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Original Research Article

Synthesis of Novel Isoxazole Derivatives as Analgesic Agents by Using Eddy's Hot Plate Method

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Abstract: The Isoxazole ring system belongs to a much studied class of compound. In the last few decades, the chemistry of Isoxazoles and their fused heterocyclic derivatives have received considerable attention owing to their significant and effective biological activity. The present study aimed to design and synthesize novel derivatives of Isoxazole from 4-methoxy aniline gives N-(4-methoxyphenyl) acetamide which was hydrolysis with sodium hydroxide and treated aromatic aldehydes yields resultant compound N-(4-methoxyphenyl) 3-phenyl propanamide (BSM-IIIA-IIIJ). Title compound were synthesized and the structures of newly synthesized compounds were confirmed by IR, Mass and ^{1}H-NMR spectroscopy. All the compounds synthesized were evaluated for their analgesic activity by using Eddy's hot plate method. The compounds 5- (4-bromophenyl)-N-(4- methoxyphenyl) 4,5- dihydroisoxazole-3-amine (BSM-IIID) and 5- (4-chloro-3-nitrophenyl)-N-(4- methoxyphenyl) 4,5- dihydroisoxazole-3-amine (BSM-IIIF) were shown good analgesic activity and remaining compounds were shown poor analgesic activity.

Keywords: Isoxazole, 4-methoxy aniline, Analgesic Activity and Eddy's hot plate method.

INTRODUCTION

Isoxazole heterocycles are of great interest due to their exceptional biological activity. The treatment of pain continues to be the subject of considerable pharmaceutical and clinical research in recent years [1, 2]. A systematic investigation of this class of heterocycle revealed that isoxozole containing pharmacoactive agents play important role in medicinal chemistry. Chemotherapeutic, analgesic and anti–inflammatory drugs are prescribed simultaneously in normalpractice [3]. There is also evidence that novel synthetic methods can be applied to develop small molecules with anti-retroviral activity that target host factors important for HIV–1 replication [4].

Isoxazoles are five-membered aromatic heterocycles containing adjacent oxygen and nitrogen atoms. The structure of Isoxazoles was shown in Fig 1. The isoxazole ring system is found in a variety of naturally occurring compounds and biologically active molecules Also varied medicinal activities such as which is 4–amino – 3 – isoxazolidine possessing antibacterial [5], antibiotic, antioxidant [6], Anti-diabetic [7], antidepressant and anxiolyticactivity [8], anticancer activities [9], anti-fungal [10] have been reported for isoxazole derivatives. Isoxazole moiety has been incorporated into a wide variety of therapeutically interesting drug candidates including AMPA receptor agonist, antithrombin activity, anti-rhinovirus agents, antidepressants, antinociceptive activity, antibacterial, anticonvulsant activity, nonnucleoside HIV-1 reverse transcriptase inhibitor, antitumor, cox-1/cox-2 inhibitor, HDAC inhibitor, antitubulin activity, 5-HT reuptake inhibitor, adrenoceptor antagonist, humoral immune response inhibitor and the neurological disorders such as schizophrenia. An attempt is being further made to explore it in an illustrated manner

owing to their clinical significance in medicinal chemistry research. The new isoxazole derivatives from 4-methoxy aniline generate N-(4-methoxyphenyl) acetamide, which was hydrolyzed with sodium hydroxide and treated aromatic aldehydes provides the final chemical N-(4-methoxyphenyl) 3-phenyl propanamide, which is tested for analgesic action.

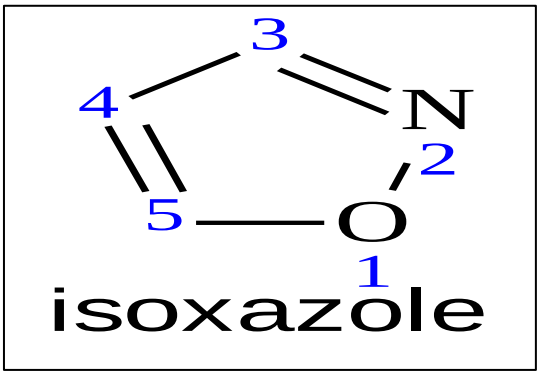


Figure 1: Structure of Isoxazole

MATERIALS AND METHODS

The entire all chemicals used were procured from Loba chemie Pvt. Ltd., Mumbai. Purity of starting materials used for reaction was confirmed by checking their melting point and by thin layer chromatography. All the reactions were monitored using thin layer chromatography. The FT-IR spectrum of the synthesized compounds has been obtained from oxygen health care and research center Pvt, Ltd Ahmadabad, Gujarat. The IR spectra were carried out by FT-IR (KBr Press Pellet) spectra were recorded on SHIMADZU Spectrophotometer (λ_{max}).

METHODOLOGY

Method of Preparation of Synthesis of N-(4-methoxyphenyl) acetamide:

The N-(4-methoxyphenyl) acetamide was prepared by the condensation of 4-methoxy anilline (1.09 gm, 0.01 mol) with acetyl chloride (0.78 ml, 0.01 mol) by refluxing for 20-30 mins. The product obtained was isolated dried overnight, which was confirmed through TLC and recrystallized with ethanol.

