Synthesis, Anti-bacterial, Anti-asthmatic and Anti-diabetic Activities of Novel *N*-Substituted-2-(benzo[*d*]isoxazol-3-ylmethyl)-1*H*-benzimidazoles

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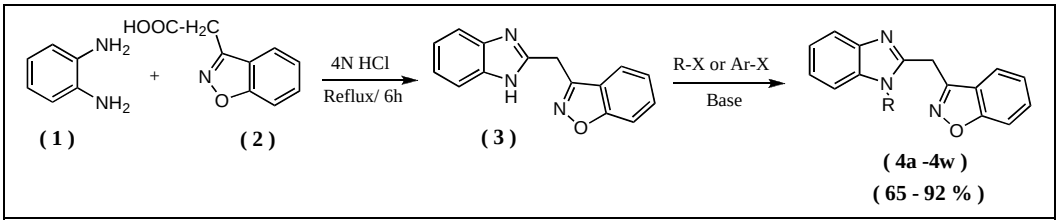

Synthesis of a series of novel class of *N*-substituted-2-(benzo[*d*]isoxazol-3-ylmethyl)-1*H*-benzimidazoles (**4**) by the condensation of *o*-phenylenediamine (**1**) with benzo[*d*]isoxazol-3-yl-acetic acid (**2**) and subsequent reactions with different types of electrophiles have been reported. Some compounds exhibited promising anti-bacterial activity against *Salmonella typhimurium*, however poor activity against *Staphylococcus aureus*. The compound **4t** was found to have high activity even at 1 μg/ml compared to Cephalexin against *S. aureus*. The biological activity against PDE-IV for potential anti-asthmatic effect and against DP-IV and PTP-1B for potential anti-diabetic effects was disappointing.

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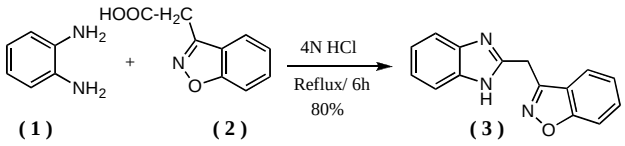
INTRODUCTION

Benzimidazole and its derivatives are marked as prominent heterocyclic compounds that exhibit a large number of biological activities [1]. Significantly, the benzimidazole moiety is a constituent part of Vitamin-B12 core structure [2]. Some, like thiabendazole, mebendazole and albendazole, are widely used as antihelmintic drugs [3] (Figure 1). Similarly, 2-substituted benzimidazoles and their derivatives have been found to be potent biologically active compounds as well [4]. The activity and structural diversity exhibited by compounds containing the benzimidazole moiety has led to the discovery and development of novel and useful bioactive benzimidazole libraries [5]. We have been interested in the synthesis of novel benzimidazole ring systems in connection with our on-going project on benzimidazoles [6]. In continuation of our work on bioactive benz-imidazole libraries, we herein describe our efforts towards the synthesis of a novel class of benzimidazole derivatives and their biological activity screening studies.

RESULTS AND DISCUSSION

Condensation of *o*-phenylenediamine **1** (OPDA) with benzo[*d*]isoxazol-3-yl-acetic acid [7], **2** under Phillips' condition [8] in refluxing 4 *N* HCl for 6 hr and subsequent work-up resulted in the formation of a white solid having m.p.174-176 °C and in 80% yield. Based on the spectral and analytical data the compound was assigned to be 2-(benzo[*d*]isoxazol-3-ylmethyl)-1*H*-benzimidazole **3** [9] (Scheme 1).

Scheme-1



Compound **3** was also synthesized by the condensation of **1** with **2** in the presence of Eaton's reagent [10] (1:10 mixture of phosphorous pentoxide - methanesulfonic acid,

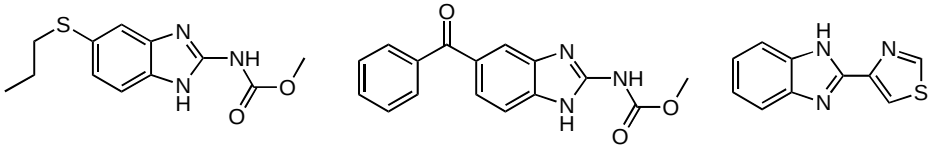
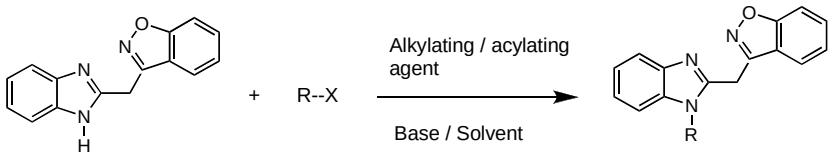


Figure -1

an efficient and convenient alternative to polyphosphoric acid (PPA) [11] for cyclodehydration reactions). In order to reduce the reaction time, the condensation of **1** and **2** was carried out in PPA under microwave irradiation [12] for 3 minutes that also yielded compound **3** in comparable and sometimes in higher yield than conventional methods. The alkylation and acylation of **3** with various electrophilic reagents yielded the N-alkylated/ acylated derivatives (Scheme 2). The physical and spectral data of the compounds **4a-4w** is presented in Table 3.

Biological Activity. All the compounds prepared herein were screened for their potential biological activities such as, anti-bacterial activity against *Staphylococcus aureus* (gram positive) and *Salmonella typhimurium* (gram negative) bacterial strains. Cephalexin was used as a reference standard. The results of the antibacterial activity screening of the tested compounds are summarized in Table 1. Most of the compounds tested were found to have good anti-bacterial activity against *Salmonella typhimurium*, however, they

Scheme-2



(**4a**, R = -CH_3), (**4b**, R = -CH_2-CH_3), (**4c**, R = -CO-O-Ethyl), (**4d**, R = -CO-O-CH(Cl)-CH_3),
(**4e**, R = -CO-O-Butyl), (**4f**, R = -CO-O-Iso-butyl), (**4g**, R=-CO-O-benzyl),
(**4h**, R = -CO-O-C_6H_4-NO_2(p), (**4i**, R = -CO-CH_3), (**4j**, R = -CO-CH_2-CH_3)
(**4k** ,R = -CO-CH_2-CH_2-CH_3), (**4l**, R = -CO-Ph), (**4m**, R =-CO-C_6H_4-(*tert*.butyl-(p)),
(**4n**, R = -SO_2-CF_3), (**4o**, R =-SO_2-CH_2-CH_2-CH_2-Cl), (**4p**, R =-SO_2-Ph)
(**4q**, R = -SO_2-C_6H_4-CH_3), (**4r**, R= -CH_2-Ph), (**4s,** R =-CH_2-C_6H_4-F(p),
(**4t**, R = -CH_2-C_6H_4-Br(p), (**4u**, R = -CH_2-C_6H_4-CH_3(p), (**4v**, R = -CH_2-C_6H_4-*t.b*utyl-(p)),
(**4w**, R = -CO-O-C(CH_3)$_3$

In an alternate route compound **4a** has also been synthesized by direct condensation of N-methyl-OPDA dihydrochloride [13] (**5**) with **2** in refluxing 4 *N* HCl as in the case of preparation of compound **3** described above.

were found to have poor activity against *Staphylococcus aureus*. The compound **4t** was found to have high activity even at 1μg/ml compared to Cephalexin against *Staphylococcus aureus*. Also they were tested against

Table 1

Antibacterial activity of compounds against *Staphylococcus aureus*.

