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Synthesis, Characterization and Biological Evaluation of Dihydropyrimidinone and Dihydropyrimidine thionones Derivatives of Naphthofuran via one pot Reaction

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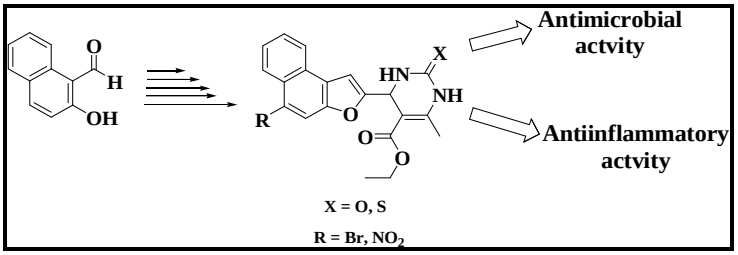
ABSTRACT

In the present study one pot condensation reaction of napthafuran-2-carbaldehyde, ethyl acetoacetate and thiourea or urea via Biginelli reaction was carried out and characterization of the derivatives was done by spectroscopic techniques. The newly synthesized compounds showed moderate to good antimicrobial as well as anti-inflammatory activities compared to standard drugs.

Graphical Abstract



Keywords: Naphthofuran-2-carbaldehyde**,** three component reaction, *in-vitro* antimicrobial and anti-inflammatory activity.

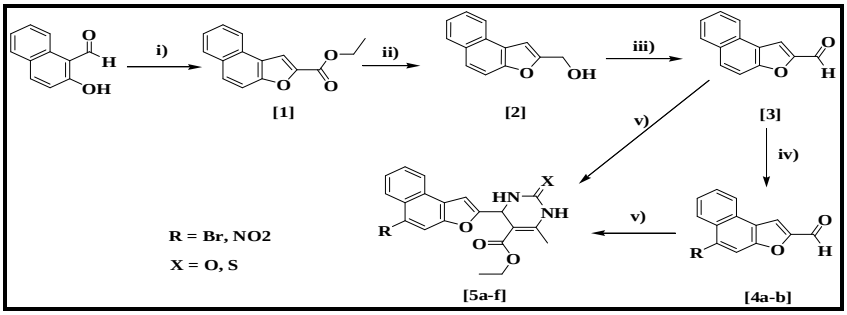
INTRODUCTION

Multicomponent reactions (MCRs) such as Biginelli reaction is a condensation reaction of an aldehyde, β-keto ester and urea or thioureain presence of an acid catalyst to give a dihydropyrimidine [**1**]. This reaction is used to prepare dihydropyrimidinone and their sulphur analogues dihydropyrimidinethiones compounds possessing wide range of biological and pharmacological activitiesand they have been known to possess antibacterial, antiviral, antitumor, anti-inflammatory [**2**] and antihypertensive along with calcium channel blocker [**3–5**], α-la-antagonist [**6–8**] and neuropeptide Y (NPY) antagonist [**9**] activities. On the other hand naphthofuran also has diverse pharmacological as well as biological properties such as antibacterial, antitumor and anthelmintic activities [**10**]. With these properties possessed by dihydropyrimidines, naphthofuran derivatives and

also in search of new drugs with antimicrobial and anti-inflammatory activity with a minimal side effects are still main objective for medicinal chemists, hence in this article we designed a synthetic pathway to synthesise a novel molecule containing both dihydropyrimidinone and naphthofuran motifs in one pot three component condensation reaction. In order to check potency the synthesized compounds were screened for their *in-vitro* antimicrobial and anti-inflammatory activities.

MATERIALS AND METHODS

The chemical reagents and solvents used in the reactions were purchased from Merck, Sigma Aldrich, SD fine and wereusedwithout further purification. FTIR spectra were recorded in KBr pellets on a Perkin- Elmer Spectrometer. ^{1}H NMR spectra (400 MHz) was recorded in $CDCl_3$/DMSO-d_6 solvent on a Bruker Avance DPX-250 FT-NMR spectrometer using internal standard (TMS). Melting points of all the solid derivatives were recorded in open capillary tubes using Stuart Scientific Apparatus SMP3 (UK). TLC was used to check the purity of the compounds and progress of reaction.