Method of Preparation of Synthesis of N-(4-methoxyphenyl) 3-phenyl propanamide:

To a mixture of equimolar quantities of N-(4-methoxyphenyl) acetamide and aromatic aldehydes in ethanol (25 ml), 2 % NaOH solution (1 ml) was added and stirred for 10.00 hrs at room temperature. Then it was refluxed for 6.00 hrs on a water bath. The excess of solvent was removed under reduced pressure. It was poured into ice-cold water. The solid thus separated was filtered, dried and recrystallized from ethanol to obtain the N-(4-methoxyphenyl) 3-phenyl propanamide in pure form. Scheme for the synthesis of N-(4-methoxyphenyl)-5-phenyl-4,5-dihydroisoxazol-3-amine (BSM-IIIA-IIIJ) shown in Figure 2.

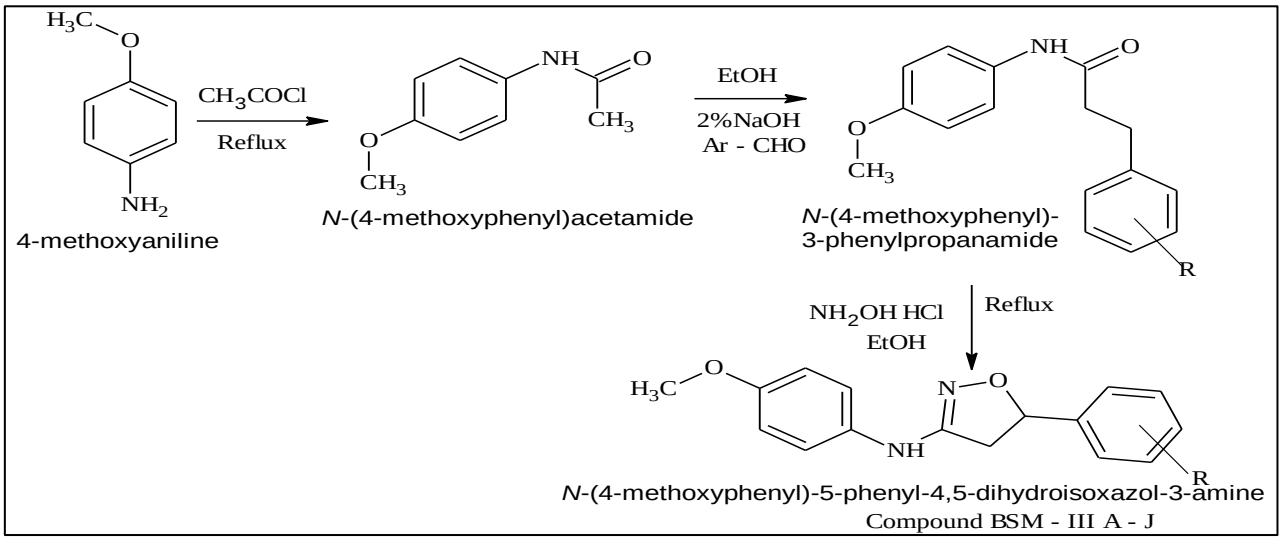
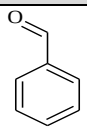
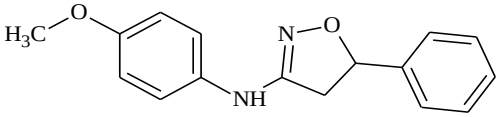
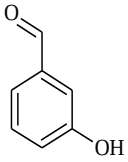
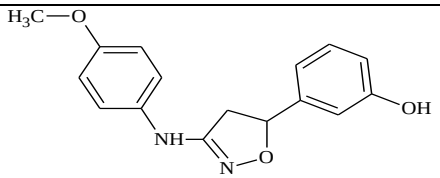
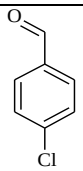
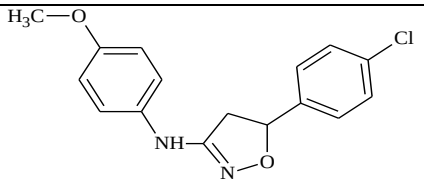
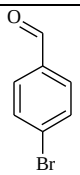
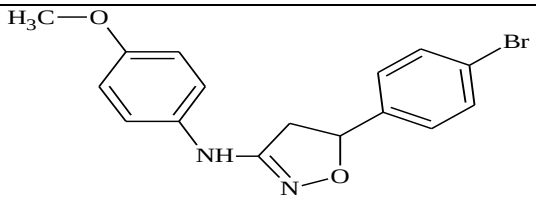
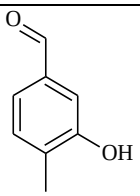
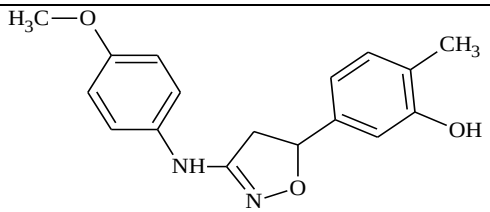
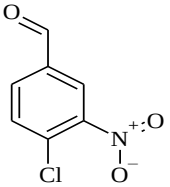
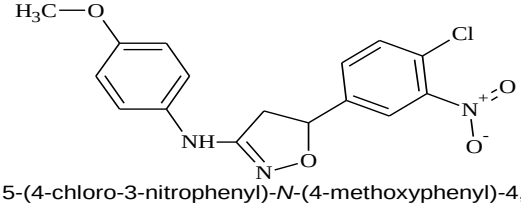


