR, ^{1}H NMR spectral data. The compounds **5a-b 9a-b, 13a-d** are screened for Antibacterial and Antifungal activities.

Keywords: 8-Bromo/Nitronaphtho[2,1-b]furan, antibacterial activity and antifungal activity.

INTRODUCTION

Now a days research is concentrated toward the introduction of new and safe therapeutic agents of clinical importance. The heterocycles are enjoying their importance as being the centre of activity. 1,4-Diazepines have been the object of intense studies because of their biological activities such as anticancer[1-2], antimicrobial[3], psychotopics, anticonvulsant[4] and antiviral[5]. Various diazepines have been reported as antimicrobial and antiaxidant[6]. Molecular docking of pyrimidine and quinazoline derivatives of 1,5-benzodiazepine as potential anticancer agents[7].Bromazepam is used for muscle relaxant and agitation in the patient[8]. Bromazepam belongs to the group of 1,4-benzodiazepines, compounds which are widely used as psychotropic drugs [9]

Several derivatives of naphtho[2,1-*b*]furan synthesized have been reported to possess many biological and pharmacological activities such as antimicrobial, analgesic, anti-inflammatory, diuretic, anthelmintic, antipyretic[10-14] etc

Some of 1,5-benzodiazepine derivatives with substituted nitrogroup possesses good antimicrobial activity[15].

Encouraged by their potential clinical application and as part of our search for the synthesis of pharmacologically potent naphtho[2,1-*b*]furan derivatives[16-20], Molecular docking of pyrimidine and quinazoline derivatives of 1,5-benzodiazepine as potentialanticancer agents

we report herein a successful annulation of 1,4-diazepine and 1,3,4-triazepine moieties on 8-Bromo/Nitro naphtho[2,1-*b*]furan, and screening them for antimicrobial activities.

The method adopted for the synthesis of these new condensed tetracyclic heterocyclic compounds involved successive building up of furan and 1,4-diazepine or 1,3,4-triazepine rings on bromo/nitro substituted naphthalene.

MATERIALS AND METHODS

Melting points were determined in open capillary tubes and are uncorrected. Purity of the compounds was checked by TLC on silica gel G. 1H NMR spectra (300 MHz) were recorded on a Brucker Supercon FT NMR instrument using TMS as internal standard (chemical shifts in δ, ppm) IR spectra on a Perkin Elmer 157 infra red spectrophotometer (V_{max} cm^{-1}) and mass spectra on a Jeol JMS-D 300 mass spectrometer operating at 70 eV.

EXPERIMENTAL

Synthesis of 2-benzoyl-3-aminonaphtho [2,1-*b*]furans (6)

To a solution of 2-hydroxy-1-naphthaldehyde oxime**1** (1.87 g, 0.01 mol) in dry acetone (50 mL), phenacyl bromide (1.4 g, 0.01 mol) and anhydrous potassium carbonate (13.8 g, 0.1 mol) were added and reaction mixture was refluxed on a water bath for 12 hr. The potassium salt was filtered off and washed thoroughly with acetone. Removal of the solvent from the filtrate and subsequent trituration with ethanol gave 2-benzoyl-3-aminonaphtho[2,1-*b*]furan **6** as a light brown coloured solid, which was purified by column chromatography using 60-120 mesh silica gel and 5% methanol in chloroform as eluting solvent.

Synthesis of ethyl 3-aminonaphtho [2,1-*b*]furan-2-carboxylate (2)

To a solution of 2-hydroxy-1-naphthaldehyde oxime **1** (1.87 g**,** 0.01 mol) in dry DMF (25 mL), ethyl bromoacetate (1.67 g, 0.01 mol) and anhydrous potassium carbonate (13.8 g,0.1 mol) were added and reaction mixture was heated on a water bath for 24 hr. The reaction mixture was poured in to crushed ice, and kept overnight. The pasty product on trituration with cold and dilute sodium hydroxide gave ethyl 3-aminonaphtho[2,1-*b*]furan-2-carboxylate **2** as a brown coloured solid, which was purified by column chromatography using 60-120 mesh silica gel and 10% ethyl acetate in hexane as eluting solvent.

Synthesis of ethyl 3-chloroacetamido naphtho[2,1-b]furan-2-carboxylate 3

A mixture of **2** (0.01 mole) and chloroacetyl chloride (5ml) was gently heated under reflux for 3 hr. The reaction mixture on pouring into ice water furnished a solid, which on recrystallisation from ethanol gave **3** as brown crystalline solid.