Scheme 1. Synthetic route for the preparation of dihydropyrimidinone and dihydropyrimidinethionones derivatives of Naphthofuran

Reagents and conditions: i) $ClCH_2COOEt$, K_2CO_3, DMF, reflux; ii) $LiAlH_4$, THF, 0°C; iii) IBX, EtOAc, reflux; iv) Br_2/AcOH and KNO_3/H_2SO_4; v) Urea/Thiourea, Ethyl acetoacetate, PTSA, EtOH, reflux.

Preparation of Ethyl naphthofuran-2-carboxylate [1]: 2-hydroxy-1-naphthaldehyde (0.03 mol) was taken in dry N, N dimethylformamide (25 mL), to this ethylchloroacetate (0.03 mol) and anhydrous potassium carbonate (0.9 mol) were added and the reaction mixture was heated on water bath for 24 h. The conversion was monitored by TLC. After completion of reaction, the reaction mixture was then poured into ice cold water, to obtain the product ethyl naphthofuran-2-carboxylate as solid, which was collected by filtration, dried. The pure compound was obtained through recrystallization using ethanol.

Preparation of Naphthofuran-2-ylmethanol [2]: To a cooled (0°C) and continuous stirring solution of Lithium aluminum hydride (0.04 mol) in tetrahydrofuran (5 mL), ethyl naphthofuran-2-carboxylate (0.01 mol) in tetrahydrofuran (5 mL) was added drop wise and the resulting mixture was stirred at lab temperature for 2 h. The formation of product was monitored by thin layer chromatography. Towards the end of the reaction, ammonium chloride solution was added to the whole mixture and extracted to organic layer (EtOAc) and concentrated in vacuuo to get crude product. Further pure product was obtained by column chromatography on silica gel.

Preparation of Naphthofuran-2-carbaldehyde [3]: To a solution of Naphthofuran-2ylmethanol (0.01 mol) in ethyl acetate (7 mL) and IBX (0.03 mol) was added. The resulting mixture was refluxed with calcium chloride guard tube at 80°C. After 3.5 h as TLC indicated disappearance of the reactant, the reaction mixture was cooled to lab temperature and filtered through a celite, washed with ethyl acetate (5 mL) and concentrated to obtain naphthofuran-2-carbaldehyde.

Preparation of8-Nitronaphthofuran-2-carbaldehyde [4a]: In a round bottom flask containing ethyl naphthofuran-2-carbaldehyde (0.1 mol) in glacial CH_3COOH (20 mL), conc. H_2SO_4 (2 mL) and potassium nitrate (2 g) were added with stirring for 1h at 0°C and further stirring was continued for 2h at lab temperature. As the thin layer chromatography observation indicated the completion, the reaction mixture was decanted into ice-cold water to get solid product. The obtained solid was filtered off, washed with water and dried. The pure compound was obtained by column chromatography on silica gel using eluents EtOAc: n-hexane in 9:1ratio.

Preparation of 8-Bromonaphthofuran-2-carbaldehyde [4b]: To a previously cooled solution (10-20^oC) of ethyl naphthofuran-2-carbaldehyde (0.1 mol) in glacial acetic acid (20 mL), bromine (0.1 mol) in acetic acid (20 mL) was added drop wise for1h and the stirring was continued for 3h after complete addition at lab temperature. After the formation of product as indicated by TLC, the reaction mixture was poured into cold water and the solid obtained was filtered off, washed with water and dried. The crude product was subjected to purification by column chromatography using silica gel (EtOAc: n-hexane- 9:1) to get pure compound.

General method for the preparation of ethyl 6-methyl-4-(naphtho[2,1-b]furan-2-yl)-2-oxo/thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate[5a-f]:A mixture of substituted naphtho-furan-2-carbaldehyde (0.0025 mol), urea/thiourea (0.00375 mol), ethylacetoacetate (0.00275 mol) and *p*-toluene sulphonic acid (0.00025 mol) in EtOH (10 mL) was heated at 80°C. After the completion of the reaction as observed through TLC, the solvent was evaporated in vacuuo under reduced pressure to get product **[5a-f].** Further to get pure compounds it was subjected to column chromatography using $CHCl_3$-MeOH (8:2) as eluent to afford pure product [**5a-f]**.