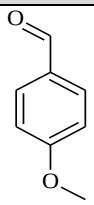
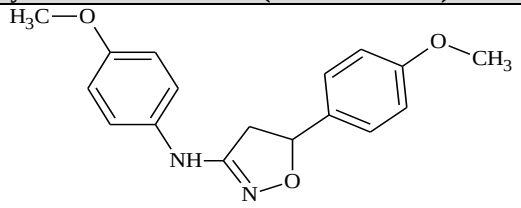
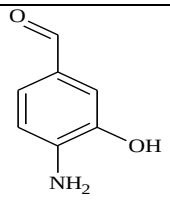
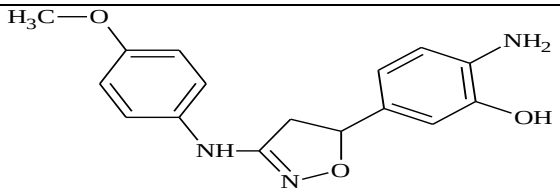
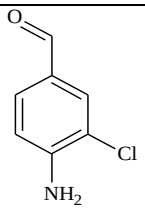
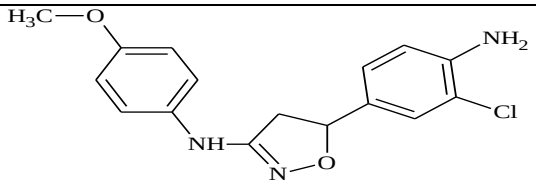
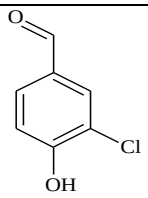
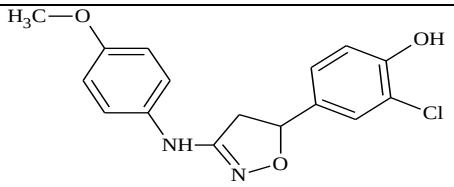
Figure 2: Representative Scheme for the synthesis of N-(4-methoxyphenyl)-5-phenyl-4,5-dihydroisoxazol-3-amine

Method of Preparation of Derivatives of N-(4-methoxyphenyl)-5-phenyl-4,5-dihydroisoxazol-3-amine (BSM-IIIA-IIIJ):

To a mixture of N-(4′-methoxyphenyl)-3-substituted-propanamides (0.01mol) and hydroxylamine hydrochloride (0.69 gm, 0.01mol) in ethanol (25ml) was refluxed on a water bath for 6.00 hrs. The reaction mixture was concentrated under reduced pressure. It was cooled and poured into ice-cold water. The solid separated was filtered, dried and recrystallized from ethanol. Derivatives of N-(4-methoxyphenyl)-5-phenyl-4,5-dihydroisoxazol-3-amine (BSM-IIIA-IIIJ) was shown in Table 1.

Table 1: Derivatives of N-(4-methoxyphenyl)-5-phenyl-4, 5-dihydroisoxazol-3-amine (BSM-IIIA-IIIJ)

Compound Code	Substituted Name With Structure	Derivatives of N-(4-methoxyphenyl)-5-phenyl-4,5-dihydroisoxazol-3-amine (BSM-IIIA-IIIJ)
BSM-IIIA	 benzaldehyde	 *N*-(4-methoxyphenyl)-5-phenyl-4,5-dihydroisoxazol-3-amine
BSM-IIIB	 3-hydroxybenzaldehyde	 3-{3-[(4-methoxyphenyl)amino]-4,5-dihydroisoxazol-5-yl}phenol
BSM-IIIC	 4-chlorobenzaldehyde	 5-(4-chlorophenyl)-*N*-(4-methoxyphenyl)-4,5-dihydroisoxazol-3-amine
BSM-IIID	 4-bromobenzaldehyde	 5-(4-bromophenyl)-*N*-(4-methoxyphenyl)-4,5-dihydroisoxazol-3-amine
BSM-IIIE	 3-hydroxy-4-methylbenzaldehyde	 5-{3-[(4-methoxyphenyl)amino]-4,5-dihydroisoxazol-5-yl}-2-methylphenol
BSM-IIIF	 4-chloro-3-nitrobenzaldehyde	 5-(4-chloro-3-nitrophenyl)-*N*-(4-methoxyphenyl)-4,5-dihydroisoxazol-3-amine

Compound Code	Substituted Name With Structure	Derivatives of N-(4-methoxyphenyl)-5-phenyl-4,5-dihydroisoxazol-3-amine (BSM-IIIA-IIIJ)
BSM-IIIG	 4-methoxybenzaldehyde	 *N*,5-bis(4-methoxyphenyl)-4,5-dihydroisoxazol-3-amine
BSM-IIIH	 4-amino-3-hydroxybenzaldehyde	 2-amino-5-{3-[(4-methoxyphenyl)amino]-4,5-dihydroisoxazol-5-yl}phenol
BSM-IIII	 4-amino-3-chlorobenzaldehyde	 5-(4-amino-3-chlorophenyl)-*N*-(4-methoxyphenyl)-4,5-dihydroisoxazol-3-amine
BSM-IIIJ	 3-chloro-4-hydroxybenzaldehyde	 2-chloro-4-{3-[(4-methoxyphenyl)amino]-4,5-dihydroisoxazol-5-yl}phenol

BIOLOGICAL EVALVATION

The animals used in the examination were sheltered in analogy of the Maratha Mandal's Nathajirao G Halgekar Institute of Dental Sciences and Research Centre Belgaum animal house, which follows the guidelines and regulation set by the committee for the control and administration of experiments on animals (CPCSEA), Ministry of social justice and empowerment, Government of India. The studies were attempted with previous approval from the Institutional Animal Ethics committee (IAEC) and ultimate care was taken to establish that the animals were handling in the most kind and satisfactory manner. Wister rats and albino mice of either sex, weighing 150-200 gm and 20-25 gm, respectively, were used. Pregnant females were eliminated.