Synthesis of 2-Benzoyl-3-chloroaceamido naphtho[2,1-*b*]furan 7

A mixture of **6** (0.02mole) and chloroacetyl chloride (5ml) was warmed on water bath for 1 hr and poured into ice water with constant stirring. The solid separated was collected and recrystallized from aqueous ethanol to give **7** as brown solid.

Synthesis of Ethyl 1-[(chloroacetyl)amido]-8 bromonaphtho[2,1-*b*]furan-2-carboxylate 4a

To a solution of ethyl naphtho[2,1-*b*]furan-2-carboxylate **3** (2.4 g, 0.01 mol) in glacial acetic acid (50 mL), bromine (0.8 g, 0.01 mol) in glacial acetic acid (20 mL) was slowly added with stirring over a period of 1 hr at 0-5˚C temperature and the stirring was continued for 3 hrs. The reaction mixture was poured in to ice cold water and the solid Ethyl 1-[(chloroacetyl)amino]-8 bromonaphtho[2,1-*b*]furan-2-carboxylate **4a** obtained was filtered out. It was washed with water, dried and the product was recrystallised from ethanol.

Synthesis of Ethyl 1-[(chloroacetyl)amido]-8 nitronaphtho[2,1-*b*]furan-2-carboxylate 4b

A cooled nitrating mixture of concentrated nitric acid and concentrated sulphuric acid in the ratio 1:2 (6.5ml: 13ml) was added very slowly to a cooled solution of ethyl 3-chloroacetamidonaphtho[2,1-b]furan-2-carboxylate **3.** (2.1g.0.01mol) in glacial acetic acid(4ml) and the mixture was stirred for about 30 min at 0-5ºC.The stirring was continued for 3hrs at the same temperature and the reaction mixture was poured on to crushed ice. The product which was separated as solid was collected and dried. Recrystallised from aqueous ethanol.

Synthesis of 1*H*-2,3,4,5-tetrahydro-(8-substitutednaphtho[2,1-b]furo[3,2-e])-1,4-diazepine- 2,5-dione 5a-b

Through a cooled suspension of **4a-b** (0.005 mole) in absolute methanol (25 ml), dry ammonia gas was bubbled till saturation. The resulting solution was left at room temperature for three days. the cloudy solution was concentrated under reduced pressure. The solid that separated was filtered and on recrystallization from aqueous dimethyl formamideofforded**5a-b** as colourless solid.

Synthesis of *N*-(2-benzoyl-8-bromonaphtho [2,1-*b*]furan-1-yl)-2-chloroacetamide 8a

To a solution of 2-Benzoyl-3-chloroaceamidonaphtho[2,1-*b*]furan **7** (2.4 g, 0.01 mol) in glacial acetic acid (50 mL), bromine (0.8 g, 0.01 mol) in glacial acetic acid (20 mL) was slowly added with stirring over a period of 1 hr at 0-5˚C temperature and the stirring was continued for 3 hrs. The reaction mixture was poured in to ice cold water and the solid *N*-(2-benzoyl-8-bromonaphtho[2,1-*b*]furan-1-yl)-2-chloroacetamide **8a.** obtained was filtered out. It was washed with water, dried and the product was recrystallised from ethanol

Synthesis of *N*-(2-benzoyl-8-nitronaphtho [2,1-*b*]furan-1-yl)-2-chloroacetamide 8b

A cooled nitrating mixture of concentrated nitric acid and concentrated sulphuric acid in the ratio 1:2 (6.5ml: 13ml) was added very slowly to a cooled solution of 2-Benzoyl-3-chloroaceamidonaphtho[2,1-*b*]furan **7** (2.1g.0.01mol) in glacial acetic acid(4ml) and the mixture was stirred for about 30 min at 0-5ºC.The stirring was continued for 3hrs at the same temperature and the reaction mixture was poured on to crushed ice. The product which was separated as solid was collected and dried. Recrystallised from aqueous ethanol.