Antibacterial activity: The *in vitro* antimicrobial activity screening cup plate method [**11**] was employed against two bacterial and two fungal strains such as *Escherichia coli*, *Staphylococcus aureus*, *Candida albicans* and *Asparagus Niger* respectively. In this method wells of diameter 6 millimeters were made with the help of sterile cork borer and wells were numbered. Using sterile micropipettes control (DMF) and solutions of **[5a-f]**(0.1 mL) of known concentration were added into the bored cups along with standard drug. The petri plates were left standing for 2 h at room temperature and then incubated for 24 h at 37°C.

Antifungal activity: For antifungal activity, potato dextrose agar (PDA) medium was used and the incubation period of 24-48 h at 27±0.2°C was maintained. The zone of inhibition was recorded.

Anti-inflammatory activity: The protocol for the anti-inflammatory assay was performed as per Ling et al and Sigma [**12**]. In this method the concentration of the compounds **[5a-f]** tested were in the range of 10-100 µg and the inhibitory property was compared by measuring the absorbance of the mixture at 600 nm with that of the reference drug Indomethacin.

Spectral Interpretation

Ethyl naphthofuran-2-carboxylate [1]: FTIR (KBr): 3058 (ArH str), 2907 (CH str), 1724 (CO str), 1364 cm^{-1}(CO). **^{1}H NMR ($CDCl_3$, 400MHz):δ**8.46-8.44 (d, 2H, ArH), 8.08-8.02 (m, 2H, ArH), 7.88-7.86 (d, 1H, ArH), 7.70-7057 (m, 2H, ArH), 4.41-4.36 (q, 2H, CH_2-CH_3), 1.38-1.34 (t, 3H, CH_2-CH_3). **MS (m/z):** 242.0 (M+).

Naphthofuran-2-ylmethanol [2]: FTIR (KBr): 3225 (OH str), 3052 (ArH), 2860 (CH str), 1381 cm^{-1}(CO). **^{1}H NMR ($CDCl_3$, 400MHz): δ** 8.27-8.25 (d, 2H, ArH), 8.03-8.01 (d, 1H, ArH), 7.81-7.74 (m, 2H, ArH), 7.62-7.39 (m, 3H, ArH), 5.54-5.51 (t, 1H, OH), 4.66-4.65 (d, 1H, CH_2). **MS (m/z):** 181.0 (M+).

Naphthofuran-2-carbaldehyde [3]: FTIR (KBr): 2918 (ArH str), 2535 (CHO str), 1695 (CO str), 1324 cm^{-1}(CO). **^{1}H NMR ($CDCl_3$, 400MHz):δ**9.89 (s, 1H, CHO), 8.63 (d, 1H, ArH), 8.46--8.44 (d,

1H, ArH), 8.13-8.10 (m, 2H, ArH), 7.91-7.89 (d, 1H, ArH), 7.76-7.61 (m, 2H, ArH). **MS (m/z):** 198.0 (M+).

8-Nitronaphthofuran-2-carbaldehyde [4a]: FTIR (KBr): 3099 (ArH str), 2920 (CHO str), 1683 (CO str), 1518 (NO_2Asym), 1444 (NO_2 sym), 1313cm^{-1}(CO). **^{1}H NMR ($CDCl_3$, 400MHz):δ**10.00 (s, 1H, CHO), 8.63 (d, 1H, ArH), 8.44--8.26 (d, 1H, ArH), 8.13-8.10 (m, 2H, ArH), 8.08-8.02 (d, 1H, ArH), 7.81-7.76 (m, 2H, ArH). **MS (m/z):**255.05 (M+).

8-bromonaphthofuran-2-carbaldehyde [4b]: FTIR (KBr): 3097 (ArH str), 2983 (CHO str), 1703 (CO str), 1315cm^{-1}(CO).b **^{1}H NMR ($CDCl_3$, 400MHz):δ**10.00 (s, 1H, CHO), 8.62 (d, 1H, ArH), 8.46--8.44 (d, 1H, ArH), 8.13-8.10 (m, 1H, ArH), 7.91-7.89 (d, 1H, ArH), 7.76-7.61 (m, 2H, ArH). **MS (m/z):**287.0 (M+), 289 (M+2).