IN-VIVO ANALGESIC ACTIVITY

In-Vivo Analgesic Evaluation

Analgesic activity was carried out by Eddy's hot plate method. Six groups of albino mice of either sex each comprising of four animals, weighing between 20-25gms were deprived of food and water for 12hrs prior to the experiment. The animal with a basal reaction time of less than 8 seconds were considered for the study. The hot plate was stabilized at 55±1°C, the animals are placed on the hot plate and the time until either licking or jumping response with the animals is recorded by a stopwatch, the time taken as the end point. The reaction time was recorded at prefixed time interval i.e., 0, 20, 40, 60, 80, 100 and 120 minutes following oral or subcutaneous administration of the standard or the test compound. The animal experimental data were indicated as mean± SEM. Statistical characteristic between the treatments and the standard were approved by one-way ANOVA pursue by Dunnett's multiple comparison test.

RESULTS AND DISCUSSION

The new Isoxazole derivatives have been successfully synthesized by from 4-methoxy aniline gives N-(4-methoxyphenyl) acetamide which was hydrolysis with sodium hydroxide and treated aromatic aldehydes yields resultant compound N-(4-methoxyphenyl) 3-phenyl propanamide (BSM-IIIA-IIIJ).

A synthesized compound BSM-IIIF i.e. 5-(4-chloro-3-nitrophenyl)-*N*-(4-methoxyphenyl)-4,5-dihydroisoxazol-3-amine was confirm by IR spectra characteristic peak of -NH Hydroxy at 1690-1750cm^{-1}**,** Aromatic CH stretching at 2900-3180cm^{-1}, Aliphatic CH at 2390-2550cm^{-1}, -NO_2 at 1480-1590 cm^{-1}, Alkyl Group –OCH_3 at 1100-1210 cm^{-1}. An IR spectrum was shown in Figure 3.

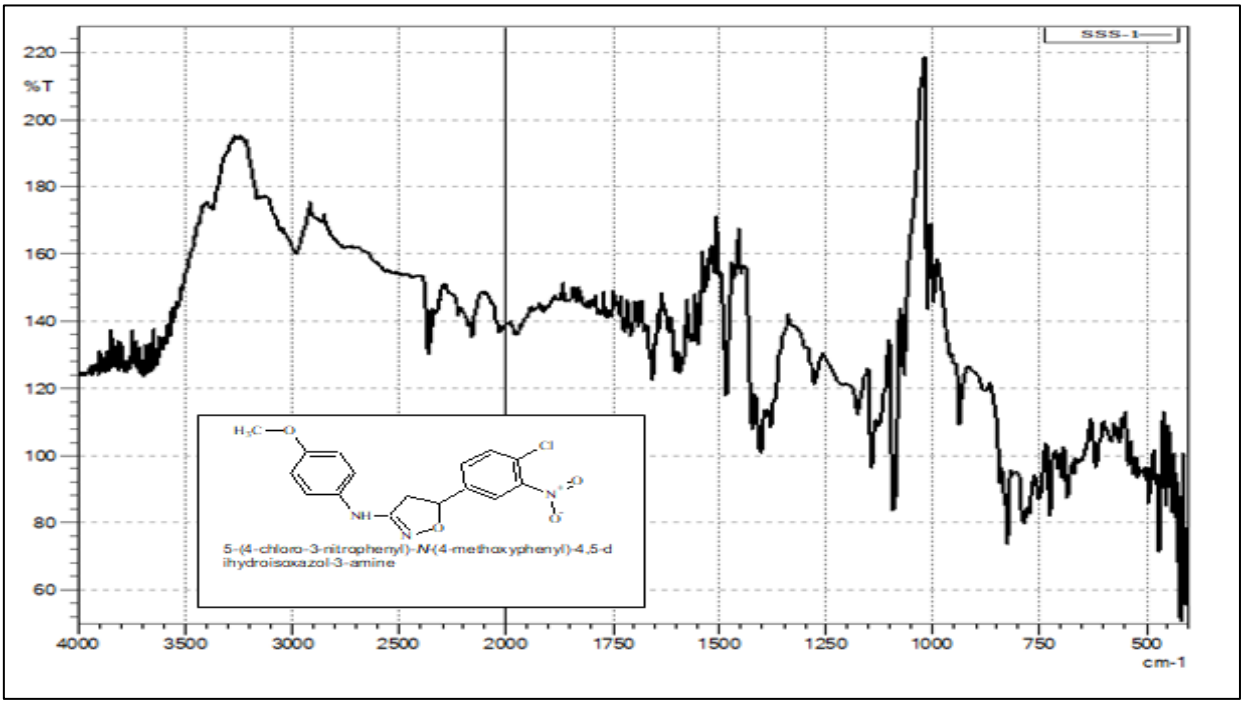


Figure 3: FT-IR Spectrum of Compound BSM-IIIF

A synthesized compound BSM-IIIH i.e. 2-amino-5-{3-[(4-methoxyphenyl)amino]-4,5-dihydroisoxazol-5-yl}phenolthe was confirm by IR spectra characteristic peak of-OH Hydroxy at 3010-3150cm^{-1}, Aromatic CH stretchingat 2920-3140cm$^{-1,}$ Aliphatic CH at 2405-2550cm^{-1}, -NH_2 at 1530-1620 cm^{-1}, Alkyl Group –OCH_3 at 950-1010 cm^{-1}. An IR spectrum was shown in Figure 4.