Synthesis of 5-phenyl-1H-2,3-dihydro-(8-substituted naphtho[2,1-*b*]furo[3,2-*e*])-1,4-diazepine- 2-one 9a-b

Ammonia was bubbled through a suspension of **8a-b** (0.01 mole) in methanol (100 ml) at moderate rate at 10-15º C over a period of 30 min. It was allowed to stand at room temperature overnight. The solution was filtered and evaporated to dryness in vacuum. The residue was dissolved in chloroform (150ml), washed with water and hydrochloric acid (5X50 ml of 2N). The aqueous extracts were combined, make alkaline with ammonia and extracted with chloroform. The organic layer was dried over sodium sulphate, filtered, evaporated and the residue was recrystallized from methanol to get.

9a-b

Synthesis of 2-benzoyl-3-carbethoxyamino naphtho[2,1-*b*]furan 10

A mixture of 2-benzoyl-3-aminonaphtho[2,1-*b*]furans **6** (0.01 mole) ethyl chloroformate (10ml) and anhydrous potassium carbonate (2.5 g) in ethanol (30ml) was heated under reflux for 8 hr. The reaction mixture was filtered and the potassium salt was thoroughly washed with ethanol. Remove of solvent under reduced pressure and on recrystallization from aqueous dimethyl formamide gave **10** as brown solid.

Synthesis of 2-benzoyl-3-carbethoxyamino-8-bromonaphtho[2,1-*b*]furan 11a

To a solution of **10** (2.4 g, 0.01 mole) in glacial acetic acid (50 mL), bromine (0.8 g, 0.01 mol) in glacial acetic acid (20 mL) was slowly added with stirring over a period of 1 hr at 0-5˚C temperature and the stirring was continued for 3 hrs. The reaction mixture was poured in to

ice cold water and the 2-benzoyl-3-carbethoxyamino-8-bromonaphtho [2,1-*b*]furan **11a** obtained was filtered out. It was washed with water, dried and the product was recrystallised from ethanol.

Synthesis of 2-benzoyl-3-carbethoxyamino-8-nitronaphtho[2,1-*b*]furan 11b

A cooled nitrating mixture of concentrated nitric acid and concentrated sulphuric acid in the ratio 1:2 (6.5ml: 13ml) was added very slowly to a cooled solution of 2-benzoyl-3-carbethoxyaminonaphtho[2,1-*b*]furan **10** (2.1g.0.01mol) in glacial acetic acid(4ml) and the mixture was stirred for about 30 min at 0-5ºC.The stirring was continued for 3hrs at the same temperature and the reaction mixture was poured on to crushed ice. The product which was separated as solid was collected and dried. Recrystallised from aqueous ethanol.

Hydrazones of 2-benzoyl-3-carbethoxyamino-8-bromonaphtho[2,1-*b*]furan 12a and 12d

Compounds **11a-b** (0.01 mol) were refluxed with hydrazine hydrate (99%. 0.01 mole) in absolute ethanol (10 ml). The reaction mixture was cooled and the products separated as solid were recrystallized from aqueous dimethyl formamide to obtain **12a, 12d** as light brown crystalline solids.

The compound **12b and 12c** were synthesized similarly by reacting **11a-b** with phenyl hydrazine.

Synthesis of 5-phenyl-3-substituted-1*H*-2,3-dihydro-8-substituted naphtha [2,1-*b*] furo[3,2-*e*]-1,3,4-trizapine-2-ones 13a-d

Compounds **12a-d** (0.01 mole) were heated under reflux in glacial acetic acid (10ml) for 20 min and cooled. The products **13a-d,** separated as brown solid were collected and recrystallized from aqueous dimethyl formamide. The characteristic and spectral data of all the synthesized compounds are given in **Table I.**

EVALUATION OF ANTIBACTERIAL ACTIVITY

The newly synthesized diazepine and trazepine compounds have been screened for antibacterial activity against *Staphycoccus aureus*, and *Klebsiclla pneumoniae* by using cup plate method[24]. Ciprofloxacin was used as standards for comparison of antibacterial activities.

The zone of inhibition developed was measured accurately and recorded in the **table II.**

RESULT AND DISCUSSION

The key starting material, 2-hydroxy-1-naphtholdoxime **1** was synthesized from naphtholdehyde and converted to ethyl -3-aminonaphtho[2,1-*b*]furan-2-carboxylate **2**. Similarly the reaction **1** with phenacyl bromide in the presence of anhydrous potassium carbonate in anhydrous acetone afforded 2-benzoyl-3-aminonaphtho [2,1-*b*]furan **6** by a known method[24]**.** In this case condensation and Thorpe-Ziegler cyclization occurred in a single step.