6-methyl-4-(naphthofuran-2-yl)-2-oxo-1,2,3,4-tetrahydropyrimidine ethyl carboxylate [5a]: FTIR (KBr): 3216 (NH str), 3097 (ArH str), 2983 (CH_3 str), 1703 (CO str), 1651 (CO str), 1315cm^{-1}(CO).
^{1}H NMR ($CDCl_3$, 400MHz):δ9.40 (s, 1H, NH), 8.31-8.29 (d, 1H, ArH), 8.02-8.00 (d, 2H, ArH), 7.81-7.74 (m, 2H, ArH), 7.62-7.49 (m, 2H, ArH), 7.27 (s, 1H, ArH), 5.47 (s, 1H, CH), 4.09-4.03 (m, 2H, CH_2), 2.32 (s, 3H, CH_3), 1.16-1.13 (t, 3H, CH_3). **MS (m/z):**351.47 (M+).

6-methyl-4-(5-bromonaphthofuran-2-yl)-2-oxo-1,2,3,4-tetrahydropyrimidine ethyl carboxylate [5b]: FTIR (KBr): 3226 (NH str), 3087 (ArH str), 2985 (CH_3 str), 1713 (CO str), 1652 (CO str), 1310cm^{-1}(C-O). **^{1}H NMR ($CDCl_3$, 400MHz):δ**9.06 (s, 1H, NH), 8.28-7.80 (d, 2H, ArH), 7.77-7.69 (m, 2H, ArH), 7.62-7.49 (m, 2H, ArH), 5.45 (s, 1H, CH), 4.00-3.89 (m, 2H, CH_2), 2.35 (s, 3H, CH_3), 1.11-1.08 (t, 3H, CH_2-CH_3). **MS (m/z):**430.0 (M+), 432 (M+2).

6-methyl-4-(5-nitronaphthofuran-2-yl)-2-oxo-1,2,3,4-tetrahydropyrimidine carboxylate[5c]: FTIR (KBr): 3216 (NH str), 3097 (ArH str), 2983 (CH_3 str), 1713 (CO str), 1651 (CO str), 1514 (NO_2Asym), 1414 (NO_2 sym), 1315 cm^{-1}(CO). **^{1}H NMR ($CDCl_3$, 400MHz,):δ**9.00 (s, 1H, NH), 8.22-7.68 (d, 2H, ArH), 7.71-7.58 (m, 2H, ArH), 7.60-7.50 (m, 2H, ArH), 5.39 (s, 1H, CH), 4.01-3.88 (m, 2H, CH_2), 2.30 (s, 3H, CH_3), 1.12-1.02 (t, 3H, CH_2-CH_3). **MS (m/z):**395.1 (M+).

6-methyl-4-(naphthofuran-2-yl)-2-thioxo-1,2,3,4-tetrahydropyrimidine ethyl carboxylate[5d]: FTIR (KBr): 3361 (NH str), 3057 (ArH str), 2928 (CH str), 1720 (CO str), 1663 (CO str), 1311cm^{-1}(CO). **^{1}H NMR ($CDCl_3$, 400MHz):δ**8.06 (s, 1H, NH), 8.04-7.41 (m, 7H, ArH), 5.70-5.69 (d, 1H, CH), 4.18-4.09 (m, 2H, CH_2), 2.43 (s, 3H, CH_3), 1.28-1.24 (t, 3H, CH_3). **MS (m/z):**366.10 (M+).

6-methyl-4-(5-bromonaphthofuran-2-yl)-2-thioxo-1,2,3,4-tetrahydropyrimidineethylcarboxylate [5e]: FTIR (KBr): 3225 (NH str), 3067 (ArH str), 2999 (CH_3 str), 1705 (CO str), 1645 (CO str), 1315 cm^{-1}(C-O). **^{1}H NMR ($CDCl_3$, 400MHz):δ**8.00 (s, 1H, NH), 7.80--7.32 (m, 5H, ArH), 6.42 (m, 1H, ArH), 5.70-5.69 (d, 1H, CH), 4.19-4.07 (m, 2H, CH_2), 1.71 (s, 3H, CH_3), 1.30-1.28 (t, 3H, CH_3). **MS (m/z):**445.01 (M+), 447 (M+2).