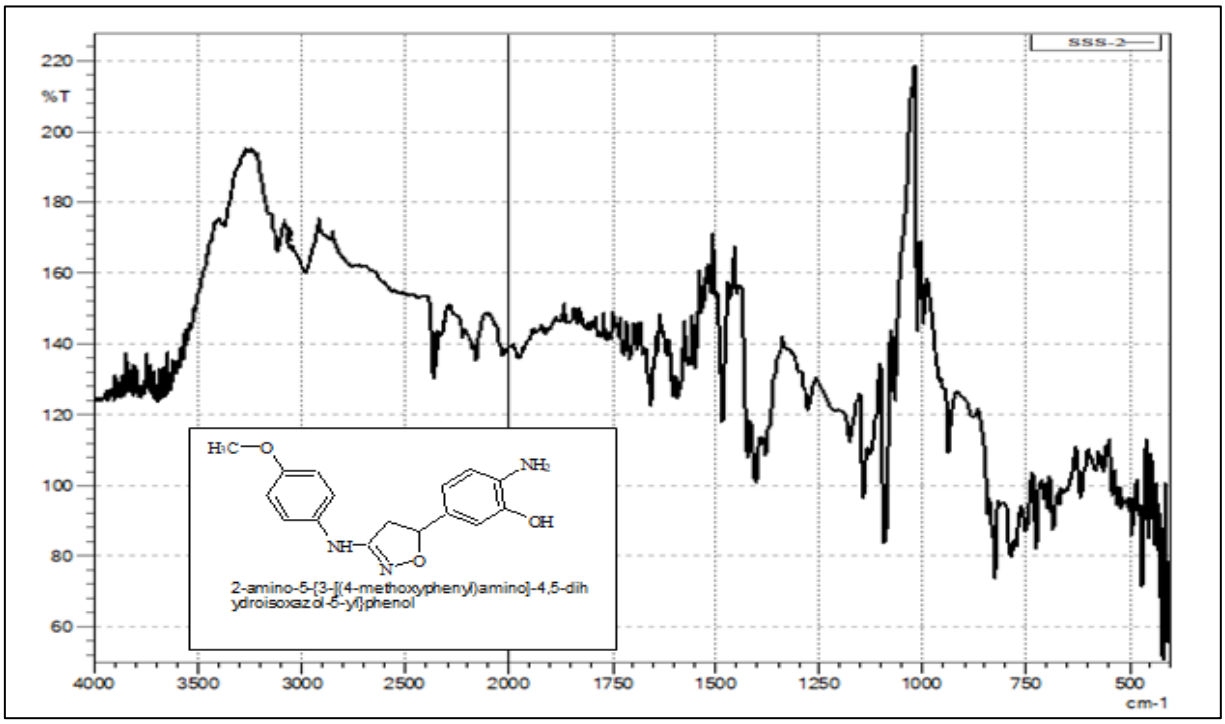


Figure 4: FT-IR Spectrum of Compound BSM-IIIH

A synthesized compound BSM-IIIF confirm by 1H-NMR spectra characteristic peak of δ 1.00-2.00(-OCH3), δ 4.1-5.0 (-NH), δ 6.6-8.9 (Ar-H multiplate). 1H-NMR spectrum was shown in Figure 5.