2-Benzoyl-3-aminonaphtho[2,1-*b*]furan **6** on treatment with chloroacetyl chloride give corresponding a chloroacetamido compound **7** which on Bromination and Nitration gave *N*-(2-benzoyl-8-substitutednaphtho[2,1-*b*]furan-1-yl)-2-chloroacetamide **8a-b.** The compounds **8a-b** underwent cyclization in methanolic ammonia to produce 5-phenyl-1H-2,3-dihydro-(8-substituted naphtho[2,1-*b*]furo[3,2-*e*])-1,4-diazepine-2-one **9a-b**.**(Scheme-1).**Structure of **9a** which was established by spectral studies. The 300 MHz 1H NMR (DMSO-d_6) spectrum showed the signal at δ 3.8singlet (2H, CH_2) protons , signals at δ 9.4 (1H, NH) protons and multiplets at δ 6.8 – 8.0 (10H, ArH).

Another method for the formation of 1,4-diazepine ring has been devised. In this method ethyl -3-aminonaphtho[2,1-*b*]furan-2-carboxylate **2** was converted into corresponding chloroacetyl compound **3** which on Bromination and Nitration gave ethyl 1-[(chloroacetyl)amino]-8 substituted naphtho[2,1-*b*]furan-2-carboxylate **4a-b.** The compounds **4a-b** underwent cyclization in methanolic ammonia to produce 1*H*-2,3,4,5-tetrahydro-(8-substitutednaphtho[2,1-**b**]furo[3,2-e])-1,4-diazepine-2,5-dione **5a-b.**Structure of **5b**which was established by spectral studies. The 300 MHz 1H NMR (DMSO-d6) spectrum showed the signal at δ 3.9singlet (2H, CH_2) protons , broad signals at δ 8.9 and at δ 9.4 (2H, NH) protons and multiplets at δ 7.0 – 9.5 (5H, ArH).

There are several synthetic routes are available in the literature for 1,3,4-triazepine nucleus from 3-aminoketones[22-23]. The method adopted here involved the condensation of **6** with ethyl chloroformate in the presence of anhydrous potassium carbonate in absolute ethanol to afford 2-benzoyl-3-carbethoxyaminonaphtho[2,1-*b*]furan **10a-b.** The compounds 10a-b on bromination and nitration yields 2-benzoyl-3-carbethoxyamino-8-substitutednaphtho[2,1-*b*]furan **11a-b.** Structure of **11b**which was established by spectral studies. The 300 MHz 1H NMR (DMSO-d6) spectrum showed the signal at δ 1.27

triplet (3H, CH_2) (J=7.12 Hz) and δ 4.2 quartet (2H, CH_3) (J=7.11) indicating the presence of an ethyl group of ester, at δ 10.5single(1H, NH) and δ 7.5-9.0multiplet (6H, 10 ArH).

The compound **11a-b** was further reacted with derivatives of hydrazine in refluxing ethanol **(Scheme-2).** The products formed were identified as the hydrazones**12a-d** and not the alternatively possible caroxyhydrazides, on the basis of spectral data (**Table I**).

The cyclization of hydrazones**12a-d** was brought about by refluxing these compounds with acetic acid to obtain 5-phenyl-3-substituted-1*H*-2,3-dihydro-8-substituted naphtho[2,1-*b*]furo[3,2-*e*]-1,3,4-trizapin-2-ones **13a-d**.The 300 MHz 1H NMR (DMSO-d6) spectrum of **13b**showed the broad signal at δ 9.4singlet (1H, NH) protons and multiplets at δ 7.3 – 8.4 (15H, ArH). The absence of triplet and quartet which was found in its precursor confirms the formation of the product.