Compound No.	Concentration						
	0.1μg/ml	1μg/ml	10μg/ml	100μg/ml	200μg/ml	500μg/ml	APP.MIC
3	++	++	+	--	--	--	100 μg/ml
4a	++	++	++	+	--	--	200 μg/ml
4b	++	++	+	P	--	--	200 μg/ml
4c	++	++	++	+	P	--	500 μg/ml
4d	++	++	++	+	P	--	500 μg/ml
4e	++	++	+	+	P	--	500 μg/ml
4f	++	++	+	+	P	--	500 μg/ml
4g	+	+	P	P	--	--	200 μg/ml
4h	++	+	P	P	--	--	200 μg/ml
4i	++	++	P	P	--	--	200 μg/ml
4j	++	++	++	+	--	--	200 μg/ml
4k	++	+	+	P	--	--	200 μg/ml
4l	++	+	+	P	--	--	200 μg/ml
4m	++	++	+	+	P	--	200 μg/ml
4n	+	+	P	P	P	--	500 μg/ml
4o	++	+	+	P	P	--	500 μg/ml
4p	+	+	P	--	--	--	100 μg/ml
4q	++	+	+	P	P	--	500 μg/ml
4r	++	++	+	P	--	--	200 μg/ml
4s	++	++	++	+	P	--	500 μg/ml
4t	+	--	--	--	--	--	1μg/ml
4u	++	++	++	+	P	--	500 μg/ml
4v	++	++	+	+	P	--	500 μg/ml
4w	++	++	++	+	P	--	500 μg/ml
Cephalexin	++	++	--	--	--	--	10 μg/ml

PDE - IV for potential anti-asthmatic effect, and against DP-IV and PTP-1B for potential anti-diabetic effects. Unfortunately, the results were disappointing.

Table 2

Antibacterial activity of compounds against *Salmonella typhimurium*.

Compound No.	Concentration						
	0.1μg/ml	1μg/ml	10μg/ml	100μg/ml	200μg/ml	500μg/ml	APP.MIC
3	++	++	++	P	--	--	200 μg/ml
4a	++	++	++	P	--	--	200 μg/ml
4b	++	++	++	+	--	--	200 μg/ml
4c	++	++	++	+	--	--	200 μg/ml
4d	++	++	++	+	P	--	500 μg/ml
4e	++	++	+	P	--	--	200 μg/ml
4f	++	++	++	+	+	--	500 μg/ml
4g	++	+	+	--	--	--	100 μg/ml
4h	++	++	+	P	--	--	200 μg/ml
4i	++	++	++	P	--	--	200 μg/ml
4j	++	++	++	P	--	--	200 μg/ml
4k	++	++	++	P	--	--	200 μg/ml
4l	++	++	+	+	--	--	200 μg/ml
4m	++	++	+	+	--	--	200 μg/ml
4n	++	++	++	+	--	--	200 μg/ml
4o	++	++	++	+	--	--	200 μg/ml
4p	++	++	++	--	--	--	100 μg/ml
4q	++	++	+	P	--	--	200 μg/ml
4r	++	++	++	+	--	--	200 μg/ml
4s	++	++	++	+	--	--	200 μg/ml
4t	++	++	++	--	--	--	100μg/ml
4u	++	++	+	+	--	--	200 μg/ml
4v	++	++	++	P	--	--	200 μg/ml
4w	++	++	P	P	--	--	200 μg/ml
Cephalexin	++	++	+	P	--	--	200μg/ml

Symbols: Total Inhibition, no growth of organism = --
Poor growth compared to controls = P
Medium growth compared to controls = +
Confluent growth, no inhibition = ++

CONCLUSION

In conclusion, we have demonstrated the synthesis of a series of novel benzimidazole derivatives by the condensation of OPDA with benzo[*d*]isoxazol-3-yl-acetic acid and subsequent reactions at the benzimidazole -NH with different electrophilic reagents under different conditions. Some of the compounds were found to have good anti-bacterial activity against *S. typhimurium*, however they were found to have less activity against *S. aureus*. The compound **4t** was found to have high activity even at 1μg/ml compared to Cephalexin against *S. aureus*. These compounds were also tested against PDE-IV for potential anti-asthmatic effect, and against DP-IV and PTP-1B for potential anti-diabetic effects. Unfortunately, the results were disappointing.

EXPERIMENTAL

Melting points are uncorrected and were recorded on a MRVIS Series, Lab India Instrument. TLC analysis was carried out using pre-coated silica gel plates and visualization was done using Iodine/UV lamp. IR spectra were recorded on a Perkin-Elmer Spectrum One FT-IR spectrometer. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Varian Mercury Vx SWBB 300 MHz spectrometer. Elemental analysis was carried out on a Perkin-Elmer Series-II CHNS/O Analyzer 2400. *o*-Phenylenediamine, alkylating, acylating and aroylating agents were obtained from commercial suppliers. Benzo[*d*]-isoxazol-3-yl-acetic acid was prepared by the reported procedure [7]. All the solvents used were of commercial grade only.

Synthesis of 2-(benzo[*d*]isoxazol-3-ylmethyl)-1*H*-benzimidazole (3). A mixture of OPDA (1.08 g, 10 mmoles), **2** (1.77g, 10 m moles) was taken in a solution of 4 *N* HCl (10 ml) and refluxed in a water bath for 6 hr (tlc monitoring). The reaction mixture was then cooled to room temperature and neutralized with aq. $NaHCO_3$ (10%), till neutral to pH. A sticky solid was obtained, which on further stirring for 30 minutes yielded a solid suspension that was free flowing. The solid was collected by filtration, washed with water (2 x 25 ml) and dried under vacuum to obtain **3** (1.99 g, 80 %). A part of the crude product was recrystallized from hot aq. ethanol to obtain a white crystalline compound. (M.P.-174-176[9] °C).