6-methyl-4-(5-nitronaphthofuran-2-yl)-2-thioxo-1,2,3,4-tetrahydropyrimidineethylcarboxylate [5f]: FTIR (KBr): 3250 (N-H str), 3057 (ArH str), 2984 (CH_3 str), 1710 (CO str), 1655 (CO str), 1525 (NO_2Asym), 1399 (NO_2 sym), 1300cm^{-1}(CO). **^{1}H NMR ($CDCl_3$, 400MHz):δ**8.16 (s, 1H, NH), 8.00-7.45 (m, 5H, ArH), 6.44 (m, 1H, ArH), 4.82-5.09 (d, 1H, CH), 4.19-4.00 (m, 2H, CH_2), 2.36 (s, 3H, CH_3), 1.28-1.24 (t, 3H, CH_3). **MS (m/z):**411.0 (M+).

RESULTS AND DISCUSSION

Synthetic pathway for the one pot condensation reaction is as shown in the scheme 1. The key starting material for the synthesis Ethylnaphthofuran-2-carboxylate **[1]** was obtained by the reaction of

hydroxyl naphthaldehyde with ethylchloroacetate in presence of base under reflux condition. Further, reduction of **[1]** with LAH gave corresponding reduction product alcohol **[2]** and further the obtained compound **[2]** was oxidized with IBX to get naphthofuran-2-carbaldehyde **[3].** Finally, compound **[3]** subjected to bromination and nitration reaction to get **[4a-b].** Finally compounds **[3]** and **[4a-b]** underwent acid catalyzed three component condensation reaction withethyl acetoacetate and urea/thiourea to give corresponding condensation products **[5a-f]**. Physical characterization data of the dihydropyrimidinone and dihydropyrimidinethionones derivatives of Naphthofuran **[5a-f]** along with yield are tabulated in table 1. The structures of the new derivatives **[5a-f]** were confirmed by their spectral data (FT IR, ^{1}H NMR and mass) analysis figure 1.

Table 1. Physical characterization data of the dihydropyrimidinone and dihydropyrimidinethionones derivatives of Naphthofuran

Comp Name	R	X	Molecular formula	Melting point (°C)	Yield (%)
1	-	-	$C_{15}H_{12}O_3$	100	77
2	-	-	$C_{13}H_{10}O_2$	135	91
3	-	-	$C_{13}H_8O_2$	258	90
4a	Br	-	$C_{13}H_7BrO_2$	185	80
4b	NO_2	-	$C_{13}H_7NO_4$	250	79
5a	H	O	$C_{20}H_{18}N_2O_4$	340	91
5b	Br	O	$C_{20}H_{17}BrN_2O_4$	318	84
5c	NO_2	O	$C_{20}H_{17}N_3O_6$	346	86
5d	H	S	$C_{20}H_{18}N_2O_3S$	269	81
5e	Br	S	$C_{20}H_{18}BrN_2O_3S$	217	79
5f	NO_2	S	$C_{20}H_{17}N_3O_5S$	289	76

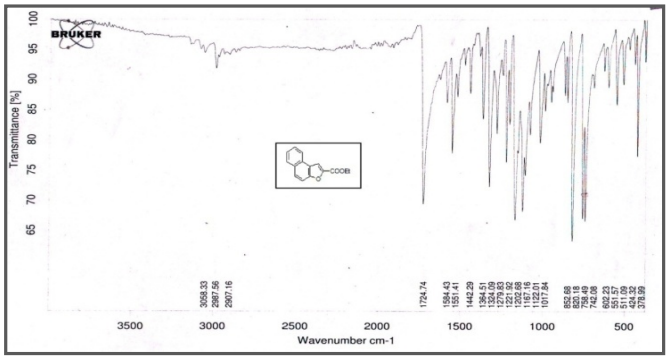


Figure 1. IR spectrum of ethyl naphthofuran-2-carboxylate [**1].**

Antimicrobial studies: The screening data of the antibacterial activity indicated that among the dihydropyrimidinone and thionone derivatives of Naphthofuran **[5a-f]** tested, compounds **[5b**] and **[5e]** with bromo substituents showed moderate antibacterial activity against *Staphylococcus aureus* and *Escherichia coli.* However, the remaining compounds showed antibacterial activities lesser than that of the standard drug.

The result of the antifungal activity revealed that the compounds **[4b]** and **[5b]** carrying bromo substituent along with compound **[5c]** carrying nitro substituent showed moderate activity against *Asparagus niger* and *Candida Albicans.* However, the remaining compounds did not show any appreciable activity. The results of the both activities are tabulated in the table 2.