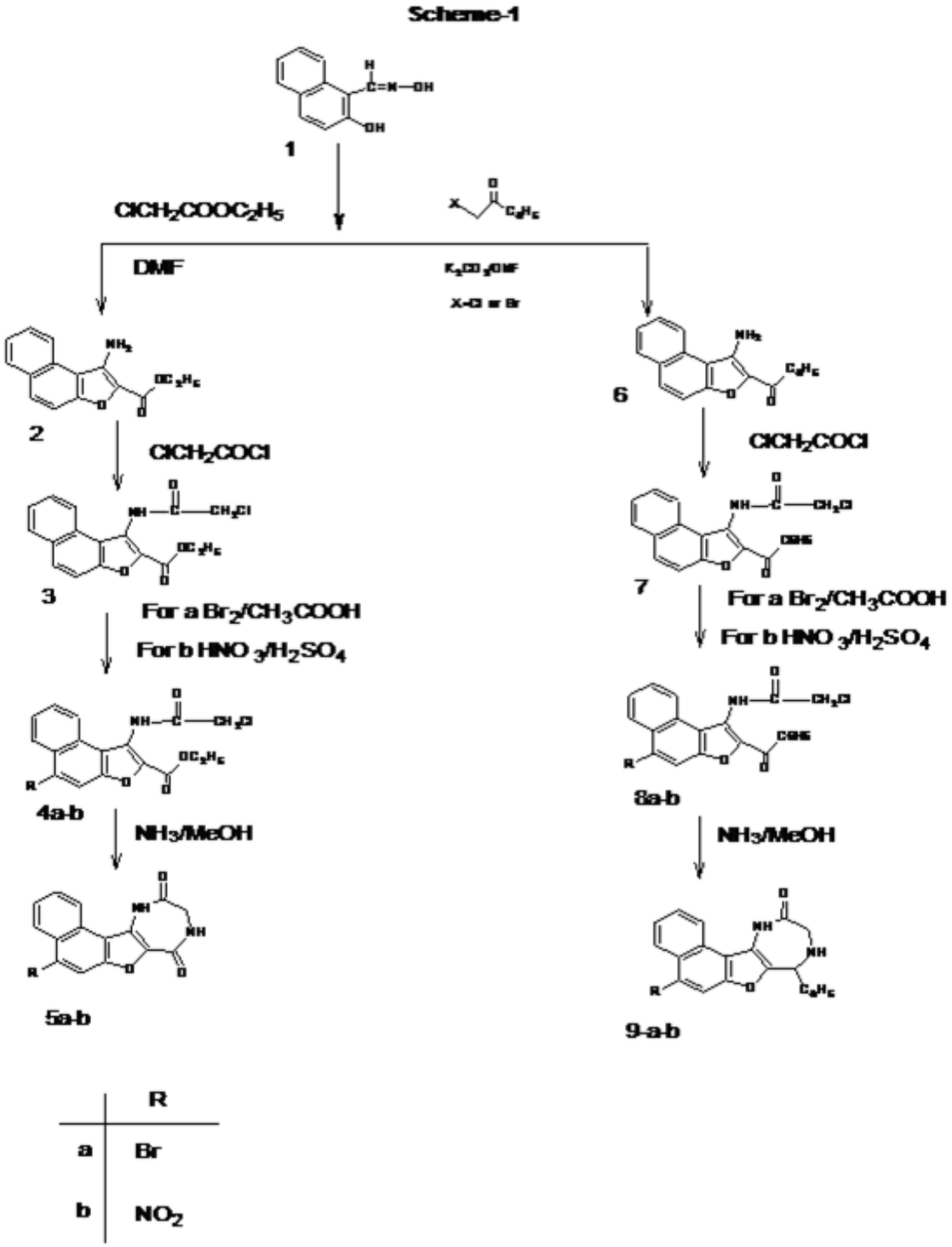
CONCLUSION

All compounds are isolated in good yield. The compounds were exhibited good antibacterial and antifungalactivity against *S. aureus, K. pneumoniae and A .niger,* and *C. Albicans* respectively. The above observation also reveals that the presence of the Bromine atom in the furan ring enhanced microbial activity of the compounds.