Synthesis of compound (3) *via* Eaton's Reagent. A mixture of OPDA (1.08g, 10 mmole), **2** (1.77g, 10 m mole), and P_2O_5-MSA (1: 10 mixture) (Eaton's Reagent) was heated with stirring at 100 °C for 5 hrs. The reaction was then quenched with aq. saturated bicarbonate (2 x 25 ml) and extracted with ethyl acetate (3 x 50 ml). The organic layer was washed with water (2 x 25 ml), brine (2 x 25 ml and dried over anhydrous magnesium sulfate and evaporated to get compound **3** (1.99 g, 80%), which

Table 3

Physical and Analytical Data of Compounds **3, 4a - 4w** Ψ

Compound	R	Time hours	Mp (°C)	Yield %	Molecular Formula	Analysis % Calcd./Found		
						C	H	N
3	H	6	174-176	80	$C_{15}H_{11}N_3O$	72.28	4.45	16.86
						72.30	4.56	16.85
4a	Methyl	2	141-142	90	$C_{16}H_{13}N_3O$	72.99	4.98	15.96
						72.86	5.27	15.90
4b	Ethyl	24	145-150	92	$C_{17}H_{15}N_3O$	73.63	5.45	15.15
						73.37	5.27	15.23
4c	Ethyl-O-CO-	3	146-147	72	$C_{18}H_{15}N_3O_3$	67.28	4.71	13.08
						67.19	4.93	12.96
4d	CH_3-CH(Cl)-O-CO-	3	152-153	87	$C_{18}H_{14}ClN_3O_3$	60.77	3.97	11.81
						60.85	4.10	11.90
4e	Butyl-O-CO-	3	108-109	71	$C_{20}H_{19}N_3O_3$	68.75	5.48	12.03
						68.67	5.74	11.93
4f	Iso-butyl-O-CO-	3	115-116	85	$C_{20}H_{19}N_3O_3$	68.75	5.48	12.03
						68.58	5.68	12.01
4g	Benzyl-O-CO-	3	122-123	65	$C_{23}H_{17}N_3O_3$	72.05	4.47	10.96
						71.86	4.67	10.79
4h	4-nitro-phenyl-O-CO-	3	171-172	90	$C_{22}H_{14}N_4O_5$	63.77	3.41	13.52
						63.59	3.57	13.23
4i	CH_3-CO-	3	165-166	77	$C_{17}H_{13}N_3O_2$	70.09	4.50	14.42
						69.81	4.77	14.41
4j	CH_3-CH_2-CO-	3	185-187	80	$C_{18}H_{15}N_3O_2$	70.81	4.95	13.76
						70.62	5.19	13.60
4k	CH_3-CH_2-CH_2-CO-	3	144-145	80	$C_{19}H_{17}N_3O_2$	71.46	5.37	13.16
						71.30	5.64	12.93
4l	C_6H_5-CO-	3	117-118	84	$C_{22}H_{15}N_3O_2$	74.78	4.28	11.89
						74.43	4.50	11.72
4m	(4)-Tert-butyl-C_6H_4-CO-	3	144-145	80	$C_{26}H_{23}N_3O_2$	76.26	5.66	10.26
						76.05	5.97	10.12
4n	CF_3-SO_2-	3	140-141	91	$C_{16}H_{10}F_3N_3O_3S$	50.40	2.64	11.02
						50.43	2.51	11.00
4o	Cl-CH_2-CH_2-CH_2-SO_2-	3	107-108	91	$C_{18}H_{16}ClN_3O_3S$	55.46	4.14	10.78
						55.24	4.25	10.71
4p	Ph-SO_2-	3	140-141	77	$C_{21}H_{15}N_3O_3S$	64.77	3.88	10.79
						64.66	3.98	10.62
4q	(4)-CH_3-C_6H_4-SO_2-	3	135-136	86	$C_{22}H_{17}N_3O_3S$	65.49	4.25	10.41
						65.46	4.24	10.26
4r	Benzyl	5	148-149	87	$C_{22}H_{17}N_3O$	77.86	5.05	12.38
						77.80	5.20	12.47
4s	(*p*)F-C_6H_4-CH_2-	5	148-150	90	$C_{22}H_{16}FN_3O$	73.94	4.51	11.76
						73.95	4.62	11.80
4t	(*p*)Br-C_6H_4-CH_2-	5	174-175	85	$C_{22}H_{16}BrN_3O$	63.17	3.86	10.05
						63.04	3.93	10.00
4u	(*p*)CH_3-C_6H_4-CH_2-	5	175-176	85	$C_{23}H_{19}N_3O$	78.16	5.42	11.89
						78.00	5.54	11.87
4v	(*p*)Tert.butyl-C_6H_4-CH_2-	5	146-147	88	$C_{26}H_{25}N_3O$	78.96	6.37	10.62
						79.05	6.50	10.56
4w	$(CH_3)_3$C-O-CO-	3	115-116	78	$C_{20}H_{19}N_3O_3$	68.75	5.48	12.03
						68.62	5.66	11.92

Ψ All products were recrystallized from hot aq. ethanol.

was recrystallized from aq. ethanol to obtain the pure compound **3**. M.P.-174-176 °C.

Synthesis of compound (3) *via* Microwave Irradiation. A mixture of OPDA (1.08 g, 10 mmole) and **2** (1.77 g, 10 mmole), in polyphosphoric acid (10 ml) were stirred and irradiated in a microwave oven at 100 W for 3 min at 170 °C. The reaction mixture was then cooled to room temperature and the reaction mass was neutralized with ice-cold concentrated potassium hydroxide solution (50 ml) to obtain neutral pH. The solid that separated out was collected by filtration, washed with water (3 x 50 ml) and dried under vacuum afforded an off-white solid (1.94 g, 78%). The crude product was recrystallized from aq. ethanol to obtain the pure compound **3**. M.P.-174-176 °C.

General Procedure for the synthesis of compounds 4a and 4b. To a solution of compound **3** (2 mmoles) in acetone (50 ml) was added finely grounded anhydrous K_2CO_3 (4 mmoles), triethylbenzylammonium bromide (TEBAB, 1 mmole) followed by the addition of alkylating agent (3 mmoles). The reaction mixture was then refluxed for 5 hrs in case of **4a** and 24 hrs in case of **4b** (tlc monitoring). Acetone from the reaction mixture was evaporated under vacuum, water (50 ml) was added to the residue and extracted with ethyl acetate. The ethyl acetate layer

was washed with water (2x50 ml), brine (20 ml) and dried over anhydrous sodium sulfate. Evaporation of the solvent yielded the corresponding alkylated product **4a** or **4b** (for details please see Table 3).