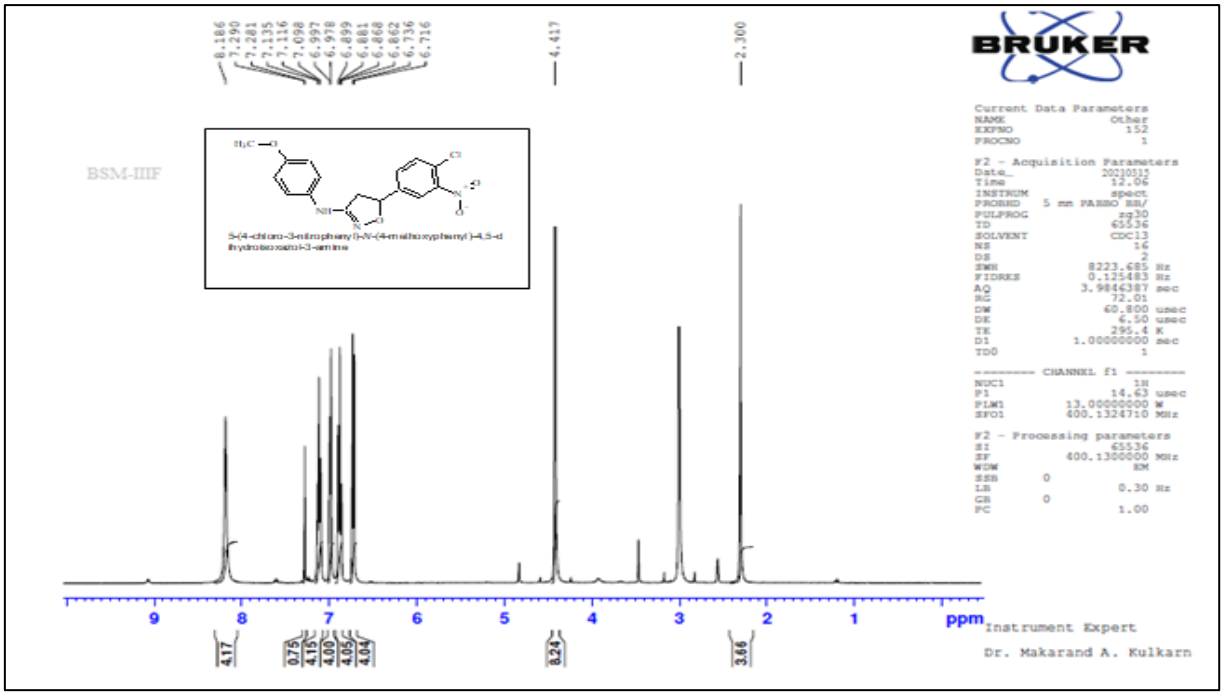


Figure 5: 1H-NMR Spectrum of Compound BSM-IIIF

A synthesized compound BSM-IIIH confirm by 1H-NMR spectra characteristic peak of δ 2.00-3.00 (-CH3), δ 4.0-5.0 (-NH singlet) δ 6.1-8.8(Ar-H multiplate),δ8.9-9.1 (-OCH3),δ11.01 (-OH) 1H-NMR spectrum was shown in Figure 6.

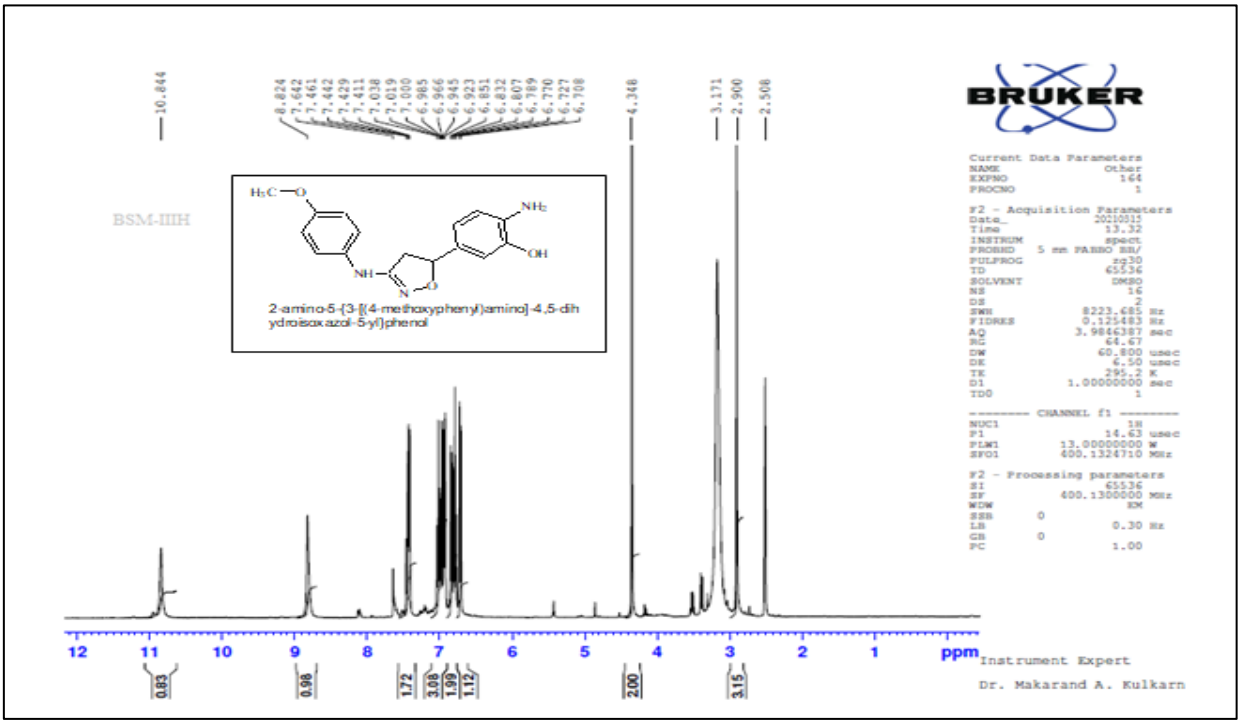


Figure 6: 1H-NMR Spectrum of Compound BSM-IIIH

Synthesized compounds BSM-IIIF confirm by mass spectra of M^+ Peaks at m/z 347 and Base Peak was 314.6 and molecular weight of compound BSM-IIIF was 347 mass spectrums was shown in Figure 7.