ACKNOWLEDGEMENTS

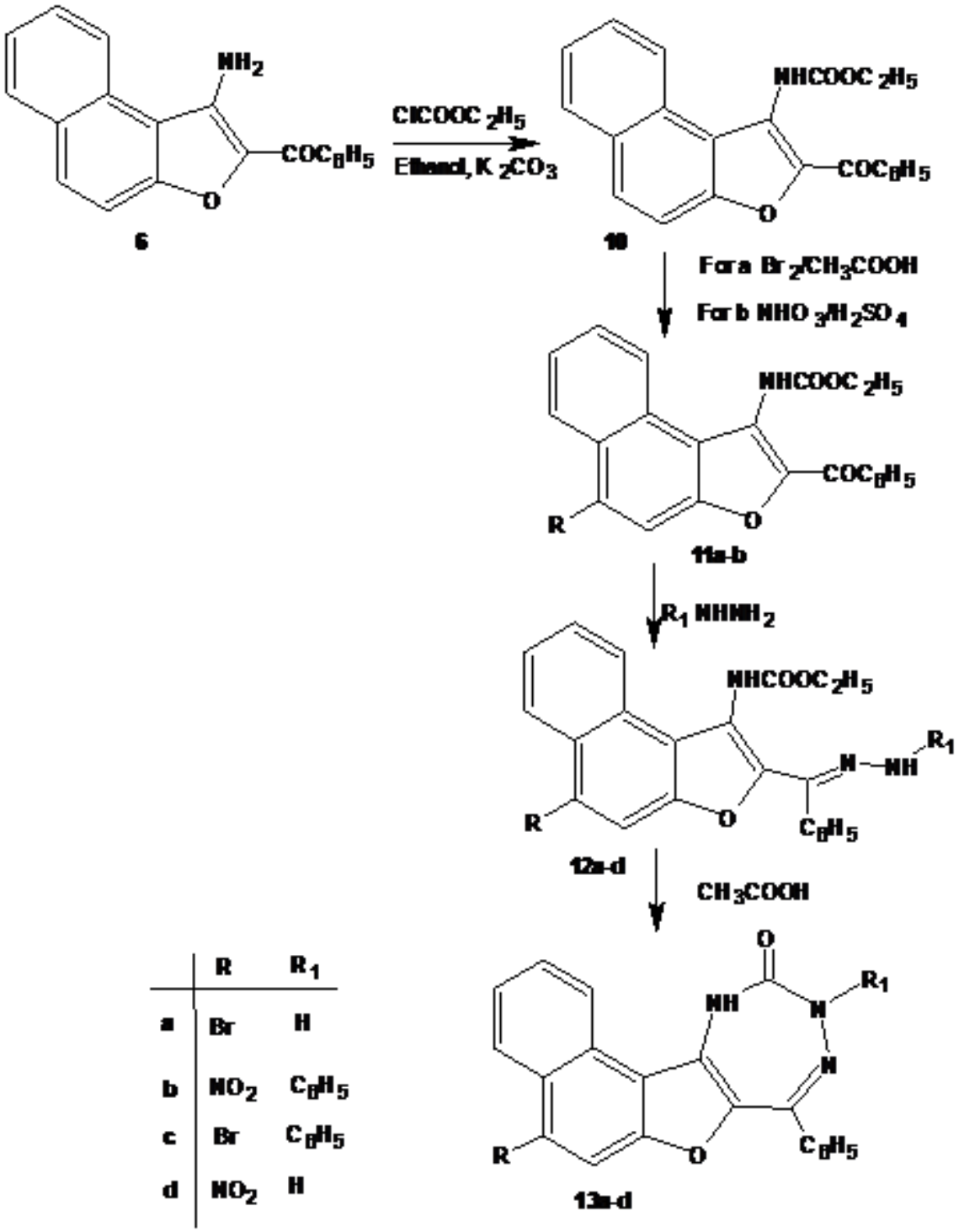
The authors are thankful to Head, SAIF, CDRI, Lucknow and IISc, Bangalore for providing the spectral analysis. One of the authors (DR) is grateful to UGC, New Delhi for awarding teacher fellowship.