Alternate synthesis of compound 4a. A mixture of *N*-methy1-*o*-phenylenediamine dihydrochloride, **5** (1.95 g, 10 mmoles), **2** (2.12 g, 12 mmoles) was taken in a solution of 4 *N* HCl (10 ml) and refluxed in a water bath for 6 hr (tlc monitoring) The reaction mixture was then cooled to room temperature and neutralized with aq. $NaHCO_3$ (10%), till basic pH to obtain a sticky oily mass which was then extracted with ethyl acetate and was washed with aq. $NaHCO_3$ (10%, 2 x 25 ml), water (2 x 50 ml), brine (15 ml) and dried over anhydrous sodium sulfate. After evaporation of the solvent **4a** was obtained in 83% yield (2.18 g).

General Procedure for the synthesis of compounds 4c – 4q. To a solution of compound **3** (2 mmoles) in pyridine (5 ml) was added acyl/aroyl chloride (3 mmoles) drop-wise at 0 °C. After the addition was complete, the temperature of the reaction mixture was slowly raised to room temperature and stirred at this temperature for 2 hrs (tlc monitoring). A solution of 2 *N* HCl was added to the reaction mixture until pH at which point a solid separated out and was collected by filtration, washed with water (2 x 30 ml) and dried under vacuum to obtain the corresponding acyl or aroyl derivatives **4c-4** (for details see Table 3).

General Procedure for the synthesis of compounds 4r - 4v. To a solution of compound **3** (2 mmoles) in acetonitrile (20 ml) was added aqueous sodium hydroxide solution (10%, 5 ml) and the mixture was stirred for 15 minutes. Benzyl bromide (2.4 mmole) was then added slowly with stirring to the reaction mixture at 0 °C. After the addition was complete, the temperature of the reaction mixture was allowed to slowly rise to room temperature and was stirred at this temperature for 24 hrs (tlc monitoring). After the completion of the reaction, acetonitrile from the reaction mixture was evaporated under vacuum to obtain a residue. The residue was then extracted with ethyl acetate and the organic layer was washed with water (2 x 50 ml), brine (2 x 20 ml) and dried over anhydrous sodium sulfate. Evaporation of the solvent under vacuum gave the corresponding N-substituted derivatives **4r - 4v** respectively. The crude compounds were recrystallized from hot aq. ethanol to obtain pure products (For details see Table 3).

Synthesis of compound 4w. To a solution of compound **3** (2 mmoles) in THF (10 ml) was added aq. NaOH (10%, 10 ml), Boc anhydride (2 mmoles) in THF (5 ml) drop-wise at 0 °C. After the addition was complete, the temperature of the reaction mixture was slowly raised to room temperature and stirred at this temperature for 2 hrs (tlc monitoring). The reaction mixture was then diluted with water (30 ml) and extracted with ether. The ethereal layer was washed with 1 *N* HCl (50 ml), brine (30 ml) and dried over anhydrous sodium sulfate. Evaporation of the solvent yielded an off white solid **4w** (for details see Table 3).

Spectral and Analytical Data for Compounds 3, 4a-4w.

2-((Benzo[*d*]isoxazol-3-yl)methyl)-1*H*-benzimidazole (3). ir(KBr): 2900(-NH) cm^{-1}. ^{1}H-nmr (DMSO-d_6): δ 4.67 (s, 2H,-CH_2-), 7.10-7.19 (m, 2H, Ar-H), 7.35 (t, *J*=6.9Hz, 1H, Ar-H), 7.45 (t, *J*=6.6Hz,1H, Ar-H), 7.54 (t, *J*=7.2Hz,1H, Ar-H), 7.61-7.67 (m,1H, Ar-H), 7.73-7.77 (m, 2H, Ar-H), 12.58 (s, 1H, -NH). ^{13}C-nmr (DMSO-d_6) (75 MHz): 26.11(-CH_2-), 109.77, 120.91, 121.59, 122.62, 123.90, 130.41, 148.81, 154.48, 163.07 (aromatic carbons). EI-MS: 250 (M^++1).

2-((Benzo[*d*]isoxazol-3-yl)methyl)-1-methyl-1*H*-benzimidazole (4a). ir (KBr): 3020 (CH) cm^{-1}. ^{1}H-nmr ($CDCl_3$): δ 3.84 (s, 3H, N-CH_3), 4.79 (s, 2H, -CH_2-), 7.14-7.26 (m, 2H, Ar-H), 7.36 (t, *J*=7.35 Hz, 1H, Ar-H), 7.54 (d *J*=7.8Hz, 2H, Ar-H), 7.65 (t, *J*=7.6Hz, 1H, Ar-H), 7.74-7.78 (m, 2H, Ar-H).^{13}C-nmr($CDCl_3$)(75 MHz): 25.66 (-CH_2-), 30.21(N-CH_3), 109.25, 109.73, 119.63, 120.96, 122.21, 122.25, 122.76, 123.75, 130.16, 136.09, 142.33, 148.87, 153.99, 163.38. (aromatic carbons). EI-MS: 264 (M^++1).

2-((Benzo[*d*]isoxazol-3-yl)methyl)-1-ethyl-1*H*-benzimidazole (4b). ir (KBr): 3043(CH) cm^{-1} ^{1}H-nmr ($CDCl_3$): δ 1.23 (t, *J*=7.2Hz, 3H, -CH_3), 4.26 (q, *J*=7.2Hz, 2H, N-CH_2), 4.72 (s, 2H, -CH_2-), 7.19-7.32 (m, 4H, Ar-H), 7.47-7.55 (m, 2H, Ar-H), 7.76-7.80 (m, 2H, Ar-H). ^{13}C-nmr ($CDCl_3$) (75 MHz): 14.72(CH_3), 25.69(CH_2), 38.79(N-CH_2), 109.49, 109.68, 119.72, 120.98, 122.12, 122.42, 122.68, 123.73, 130.14, 134.96, 142.55, 148.22, 154.15, 163.34(aromatic carbons). EI-MS: 278 (M^++1).

Ethyl 2-((benzo[*d*]isoxazol-3-yl) methyl)-1*H*- benzimidazole-1-carboxylate (4c). ir (KBr): 2999(CH), 1742(C=O)cm^{-1}. ^{1}H-nmr ($CDCl_3$): δ 1.42 (t, *J*=6.9Hz, 3H, -CH_3), 4.49 (q, *J*=6.9Hz, 2H, O-CH_2), 4.97 (s, 2H, -CH_2-), 7.23-7.28 (m, 1H, Ar-H), 7.35-7.40 (m, 2H, Ar-H), 7.50-7.62 (m, 3H, Ar-H), 7.72-7.76 (m, 1H, Ar-H), 7.96-7.99 (m, 1H, Ar-H).^{13}C-nmr ($CDCl_3$) (75 MHz): 13.97(CH_3), 28.56(CH_2), 64.29(O-CH_2), 109.79, 114.99, 119.98, 121.28, 121.56, 123.39, 124.47, 125.04, 129.76, 132.95, 141.93, 149.95, 150.07, 154.30 (C=O), 163.06.EI-MS: 322 (M^++1).