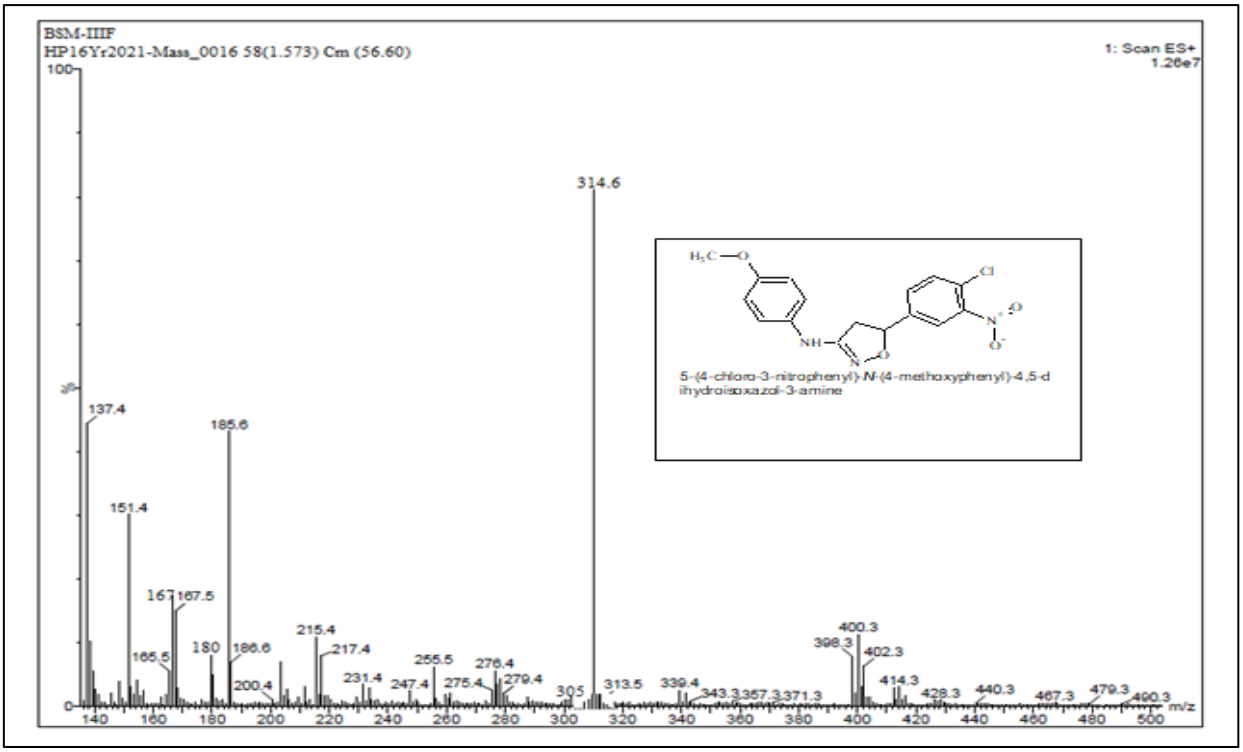


Figure 7: Mass Spectrum of Compound BSM-IIIF

Synthesized compounds BSM-IIIH confirm by Mass spectra of M^+ Peaks at m/z 299 and Base Peak was 248 and molecular weight of compound BSM-IIIH was 299 mass spectrums was shown in Figure 8.

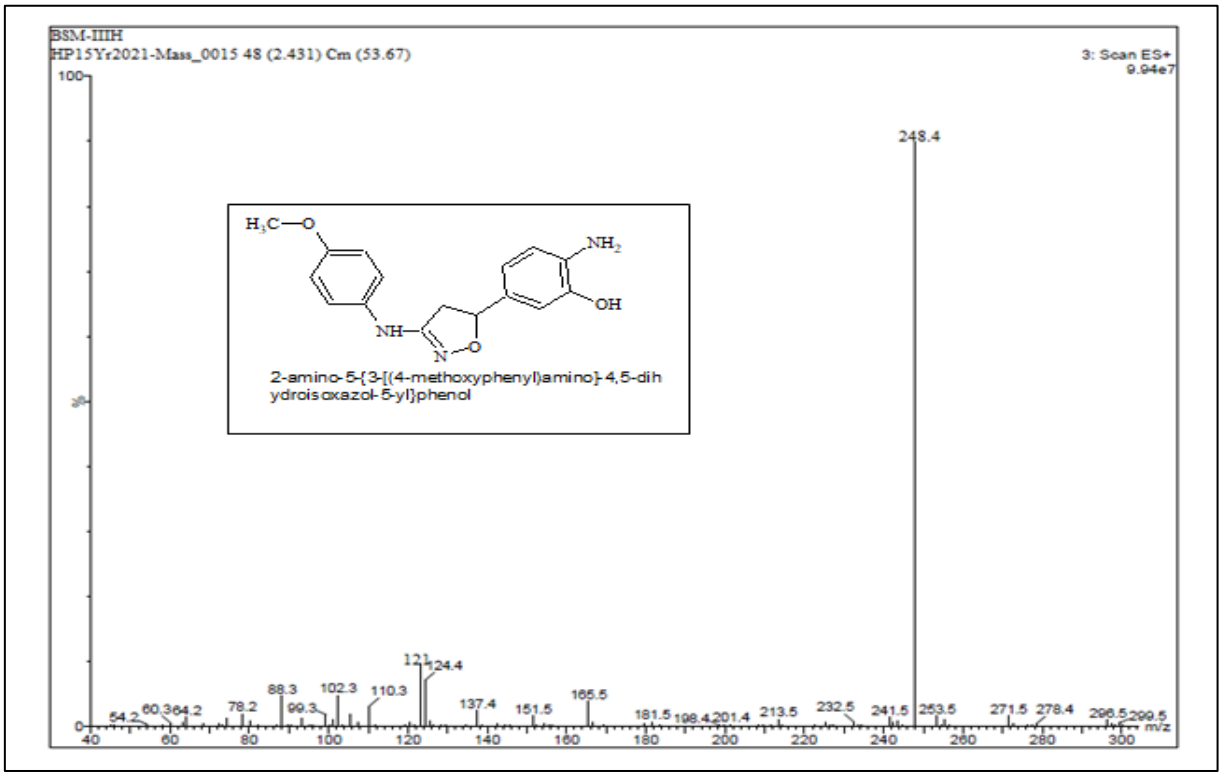


Figure 8: Mass Spectrum of Compound BSM-IIIH

***In-vivo* analgesic activity**

The derivatives of N-(4-methoxyphenyl)-5-phenyl-4,5-dihydroisoxazol-3-amine (BSM- IIIA-IIIJ) have shown a significant Analgesic activity. Results are tabulated in table no.2 and graph was shown in Figure 9.

The compounds BSM-IIIC and BSM-IIIF have shown potent Analgesic activity. The compounds BSM-IIIA and BSM-IIID showed a moderate analgesic activity. The other compound also showed a significant analgesic activity till 120 minutes.