Scheme-1



	R
a	Br
b	NO_2

Scheme-2



	R	R_1
a	Br	H
b	NO_2	C_6H_5
c	Br	C_6H_5
d	NO_2	H

Table I: Characteristic and spectral data of compounds 5a-b, 9a-b and 13a-d

Comp	R	R^1	Mol. formula	m.p ºC	1H NMR (δ,ppm)and MS
5a	Br	-	$C_{15}H_{19}N_2O_3Br$	201	3.7(s,2H,CH_2), 6.8-8.1(m,10H,ArH), 9.3(1H, NH)
5b	NO_2	-	$C_{15}H_{19}N_3O_5$	210	3.9(s, 2H,CH_2), 8.9(bs,1H, HN), 9.4(bs,1 H, NH),7-9.5(m,5H, ArH)
9a	Br	-	$C_{21}H_{13}N_2O_2Br$	260	3.8(s,2H,CH_2), 6.8-8, (m,10H,ArH), 9.4, 1H(NH)
9b	NO_2	-	$C_{21}H_{13}N_3O_4$	268	3.9(s, 2H,CH_2), 9.3(bs,1H, HN), 6.9-9.6(m,5H, ArH)
11b	NO_2	-	$C_{22}H_{16}N_2O_6$	146	1.27(t,3H,CH_3), 4.2(q, 2H, CH_2), 10.5(s, 1H, NH), 7.5-9.0 (m, 10H,ArH)
13a	Br	H	$C_{20}H_{12}N_3O_2Br$	186	7.2-8.5(m,10ArH), 9.3(bs, 1H, NH)
13b	NO_2	C_6H_5	$C_{26}H_{16}N_4O_4$	290	7.3-8.4(m,15ArH), 9.4(bs, 1H,NH)
13c	Br	C_6H_5	$C_{26}H_{16}N_3O_2Br$	195	7.2-8.3(m,15ArH), 9.2(bs, 1H, NH)
13d	NO_2	H	$C_{20}H_{12}N_4O_4$	201	7.4-8.5(m,10ArH), 9.4(bs, 1H, NH)

Table II: Antimicrobial activities of compounds 5a-b, and 13a-d

Compounds	Antibacterial activity zone of inhibition in mm		Antifungal activity zone of inhibition in mm	
	S. aureus	***K.pneumoniae***	***A. niger***	***C. albicans***
5a	18	16	18	22
5b	15	14	16	17
9a	20	21	18	21
9b	17	17	16	15
13a	18	20	21	19
13b	16	18	18	16
13c	21	22	20	23
13d	20	20	19	21
Std	**24**	**26**	**23**	**24**

REFERENCES

1. Krezel I, Mikiciuk Olasik E, Zurrek E and Glowka ML. New mitoguazone analogues with anticancer activity. Pharm Pharmacol Commun. 1999;5:458.
2. Sandra Cortez, María Teresa RamírezApan, Simón Hernández-Ortega, Antonio Nieto, Irina V Lijanovab and Martínez-GarcíaMarcosa,Anti-cancer agents in medicinal chemistry, Anticancer Activity and Anti-inflammatory Studies of 5-Aryl-1,4-benzodiazepine Derivatives. 2012;12(6):611-619.
3. Priti U Warbhe and Reshal A Deshmukh. Synthesis, spectral studies and antimicrobial studies of 7-[phenylamino]-5-methyl-1,4-diazepines and its derivatives,Journal of Chemical and Pharmaceutical Research. 2016;8(8):364-368.
4. Rashid M, Mishra R, Husain A and Ahmad B. Synthesis of some novel C_3 Substituted New Diazo-[1,4]-Benzodiazepine-2-One Derivatives As potent anticonvulsants, Chemical Sciences Journal. 2010:5:1-9.
5. Phillips OA, Murthy KSK, Ciakpuri CY and Knaus EE. Can J Chem. 1999;77:216.
6. Parmar NJ, Barad HA, Pansuriya BR, Teraiya SB, Gupta VK and Kant R. An efficient one-pot synthesis, structure, antimicrobial and antioxidant investigations of some novel quinolyldibenzo[b, e][1,4]diazepinones. Bioorg Med Chem Lett. 2012;22(11):3816–21.
7. Apoorva M, Dharma K, Ved Prakash V, Sunil D, Subhash Chandra, Neha Gupta, Sameer Bhagyawant, Jaya Dvivedi, Zeid A Alothman, Saik Mohammad Wabaidur and Swapnil Sharma. Synthesis, biological evaluation and molecular docking of pyrimidine and quinazoline derivatives of 1,5-benzodiazepine as potential anticancer agents, Journal of King Saud University Science. 2020;32(2):1486-1495.
8. Sternbach LH. The benzodiazepine story. J Med Chem. 1979;22.
9. Pfendt LB, Popovi GV and Damjanovi T. Protolyticequilibria of bromazepam. J Serb Chem Soc. 2002;67:187.