1-Chloroethyl-2-((benzo[*d*]isoxazol-3-yl)methyl)-1*H*-benzimidazole-1-carboxylate (4d). ir(KBr): 1755(C=O)cm^{-1}.^{1}H-nmr ($CDCl_3$): δ 1.93 (d, *J*=5.7Hz, 3H, CH_3), 4.95 (s, 2H, CH_2), 6.72 (q, *J*=6Hz, 1H, CH), 7.24-7.29 (m, 1H, Ar-H), 7.37-7.47 (m, 2H, Ar-H), 7.50-7.63 (m, 3H, Ar-H), 7.72-7.75 (m, 1H, Ar-H), 7.96-7.99 (m, 1H, Ar-H) .^{13}C-nmr($CDCl_3$)(75 MHz): 24.96(CH_3), 28.63(CH_2), 83.72(CH), 109.94, 115.07, 120.31, 121.23, 121.49, 123.54, 125.08, 125.54, 129.94, 132.68, 142.00, 147.78, 149.97, 154.11 (C=O), 163.16. EI-MS: 356 (M^++1).

Butyl 2-((benzo[*d*]isoxazol-3-yl)methyl)-1*H*-benzimidazole-1-carboxylate (4e). ir (KBr): 1758(C=O)cm^{-1}. ^{1}H-nmr ($CDCl_3$): δ 0.94 (t, *J*=7.2Hz, 3H, CH_3), 1.36-1.48 (m, 2H, CH_2), 1.71-1.84 (m, 2H, CH_2), 4.43 (t, *J*=7.2Hz, 2H,O-CH_2), 4.96 (s, 2H,-CH_2), 7.22-7.27 (m, 1H, Ar-H), 7.32-7.39 (m, 2H, Ar-H), 7.49-7.61 (m, 3H, Ar-H), 7.72-7.75 (m, 1H, Ar-H), 7.94-7.97 (m, 1H, Ar-H).^{13}C-nmr($CDCl_3$) (75 MHz): 13.55(CH_3), 19.01(CH_2), 28.61(CH_2), 30.35(CH_2), 68.16(O-C), 109.87, 114.98, 120.08, 121.34, 121.59, 123.43, 124.52, 125.10, 129.80, 132.99, 142.00, 150.16, 154.35 (C=O), 163.13 EI-MS**:** 350 (M^++1).

Isobutyl 2-((benzo[*d*]isoxazol-3-yl)methyl)-*1H*-benzimidazole carboxylate (4f). ir (KBr): 1751(C=O) cm^{-1}. ^{1}H-nmr ($CDCl_3$): δ1.01 (s, 3H,CH_3), 1.03 (s, 3H, CH_3), 2.12-2.17 (m, 1H, CH_2), 4.24 (d, *J*=6.6Hz, 2H, -O-CH_2), 4.97 (s, 2H, -CH_2), 7.23-7.29 (m, 1H, Ar-H), 7.35-7.39 (m, 2H, Ar-H), 7.53-7.62 (m, 3H, Ar-H), 7.72-7.75 (m, 1H, Ar-H), 7.95-7.98 (m, 1H, Ar-H). ^{13}C-nmr ($CDCl_3$) (75 MHz): 19.03(CH_3), 27.61(CH), 28.55(CH_2), 74.30(O-CH_2), 109.86, 114.93, 120.11, 121.36, 121.60, 123.41, 124.51, 125.09, 129.78, 132.91, 142.01, 150.28, 154.33 (C=O), 163.12. EI-MS**:** 350 (M^++1)

Benzyl-2-((benzo[*d*]isoxazol-3-yl)methyl)-*1H*-benzimidazole-1-carboxylate (4g). ir (KBr): 1758(C=O)cm^{-1}.^{1}H-nmr ($CDCl_3$): δ 4.93 (s, 2H, -CH_2-), 5.48 (s, 2H, O-CH_2-), 7.32-7.39 (m, 6H, Ar-H), 7.44-7.48 (m, 2H, Ar-H), 7.61-7.68 (m, 2H, Ar-H), 7.73-7.80 (m, 2H, Ar-H), 7.92-7.95 (m, 1H, Ar-H). ^{13}C-nmr

($CDCl_3$) (75 MHz): 28.67(-CH_2-), 69.85 (O-CH_2), 109.90, 115.07, 120.10, 121.32, 121.58, 123.46, 124.62, 125.22, 128.80, 128.88, 129.07, 129.82, 132.97, 133.85, 141.99, 149.97, 150.11, 154.36 (C=O), 163.13. EI-MS**:** 384 (M^++1).

4-Nitrophenyl 2-((benzo[*d*]isoxazol-3-yl)methyl)-*1H*-benzimidazole-1-carboxylate (4h). ir (KBr): 1765(C=O)cm^{-1}.^{1}H-nmr ($CDCl_3$): δ 5.02 (s, 2H,-CH_2), 7.28-7.31 (m, 1H, Ar-H), 7.42-7.45 (m, 4H, Ar-H), 7.55 (d, *J*=6.6Hz, 2H, Ar-H), 7.67 (d, *J*=8.1Hz, 1H, Ar-H), 7.79-7.82 (m, 1H, Ar-H), 8.01-8.04 (m, 1H, Ar-H), 8.34 (d, *J*=6.6Hz, 2H, Ar-H).^{13}C-nmr ($CDCl_3$) (75 MHz): 28.76(CH_2), 110.03, 115.03, 120.56, 121.15, 121.46, 122.38, 123.73, 125.42, 125.53, 125.84, 130.16, 132.79 (C=O), 142.10, 147.56, 149.95, 153.86, 154.08, 163.19 (aromatic carbons & carbonyl carbon) EI-MS: 415 (M^++1).

1-(2-((Benzo[*d*]isoxazol-3-yl)methyl)-1*H*-benzimidazole-1yl)-ethanone (4i). ir (KBr): 1720(C=O)cm^{-1} .^{1}H-nmr($CDCl_3$)**:** δ 2.87 (s, 3H, CH_3), 4.95 (s, 2H, CH_2), 7.31-7.42(m, 3H, Ar-H), 7.60-7.68 (m, 2H, Ar-H), 7.74-7.82 (m, 2H, Ar-H), 7.96 (d, *J*=8.1Hz, 1H, Ar-H). ^{13}C-nmr ($CDCl_3$) (75 MHz): 26.80(CH_3), 29.19(-CH_2), 109.90, 113.54, 120.78, 121.42, 121.54, 123.45, 124.56, 125.00, 129.85, 132.45, 142.55, 150.89, 154.54, 163.06, 169.00 (C=O). EI-MS**:** 292 (M^++1).