Table 2: Data showing *In-vivo* analgesic activity of Derivatives of N-(4-methoxyphenyl)-5-phenyl-4,5-dihydroisoxazol-3-amine (BSM-IIIA-IIIJ)

Sr. No	Compound	Basal reaction time(Sec.)after						
		0min	20min	40min	60min	80min	100min	120min
1	Control (Gum Acacia)	3.27±0.60	4.32±0.65	4.6±0.53	4.22±0.25	4.14±0.70	4.50±0.81	5.03±0.47
2	Standard (Pentazocin 10mg/kg)	7.45±1.02	16.23±0.22	16.45±1.13	17.48±0.67	17.47±1.56	15.22±0.78	19.73±0.89
3	BSM-IIIA	5.20±0.32	11.23±1.12	12.26±0.35	11.65±0.70	12.56±1.11	14.37±0.34	14.22±0.19
4	BSM-IIIB	4.21±1.10	5.28±0.19	13.44±0.45	12.57±0.82	10.25±1.09	11.66±0.79	11.47±1.25
5	BSM-IIIC	4.44±0.56	10.23±0.22	12.45±1.13	12.48±0.67	14.48±1.06	14.22±0.18	16.73±0.89
6	BSM-IIID	5.85±0.66	9.03±0.94	13.21±0.85	13.71±0.70	14.58±1.56	15.74±0.78	14.23±0.56
7	BSM-IIIE	4.89±1.74	6.13±0.62	6.45±1.05	11.45±0.97	12.44±1.33	11.27±0.19	13.52±0.67
8	BSM-IIIF	5.78±1.62	10.03±0.22	13.54±1.54	15.27±0.67	15.87±0.45	16.01±0.70	16.73±0.13
9	BSM-IIIG	3.45±1.02	6.32±0.22	6.45±1.63	7.88±0.98	9.47±1.86	10.22±1.08	11.03±0.09
10	BSM-IIIH	2.35±0.36	5.20±0.35	6.05±1.30	6.88±0.90	7.47±0.20	9.32±1.30	12.10±0.39
11	BSM-IIII	3.15±0.72	6.10±0.15	8.15±1.91	8.78±1.10	8.80±1.36	9.75±1.45	11.63±0.80
12	BSM-IIIJ	2.80±1.60	5.02±1.10	7.45±0.63	7.90±0.75	8.17±1.05	10.05±1.58	12.54±1.23

Dose 20, 25 mg/kg for analgesic activity, Mean ± SEM, n=4

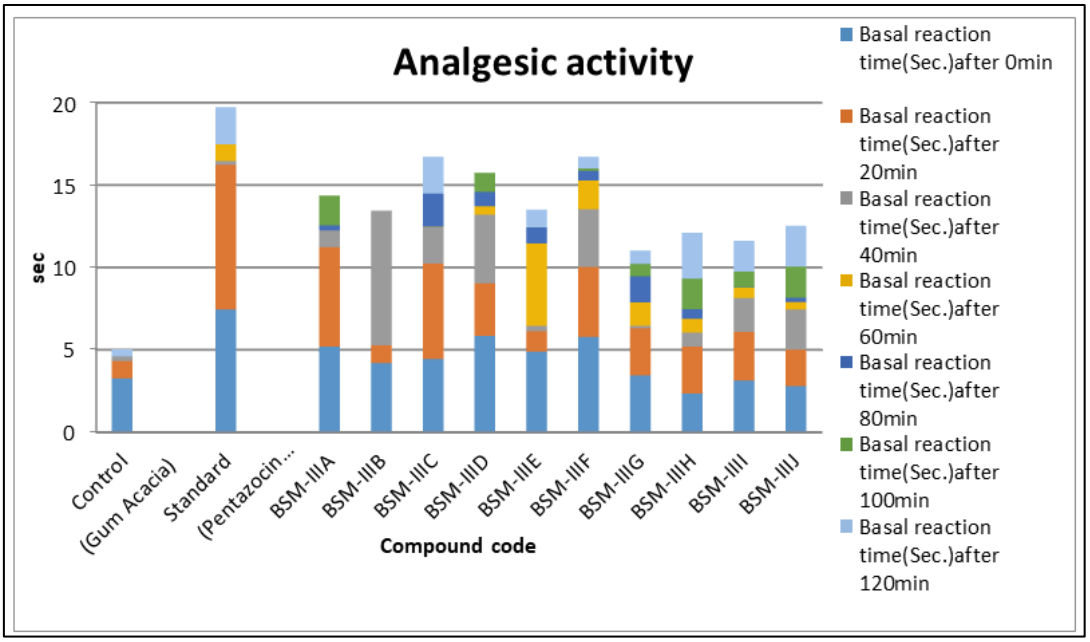


Figure 9: Data showing analgesic activity of Derivatives of N-(4-methoxyphenyl)-5-phenyl-4,5-dihydroisoxazol-3-amine (BSM-IIIA-IIIJ)

CONCLUSION

Synthesize new derivatives of Isoxazole which has been considered as active moiety and is a core structure in a various synthetic pharmaceuticals displaying a wide spectrum of biological activities. All the derivatives synthesized were screened for their analgesic activity. The analgesic activity screening of the compounds suggests that these possessed significant analgesic activities that are comparable with the standard drug. Hence, in search for new generation of drugs with high potency, selectively and reduced toxicity, it may be worthwhile to explore the possibility in this area by fusing different moieties. If suitably exploited it may results in better compounds.

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