10. Kumaraswamy MN, Prathima Mathias DA, Chandrashekhar C and Vaidya VP. Synthesis and pharmacological evaluation of 2-mercapto-4-substitutednaphtho [2,1-b]furo[3,2-d] pyrimidines. Indian J Pharma Sci. 2006;68(6):731-735.
11. Kumaraswamy MN, Prathima Mathias DA, Chandrashekhar C, Shivakumar H, Mahadevan KM and Vaidya VP. Novel approach towards the synthesis of 2-(1-naphtho[2,1-b]furan-2-ylcarbonyl)-3,5- disubstituted-2,3-dihydro-1H pyrazoles. As a new class of antimicrobial and pharmacological agents. Indian J Pharma Sci. 2008;70(6):715-720.
12. Nagaraj GK, Prakash GK, Kumaraswamy MN, Vaidya VP and Mahadevan KM. Synthesis of novel nitrogen containing naphtho[2,1-b]furan derivatives and investigation of their antimicrobial activities. Arkivoc. 2006;15:160-168.
13. Vaidya VP, Shruthi E and Yamuna AJ. Synthesis of Substituted Urea Derivatives Encompassing Naphtho[2,1-b]Furan and Evaluation of Their Antimicrobial Activity. Res J Pharma Bio Chem Sci. 2011;2(4):35-43.
14. Kumaraswamy MN, Vaidya VP, Chandrasekhar C, Prathima Mathias DA, Shivakumar H and Mahadevan KM. Synthesis of Novel 5,8-Dihydro[1,2,4]Triazolo[3,4-b] [1,3,4]Thiadiazepines Derivatives Involving Naphtho[2,1-b] Furan and Evaluation of their possible pharmacological activities. International journal of Pharmaceutical and Chemical Sciences. 2016;5(4):245-251.
15. Kumaraswamy MN, Vaidya VP, Chandrashekhar C, Prathima Mathias DA, Shivakumar Hand and Mahadevan KM, Synthesis of Novel 2,5-Dihydro-1H-1,5- Benzodiapenes encompassing Naphtho[2,1-b]furan and Evaluation of their pharmacological activities. International Journal of Pharmaceutical, Chemical and Biological Science. 2013;3(2):281-287.
16. Vagdevi HM and Vaidya VP. Studies in naphthofurrans: Part III-Synthesis of 2- substituted naphtha[2,1]furans, 2-(2'- aryl-3'-acetyl-1',3'4'-oxadiazolyl) amino naphtha[2,1-b]furans and their biological activities. India J Heterocyclic Chem. 2001;10:253-260.
17. Chandrashekhar CH, Latha KP, Vagdevi HM and Vaidya VP. Synthesis and antimicrobial activity of chalcones of naphtho [2, 1-b] furan condensed with barbituric acid. Der Pharma chemica. 2011;3(5):329-333;3.
18. Basavaraj Padmashalil, Vaidya VP and Vijaya Kumar ML. Synthesis and Pharmacological Evaluation of some naphtha[2-b]furo[3-2-d] pyrimidines. Indian J Heterocycl Chem. 2002;12:89-94.
19. Mahadevan KM and Vaidya VP. Studies in Naphthofurans: Part IV-Synthesis of some 2-Isoxazolyl, Pyrazolyl, Pyrimidyl and Quinolinyl Naphtho[2,1-b]furan Derivatives and their Biological Activities. Journal of Indian Council Chemists. 2001;18(2):78-82.
20. Mahadevan KM, Basavarajj Padmashali and Vaidya VP. Studies in Naphthofurans: Part V-Synthesis of 2aryl-1,2,3,4,-tetrahydropyrido(Naphto[2,1-b]furan)-4-ones and their Biological Activities. Indian J Heterocycl Chem. 2002;11:15-20.
21. Ramesh D, Chandrashekhar and Vaidya VP. Synthesis of novel naphtho[2,1-b]furo[3.2-b]pyridine derivatives as potential antimicrobial agents. Indian Journal of Chemistry. 2008;47B:753.
22. Vaidya VP, Vagdevi HM and Mahadevanand Shreedhara CS. Synthesis of naphtho[2,1-b]furo[3,2-e]-1,4-diazepin-2-ones and naphtho[2,1-b]furo[3,2-e]-triazepine-2-ones of pharmacological interest. Indian Journal of Chemistry. 2004;43B:1537.
23. Basavaraja KM, Vaidya VP and Chandrashekhar C. Synthesis of Benzofuro[3,2-e]-diazepines of pharmacological Interest. E-Journal of Chemistry. 2008;5(3):567.
24. Indian Pharmacopoeia. Antimicrobial Controller of Publications. Delhi. 1996;2:100-106.