1-(2-((Benzo[*d*]isoxazol-3-yl)methyl)-1*H*-benzimidazole-1-yl)propan-1-one (4j). ir (KBr): 2982(CH), 1728(C=O) cm^{-1}.^{1}H-nmr ($CDCl_3$): δ 1.32 (t, *J*=7.2Hz, 3H, CH_3), 3.14 (q, *J*=7.2Hz, 2H, CO-CH_2), 4.98 (s, 2H, -CH_2-), 7.26-7.31 (m, 1H, Ar-H), 7.36-7.40 (m, 2H, Ar-H), 7.54-7.56 (m, 2H, Ar-H), 7.64-7.71 (m, 2H, Ar-H), 7.75-7.79 (m, 1H, Ar-H).^{13}C-nmr($CDCl_3$) (75 MHz): 8.41(CH_3), 29.37(-CH_2-), 32.20(CH_2), 109.92, 113.77, 120.82, 121.46, 121.60, 123.44, 124.46, 124.93, 129.84, 132.20, 142.64, 151.04, 154.61, 163.09, 173.02 (C=O). EI-MS**:** 306 (M^++1).

1-(2-((Benzo[*d*]isoxazol-3-yl)methyl)-1*H*-benzimidazole-1-yl)butan-1-one (4k). ir (KBr): 2965(CH), 1714(C=O)cm^{-1}. ^{1}H-NMR ($CDCl_3$)**:** δ 0.99 (t, *J*=7.2Hz, 3H, CH_3), 1.82 (q, *J*=7.2Hz, 2H, CH_2), 3.05 (t, *J*=7.2Hz, 2H, -CH_2-CO), 4.97 (s, 2H,-CH_2-), 7.24-7.29 (m, 1H, Ar-H), 7.33-7.40 (m, 2H, Ar-H), 7.49-7.57 (m, 2H, Ar-H), 7.62-7.67 (m, 2H, Ar-H), 7.74-7.77 (m, 1H, Ar-H).^{13}C-nmr($CDCl_3$) (75 MHz): 13.40(CH_3), 17.52(CH_2), 29.27(-CH_2-), 40.39(CH_2), 109.86, 113.69, 120.76, 121.43, 121.55, 123.41, 124.39, 124.87, 129.81, 132.16, 142.59, 151.00, 154.57, 163.05, 172.17 (C=O). EI-MS**:** 320 (M^++1).

(2-((Benzo[*d*]isoxazol-3-yl)methyl)-1*H*-benzimidazole-1-yl)-(phenyl)methanone (4l). ir (KBr): 3065(CH), 1688(C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$)**:** δ 4.95 (s, 2H, -CH_2-), 6.62 (d, *J*=8.4Hz, 1H, Ar-H), 7.10 (t, *J*=7.2Hz, 1H, Ar-H), 7.26-7.31 (m, 2H, Ar-H), 7.46-7.50 (m, 4H, Ar-H), 7.65-7.77 (m, 5H, Ar-H).^{13}C-NMR($CDCl_3$) (75 MHz): 27.28(-CH_2-), 109.89, 113.32, 120.18, 121.15, 121.39, 123.50, 124.00, 124.14, 128.91, 129.93, 130.05, 132.82, 133.92, 134.05, 142.15, 150.80, 154.36, 163.07, 168.64 (C=O). EI-MS: 354 (M^++1).

(4-*tert*-Butylphenyl)(2-((benzo[*d*]isoxazol-3-yl)methyl)-1*H*-benzimidazole-1-yl)methanone(4m). ir (KBr): 1697(C=O) cm^{-1}.^{1}H-nmr ($CDCl_3$): δ 1.36 (s, 9H, CH_3), 4.93 (s, 2H, -CH_2-), 6.74 (d, *J*=8.4Hz, 1H, Ar-H), 7.12 (t, *J*=7.05Hz, 1H, Ar-H), 7.25-7.31 (m, 2H, Ar-H), 7.47-7.53 (m, 4H, Ar-H), 7.64-7.69 (m, 3H, Ar-H), 7.76 (d, *J*=7.2Hz, 1H, Ar-H). ^{13}C-nmr ($CDCl_3$) (75 MHz): 27.20(-CH_2-), 31.01(CH_3), 35.33(C-), 109.89, 113.35, 120.14, 121.21, 121.46, 123.49, 123.88, 124.09, 125.91, 129.84, 129.90, 130.21, 134.09, 142.16, 150.75, 154.40, 158.32, 163.09, 168.50 (C=O). EI-MS: 410 (M^++1).

2-((Benzo[*d*]isoxazol-3-yl)methyl)-1-trifluoromethanesulfonyl-1*H*-benzimidazole (4n). ir (KBr): 1044(S=O) cm^{-1}. ^{1}H-nmr ($CDCl_3$): δ 4.86 (s, 2H, -CH_2-), 7.27-7.33 (m, 1H, Ar-H), 7.40-7.47 (m, 2H, Ar-H), 7.53-7.64 (m, 3H, Ar-H), 7.68-7.73 (m, 1H, Ar-H), 7.83-7.86 (m, 1H, Ar-H).^{13}C-NMR($CDCl_3$) (75 MHz): 26.76(-CH_2-), 110.12, 113.56, 117.31, 121.09, 121.43, 121.60, 123.67, 126.33, 126.55, 130.05, 132.72, 141.51, 149.21, 153.16, 163.40. (aromatic and CF_3 carobons). EI-MS: 382 (M^++1).

2-((Benzo[*d*]isoxazol-3-yl)methyl)-1-(3-chloropropanesulfonyl)-1*H*-benzimidazole (4o). ir (KBr): 1054(S=O) cm^{-1}. ^{1}H-nmr ($CDCl_3$): δ 2.18-2.27 (m, 2H, CH_2), 3.53-3.64 (m, 4H, CH_2), 4.95 (s, 2H, -CH_2-), 7.32-7.44 (m, 3H, Ar-H), 7.57-7.58 (m, 2H, Ar-H), 7.74-7.79 (m, 2H, Ar-H), 7.83-7.86 (m, 1H, Ar-H). ^{13}C-nmr ($CDCl_3$) (75 MHz): 25.74(CH_2), 26.92(-CH_2-), 41.89(CH_2), 51.96 (CH_2Cl), 109.97, 113.07, 120.61, 121.01, 121.58, 123.84, 125.04, 125.60, 130.33, 133.12, 141.62, 148.76, 154.76, 163.19. (aromatic carbons). EI-MS: 390(M^++1).