Anti-inflammatory studies: Anti-inflammatory activity by hyaluronidase enzyme method indicated all the compounds **[5a-f]** tested did not show any significant anti-inflammatory activity at concentration 10µg and 50 µg. However, at 100 µg concentration, all the synthesized derivatives **[5a-f]** showed moderate activity, but less than that of the standard drug Indomethacin which has %

inhibition of 77.95 at concentration of 10µg as shown in the table 3 and depicted graphically in figure 2.

Table 2. Antibacterial and antifungal activity of dihydro pyrimdinone and thionone derivatives of naphthofurans [5a-f]

Compounds	Conc. 2 mg Zone of inhibition (in mm)			
	S. aureus	*E.coli*	*A.niger*	*C.albicans*
5a	3	4	2	2
5b	16	14	10	9
5c	9	8	5	6
5d	5	7	4	5
5e	15	16	11	10
5f	12	11	13	14
Gentamycin	18	18	-	-
Amphotericin	-	-	18	18
Control	-	-	-	-

Table 3. Antiinflammatory activity of dihydropyrimdinone and thianone derivatives of naphthofuran [5a-f]

Sample	R	Test concentration (in µg)	% inhibition
Ref		-	100
		10	4.86
4a	**H**	50	15.75
		100	25.59
		10	5.25
4b	**Br**	50	21.52
		100	32.41
		10	1.97
4c	**NO_2**	50	22.18
		100	39.50
		10	7.22
5d	**H**	50	13.78
		100	25.98
		10	9.71
5e	**Br**	50	31.63
		100	58.66
		10	77.95
Indomethacin	**Standard**	50	*
		100	*

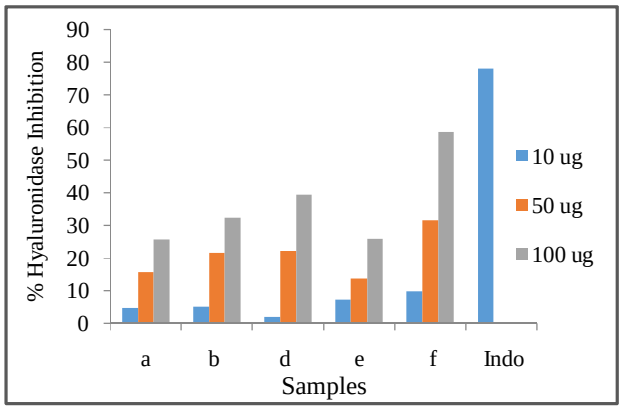


Figure 2. Hyaluronidase inhibition profile as demonstrated by the samples.
(Labels: Sample **4**a= a, **4b**=b, **4d**= d, **5e**= e, **5f**= f, **Indomethacin**= Indo)

APPLICATION

Condensed products of dihydropyrimdinone and thionone derivatives of Naphthofuran with bromo substituent are useful against the bacterial function.

CONCLUSION

In summary we have synthesized novel condensation product dihydropyrimdinone and thionone derivatives of naphthofuran **[5a-f]** through one pot three component reaction and characterized the synthesized molecules by spectroscopic techniques. The *in-vitro* antimicrobial and anti-inflammatory screening of the compounds **[5a-f]** revealed that the derivatives with bromo substituent have moderate activity, whereas other derivatives did not show any appreciable activity.