2-((Benzo[*d*]isoxazol-3-yl) methyl)-1-benzenesulfonyl-1*H*-benzimidazole (4p). ir (KBr): 3059(CH)**,** 1054(S=O) cm^{-1}.^{1}H-nmr($CDCl_3$): δ 4.98 (s, 2H,-CH_2-), 7.19-7.24 (m, 1H, Ar-H), 7.34-7.42 (m, 4H, Ar-H), 7.48-7.57 (m, 4H, Ar-H), 7.68 (d, *J*=7.2Hz, 1H, Ar-H), 7.84 (d, *J*=7.5Hz, 2H, Ar-H), 8.03 (d, *J*=7.8Hz, 1H, Ar-H). ^{13}C-nmr($CDCl_3$) (75 MHz): 27.03 (-CH_2-), 109.89, 113.53, 120.52, 121.24, 121.78, 123.52, 124.91, 125.48, 126.73, 129.50, 129.88, 133.16, 134.66, 137.83, 141.68, 148.86, 153.81, 163.26 (aromatic carbons). EI-MS: 390(M^++1).

2-((Benzo[*d*]isoxazol-3-yl)methyl)-1-(4-methylbenzenesulfonyl)-1*H*-benzimidazole (4q). ir (KBr): 3058(CH)**,**1050 (S=O) cm^{-1}.^{1}H-nmr ($CDCl_3$): δ 2.36 (s, 3H,CH_3), 5.09 (s, 2H, -CH_2-), 7.32-7.45 (m, 5H, Ar-H), 7.62-7.78 (m, 3H, Ar-H), 7.77 (d, *J*=8.4Hz, 1H, Ar-H), 7.96 (d, *J*=7.5Hz, 1H, Ar-H), 8.02 (d, *J*=8.4Hz, 2H, Ar-H). ^{13}C-nmr ($CDCl_3$) (75 MHz): 21.55(CH_3), 26.98(-CH_2-), 109.78, 113.53, 120.40, 121.22, 121.79, 123.44, 124.75, 125.34, 126.75, 129.77, 130.05, 133.12, 134.80, 141.64, 146.02, 148.81, 153.82, 163.21(aromatic carbons). EI-MS: 404(M^++1).

2-((Benzo[*d*]isoxazol-3-yl)methyl)-1-benzyl-1*H*-benzimidazole (4r). ir (KBr): 3026(CH) cm^{-1}.^{1}H-nmr ($CDCl_3$): δ 4.61 (s, 2H,-CH_2-), 5.40 (s, 2H, N-CH_2-), 6.91 (s, 2H, Ar-H), 7.17-7.28 (m, 7H, Ar-H), 7.47 (s, 2H, Ar-H), 7.71 (d, *J*=7.5Hz,1H, Ar-H), 7.82 (d, *J*=7.2Hz, 1H, Ar-H).^{13}C-NMR($CDCl_3$) (75 MHz): 25.73(-CH_2-), 47.01(N-CH_2), 109.60, 109.75, 119.72, 120.95, 122.13, 122.30, 122.99, 123.56, 126.02,127.68, 128.68, 129.97, 135.27, 135.79, 142.35, 148.93, 153.82, 163.21(aromatic carbons).EI-MS: 340(M^++1).

1-(4-Fluorobenzyl)-2-((benzo[*d*]isoxazol-3-yl)methyl)-1*H*-benzimidazole (4s). ir (KBr): 3033(CH)cm^1. ^{1}H-nmr ($CDCl_3$): δ 4.64 (s, 2H, -CH_2-), 5.34 (s, 2H, N-CH_2), 6.80-6.82 (m, 4H, Ar-H), 7.18-7.44 (m, 4H, Ar-H), 7.44 (s, 2H, Ar-H), 7.68 (d, *J*=7.8Hz, 1H, Ar-H), 7.83 (d, *J*=7.5Hz, 1H, Ar-H) .^{13}C-nmr ($CDCl_3$) (75 MHz): 25.75(-CH_2-), 46.34(N-CH_2), 109.56, 109.59, 109.62, 115.33, 115.61, 119.77, 120.85, 122.02, 122.38, 123.07, 123.56, 127.62, 127.73, 129.99, 130.89, 130.93, 135.64, 142.30, 148.76, 153.70, 160.31, 163.15, 163.58(aromatic carbons).EI-MS: 358(M^++1).

1-(4-Bromobenzyl)-2-((benzo[*d*]isoxazol-3-yl)methyl)-1*H*-benzimidazole (4t). ir (KBr): 3055(CH) cm^{-1}.^{1}H-nmr($CDCl_3$): δ 4.65 (s, 2H, -CH_2-), 5.33 (s, 2H, N-CH_2), 6.68 (d, *J*=8.1Hz, 2H, Ar-H), 7.15-7.32 (m, 6H, Ar-H), 7.43-7.50 (m, 2H, Ar-H), 7.66 (d, *J*=8.1Hz, 1H, Ar-H), 7.83 (d, *J*=7.8Hz, 1H, Ar-H).^{13}C-nmr ($CDCl_3$) (75 MHz): 25.87(-CH_2-), 46.52(N-CH_2), 109.59, 109.70, 119.88, 120.88, 121.56, 122.03, 122.52, 123.22, 123.64, 127.62, 130.05, 131.64, 134.16, 135.71, 142.32, 148.77, 153.69, 163.21(aromatic carbons).EI-MS: 418(M^++1).

1-(4-Methylbenzyl)-2-((benzo[*d*]isoxazol-3-yl)methyl)-1*H*-benzimidazole (4u). ir (KBr): 3056(CH) cm^{-1}.^{1}H-nmr ($CDCl_3$): δ 2.24 (s, 3H, CH_3), 4.63 (s, 2H, -CH_2-), 5.33 (s, 2H, N-CH_2-), 6.80 (d, *J*=7.8Hz, 2H, Ar-H), 6.95 (d, *J*=7.8Hz, 2H, Ar-H), 7.14-7.28 (m, 4H, Ar-H), 7.44-7.45 (m, 2H, Ar-H), 7.68 (d, *J*=7.8Hz, 1H, Ar-H), 7.81 (d, *J*=7.8Hz, 1H, Ar-H).^{13}C-nmr ($CDCl_3$) (75 MHz): 20.91(CH_3), 25.73(-CH_2-), 46.83(N-CH_2-), 109.54, 109.77, 119.66, 120.96, 122.15, 122.21, 122.92, 123.51, 126.04, 129.30, 129.89,132.24, 135.80, 137.38, 142.32, 148.90, 153.83, 163.19 (aromatic carbons). EI-MS: 354(M^++1).