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REFERENCES

[1]. P. Biginelliand Gazz, Synthesis of 3,4-Dihydropyrimidin-2(1H)-Ones,*Chim. Ital*, **1983**, 23, 360-416.
[2]. C. O. Kappe, Biologically active dihydropyrimidones of the Biginelli-type- a literature survey. *Eur. J. Med. Chem.*, **2000**, 35, 1043-1052.
[3]. K. S. Atwal, B. N. Swanson, S. E. Unger, D.M. Floyd, S. Moreland, A. Hedberg, O'Reilly, Dihydropyrimidine calcium channel blockers. 3. 3-Carbamoyl-4-aryl-1,2,3,4-tetrahydro-6-methyl-5-pyrimidinecarboxylic acid esters as orally effective antihypertensive agents, *J. Med. Chem.*, **1991**, 34, 806.
[4]. G. C. Rovnyak, K. S. Atwal, A. Hedberg, S. D. Kimball, S. Morel, J. Z. Gougoutas, O'Reilly, B. C. J.Schwartz, M. F.Malley, Dihydropyrimidine calcium channel blockers. 4. Basic 3-substituted-4-aryl-1,4- dihydropyrimidine-5-carboxylic acid esters. Potent antihypertensive agents, *J. Med. Chem.*, **1992**, 35, 3254.
[5]. G. J. Grover,S. Dzwonczyk, D. M. McMullen, D. E. Normandin, C. S. Parham, P. GSleph Morel, Pharmacologic Profile of the Dihydropyrimidine Calcium Channel Blockers SQ 32,547 and SQ 32,946, *J Cardiovasc. Pharmacol.*, **1995**, 26, 289.
[6]. D. Nagarathnam, S. W. Miao, B. Lagu, G.Chiu ,J.Fang, T. G. M., Dhar, J.Zhang,S.Tyagarajan, M. R. Marzabadi,F. Q. Z hang,W. C. Wong, W. Y. Sun, D.Tian, J. M.Wetzel, C.Forray, R. S. L. Chang, T. P.Broten, R. W. Ransom, T. W. Schorn, T. B. Chen, S. MalleyO', P. Kling, K.. Schneck, R.Benedesky, C. M.Harrell, K. P. Vyas, C. Gluchowski, Design and Synthesis of Novel α1a Adrenoceptor-Selective Dihydropyridine Antagonists for the Treatment of Benign Prostatic Hyperplasia. *J.Med. Chem.*, **1999**, 42, 4764.
[7]. T. G. MuraliDhar, D. Nagarathnam, M. R. Marzabadi, B. Lagu, G. Wong, W. C. Chiu, S. Tyagarajan, S. W. Miao, F. Zhang, W. Sun, D. Tian, Q. Shen, J. Zhang, J. M.Wetzel, C.Forray, R. S. L. Chang, T. P. Broten, . W. Schorn, T. B. Chen, S. MalleyO', R. Ransom, K. Schneck, R. Bendesky, C. M. Harrell, K. P. Vyas, K..Zhang, J. Gilbert, D. J. Pettibone, M. A. Patane, M. G. Bock, R. M. Freidinger, C. Gluchowski, Design and Synthesis of Novel α_{1a} Adrenoceptor-Selective Antagonists. 2. Approaches to Eliminate Opioid Agonist Metabolites via Modification of Linker and 4-Methoxycarbonyl-4-phenylpiperidine Moiety, *J. Med. Chem.*, **1999**, 42, 4778.
[8]. J. C. Barrow, P. G. Nantermet, H. G. Selnick, K. L. Glass, K. E. Rittle, K. F. Gilbert, T. G.Steele, C. F. Homnick, R. M. Freidinger, R. W. Ransom, P. Kling, D. Reis, T. P. Broten, T. W. Schorn, Chang, S. SmalleyO', T. V. Olah, J. D. Ellis, A. Barrish, K. Kassahun, P. Leppert, D. Nagarathnam, C. Forray,.*In Vitro* and *in Vivo* Evaluation of Dihydropyrimidinone C-5

Amides as Potent and Selective r1A Receptor Antagonists for the Treatment of Benign Prostatic Hyperplasia, *J.Med. Chem.*, **2000**, 43, 2703.

[9]. M. A. Bruce, G. S. Pointdexter, G. Johnson, Preparation of dihydropyrimidones as NPY antagonist, *PCT Int. App.l*, **1998**, WO 99 07695.

[10]. H. M. Vagdeviand V. P. Vaidya, Studies in naphthofurans: Part III. Synthesis of 2-substituted naphtho[2,1-b]furans, 2- (2'-aryl-3'-acetyl-1',3',4'-oxadiazolyl)aminonaphtho [2,1- b]furans and their biological activities,. *Indian J. Heterocyclic Chem.*, **2001**, 10, 253.

[11]. *"Indian Pharmacopoeia"*. Controller of Publications, Delhi, India, **1996**, 2, A-9.1-100.

[12]. S. K. Ling, T. Tanakaand I. Kouno, Effects of iridoids on lipoxygenase and hyaluronidase activities and their activation by β-glucosidase in the presence of amino acids, *Biol Pharm Bull*, **2003**, 26(3), 352-356.