1-(4-*tert*-Butylbenzyl)-2-((benzo[*d*]isoxazol-3-yl)methyl)-1*H*-benzimidazole (4v). ir (KBr): 3058(CH) cm^{-1}.^{1}H-nmr ($CDCl_3$): δ 1.25 (s, 9H, CH_3), 4.65 (s, 2H, -CH_2-), 5.36 (s, 2H, N-CH_2), 6.86 (d, J=7.5Hz, 2H,Ar-H), 7.17-7.28 (m, 6H, Ar-H), 7.43 (s, 2H, Ar-H), 7.69 (d, J=7.8Hz, 1H, Ar-H), 7.84 (d, J=7.5Hz, 1H, Ar-H) . ^{13}C-nmr ($CDCl_3$) (75 MHz): 25.67(-CH_2-), 31.08(CH_3), 34.26(C), 46.61(N-CH_2), 109.49, 109.72, 119.61, 120.94, 122.07, 122.17, 122.86, 123.43, 125.48, 125.70, 129.82, 132.21, 135.80, 142.27, 148.87, 150.52, 153.75, 163.11(aromatic carbons). EI-MS: 396(M^++1).

***tert*-Butyl-2-((benzo[*d*]isoxazol-3-yl)methyl)-1*H*-benzimidazole-1-carboxylate (4w).** ir (KBr): 1751(CO) cm^{-1}.^{1}H-nmr ($CDCl_3$): δ 1.62 (s, 9H, CH_3), 4.96 (s, 2H, -CH_2-), 7.22-7.38 (m, 3H, Ar-H), 7.50-7.56 (m, 3H, Ar-H), 7.70-7.73 (m, 1H, Ar-H), 7.93-7.96 (m, 1H, Ar-H). ^{13}C-NMR ($CDCl_3$) (75 MHz): 27.84(-CH_2-), 28.56(CH_3), 86.09(O-C), 109.81, 114.95, 119.92, 121.36, 121.64, 123.38, 124.22, 124.82, 129.74, 133.15, 141.87, 148.50, 150.13, 154.41 (C=O), 163.06. EI-MS: 350 (M^++1).

REFERENCES

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[1a] Wright, J. B. *Chem. Rev.*, **1951**, *48*, 397; [b] Amari, M.; Fodili, M.; Nedjar-Kolli, B. *J. Heterocycl. Chem.*, **2002**, *39*, 811.

[2] The Merck Index, 13th Edition, Ed. M. J. O'Neil; M. Smith; P. E Heckelman, Merck & Co. Inc., NJ. **2001**, P-1785, Monograph Number: 10074.

[3] Kohler P. *Int. J. Parasitol.*, **2001**, *31*, 336.

[4] Preston, P. N. *Chem. Rev.*, **1974**, *74*, 279.

[5a] Breslin, H. J.; Miskowski, T. A.; Kukla, M. J.; De Winter, H. L.; Somers, M. V. F.; Roevens, P. W. M.; Kavash, R. W. *Bioorg. & Med. Chem. Lett.*, **2003**, *13*, 4467; [b] Spasov, A. A.; Yozhitsa, L. N.; Bugaeva, L. I.; Anisimova, V. A. *Pharmaceutical Chem. Journal*, **1999**, *33*, 232; [c] Valdez, J.; Cedillo, R.; Hernandez-Campos, A.; Yepez, L.; Hernandez-Luis, F.; Navarrete-Vazquez, G.; Tapia, A.; Cortes, R.; Hernandezc, M.; Castillo, R. *Bioorg. & Med. Chem. Lett.,* **2002**, *12*, 2221.

[6a] Vinod Kumar, R.; Raja Gopal, K. and Seshu Kumar, K. V. S. R. *J. Heterocycl. Chem.*, **2005**, *42*, 1405; [b] Siva Kumar, B. V.; Vaidya, S. D.; Vinod Kumar, R.; Bhirud, S. B.; Mane, R. B. *Euro. J. Med. Chem.,* **2006**, *41*, 599 .

[7a] Mustafa, A.; Hsihmat, O. H.; Zayed, S. M. A. D.; Nawar, A. A. *Tetrahedron*, **1963**, *19*, 1831; [b] Casini, G.; Gualtieri, F.; Stein, M. L. *J. Heterocycl. Chem.*, **1965**, *2*, 385; [c] Giovanni, C.; Gualtieri, F.; Stein, M. L. *J. Heterocycl. Chem.* **1969**, *6*, 279.

[8] Phillips, M. A. *J. Chem. Soc.*, **1928**, 2393.

[9] For a preliminary communication of this work please see. Vaiday, S. D.; Siva Kumar, B. V.; Vinod Kumar, R.; Bhirud, S. B.; Mashelkar, U. C. *Indian J. Heterocycl. Chem*, **2005**, *14*, 197.

[10] Eaton, P. E.; Carlson, G. R.; Lee, J. T. *J. Org. Chem.* **1973**, *38*, 4071.

[11] Kauffman, J. M.; Khalaj, A.; Litak, P. T.; Novinski, J. A.; Bajwa, G. S. *J. Heterocycl. Chem.*, **1994**, *31*, 957.

[12] Reviews on microwave chemistry include: [a] Gabriel, C.; Gabriel, S.; Grant, E. H.; Halstead, B. S. J.; Mingos, D. M. P. *Chem. Soc. Rev.*, **1998**, *27*, 213; [b] Kuhnert, N. *Angew. Chem. Int. Ed. Eng.*, **2002**, *41*, 1863; [c] Lidström, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron*, **2001**, *57*, 9225; [d] Loupy, A.; Petit, A.; Hamelin, J.; Texier-Boullet, F.; Jacquault, P.; Mathé, D. *Synthesis*, **1998**, *9*, 1213; [e] Galema, S. A. *Chem. Soc. Rev.,* **1997**, *26*, 233; [f] Caddick, S.; *Tetrahedron,* **1995**, *51*, 10403; [g] Strauss, C. R.; Trainor, R. W. *Aust. J. Chem.*, **1995**, *48*, 1665; [h] Microwaves in Organic Synthesis, Danks, T. N. *Tetrahedron. Lett.,* **1999**, *40,* 3957; (h) Microwaves in Organic Synthesis, Loupy, A. Ed.; Wiley VCH: Weinheim, (**2002**).

[13a] Elderfield, R. C.; Meyer, V. B. *J. Am. Chem. Soc.*, **1954**, *76*, 1891; [b] Cheeseman, G.W.H. *J. Chem. Soc.*, **1955**, 3308; [c] Irving, H.; Weber, O. *J. Chem. Soc.*, **1959**, 2296.